Impacts, Assimilations, and Adaptations within the Architectures of Regulatory Oversight, Capital Structures, Medicalization, and Governance of Precision Medical Technologies

by

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ABSTRACT

This dissertation investigates and describes the concept of precision medicine from historical, conceptual, capital investment, industry strategic, regulatory oversight, and medicalization perspectives. The study examines the various current and ongoing challenges, impacts, assimilations, and actual adaptive measures occurring within each of these areas as a result of the emergence and continued evolution of precision medicine as a medical discipline, as well as the technosocial advancements characteristic of precision medical products, such as companion diagnostics and targeted therapeutics, seeking market entry in the United States. The dissertation argues that there is a disjunction between precision medicine and historical governance, oversight, and medical practice mechanisms. Through case studies of two case products, Foundation Medicine's F1CDx companion diagnostic and Novartis' Kymriah CAR-T Cell therapeutic, the dissertation illustrates the impacts, destabilization and destandardization effects, and re-standardization efforts around a precision medicine diagnostic and therapy. As a central contribution, this dissertation demonstrates and illustrates the impact(s) that precision medicinal technologies are having on the technoscientific network involved in the creation, development, evaluation, governance, and implementation of medical products in the United States. Results revealed an emerging precision medical innovation model between and among member components of a precision medical ecosystem comprised of the above-mentioned focal areas and that, to fully understand the emerging precision medical innovation model, it is critical to understand not only the impacts of precision medical technologies on the individual components of the precision medicine ecosystem, but also

the impacts, adaptations, assimilations, and occlusions inherent to the ecological relations within and across the ecosystem itself. Findings include the destabilization of the traditional drug development process across all stakeholder areas, characterized by the development of non-linear adaptive processes at both the premarket and post-market phases. Although the findings from this study are significant, it is likely that they are temporary in nature and will continue to evolve in accordance with the further advancement of precision medicine, ultimately re-stabilizing the precision medical development ecosystem.

DEDICATION

I would like to thank my family for their unwavering support, confidence, patience, and inspiration. None of this would have been possible without you and I thank you with all of my heart and soul.

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TABLE OF CONTENTS

APPENDIX Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

Chapter 1 – Introduction

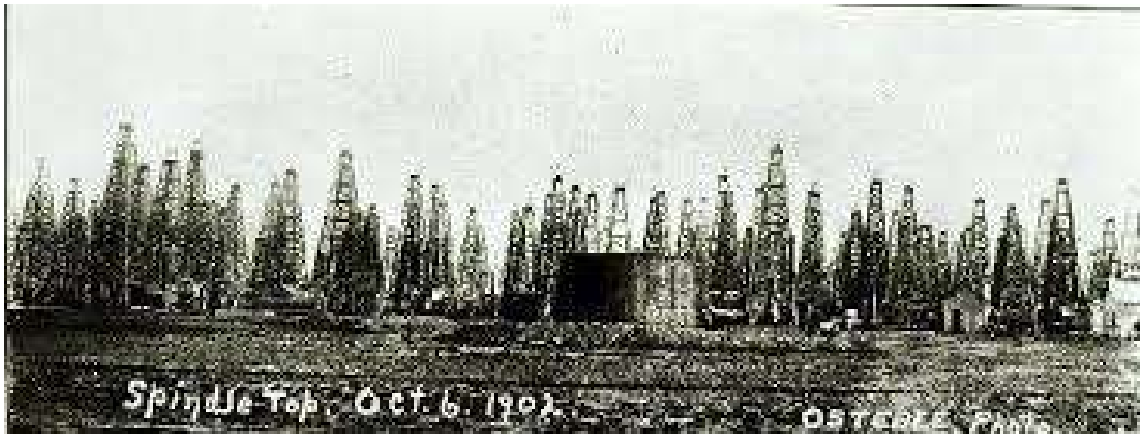
On January 10, 1901, an enormous geyser of oil exploded from a drilling site at Spindletop Hill (see Figure 1), a mound created by an underground salt deposit located near Beaumont in Jefferson County, southeastern Texas (History, 2019).

Figure 1: Spindletop Oil Geyser

Reaching a height of more than 150 feet and producing close to 100,000 barrels a day, the "gusher" was more powerful than any previously seen in the world. A booming oil industry soon emerged around the oil field at Spindletop (see Figure 2), and many of the major oil companies in America, including Gulf Oil, Texaco, and Exxon, can trace their origins

to this location (History, 2019). This event is credited with launching America's oil boom and transforming the energy industry in the United States.

Figure 2: Spindletop-October 1902



Similar to the alacrity that ensued following the Spindletop geyser, in 2000 President Clinton, along with NIH Director Dr. Francis Collins, announced the successful sequencing of the human genome, which indicated the successful culmination of the Human Genome Project (HGP). This monumental accomplishment was enabled by advances in DNA sequencing technology that allowed data production to far exceed the original description of Sanger sequencing (Sanger, Nicklen, and Coulson, 1977). In doing so, they spoke to the enormous promise such advancements held for the treatment and potential eradication of the most devastating diseases of our time. Just as the Spindletop geyser impacted the American energy industry, this event served as an inflection point for the medical and biomedical research communities. Such an accomplishment has led to unprecedented

advancements in the areas of next generation DNA high throughput sequencing, making it possible to delineate genetic variances and molecular aberrations consistent with the presence of and susceptibility to diseases. What emerged is the nascent field of precision medicine, carrying the promise that a person's medical care can one day be tailored to their individual needs based upon data gathered through the sequencing of their genetic information and the subsequent delineation of molecular aberrations consistent with one's individual instance of illness or disease.

More than two decades have passed since President Clinton's announcement and genetic sequencing technologies have become more efficient, readily accessible within the scientific community, and cost effective. As Collins stated, now "the challenge is to deliver the benefits of this work to patients" (Hamburg and Collins 2010). According to the FDA (2019), precision medicine involves aligning the right drugs or treatments with the right patient, based on a genetic or molecular understanding of their disease. The idea behind this concept is that one person's disease isn't the same as someone else who seemingly has the same disease.

Genetic attributes inherited by an individual and influenced by their environment can impact health, disease symptomatology, and the efficacy of treatments. Precision medicine attempts to understand more about how such variations in our genes, proteins, and other factors influence our health and response to medical interventions. This approach has been

enabled by technoscientific developments in sequencing technologies, analytics, and scalability from DNA strand to genomic level interrogation.

DNA Sequencing

The advancements discussed by President Clinton and Dr. Collins in 2000 were predicated by genetic discoveries that occurred several decades earlier. Frederick Sanger's studies of insulin first demonstrated the importance of sequence in biological macromolecules and, in 1953, James Watson and Francis Crick reported the discovery of the DNA double helix, the molecule that carries genetic information from one generation to the other, and that genes are made up of, deoxyribo-nucleic-acid (DNA). Fifteen years elapsed between Watson and Crick's discovery of the DNA double helix and the first experimental determination of a DNA sequence, reported by Sinsheimer to be the genome of bacteriophage X174 (1959).

The next major discovery, leading to the eventual path of DNA sequencing, was the discovery of type II restriction enzymes by Hamilton Smith and his colleagues. In addition, it was soon found that enzymes recognizing many different sequences could be identified by screening bacterial strains (Middleton, Edgell, & Hutchison, 1972). The restriction enzymes provided a method for cutting a large DNA molecule into a number of smaller pieces that could be separated by size using gel electrophoresis. These pieces had specific ends that could function as starting points for the sequencing methods that developed over the next few years.

Unlike amino acid sequences of proteins, the DNA sequence of the X genome could be interpreted to tell a fascinating story based upon interpretation of the sequence in terms of the genetic code (Barrell & Hutchison, 1976). Analysis of mutations in genes identified by traditional phage genetics, combined with amino acid sequence information for protein components of the X virion, allowed phage genes to be located on the DNA sequence. For the first time translation of a DNA sequence in all possible reading long open reading frames that could be assigned to genes identified by traditional genetic methods. And, most surprising, it was clear that significant portions of the genome were translated in more than one reading frame to produce two different protein products. According to Barrell and Hutchison, these pairs of 'overlapping genes' had not been detected by recombination mapping of the X genome, but their existence was indisputable when the sequence was analyzed in light of genetic and protein sequence information (1976).

Bioinformatics

Beginning with the X genome, the management and analysis of sequencing data became, and continues to be, a major undertaking. The original X genome data was contained in the notebooks of nine different workers each concerned with particular portions of the molecule (Smith & McCallum, 1977). Smith and McCallum wrote the first programs to help with the compilation and analysis of DNA sequence data in COBOL by transcribing manually deduced sequences onto paper forms, which were entered on punched cards (1977).

Subsequently, and with the proliferation of DNA sequence data, came the need for a DNA sequence database. Margaret Dayhoff was the early pioneer in this area. She had previously established a protein sequence database and published the first collection of nucleotide sequencing information in 1981 (Dayhoff, Schwartz, Chen, Hunt, Barker, & Orcutt, 1981). Shortly thereafter, GenBank was created by the NIH to provide a 'timely, centralized, accessible repository for genetic sequences' (Bilofsky, Burks, Fickett, Goad, Lewitter, Rindone, Swindell & Tung, 1986).

As the sequence databases grew, methods to compare and align sequences soon became a rate-limiting step in the analysis of sequence data. The development of rapid search programs such as FASTA (Pearson & Lipman, 1988) and BLAST (Altschul, Gish, Miller, Myers, Lipman, 1990) made it practical to identify genes in a new sequence by comparison to all sequences already in the databases.

The Human Genome

Eventual sequencing of the human genome became an imaginable goal at the outset of the sequencing era over 30 years ago. In 1990, the U.S. Department of Energy and National Institutes of Health presented a joint 5-year US Human Genome Project plan to Congress. The U.S. Human Genome Project established goals of mapping, and in some cases sequencing, several model organisms as well as humans. These included *E. coli*, yeast (*S. cerevisiae*), the worm (*C. elegans*), drosophila (*D. melanogaster*) and mouse (laboratory strains of *Mus domesticus*). It was estimated that the project would take 15 years and cost approximately 3 billion U.S. dollars.

Concurrently, under the guidance of President Dr. J. Craig Venter, Celera Corporation was performing human genome sequencing using the Whole Genome Shotgun WGS) strategy. The WGS approach involves the whole genome being separated into millions of fragments, which are sequenced individually and reassembled to produce a series of sequence "scaffolds". This approach was used to sequence several genomes.

Human genome sequencing began in September 1999 and continued until June 2000, when data collection was completed and an initial assembly was achieved. Sequencing of the human genome captured public attention in a way that is extremely rare for a scientific topic. Several books for the general public have centered around the 'race' for the human genome sequence (Wickelgren, 2002). Leaders of the public and the private projects have even published books describing events from their own personal perspectives.

Next Generation Sequencing

In the years that followed, methods emerged that challenged the supremacy of the previous dideoxy method. These methods are commonly called Next Generation Sequencing (NGS). A significant feature of NGS methods is that they are characterized as 'massively parallel', meaning that the number of sequence reads from a single experiment is vastly greater than those of prior methods. That being said, this very high throughput is achieved with substantial sacrifices in length and accuracy of the individual reads when compared to Sanger sequencing. Nonetheless, assemblies of such data can be highly accurate because of the high degree of sequence coverage obtainable. The methods are designed for projects that employ the whole genome sequencing approach and are most readily applied to

resequencing, in which sequence data is aligned with a reference genome sequence in order to look for differences from that reference. The continued emergence of NGS technologies makes it possible to analyze massive amounts of data in a matter of seconds or minutes, instead of days or weeks as in the past. It is this type of efficiency that has provided the medical community with optimism that incorporation of genetic and genomic information into medical practice may, in fact, be achievable and cost effective.

Project Overview

My research focused on the complex sociotechnical intersection of precision medical technologies, regulatory processes, capital structures, methods of governance, and patient-consumers. Specifically, I utilized science and technology studies concepts such as bioconstitutionalism, actor network theory, biocapitalism, and co-production to augment my understanding, conceptualization, and theorize the challenges and ongoing adaptive measures being implemented by various precision medical stakeholders surrounding risk, investment, capital structures, regulatory science, medicalization, and governance of precision medical technologies deliberated and considered for release into the U.S. market. As I will present in this dissertation, these focal areas represent a precision medical ecosystem comprised of interdependent essential components within which novel therapeutics and diagnostics are created, validated, tested, evaluated, and ultimately approved for market.

This project sought to capture and theorize the implications for patients and society in the context of a co-produced complex technoscientific regime comprised of regulatory,

governance structures, and ethical doctrine surrounding precision medical technologies and their approval for marketing in the United States (U.S.). This approach provides a different kind of insight into the field of precision medicine – allowing for an understanding of co-produced knowledge and adaptive measures within a complex and inter-related sociotechnical regulatory, capital, and governance regime in response to technoscientific advancements such as NGS, companion diagnostics, and targeted therapeutic compounds.

This dissertation is not simply concerned with plans, espoused values, and ideas about the field of precision medicine, but also how decisions are actually made in practice with regard to investment, risk analysis, and considerations for precision medical technologies as they proceed from pre-market application to post-marketing approval by the U.S. Food and Drug Administration (FDA). To address this question, I built my project around two case studies for precision medical technologies and their journeys from pre-market application to post-market approval, Foundation One's F1CDx test and Novartis' Kymriah (tisagenlecleucel) gene therapy treatment. These case studies are relevant to such an analysis in that they represent the first products of their kind to seek marketing approval in the US. As such, their transition from pre-market application to post-market approval required the co-production and adaptation of approaches toward risk analysis and regulation of novel precision-medical technologies, which differ from traditional non-molecular therapeutic and diagnostic products.

Methodology for this project included qualitative methods involving the accession and analysis of both primary and secondary sources as a means of describing and analyzing regulatory, ethical, and scientific policy aspects of the evolving field of precision medicine. Primary sources included archived regulatory submissions, correspondence, documentation of deliberations, press releases, and approval documents. In addition, documentation of interviews with the FDA, medical practitioners, technology transfer/venture capital firms, and biopharmaceutical and medical device companies are included as primary sources.

For the background and overview of precision medicine, I accessed and interrogated primary and secondary sources to characterize the construct of precision medicine with an in-depth analysis of what constitutes a disease in the precision medicine era, how treatments can be tailored to patients and their individual instances of disease, and sources of knowledge development and mobilization. Primary sources include regulatory, governance, and policy-related documentation from the FDA, NIH, and National Science Foundation (NSF). Secondary sources include current STS scholarship, as well as journal articles and publications relevant to the precision medical field.

For the F1CDx test case study, primary sources include Foundation One's *Summary of Safety and Effectiveness* application to the FDA, as well as FDA labeling, fact sheets, premarket approval letter, product classification, approval letter, press releases, and other archived documents. Objectives associated with the review and analysis of the F1CDx

test include the description and delineation of the product and its regulatory review and approval process, including applicable historical and exploratory governance policies (as applicable) allowing for its market approval and risk analysis deliberations *vis-a-vis* clinical efficacy warranting U.S. market approval. My analysis of the F1CDx case study sought to address the following questions:

1. What aspects of the F1CDx test make it applicable to the evolving field of precision medicine and its new taxonomy of disease?
2. What aspects of the F1CDx test make it relevant to precision medicine's espoused promise to provide the right treatment to the right patient at the right time?
3. What is the development and regulatory approval process for F1CDx and similar technologies?
4. What governance structures, civic epistemologies, capital structures, policies, and actions played a role in the development of a complex technoscientific review and approval regime, rendering it capable of evaluating and approving such a technology?
5. Whose well-being is being prioritized or invoked in the creation of such knowledge and risk/benefit analysis from this regime and what bioconstitutional consequences emerge as a result of such knowledge mobilization?
6. What theoretical frameworks and implications lend themselves to the analysis of these technologies and their impacts on the co-production of knowledge, process, and biosociality?

For the Kymriah (tisagenlecleucel) case study, primary sources included Novartis' *Biologics License Application (BLA)*, information requests, risk evaluation and mitigation strategies, meeting proceedings, approval letters, and other archived documents. Objectives associated with the review and analysis of Kymriah included the description and delineation of the product and its regulatory review and approval process, including applicable historical and exploratory governance policies (as applicable) allowing for its market approval and risk analysis deliberations vis a vis clinical efficacy warranting U.S. market approval. Similar to F1CDx, my analysis of the Kymriah case study sought to address the following questions:

1. What aspects of Kymriah make it applicable to the evolving field of precision medicine and its new taxonomy of disease?
2. What aspects of Kymriah make it relevant to precision medicine's espoused promise to provide the right treatment to the right patient at the right time?
3. What is the development and regulatory approval process for F1CDx and similar technologies?
4. What governance structures, civic epistemologies, capital structures, policies, and actions played a role in the development of a complex technoscientific review and approval regime, rendering it capable of evaluating and approving such a technology?

5. Whose well-being is being prioritized or invoked in the creation of such knowledge and risk/benefit analysis from this regime and what bioconstitutional consequences emerge as a result of such knowledge mobilization?
6. What theoretical frameworks and implications lend themselves to the analysis of these technologies and their impacts on the co-production of knowledge, process, and biosociality?

I also provide a description of the similarities and differences of the regulatory, scientific policy, and ethical considerations related to the market approval processes for both F1CDx and Kymriah. Such comparisons include STS framework characterization and analyses. To assist with this process, I drew upon salient STS scholarship, theorists, frameworks, and writings. Examples of such frameworks include biocapital (Sunder Rajan), bioconstitutionalism (Jasanoff), and actor network theory (Latour).

For my capital structures analysis, I identified and interviewed a prominent university-based technology-transfer office and venture capital firm. In doing so, I sought to evaluate the processes and decision points they assess when considering issues like potential return on investment, market valuation, and their associated invest or decline decision points as they relate to medical technologies. I also presented the construct of precision medicine and asked them to describe the impact(s) such technologies have had on the above-mentioned funding evaluation process. Specific questions addressed were the following:

1. What attributes, return on investment opportunities, or potential market value characteristics do you seek to identify when considering providing capital investment in medical technologies and interventions?
2. How have those attributes changed or been impacted by the emergence of precision medical therapeutics and diagnostics and how are such products evaluated differently than traditional medical products when considering capital investment?

The central aim of this dissertation was to illuminate, understand and offer novel insight into the impacts of precision medical technologies as they relate to the co-production of real adaptive mechanisms within governance structures, the practice of medicine, capital investment, and the resulting bioconstitutional, and biocapital frameworks through which patients, practitioners, regulators, and investors interact with such technologies. The overarching question for this project can be summarized as the following: **What assimilations, occlusions, or adaptations have been co-produced or occurred secondary to the emergence of precision medical technologies with respect to patients, medicalization, regulatory processes, and investors (e.g. venture capitalists)?** This is to say that there is a disjunction between precision medicine and historical governance, oversight, and medical practice mechanisms. As a result, and as a means of illumination, I used theoretical concepts/frameworks as necessary and appropriate to describe the different elements at work in the effort to navigate this disjunction.

Given this immense potential ascribed to precision medicine and its promise to facilitate a new era of medicine, my research examines and interrogates the manners and methods through which precision medical technologies are being incorporated into the technoscientific regime of medical product development, evaluation, and market entry within the United States, unifying factors of these components, and the downstream impact(s) on the healthcare system in the United States. That is, the central contribution of this dissertation is the demonstration and illustration of the impact(s) that precision medicinal technologies are having on the technoscientific network involved in the creation, development, evaluation, governance, and implementation of medical products considered for market approval in the United States. Further, this dissertation demonstrates that that such products are necessarily impacting both the pre-market and post-market phases and the manner and methods through which such products are considered for investment by venture capital funding, the ways in which biopharmaceutical and medical device companies are configuring their business models, the manner in which the FDA identifies with risk when considering such products for market approval, and the downstream physician-patient relationship.

Each of the above-mentioned areas is representative of an individual component of a larger, inter-connected precision medical ecosystem characterized by critical contributions from each of the components, without which precision medical advancements are not possible. As such, the assimilative and adaptive measures of precision medical technologies are not limited to the respective individual components of the precision medical ecosystem, but

also the ecological relations within the ecosystem itself, and the manner in which it approaches, and collectively confronts, such technologies. In the upcoming chapters, this dissertation addresses the specific impacts within each of these essential components, their unifying factors, and the overarching impacts, interactions, and adaptations being implemented by the precision medical ecosystem as a whole.

In summary, in the upcoming chapters I will guide the reader through the concept of precision medicine as a practice, including facilitative advancements and historical milestones. In addition, I present the two case studies interrogated in support of this dissertation as means of exemplification and validation of findings. I will also present the reader with in-depth actual examples of impacts and adaptive measures occurring within the precision medical premarket product development, validation and deliberative processes, and transition to post-market implementation. Lastly, I will summarize research results, implications, driving factors, and takeaways to provide a comprehensive analysis of the current and ongoing impacts, adaptations, and occlusions associated with the continued advancement of precision medicine within each of the aforementioned focal areas, as well as broad adaptations and measures being undertaken by the precision medical ecosystem as a whole in order to advance precision medical products from development to market.

Chapter 2 – Background, Overview, and Challenges of Precision Medicine

Similar to the Pasteurian experiments of the 1800's, the growth of DNA sequencing has largely been contingent upon the development of an actor network, able to assign a value to its possibilities. As Latour characterized, "Give me a lab and I shall raise the world" (Latour, 1988). Pasteurian "applications" were "diffused", as we say, only if it were previously possible to create *in situ* the conditions of a laboratory" (Latour, 1988). But, for Pasteurians, "if these applications were to spread (to) the operating room, the hospital, the physician's office, the wine grower's winery, they had to be endowed with a laboratory" (Latour, 1988). This paradigm is not exclusive to vaccine research. The same scenario exists for DNA sequencing as well. That is, if DNA sequencing and precision medicine are to succeed in their goal to usher in a new era of medicine, one in which unforeseen treatments and curative potential are not merely potentialities, but expectations, their adoption and assimilation will need to occur within multiple settings required to transition such technologies from laboratories to patients and back. Specifically, there have been transformative discoveries in laboratories over the past few decades but, in order for sequencing to gain large scale acceptance and application throughout the medical, regulatory, and pharmaceutical/biotech communities, they must first be empowered by the presence of a macroscale laboratory comprised of physician scientists, biotechnology companies, big pharma, insurance providers, regulatory agencies, politicians, and the public. All of these actors serve to create a network of stakeholders surrounding DNA sequencing technology and they collectively hold the power to transform the construct of medicine in modernity. This is to say, recent biomedical research breakthroughs, including

the sequencing of the human genome and a deeper understanding of the molecular underpinnings of disease, have the potential to transform the taxonomy and manner in which we understand disease, as well as the practice of medicine. One of the most profound changes to medicine is the movement toward tailored therapeutics, or precision medicine. Precision medicine therefore has the potential to optimize targeted delivery and dosing of treatments so patients can receive the most benefit with the least amount of risk, cutting out the difficulties of the current trial-and-error process many patients endure to find the correct drug at the correct dose to treat a condition. For DNA sequencing, precision medicine is tantamount to Pasteur's Pouilly-le-Fort[1]. To expand upon this theme, in subsequent chapters I will describe in detail the impact that precision medicine is having on these aforementioned actors and stakeholders, as each represents an integral aspect of the precision medical ecosystem.

Precision medicine is concurrently a subject of immense public, scientific, and political interest, as well as considerable confusion and divergence regarding the exact manifestation of the practice. Is precision medicine the practice of correlating current and future therapeutic compounds with genetic variances identified through pharmacogenomic or pharmacogenetic tests, thereby retrofitting medications to genetic information? Or, in contrast, is precision medicine the practice of developing therapeutic compounds based upon prospectively gathered data revealing the genomic profile of an individual patient and well as the homogenous and heterogenous properties of their disease? Regardless of the

[1] Pouilly-le-Fort is a French village in the municipality of Vert-Saint-Denis, famous for serving as the location of Louis Pasteur's anthrax experiments with sheep.

manifestation, there are challenges associated with the implementation of precision medicine into medical practice.

It is known that all disease has a genetic basis, whether in genes inherited by the affected individual, environmentally induced genetic changes that produce a cancer, or the genes of a pathogen and their interaction with those of the infected individual. Sequencing of a patients DNA, as well as all major pathogens, is beginning to have a major impact on the diagnosis, treatment and prevention of diseases. For the purposes of this dissertation, we will consider precision medicine to be a medical intervention (e.g. drug) that is predicated by the performance of a companion diagnostic (CoDx), revealing a particular genetic variance that corresponds to the ability of the therapeutic agent to act upon the identified molecular aberration.

Modern medicine is at an inflection point secondary to technological advancements in the evolving field of precision medicine. These technologies are the downstream result of decades of research into the genetic profile of plants, animals, humans, and disease. Concurrent with such advancements and dovetailing into the political aspirations regarding the potential impact of precision medicine, the medical community in the United States, has been confronted with assimilating precision medical practice into its historic architectural underpinnings concerning both disease characterization and therapeutic intervention.

What is a Disease?

One area of impact that precision medicine is having within the medical community is what constitutes a disease in a post-genomic era. That is, advancements in the areas of NGS and the information yielded by such processes have had an impact on the public's understanding of disease, as well as the medical and scientific community seeking to develop a greater understanding of disease and provide ethical and efficacious medical care. In 2011, the National Research Council (NRC) released its vision of a new understanding and taxonomy of disease, in their report entitled *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. According to the NRC, "the rise of data-intensive biology, advances in information technology and changes in the way health care is delivered have created a compelling opportunity to improve the diagnosis and treatment of disease by developing a Knowledge Network, and associated New Taxonomy, that would integrate biological, patient, and outcomes data on a scale hitherto beyond our reach" (National Research Council, 2011, p. 19). This is to say that the concept of precision medicine has facilitated the development of a complex socio-technical network surrounding human genetic information and its characterization of what constitutes a disease. The result has been a disruptive technology for American medicine, pharmaceutical development, and regulatory oversight. Through this technology, DNA sequencing seeks to destandardize how we have historically understood and treated the prevalent diseases of our time. By comparison, Cooper reported that the process of destandardization has been perhaps most

visible in the invention of recombinant DNA, the technique that is credited with having initiated the genetic revolution (2008). Recombinant DNA (or genetic engineering) is a method that allows biologists to generalize the processes of bacterial recombination to the whole of organic life. Precision medicine carries with it the same degree of potential for destandardization for the understanding and treatment of disease.

Precision medicine can be thought of as the use of genetic, genomic, epigenetic, lifestyle, and environmental information in support of a promise that a person's medical care can one day be tailored to their individual needs based upon data gathered through the sequencing of their genetic information and the subsequent identification of genetic variants consistent with their individual instance of illness or disease. One realization that has emerged as a result of this promise is that diseases, like humans and other living organisms, have their own genetic or genomic profiles that can be delineated through advanced sequencing technologies. The World Health Organization distinguishes between genetics and genomics in that genetics scrutinizes the functioning and composition of the single gene whereas genomics addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of the organism (WHO, n.d.).

Medical care and the practice of medicine have historically relied upon the presentation of symptomatology among patients and traditional diagnostic techniques such as laboratory reports from blood draws and diagnostic imaging. Merriam-Webster defines disease as "a

condition of the living animal or plant body or one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms" (Merriam-Webster, n.d.). To frame such a construct within the medical profession, Rosenberg states that "disease begins with perceived and often physically manifest symptoms. In all those centuries before the nineteenth, physicians and their patients had to try to make sense out of these symptoms-imposing an array of speculative mechanisms on the otherwise opaque body" (Rosenberg, 1989, p.5).

The NRC envisions a "Knowledge Network of Disease and New Taxonomy" characterized by the defining and descriptions of disease based upon their intrinsic biology in addition to traditional symptomatology and physical presentation by patients (National Research Council, 2011). According to the NRC, the "physical signs and symptoms are the overt manifestations of disease observed by physicians and patients. However, symptoms are not the best descriptors of disease" (National Research Council, 2011, p. 35). Per the NRC:

> Biology-based indicators of disease such as genetic mutations, marker-protein molecules, and other metabolites have the potential to be precise descriptors of disease. They can be measured accurately and precisely–be it in the form of a standardized biochemical assay or a genetic sequence - thus enabling comparison across datasets obtained from independent studies. Particularly when multiple molecular indicators are used in combination with conventional clinical, histological, and laboratory findings, they offer the opportunity for a more accurate

> and precise description and classification of disease, particularly (National Research Council, 2011, p.36).

This approach suggests the re-characterization and defining of disease from a condition or presentation of symptoms by a patient to a stratified classification system comprised of individual or groups of molecular markers. Current molecular markers available to the medical and scientific community include its genome, transcriptome, proteome, metabolome, lipidome, and epigenome, allowing for the rich molecular characterization of patients, even prior to the expression of symptoms in a manner supportive of traditional medical diagnosis (National Research Council, 2011). Such markers are beginning to impact the ways in which physicians identify with disease and approach the practice of medicine with their patients, which I will expand upon in greater detail in Chapter 4 of this dissertation, as a means of characterizing the impacts precision medical technologies are having within the medical community.

The Right Treatment at the Right Time

In January 2015, during his State of the Union Address, President Obama announced the formation of the Precision Medicine Initiative to lead a new era of medicine – one that will deliver the right treatment, at the right time, for patients. His vision was predicated on, and enabled by, the accomplishments in DNA sequencing technology that allowed data production to far exceed the original Sanger sequencing (Sanger, Nicklen, and Coulson, 1977).

According to the U.S. Food and Drug Administration (FDA), "the concept of precision medicine is not new: The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions" (FDA, 2013, p.4).

Such aspirations and speculative promise are embedded within a highly complex socio-technical system that, in order to fulfill the vision of precision medicine, requires engagement of several components, as follow:

- Drug and biologics development by pharmaceutical and biotechnology companies based upon the collection of biological specimens from patients in the contexts of clinical trials or biomedical research studies and subsequent analysis of those specimens to identify genetic variants or biomarkers specific to a particular disease.
- Biomedical research studies conducted by industry, academic medical institutions, universities, and independent research institutes to provide *in-vitro* or *in-silico* analyses of novel compounds and their ability to act upon identified molecular targets.
- Adaptive clinical trial design, refinement, and conduct to determine safety and efficacy of novel compounds in an *in-vivo* setting, validating the viability of the target, as well as the tolerability of applicable test articles.
- Regulatory review and approval by the FDA at both investigational and market approval stages to validate findings from pre-clinical and clinical studies. This step

requires the continual advancement and refinement of regulatory scientific processes and technology in order to remain in step with the rapid advancements in precision medical technology.

- Medical practice integration of investigational and/or approved therapeutic compounds, increasingly reliant upon the ordering of pre-treatment genomic testing of patient-specific specimens to delineate the genetic profile(s) of their particular instance of disease, interpretation of such findings, and alignment with the availability of targeted compounds in the context of clinical trials or treatment of patients.
- Funding mechanisms through federal or private foundation grants, industry-sponsored clinical trials, and third-party payers to ensure coverage of precision medical interventions at both investigational and treatment stages.

Biospecimen Science

A principal enabling mechanism for the advancement of precision medicine and its potential application(s) is the collection, storage, and sequencing of high-quality biological specimens, such as residual tumor samples from surgeries and tissue harvested prospectively through biopsy procedures, which has served as a catalyst for the development and implementation of biorepositories (biobanking) facilities. In fact, one could say that biospecimens are the fuel required to run the engine powering the precision medical movement. The term biobank refers to the organized collection of biological samples and the data associated with them (Cambon-Thomsen, 2004). Biobanking

covers collections of plant and animal, including human, specimens. For the purposes of this dissertation, I focused on human biobanks. A human tissue biobank is a biorepository that accepts, processes, stores, and distributes biospecimens and associated data for use in translational and clinical research, as well as clinical care. The field of biobanking has changed tremendously over the past 30 years and, according to Vaught and Lockhart, each year millions of biospecimens are collected for a variety of purposes, including basic science research studies, clinical trials, and epidemiology studies (2012). This movement started with small, predominantly university-based, repositories that were developed for the research needs of specific projects. There gradually evolved institutional and government-supported repositories, commercial (for profit) biorepositories, population-based biobanks and, most recently, virtual biobanks. The data associated with stored biospecimens have increased in complexity from basics, such as date of collection and the clinical diagnosis, to extensive information sets including many aspects of a donor's phenotype, now rapidly extending into genetic, proteomic, transcriptomic, and other 'omics' information.

By the late 1990's, hundreds of millions of biospecimens were stored in the United States in a wide variety of public and private biobanking facilities (Eiseman & Haga, 1999). Initially, most of these biospecimens were collected during routine clinical and surgical procedures to be used for "future research". However, in recent years there has been an increasing movement by both public and private initiatives in the United States to prospectively collect and store biospecimens for defined research purposes, oftentimes

with an identified desirable downstream clinical application. The emergence of biorepositories and biobanking as a practice, when coupled with historical and current advancements in "omics" sequencing technologies, helped set the stage for the mainstream application of precision medical practice.

It is now possible to identify biomarkers corresponding with the susceptibility to disease, as well as immunity. In addition, novel therapeutic agents can be developed to act upon genetic variances associated with disease(s), holding the potential to tailor medical interventions to an individual's genetic profile and characteristics of their individual disease, thereby reducing side effects and increasing the efficacy of the clinical intervention.

To put this movement into context from a biobanking and biospecimen sciences perspective, patients are no longer merely a set of acute symptomologies for which medical interventions are prescribed. Rather, precision medicine concurrently re-characterizes patients as subjects of intervention and objects of information. This evokes Paul Rabinow's concept of biosociality (Sunder-Rajan, 2007). That is, disease risk equates to a method of self-identification and, in addition to being biosocial, also subjects individuals to potentially perpetual therapeutic consumption, turning them into almost always already patients-in-waiting (Sunder-Rajan, 2007). Somewhat unique to precision medicine, unlike traditional medical practice, is the role that the patient (or human subject in the context of research) plays in the development of therapeutic

compounds through their contribution of tissue and biological samples in the name of research. Historically, translational science has adhered to the model of developing a compound, performing *in vitro, in vivo*, and human subjects' research in an effort to translate those technologies into human medical application. In the realm of precision medicine, this 'bench to bedside' approach is supplanted by a new paradigm in which bioinformatic data is generated from patients (via biospecimens) and novel therapeutic compounds are developed based upon the information gathered, subjected to analysis, and provided back to patients in the form of pharmaceutical or biological agents. This scenario establishes patients as both subjects of therapeutic intervention and objects of knowledge consumption. This paradigm is both facilitative and ethically problematic because, according to Saha and Hurlbut (2011), "participants provide information or tissues with little or no knowledge of the researchers' priorities, goals or expected outcomes. Barriers are erected. Materials and information are 'de-identified' to protect people's identities. Participants neither see how their donations are used, nor what the research produces". This is a real opportunity for precision medicine and associated practices (e.g. biobanking). Simply put, patients are perhaps the most critical element in precision medicine's ability to succeed, so we need an alternative approach, in which donors are made partners by staying connected to research. Partnership is a win–win approach: it will build trust, make research better and faster, and generate large, diverse cohorts with longitudinal data (Saha, et al, 2011).

Despite the seemingly limitless promise of precision medicine to provide unprecedented insight into human disease and the ability to treat such conditions at the N=1 level, there are numerous ethical and operational challenges confronting the ability of precision medicine in becoming the standard of care in America, as follow:

Confidentiality

While the process of collecting, processing, and storing biological specimens and associated data is relatively straight forward, biobanks present challenges for scientific and regulatory communities, especially the concept of identifiability of biospecimens. In addition, ethical concerns represent risk for donor patients, as a lack of regulatory standardization holds the potential to foster inconsistent biobanking processes, negatively impacting sample quality and the usability of data emerging from banked specimens, thereby perpetuating ethical concerns. That is, the downstream effect of inconsistent and inadequate biospecimen collection and management processes can result in inaccurate or inconsistent data that carries the potential to negatively impact the rights and welfare of patients. According to the International Society for Biological and Environmental Repositories (ISBER), the collection of specimens and/or data for research must never adversely affect patient care ("2012 Best Practices", 2012). Every effort should be made to protect the privacy and confidentiality of data associated with the specimens ("2012 Best Practices", 2012). Despite such intent, recent studies have suggested that some analyses of high-dimensional molecular data can raise more risks to privacy than had been

appreciated (Rodriguez, Brooks, Greenberg and Green, 2013, p. 275). Gymrek M, McGuire A L, Golan D, Halperin E and Erlich Y report that surnames can be recovered from personal genomes by profiling short tandem repeats on the Y chromosome (Y-STRs) and querying recreational genetic genealogy databases (2013). According to the report, they were able to demonstrate that a combination of a surname with other types of metadata, such as age and state, can be used to triangulate the identity of the target (Gymrek, et al, 2013).

Informed Consent

Taking into consideration such technological possibility and risk *vis a vis* the rapid growth in biobanking facilities and activities illustrates the gravity of the ethical, regulatory, and scientific policy issues to consider. One area of focus is the concept of informed consent from individual donors, their family members, or the community for the collection and use of biological specimens (Licinio and Wong, 2002). The *Council for International Organizations of Medical Sciences (*CIOMS) specifies that subsequent research be circumscribed by the original informed consent, and that any conditions specified in that initial consent apply equally to secondary uses. This issue is compounded by the fact that, under the auspices of human subjects protections, current biorepository practices are largely characterized by the removal of identifiers from donated specimens, such that scientists and individuals who come into contact with them, or associated data sets, are unaware of the names and identifiable information of the donor(s). Such practices position the public as little more than a resource for mining data and materials, and as a potential

source of resistance (Saha and Hurlbut, 2011, 312). That is, participants neither see how their donations are used, nor what the research produces (Saha, et al, 2011, 312).

There is consensus among the scientific and policy development communities that, for most research involving human subjects, an ethical approach requires at least two key elements: Institutional Review Board (IRB), also known as an ethics review committee, review and approval before researchers can recruit participants, and an informed consent process on the part of the study subjects, to ensure there is no coercion and that they voluntarily agree to participate in the research. The purpose of IRB review is to ensure that persons independent of the research determine that the study's potential benefits to participants outweigh or justify the potential risks of research participation. The informed consent requirement is to ensure that individuals who enroll in a study understand its purpose and voluntarily agree to expose themselves to any potential research risks.

In the context of biobanking, the informed consent process is problematic on several levels. First, many stored specimens were collected for purposes other than research, such as specimens collected during routine clinical and surgical procedures for clinical treatment purposes. In this scenario, patients would not have given consent for their biospecimens to be used in research. Second, donors may have given consent for specific types of research but researchers may, at a later time, want to use them for other types of studies. Finally, there is some concern regarding the consent process surrounding the use and disclosure of genetic and other identifiable medical data, such as incidental findings, to

donors directly or to others potentially affected by such information, such as family members. From an ethical perspective, one would not want to expose patients or the public to undue risk or distress.

There are also ethical challenges in obtaining consent when biospecimens are collected prospectively for research purposes. Individuals who provide specimens are oftentimes providing blanket consent for research with their biological materials. For the donor(s), this suggests that no restrictions are placed on the types of research that can be conducted with their donated specimens. From an ethical perspective, it can be argued that this scenario does not, in fact, meet the definition of informed consent because individual donors do not have full information about how their specimens will be used, which would not uphold the autonomy principle of The Belmont Report.

To address these concerns, one alternative approach that has been proposed is an individualized or tailored consent process. In effect, this gives individuals a choice about the specific types of research for which their specimens and related information can be used. For example, an individual providing a specimen for research might authorize a particular type of cancer research but decline other types of research, such as Alzheimer's Disease. Within this framework, The Genetic Alliance BioBank uses a tailored consent process, allowing scientists to contact individual donors to obtain ongoing consent for new research with their individual specimens as the need or scientific desire arises. Another

approach that has been undertaken by the National Cancer Institute, as stated in its "Best Practices for Biospecimen Resources," allows NCI-funded researchers to use a tiered consent process in which human subjects could specify the types of research for which their donated specimens could be used (2011).

In contrast to the tiered approach, some believe that risk of harm from research with biospecimens is low and primarily related to the disclosure of a person's identifiable genetic and other medical information. In such a case, a blanket consent process through which biospecimens are collected and additional consent for subsequent uses is not required is considered ethically acceptable, assuming the presence of safeguarding mechanisms to protect the privacy and confidentiality of identifiable medical information. Examples of such safeguards would include ethics review boards to approve new studies with stored biospecimens and associated data, the de-identification of biospecimens and associated data with no means to relink them to identifiable persons, the establishment of guidelines or policies for linking de-identified biospecimens and associated data to identifiable persons, and the establishment of security measures (e.g. password protection) to minimize unauthorized access to information.

Disclosing Research Results

Another area of ethical concern for biobanking is the disclosure of research results, or the lack thereof as is usually the case. Specifically, when research is undertaken and completed

not all research results are published and it is often the case that, for those that are, it is usually long after the study began and in only in scientific journals. Consequently, there is a risk that biospecimen donors, along with the public *writ large*, might never learn the outcome of that research. This proposition may be poorly understood and represent an ethical shortcoming for biobanking based upon what Gottweis calls his "deficit theory", which is characterized by distrust simply based on misunderstandings and a lack of scientific information (2002). In this 'deficit theory' of the public, most difficulties in the interaction between science and the public are derived from the assumption that there is a communication gap between scientists and the public (Gottweis, 2002).

While there are reasons for not disclosing some findings (such as preliminary or inconclusive results that may not have clinical value or could provide misleading information about the etiology of disease, especially when the research involves analysis of genetic materials), there is growing support for the principle that researchers and study sponsors have an obligation to disclose both positive and negative research results, provided that certain conditions are met. How and when to do this remains unclear. In 2010, the National Science Foundation developed a policy in which "investigators are expected to share with other researchers, at no more than incremental cost and within a reasonable time, the primary data, samples, physical collections and other supporting materials created or gathered in the course of work under NSF grants" (NSF, 2013). Despite the spirit of such a mandate, there is little to no guidance regarding the proper mechanism(s) for fulfilling this obligation.

Equitable Distribution of Benefits and Risks

An additional area of ethical consideration is the equitable distribution of benefits and risks associated with precision medical products. As an analogy, within the human subjects' research arena, the equitable distribution of risks and benefits is detailed and exemplified by the *justice* principle of the Belmont Report (HHS, 1979). According to the Report, "an injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally" (1979). As will be described in later chapters, precision medical products are subject to both pre- and post-marketing research requirements, in addition to the treatment of patients through the medicalization of such products. Given this scenario, it is important for clinicians and regulators to adhere to principles such as *justice* and the equitable selection of subjects in order to share potential benefits and risks at both the individual and societal levels. In terms of individual patients, it is incumbent upon clinicians to exhibit fairness (HHS, 1979). That is, they should not offer potentially beneficial products to patients who are convenient or research subjects for whom the test article administration would be in their favor or to only undesirable patients for high-risk research (HHS, 1979). From a societal perspective, no distinction should be drawn between classes of patients or subjects for social, racial, sexual or cultural reasons, or whether they can either bear burdens of risk or financially afford treatment with precision medical products, while preventing or neglecting patients or subjects who are not in a similar position (HHS, 1979). Looked at another way, the perceived clinical promise of precision medical products should not be afforded to certain groups of patients or research subjects and concurrently denied to others.

Ownership and Intellectual Property

Another area of ethical concern for biobanking facilities is ownership and intellectual property of both the specimens and information inherent to, or resulting from, specimen processing. This is due to the fact that research with biospecimens and associated data carries the potential for inventions of some commercial value. Researchers, their institutions, and research sponsors seek to establish and protect the intellectual property rights surrounding these activities to control access to such resources. Although opinions vary, the NCI, maintains the stance that researchers and institutions should share research data and tools generated through use of biospecimens in a timely manner, and that biorepositories have no inherent rights to future intellectual property, such as those resulting from inventions made by using repository samples (2011). For specimen donors, there are ethical red flags with regard to intellectual property and ownership. That is, they are usually informed that they will have no rights to any intellectual property or inventions resulting from the scientific use of their specimen(s). Consequently, the most integral component of the scientific and knowledge development process is completely cut off from any potential downstream benefit of scientific discovery.

Policy and Governance

Science alone is not enough to translate precision medicine from the lab into medical practice. The FDA is also developing a series of regulatory policies and procedures to support its fruition. According to Gottweis, policymaking can be understood as an attempt

to manage a field of discursivity, to construct regularity in a dispersed multitude of combinable elements (2002). Since the development and continued emergence of precision medicine, there have been continual and increasing efforts on the part of policy makers and regulators to establish a political and regulatory framework accepting of such advancements.

The FDA regularly receives feedback about policies related to precision medicine from industry groups that regard precision medicine as one of the most promising avenues for new drugs and other innovative medical products. Industry is increasingly requesting that the FDA address the issue of companion diagnostics. The FDA's *In Vitro Companion Diagnostic Devices* guidance (2011) addresses several key elements for developing drug/diagnostic products, such as when an in vitro diagnostic test is considered a companion diagnostic and what requirements apply when companion diagnostics are used in clinical trials. It also outlines the steps necessary to obtain FDA approval if a company were to develop a diagnostic that identifies patients with an increased probability of responding to a therapy or an increased risk of adverse reaction to a new or existing therapy, and it specifies the information that must be included in the label of the test and its corresponding therapeutic product. That is, the FDA seeks to ensure that the tests steering patients toward targeted therapies are accurate and reliable and that the right patients receive the right drug at the right dose, promoting the basic tenets of precision medicine.

The FDA reports it is also developing a draft guidance outlining strategies for clinical trial design and regulatory considerations for co-developing a novel companion diagnostic and

therapy simultaneously, where the approval and subsequent use of the therapy would incorporate a requirement for the diagnostic test (2012). This draft guidance includes recommendations for the strategic use of biomarkers for patient selection and screening, as well as clinical trial designs that allow for ethical patient selection strategies.

The FDA understands that it is fully anticipated that the pathway to precision medicine will utilize an individual's full genomic sequence, and rapid developments in ultra-high throughput genomic sequencing technologies indicate that the era of the personal genome is fast approaching. In order to effectively utilize these new sequencing technologies for clinical applications, appropriate evaluation tools in the form of standards and criteria are needed to ensure sequencing quality and the accuracy of tests. Through public meetings and direct engagement, the FDA reports that it is actively seeking input from academia, industry, patients, and other stakeholders on validation methodologies, materials, and bioinformatics approaches needed to address these issues and accelerate and support the introduction of innovative sequencing applications (2012).

Promoting precision medicine not only means having the right policies and scientific practices in place, it means making sure the FDA medical product centers work together as a team to get safe and effective new treatments to patients as quickly as possible. In the emerging era of precision medicine, the FDA's ability to evaluate targeted therapeutics, companion diagnostics, and similar precision medical technologies is being challenged by both the technoscientific advancements themselves, as well as long-standing

standardization models for evaluating the safety and efficacy of medical products vis-à-vis disease classifications standards, which I will describe in greater detail in Chapter 3.

Within the FDA, the primary responsibility for diagnostic approvals lies within the Center for Devices and Radiological Health (CDRH), whereas the responsibility for drugs, biologics and cell-based therapies exists in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), coordination between the Centers for applications incorporating diagnostics as a requirement for therapy use will be necessary. To spearhead efforts for a seamless integration between the Centers, the FDA Commissioner appointed a new Deputy Commissioner for Medical Products to oversee and manage the three medical product development centers. The Deputy Commissioner for Medical Products will be responsible for providing overall leadership for the three medical product centers. This person will also be responsible for other programs, such as combination products, where the Centers must work together to establish cross-center programs (FDA, 2012).

Despite these efforts, reform and the political infrastructure conducive to the implementation of precision medicine cannot be accomplished by the FDA alone. As Carpenter reports, this requires congressional statute changes as well, which is a challenging proposition, considering the toxic polarization between Democratic and Republican lawmakers — and the micromanaging tendencies of Barack Obama and former President George W. Bush – which damage US public-health infrastructure and its scientific prospects, weakening one of the republic's most vital institutions (2012).

Policy and governance structures for the biobanking industry are varied and largely inadequate given recent technological advancements. While the public largely supports research with biospecimens, there is concern that biospecimens may be used for research that some find objectionable, such as cloning, or that genetic and other medical information may be used in ways that can harm individuals and their families, such as causing them undue stress resulting from a revealed genetic condition. Former President Bush's administration sought to allay such concerns by passing the Genetic Information Nondiscrimination Act (GINA), prohibiting employers and insurance companies from discriminating against individuals on the basis of their genetic information.

In the United States there is no comprehensive regulatory structure that addresses these issues and confusion has existed regarding when human subjects' protections regulations apply to research with biospecimens and their data. The interpretation of these issues determines whether IRBs must approve biospecimen research and whether individuals must give consent for use of their stored biospecimens or their identifiable genetic and private medical information. In 2015, the US Department of Health and Human Services issued a Notice of Proposed Rulemaking (NPRM), soliciting public commentary regarding proposed changes to The Common Rule (45 CFR 46) in an attempt to "...increase human subjects' ability and opportunity to make informed decisions; reduce potential for harm and increase justice by increasing the uniformity of human subject protections…" (Federal Register, 2015). From a biobanking perspective, one of the most significant proposals detailed within the NPRM would be the requirement to provide "informed consent for the use of stored biospecimens in secondary research (for example, part of a blood sample that

is left over after being drawn for clinical purposes), even if the investigator is not being given information that would enable him or her to identify whose biospecimen it is. That consent would generally be obtained by means of broad consent (i.e., consent for future, unspecified research studies) to the storage and eventual research use of biospecimens" (NPRM 2015-Summary, 2015). If such requirements were to be enacted, it would create a significant operational and policy-related impact for academic medical and hospital organizations seeking to engage in biospecimen-related research activities by necessitating a *de facto* stance that any/all clinical specimens may, in fact, be subject to future unspecified research and require the implementation of a broad consent mechanism to ensure compliance with the enacted changes to The Common Rule. The exact outcome of the NPRM process is yet to be fully realized, so historical regulatory and governance structures remain in place until such a time that some or all of the proposed changes are codified.

Minus such proposed changes, what has emerged from a risk-mitigation perspective is an environment through which independent trade organizations, such as the International Society of Biological and Environmental Repositories (ISBER), and governmental agencies, including the National Cancer Institute (NCI), have developed best-practices for biobanking activities. However, these measures have fallen short of regulatory requirements, thereby perpetuating the potential for disparate practices from one biobank to the next. Of particular concern is the lack of regulatory guidance by the U.S. Food and Drug Administration (FDA). As Lori Ball, Chief Operating Officer for Biostorage Technologies, states "Due to the lack of FDA regulations for sample management and

differences in global policies, it is imperative the industry joins together to discuss common guidelines for these invaluable assets. This is of the upmost importance as we understand that samples stored today will be held to the standards of tomorrow" (Biostorage Technologies, 2011)". Considering the continued emergence of therapeutic compounds designed to act upon specific molecular targets, it is concerning that the FDA has not developed any formal regulatory oversight of biobanking practices, which directly impact the quality of pharmaceutical and biological compounds developed within the context of precision medicine.

Despite these ethical concerns, much of the focus of OHRP and human subjects' protections regarding biobanking has centered on the "identifiability" of specimens. That is, in 2004, the OHRP published guidance clarifying its interpretation of the Common Rule as it applies to repositories comprised of de-identified samples. In this guidance, OHRP concluded that repositories including only information that is identified by a code and not by personal identifiers is not classified as human subjects research. This is because the policy defines a human subject as a person whose "identifiable private information" has been obtained (OHRP, 2004).

Under the OHRP definition, such practices do not qualify as human subjects research. It is therefore subject to a different set of rules. Requirements for human subjects research, such as review by the institutional review board and informed consent of potential participants, is not required under the Common Rule or the OHRP's interpretation of that policy.

However, research on de-identified human samples obtained without interaction by the researcher can only remain in the category of nonhuman subjects research if no intentional or routine identification occurs. That is, as soon as re-identification occurs, this research immediately shifts from the nonhuman subjects research category to the human subjects research category. This shift in category can easily place a research project into noncompliance with the Common Rule if it is not already following the requirements for human subjects research, including, for example, informed consent (Langanke, et al, 2011).

Regulatory Science

The United States Food and Drug Administration oversees the marketing approval of food, drugs, biologics, medical devices, radiation-emitting products, cosmetics, animal feed, and accounting for 25-30 cents of every dollar spent by consumers in the U.S. The FDA grew to this status from its humble beginnings as a single chemist in the U.S. Department of Agriculture in 1862 to a staff of approximately 9,100 employees and a budget of $1.294 billion in 2001. The FDA employs chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, D. C. area, staffing over 150 field offices and laboratories, including five regional offices and 20 district offices. Agency scientists evaluate applications for new human drugs and biologics, complex medical devices, food and color additives, infant formulas, and animal drugs. Also, the FDA

monitors the manufacture, import, transport, storage, and sale of about $1 trillion worth of products annually at a cost to taxpayers of about $3 per person.

For the FDA, precision medicine represents a potential inflection point from a traditional system of large-scale clinical trials involving many thousands of participants evaluated under the treatment of a standardized test article provided to all participants (assuming they were randomized into the treatment arm of a trial). Under both the promise and surplus value of precision medicine, participants would be given a therapeutic compound unique to their genetic profile.

To address this concern, the FDA has acknowledged that patients respond differently to medicines, and all medicines present the possibility of side effects. Based on the belief that these differences may be based on genetic factors, the FDA has been providing scientific and strategic input to the International Serious Adverse Events Consortium (iSAEC) to identify genetic markers that are useful in predicting the risk of drug-related serious adverse events. While the majority of iSAEC's genetic findings have been focused on a specific drug instead of across multiple drugs, a number of cross-drug inherited genes are emerging that may provide important insights into the underlying biology leading to a drug-induced serious adverse event (FDA, 2012).

Realizing the promise of precision medicine requires a sustained commitment to advancing our understanding of the structure and function of our genomes, the underlying genetic and environmental bases of human disease, and human genomic variations and the ways in which these variations influence disease or responses to therapy. This research also requires

a pathway to translate such findings to real world medical products and practices. Much of the applied regulatory science for evaluating the strategies and outcomes for precision medicine - such as standards for whole genome sequencing, fully qualified biomarkers (measurable characteristics in patients), and innovative clinical trial designs and statistics - are still underdeveloped. The move toward precision medicine is resulting in an increasing number of new products that fall within the purview of multiple centers at the FDA, creating an additional challenge during the approval process. The FDA plays a leadership role on the scientific front and build the infrastructure necessary to support the development of these more precision targeted therapies, most immediately through investments in regulatory science, clarification of FDA policies, a reorganization of leadership, and engagement of physicians, patients, and their advocacy groups (FDA, 2012).

To expand the understanding of how genomic variations contribute to an individual's disease or response to therapy and gain deeper insights into the mechanisms underlying diseases and disease subtypes, innovative medical product development will increasingly use strategies where diagnostics and drugs are "co-developed" allowing for the diagnostic to guide which patients will be more likely to benefit from the drug and less likely to be at risk for serious side effects.

To fully realize the co-development approach, clinical development programs for medical products will require increased investments in regulatory science. Regulatory science will play an important part in addressing the challenges presented by precision medicine.

Approaches that use novel clinical trial designs and statistics will also be crucial. These novel designs will allow for patient selection strategies that identify those patients who will derive the most benefit from a treatment, balancing the need for methodological rigor with the need for more rapid, targeted answers and smaller study populations. Equally important are improved approaches to identify and qualify the performance and quality metrics of biomarkers to ensure that diagnostic tools can be developed and used to guide the selection of therapies. The FDA reports that it will continue to invest in these key scientific areas through direct funding efforts and collaborations with other agencies, such as NIH. The FDA also states it will work to expand its efforts through collaborations with other government agencies and academia, as well as through public-private partnerships with industry scientists as collaborative partners to support these efforts (2012).

Funding

An additional challenge confronting the large-scale implementation efforts of precision medicine is funding for CoDx and preventative medicine. As discussed, DNA sequencing and precision medicine hold the promise of identifying unique characteristics of a person's individual genome, delineating molecular aberrations that correspond to their unique instance of disease, and targeting those variances via tailored therapeutic compounds. However, much of the success of precision medicine is contingent upon the ability to have insurance companies provide coverage for treatments. The difficulty exists in that insurance providers do not currently acknowledge genetic variances as the presence of disease. That is, simply possessing a particular biomarker does not equate to a diagnosis of disease. To address this issue, scientists, regulators, and policy-makers will have to

work in concert to develop a new ontology of disease, consistent with the promise of precision medicine.

There have been significant advancements in recent decades in terms of DNA sequencing technologies, their refinement, and potential applications. The sequencing of the human genome set the stage for a renaissance in American science and medicine, in which we find ourselves today. These developments have made it possible to challenge the manners in which we have come to understand the human condition, the composition of disease, and the methodology used to treat illnesses. It is now possible to identify biomarkers corresponding to the susceptibility to disease, as well as immunity. In addition, novel therapeutic agents can be developed to act upon genetic variances of disease, holding the potential to tailor medical interventions to an individual's genomic profile and characteristics of their disease, thereby reducing side effects and increasing the efficacy of the clinical intervention.

Despite such promise of precision medicine, there are a multitude of obstacles that must be addressed in order to facilitate the large-scale implementation of such an approach within the U.S. medical community. Specifically, regulatory science needs to develop methods of analysis consistent with the level of science associated with precision medicine. This involves the aggregation and comprehensive understanding of disease biomarkers and the development of novel clinical trial designs that will facilitate the rapid analysis of data emerging from companion diagnostics and therapeutic interventions. Congressional policy

needs to be enacted, further establishing precision medicine as a priority, facilitating the funding of increased research activities in this area. Assimilation of genomic data into insurance coverage is essential for patients to continue to embrace such technology without fear of financial hardship. In addition, patients need to be considered partners in biomedical research more than any other point throughout American scientific history. They represent both subjects of therapeutic intervention and objects of knowledge consumption in the precision medicine movement and should be provided with both a voice concerning the use of their genetic information for research and should have outcomes communicated to eliminate the public lack of trust inherent to Gottweis' Deficit Theory. Overcoming these challenges is proving both laborious and difficult but can ultimately pave the way for a transformation of medical practice and the potential for eradication of disease.

For contextual purposes, medical products, such as drugs and devices, are subject to a product life cycle involving both pre-market development and post-market implementation. That is, there are two sides to the continuum of a product's life cycle that involve creation and market actualization. One could say that equilibrium is attained when both premarket processes and post-market balance in their ability to deliver the right treatment to the right patient at the right time. To put all of this into perspective, what is emerging is a precision medical ecosystem comprised of several inter-dependent players that are each critical in their respective function in the advancement of precision medicine. To describe this ecosystem and the impacts of precision medical products on both the pre- and post-market aspects of the product development life cycle, I will address each

separately throughout the next two chapters and describe the current and ongoing adaptive measures being undertaken by each stakeholder, respectively, as well as the overarching ecosystem as a whole.

Chapter 3 – Premarket Impacts, Adaptations, and the Assimilation of Precision Medical Products

In the United States, drugs, biologics, and medical devices fall under the oversight of the U.S. Food and Drug Administration. Such products are brought to market via a historically linear process comprised of two primary phases, premarket and post-market. In this chapter, I will present the premarket aspects of the product development and approval life cycle, as well as the impacts and salient findings regarding the assimilation of precision medical products into their respective area.

For context, the FDA's Center for Drug Evaluation and Research (CDER) oversees the review and approval of prescription drugs in the United States. To manage this process, CDER has developed a drug development process comprised of five sequential phases (or steps) that must be undertaken in order to successfully market a prescription drug or biologic in the United States (FDA, 2018). Each of these steps and their specific function(s) are listed in Table 1 below.

Table 1: FDA Drug Development Process (FDA, 2018)

Step	Function
Discovery and Development	• New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease • Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases • Existing treatments that have unanticipated effects • New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material

Preclinical Research	• Before a drug is testing with human subjects, researchers try to determine it carries the potential for serious harm Types of Preclinical Research: • **<u>In Vitro</u>** - a medical study or experiment which is done in the laboratory within the confines of a test tube or laboratory dish • **<u>In Vivo</u>** - a medical test, experiment or procedure that is done on (or in) a living organism, such as a laboratory animal or human • Preclinical research activities must adhere to Good Laboratory Practices (GLP) [21 CFR 58.1], which set requirements for: study conduct, personnel, facilities, equipment, protocols, operating procedures, study reports, and quality assurance oversight These studies yield detailed information about dosing & toxicity
Clinical Research	After completion of the preclinical research phase, a drug is then tested in human subjects, • May include both domestic and foreign-gathered data • Clinical trials must adhere to Good Clinical Practice (GCP) standards • In this phase, researchers must develop a clinical protocol, which covers: • Who qualifies to participate (selection criteria) • How many people will be part of the study • How long the study will last • Whether there will be a control group and other ways to limit research bias • How the drug will be given to patients and at what dosage • What assessments will be conducted, when, and what data will be collected • How the data will be reviewed and analyzed Before proceeding with clinical trials, they must submit an Investigational New Drug (IND) [21CFR 312 – Investigational New Drugs] application to the FDA, including: • Animal study data and toxicity (side effects that cause great harm) data • Manufacturing information

	• Clinical protocols (study plans) for studies to be conducted • Data from any prior human research • Information about the investigator

FDA Drug Review	• After completing the preclinical and clinical research requirements establishing the safety and efficacy of a drug, developers can apply to market the drug, a process known as a "New Drug Application (NDA)"
	• NDAs cover every aspect of the drug and its development, including:
	  • Proposed labeling
	  • Safety updates
	  • Drug abuse information
	  • Patent information
	  • Any data from studies that may have been conducted outside the United States
	  • Institutional review board compliance information
	  • Directions for use
	• The FDA review team has 6-10 months to make a decision on the NDA. The review process includes:
	  • Each member of the review team conducts a full review of his or her section of the application
	  • FDA inspectors travel to clinical study sites to conduct a routine inspection
	  • The project manager assembles all individual reviews and other documents and the team makes a recommendation or requests additional information

Post-Market Safety Monitoring	• Clinical trials cannot fully capture all information about the safety of a drug. As a result, the true picture of a drug's safety is determined over months or years on the market • As a result, the FDA has established mechanisms to report

	problems with products that have been previously approved: • ***MedWatch*** - a gateway for reporting problems with medical products (drugs and devices) and learning about new safety information • ***Medical Product Safety Network (MedSun)*** - monitors the safety and effectiveness of medical devices and publishes a newsletter for consumers • The FDA can require action on the part of developers based upon this information, such as labeling changes or withdrawal from market

The first four steps of the above-mentioned drug development process occur during the pre-market phase of the drug life cycle. Traditionally, these steps coincide with capital investment, strategic investment by industry, regulatory governance, and the augmentation of medical practice via clinical trials to constitute the making of a drug or biologic.

Medical devices are overseen by the FDA's Center for Devices and Radiological Health (CDRH). Unlike drugs or biologics, medical devices are assigned a risk level at the initiation of the marketing application process. To evaluate risk, first a medical device must be categorized within a stratified classification system based upon the risk level consistent with the proposed used of the device, as follow:

- Class I Devices - Medical devices in the Class I category have the least amount of regulatory control and minimal potential harm to the patient. These devices are

relatively simple to design, manufacture, and use. Examples of Class I medical devices are hospital beds, oxygen masks, tongue depressors, and arm slings.

- Class II Devices - Class II medical devices require more FDA regulation to assure safety and effectiveness. X-ray systems, contact lenses, syringes, and blood transfusion kits all fall under this medical device classification.
- Class III Devices - Products used to support or sustain human life or those that present a potentially high risk for a patient are in the Class III classification. These devices are, understandably, more rigorously regulated than Class II or Class I products and require additional levels of approval. Heart valves, cochlear implants, and defibrillators are examples of Class III medical devices.

During the pre-marketing phase, once a device's risk classification is determined, the level of FDA oversight and pre-market requirements can also be determined by whether a product is deemed *de novo* (novel) or whether there exists a predicate device currently marketed in the U.S. A predicate device would be any device with the same intended use and similar risk profile as a product being submitted for a marketing application to the FDA. As an example, a new pacemaker product can be submitted to the FDA for market approval, citing existing pacemaker products as predicate devices. This is significant to the manufacturer or sponsor of a given product in that it can determine the regulatory pathway required for market approval. If a medical device is determined to be a *de novo* Class III device, suggesting that the device is both high-risk with no existing predicate device, the manufacturer is required to submit a Premarket Application (PMA) and

demonstrate safety and efficacy in the context of clinical trials. In contrast, if a product is deemed substantively equivalent to an existing marketed product, the regulatory pathway would point to a process known as 510(k), for which the manufacturer would submit a Premarket Notification to the FDA, essentially demonstrating substantive equivalence while being exempt from the presentation of safety and efficacy data for their individual product, thereby allowing the manufacturer to go directly to market with the product.

To explore the premarket phase for both drugs and devices, as well as the impacts, adaptations, and assimilations occurring within this phase for capital investors, pharmaceutical and medical device companies, regulators, and the practice of medicine as a result of precision medical products, , I am presenting the reader with two case examples, Foundation Medicine's F1CDx companion diagnostic test and Novartis' Kymriah (tisagenlecleucel) CAR T cell biologic, both of which represent early movers in the era of precision medicine, as well as disruptive technologies within applicable medical communities.

Foundation Medicine's F1CDx test was approved by the FDA on November 30, 2017 (see Appendix A- F1CDx Approval Letter). Foundation Medicine (FM) is an American assay development and genomic profiling company based out of Cambridge, Massachusetts. "Foundation Medicine was born in 2010 driven by the commitment to use genomic insights to redefine the way each person with cancer is treated. In just ten years, we've made

incredible progress—breakthroughs that have helped shift the treatment paradigm to directly impact patient care" (Foundation Medicine, ND).

Their F1CDx test was the "first breakthrough-designated, next generation sequencing (NGS)-based in vitro diagnostic (IVD) test that can detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type" (FDA, 2017a). I chose this product as one of my case studies for a couple of reasons. First, in the era of precision medicine, F1CDx is one of the first movers in the comprehensive companion diagnostic market. In addition, it also represents and exemplary product in that its goal is to provide medical practitioners with comprehensive, actionable knowledge that is expected in the era of precision medicine and, as such, it carries the potential to guide the development and refinement of future products. Unlike prior IVD tests receiving approval by the FDA, the F1CDx is a "more extensive test that provides information on a number of different genetic mutations that may help in the clinical management of patients with cancer" (FDA, 2017a). Additionally, the FDA reports that based on individual test results, the F1CDx test can identify which patients with any of five tumor types may benefit from different FDA-approved targeted treatment options (see Appendix B - F1CDx Label Document). Its results provide patients and health care professionals access to all of this information in one test report, avoiding duplicative biopsies (2017a). Concurrently, the Centers for Medicare & Medicaid Services (CMS) approved coverage of the F1CDx via their Parallel Review Program with the FDA to provide earlier access to innovative medical technologies for Medicare beneficiaries.

In my discussions with FM, they reported that they are "committed to advancing patient care by offering a proven portfolio of comprehensive genomic profiling products that help physicians make more informed care decisions" (Foundation Medicine, 2021). This is to say that, "through constant innovation in molecular insights, we are dedicated to working with our partners to deliver breakthroughs that improve outcomes for more individuals living with cancer and bringing them to routine cancer care every day" (Foundation Medicine, 2021).

Foundation's F1CDx test differed from previous in-vitro diagnostics tests in that predicate products sought to match one test to one drug, whereas the F1CDx was a more extensive test that provides information on a number of different genetic mutations that could augment the clinical management of patients with cancer. That is, based on individual test results, the new diagnostic can identify which patients with any of five tumor types may benefit from 15 different FDA-approved targeted treatment options. The F1CDx test was able to inform patients and health care practitioners with access to all of this information in one test report, avoiding duplicative biopsies.

Six months later, on May 1, 2018, the U.S. Food & Drug Administration (FDA) approved Novartis Pharmaceutical Corporation's Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL) (See Appendix C – Kymriah BLA Approval Letter).

Novartis Pharmaceuticals Corporation is a Swiss multi-national company based out of Basel, Switzerland. Novartis traces its history back more than 250 years through the convergence of three companies: Geigy, a chemicals and dyes trading company founded in Basel, Switzerland in the middle of the 18th century; Ciba, which began producing dyes in 1859; and Sandoz, a chemical company founded in Basel in 1886. From its beginning in the production of synthetic fabric dyes, the companies that eventually became Novartis branched out into producing chemicals and ultimately pharmaceuticals. Modern day Novartis Pharmaceuticals Corporation is the largest pharmaceutical company in the world but retains the culture and spirit of its founding companies and their passion for developing and marketing new products that contribute to human progress through advances in science and health (Novartis, n.d. b). Building on this heritage, today Novartis focuses its innovation prowess on addressing the unmet needs of patients worldwide. Novartis is also a global leader in the development of precision medical products and is committed to tailoring medical products that are designed for the right patient at the right dose. According to Dr. Ronenn Roubenoff, Global Translational Medicine Head, Musculoskeletal Diseases at the Novartis Institutes for BioMedical Research, "precision medicine is where we want medicine to be. It is a key evolution – it used to be about making the patient fit the treatment, but now it is about making the treatment fit the patient.

Novartis' tisagenlecleucel product, which ultimately was given the trade name Kymriah, is a cell-based gene therapy, is the first gene therapy approved for marketing in the United

States and indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse (FDA, 2017b) (See Appendix D – Kymriah Label). Similar to the F1CDx test, I chose Kymriah as a case study based upon its first-mover status, as well as its exemplary nature of a precision medical product designed to act at an individual patient level with regard to his/her specific disease. This attribute is highly representative of the goal of precision medicine to provide patients with the right treatment at the right time.

According to its Biologic License Application (BLA), tisagenlecleucel is "comprised of genetically-modified antigen-specific autologous T cells that have been modified to target cells that express CD19" (FDA, n.d.).

> CD19 is an antigen expressed on the surface of B cells and tumors derived from B cells. The tisagenlecleucel chimeric antigen receptor (CAR) protein consists of an extracellular portion that has a murine anti-CD19 single chain antibody fragment (scFv) and an intracellular portion that contains T cell signaling (CD3-ζ) and co-stimulatory (4-1BB) domains. These intracellular domains play critical roles in tisagenlecleucel's functions, including T cell activation, persistence in vivo and anti-tumor activity. In terms of treatment mechanism, each dose of Kymriah is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that

> contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells (FDA, n.d.).

Both of these products and their approvals by the FDA represent a significant development in modern medicine and, more specifically, the advancement of precision medical technologies in the U.S. market. My analysis of these technologies and their sociotechnical implications for patients, investors, regulators, and the medical community were framed by the following questions, as applicable:

1. What aspects of such technologies make them applicable to the evolving field of precision medicine and its new taxonomy of disease?
2. What aspects of such technologies make them relevant to precision medicine's espoused promise to provide the right treatment to the right patient at the right time?
3. What are the development and regulatory approval processes for F1CDx, Kymriah, and similar technologies and what impacts or adaptive measures within governance structures, regulatory science, policies, and actions allowed for the review and market approval of such technologies?
4. Whose well-being is being prioritized or invoked in the creation of such knowledge and risk/benefit analysis from this regime and what biosocietal consequences emerge as a result of such knowledge mobilization?

5. What attributes, return on investment opportunities, or potential market value characteristics do you seek to identify when considering providing capital investment in medical technologies and interventions?
6. How have those attributes changed or been impacted by the emergence of precision medical therapeutics and diagnostics and how are such products evaluated differently than traditional medical products when considering capital investment?
7. What theoretical frameworks and implications lend themselves to the analysis of these technologies and their impacts on the co-production of knowledge, process, and biosociality?

I used these questions as guidance for the evaluation and delineation of both pre-market and post-market considerations, challenges, and impacts with regard to the entire spectrum of stakeholders involved in the advancement of precision medical products. Within this framework, I will address the premarket findings in the remainder of this chapter and present post-market findings in Chapter 4.

Capital Structures

The life cycle of many potential therapeutic compounds like Kymriah and diagnostic instruments like F1CDx begin in laboratories within universities, academic medical centers, and private research institutions. Historically speaking, pharmaceutical compounds and medical products emerge when laboratory scientists develop an idea or

concept and design *in-vitro* studies to determine whether their idea represents a potentially viable approach to treatment of a representative disease(s). Much of the time, these initial steps in the drug development life cycle occur with little or no funding. However, the advancement of such products along the drug approval continuum requires substantive investment in both equity and debt-based capital structures, such as corporate investment, internal bridge funding, and external vendors or venture capital firms.

Before such investments can occur, such technologies are subject to proof-of-concept reviews and potential return on investment analyses by internal or external technology transfer firms in order to determine whether such a product can be protected by intellectual property laws. Such traditional analyses involve the identification of potential market size, as well as other factors, in determining whether novel compounds warrant investment.

The emergence and evolution of precision medical products has seen wave of new technologies such as biologics and gene and cell therapies, which develop large amounts of biodata that are highly coveted by large pharma and biotech firms. Sunder-Rajan describes this dynamic as *biocapital*, which he characterizes as a "framework for contemporary capitalism in its emergent and shifting topological manifestations and conundrums of value generation and market logic that come out of the bio-informatic (disciplinary and corporate) mergers of the genomic sequencing revolution" (1997, p. 20).

Foundation Medicine's F1CDx test and its conceptualization and development is a direct result of biocapital development secondary to the collection and analysis of large

amounts of biodata, ultimately revealing genetic variants associated with 324 genes and 2 genomic signatures for solid tumor cancers. For Foundation Medicine, the potential competitive advantage of F1CDx is the extensive nature of the test. As such, their internal investment decision-making was highly focused on time-to-market considerations because the companion diagnostic market is a rapidly evolving sector of the precision medical market and any realized competitive advantage would, at best, be short lived.

For technology transfer offices and firms, precision medicine has facilitated the co-production of strategic approaches designed to capitalize on the promise of precision medicine while concurrently recognizing that the field itself remains in a constant state of change. Much of the impact and interest in precision medical technologies has been driven by immense speculative value for unprecedented treatments and potentially curative effects for genetically esoteric and/or rare diseases. This scenario presents equity investment opportunities in the form of intellectual property rights for such organizations. To fully understand this dynamic, I spoke with a representative from a university-based technology-transfer office to understand how they evaluate precision medical technologies versus traditional medical products.

The representative informed me that they are in frequent receipt of medical technology (e.g. therapeutic compounds) applications, representing both traditional therapeutics and molecular-driven targeted therapies. He informed me that traditional medical products are evaluated in terms of previous study outcomes, novel nature of the

product(s), and marketing potential. That is, if a compound is considered different, viable, and a market exists for such a product, it would likely be determined as a product in which they are willing to invest. Depending on where the product was on the drug development continuum, the exact level of engagement and investment can vary from facilitating bridge funding to allow scientists to gather additional data, patent applications and spin-off company investments, connection with incubator laboratory space, and even leveraging pharmaceutical company contacts to seek licensing agreements for such technologies.

While the same potential investment strategies exist for precision-medical products, the pre-investment analytics diverge significantly in terms of how they are evaluated for market viability and return on investment. Simply put, the fact that precision medical products are designed to impact small numbers of patients and genetically specific instances of disease, makes them difficult to evaluate through traditional market-driven methodologies. In addition, the technoscientific attributes of such compounds make them difficult for non-scientific investors to evaluate. As a result, he stated that they have adopted an approach that largely seeks to advance such technologies during the early stages of a precision medical product's life cycle in order to not commit an error of omission by failing to invest in a potential promising technology.

Novartis' Kymriah, from an investment and development perspective, represented a potential game-changer for the American medical market. Specifically, the treatment itself would not only provide patients with a potential curative outcome for a specific

subset of ALL, but the technology represented a first of its kind gene therapy to receive market approval in the U.S. Taking this into consideration, for Novartis the product also presented a proof-of concept that may ultimately be scalable to other cancers or diseases.

From a venture capital point of view, J.P. Morgan reports that "precision medicine, over time, has the potential to bring targeted, life-saving treatments to countless individuals suffering from a wide range of previously incurable diseases, without destroying the quality of the lives it saves" (2020). That is, "precision medicine is already being closely studied for its potential in oncology. Doctors may be able to use it to create targeted cancer treatments that attack specific cells within the body. As opposed to chemotherapy, precision oncology may be less likely to harm healthy human cells because it takes aim only at specific tumor cells. What's more, the possibilities extend to conditions like genetic blindness, muscular dystrophy, diabetes, heart disease and more" (J.P. Morgan, 2020). J.P. Morgan goes on to report that "for precision medicine to become a viable option for everyone, data is needed, lots of data, well as the commitment of governments, healthcare agencies and regulators to provide a supportive framework (2020). Within this framework, and similar to technology transfer firms, the data derived from NGS technologies has resulted in a biocapital market whose nexus exists at the intersection of compound development and regulatory evaluation. To design treatments for individuals or specific groups, scientists need a vast dataset of patient histories to analyze which treatments work best for which patients" (2020). "While the FDA is still working to develop answers to the regulatory questions, there is no doubt

the field of precision medicine represents a new frontier in healthcare innovation" (J.P. Morgan, 2020).

To understand how precision medical products are impacting investment-related decisions for venture capital firms, I spoke with a managing director for an investment fund specializing in machine learning and scientific innovation in healthcare. During our conversation, I asked him to describe the decision-making process for evaluating a medical product and to describe how these processes may differ for precision medical products versus traditional medical products. He informed me that their fund, and overarching venture capital firm, have seen an increase in funding proposals for intelligent and precision medical products in recent years and acknowledged that there are some differences between precision medical products and traditional medical products, but that, for his firm, the core requirements for investment remain standard. Specifically, he reported that it is not simply about an idea or new and interesting technology. Rather, it's more of an issue of company stability, leadership, and a solid roadmap for the product. I inquired further about potential roadmaps, to which he reported that many companies lack the resources to bring a product to market and that, for those, the roadmap may involve an exit strategy through which intellectual property rights are sold to larger companies with the resources to advance the technology through validation, pre-clinical, and clinical trials, depending on where the product is in its life cycle. The approach adhered to by this firm speaks more to assimilation of precision medical products into benchmarks and standards, resulting in the imaginary of a predictable world that seeks to mitigate financial risk. In this scenario, risk is a

product of capital investment and it is the firm's portfolio whose interest is being protected via investment decision making.

As our conversation advanced, I explored my curiosity a bit and inquired how they would address a really interesting technology or therapeutic that had, by all intents and purposes, potential to help patients, but perhaps lacked a stable company and solid business plan. He then mentioned that those situations do occur, especially when his firm sends representatives to universities to meet with faculty to see a host of products over 1-2 days. In that situation, he stated that "sometimes we just buy the company and put leadership in place". I then asked what that would look like for the inventor or faculty member, to which he offered a brief chuckle and said that it usually involves moving the company to a biotech "hotbed", such as California, where there are "many experienced entrepreneurs in the medical innovation space" to quickly insert a leadership team. While venture capital firms have become active players in the biocapital network surrounding precision medical technologies, the most salient theme during our conversation was standardization through financial predictability and risk aversion, to the extent that they routinely utilized an entry point in advancing a technology through acquisition of the technology and then placed the other desirable pieces (of a business model) around the technology into their imaginary of predictable financial performance and formulaic outcomes.

In looking toward the future of capital investments in the precision medical sector, J.P. Morgan was consistent with the fund manager I spoke with and reports that "data-driven

medical research companies, particularly those with prowess in artificial intelligence and machine learning, will lead the way in researching new precision medicines for patients" (2020). Similar to financial firms being able to determine a consumer's credit score based on almost every aspect of a person's financial history, healthcare companies may soon be able to analyze a patient's entire medical history to determine which treatment could be best for that unique individual (J.P. Morgan, 2020). J.P. Morgan states that "these are the companies that will be able to take vast datasets and interpret them to determine which treatment options to explore and conduct further research on for any given patient. Large pharmaceutical companies that focus on cell therapy and/or immune-oncology treatments could be key in this category" (2020).

Bob Kocher, a partner at venture capital firm Venrock, said that these consumer-focused companies have all taken steps toward personalizing their offerings. Simply put, the promise of precision medicine is too great for such firms to ignore in their investment portfolios (Pappas Capital, 2012). Personalization increases the value of those offerings and helps the companies make delivery of services and products more efficient. "Because they can offer the right product, they can take away unnecessary costs," Kocher said. "And in healthcare, that's what we really need to do" (Pappas Capital, 2012).

Precision medicine will help doctors determine what to treat, how to treat and how much to treat. That knowledge, Kocher said, will mean fewer medicines, not more. Evidence and data will guide treatment to the optimal level that strikes a balance between risks and outcomes. Within this framework, Kymriah ultimately represented little risk to Novartis'

balance sheet due to the small numbers of patients who would be eligible for such therapy while, concurrently, providing Novartis with a high reward potential for patients and public perception.

The ongoing advancements in the precision medical sector has also been driven by lessons learned during the biotechnology boom in the 1990s, at which time venture capitalists invested significant amounts of equity into companies that ultimately failed to bring therapeutics to market or to execute an effective exit strategy such as technology licensure or the selling of intellectual property rights to larger biotechnology or pharmaceutical companies that had the resources to advance such technologies along the drug development life cycle.

According to Pappas Capital (2012), investors are interested in ideas that substantially save money. According to Kocher, "if it substantially costs money and there's little to no return on investment, the product won't do well" (Pappas Capital, 2012). As an example, Pappas is an investor in Palo Alto, California cardiovascular genomic diagnostics company CardioDx. Turner Jenkins, an associate at Durham venture capital firm Pappas Ventures, said that there is a gap between the launch of the product and its reimbursement by payers. Kocher reports that "until payers start paying for the CardioDx's genomics diagnostic, the company must subsidize its use" (Pappas Capital, 2012). If a precision medicine technology doesn't substantially save money or improve outcomes, its probably not a good idea, at least from an investment perspective, Kocher said (Pappas Capital, 2012). This

scenario aligned perfectly with the developmental investment requirements needed for Novartis to bring Kymriah to market and the downstream clinical outcomes afforded to patients prescribed its treatment.

Industry

The U.S. pharmaceutical industry has historically been built around drugs that treat conditions affecting large populations including high cholesterol, infectious diseases, high blood pressure and gastrointestinal maladies (Korn Ferry, n.d.). The model focused on patients receiving similar, if not identical, treatments (Korn Ferry, n.d.). During these times, a patented drug like Lipitor contributed a record $125 billion to Pfizer during its 12-year run, making pharma very profitable even if the companies had to replace an entire book of business every 10 to 12 years (Korn Ferry, n.d.).

With the continued emergence and maturation of the precision medical industry and its ability to analyze genomic data to unveil the abnormalities that create illness, pharmaceutical companies are increasingly being confronted with the realization that they have to reinvent themselves in order to remain competitive. This is to say that the data generated by advancements in NGS technologies have made patients and the public subjects of biocapital driven by a greater emphasis on data and tissue-based economies. As a result, pharmaceutical companies are placing an increased emphasis on the collection and genomic analysis of biospecimens as part of their clinical trial offerings in an effort to

delineate molecular markers for which they can develop advanced diagnostics and targeted therapeutics.

This paradigm is being led by discoveries and clinical trial advancements that are reported annually in forums such as the annual meeting of the American Society of Clinical Oncologists (ASCO). Each year, ASCO hosts thousands of oncologists and pharmaceutical representatives to learn about new developments in cancer treatment. In doing so, attendees hear accounts of clinical trials documenting exciting breakthroughs were presented alongside reports of gnawingly difficult challenges in developing therapies for treating stubborn cancers with therapies that bring relief to some and completely fail other patients (Korn Ferry, n.d.). As a result, more and more pharmaceutical companies are migrating business strategies away from the traditional "blockbuster" drug model to one that is focused on small sets and subsets of patients and their genetically unique instances of disease.

This new model is prompting pharmaceutical companies to examine expenses in research and development and, like enterprises in other sectors, pharmaceutical companies are divesting some operations to bring greater focus to their core business. In the realm of clinical trials, there is increased emphasis on the collection and analysis of biospecimens for known or unknown future research as a result of the need for additional genomic data and applicable disease variants so that novel diagnostics and therapeutic technologies can be developed.

In terms of the impact on pharma, Korn Ferry reports that Bristol-Myers Squibb (BMS) was one company that has experienced the highs and lows of this paradigm shift, concurrently presenting at the ASCO conference powerful data from clinical trials that showed its drug, Opdivo, could double survival for lung cancer patients while experiencing a drop in its stock price secondary to an analyst suggesting that its competitive position for Opdivo wasn't bulletproof (Korn Ferry, n.d.). In response, BMS CEO Giovanni Caforio reported that BMS "have successfully transformed the company," he said, referring to the company's hard slog in re-engineering its business, divesting its medical-imaging group, its diabetes business, wound-care division and nutritional business to focus on the high-margin specialty drug group (Korn Ferry, n.d.).

While BMS sought to allay the concerns of its investment community, the most significant trend at the conference was the announcement of NCI-Molecular Analysis for Therapy Choice program, NCI-MATCH, a clinical trial that will analyze patients' tumors to determine whether they contain genetic abnormalities for which a targeted drug exists and assign treatment based on the abnormality. NCI-MATCH seeks to determine whether treating cancers according to their molecular abnormalities will show evidence of effectiveness.

To do that, Korn ferry reports that the National Cancer Institute will work with more than 20 companies in "discovery trials" as companies provide their drugs for study on specific

mutations. The government is paying for the trials, a huge incentive to the companies to participate. The drugs included in the trial have all either been approved by the U.S. Food and Drug Administration for another cancer indication or are still being tested in other clinical trials but have shown some effectiveness against tumors with particular genetic alterations (n.d.). For pharmaceutical companies, this approach strikes a balance in the risk-benefit determination when considering the minimal financial investment due to the federal sponsorship of the trials, while also presenting companies with opportunities to demonstrate the efficacy of their products for one or more genetic variants associated with disease. From a risk perspective, it may be determined that a competitor's product is superior or non-inferior to a company's product, but this risk should be minimal and the potential subject of mitigation through the specificity of genetic targets.

"This is the largest and most rigorous precision oncology trial that has ever been attempted," said Dr. James H. Doroshow, deputy director of NCI. The trials promise new insight into treating tumors that have been particularly resistant to treatment (Korn Ferry, n.d.). According to Korn Ferry, Doroshow called the program a "paradigm shift," from treating cancer based on the organ where it originated to zeroing in on the genetic abnormality and matching it to one of the drugs being studied. Once enrolled, patients will be treated with the targeted drug for as long as their tumor shrinks or remains stable (n.d.).

Such a program is made possible by significant advancements in NGS technologies, resulting in more extensive data at lower costs. Korn Ferry reports that "while the Human

Genome Project was an immense international collaboration that took 13 years and cost $3.8 billion, Doroshow estimates that the genome mapping for NCI-MATCH is about $1,000 per patient" (n.d.).

Taking all of this into consideration, it is clear that companies are both seeking to make an impact within the precision medical sector, but that any potential competitive advantage is likely fragile and potentially short-lived. Much of this is relative to whose benefit is being considered at any specific moment in time. That is, news of an emerging therapeutic can be simultaneously good news for patients and clinical practitioners, but concurrently detrimental to stockholders and other stakeholders within competing firms. What is positive is the potential for public-private collaborations to further evaluate precision medical products across diseases beyond labeling constraints. This approach can both minimize financial risk for companies while expanding the potential patient population(s) for which a particular product can be considered as a potential therapeutic intervention, thereby minimizing downstream risk to corporate investment and investor relations. This approach also supports the notion of an emerging new taxonomy of disease, through which novel or existing precision medical products can transcend traditional diagnostics and subscribe to an amended labeling model specific to targeted genetic variants.

Regulatory Governance

In the United States, precision medical products, such as Kymriah and the F1CDx test, seeking introduction to the U.S. market are evaluated based upon concepts such as risk and

efficacy. That is., much of the determination whether to approve a product's marketing application hinges on whether the product is determined to be safer than currently marketed products and/or more effective in the fulfillment of its purpose. To fully understand the governance and oversight of concepts such as "risk", I believe it is necessary for one to have, at the very least, a basic understanding of the structures and mechanisms through which such factors emerge.

Before medical products such as pharmaceuticals, in-vitro diagnostics, and biologics reach their final marketability determination, they are subject to both pre-clinical and clinical (i.e. human subjects) research. In the United States, human subjects' research has a long history of scientific advancement, regulatory actions, and human rights violations. As such, it became necessary to create a robust regulatory oversight system to facilitate advancements in science, while seeking to mitigate or minimize violations or ethical shortcomings. An operational model emerged in which human subjects' research in the U.S. is regulated by two primary authorities, the U.S. Food and Drug Administration (FDA) and the U.S. Department of Health and Human Service's Office for Human Research Protections (OHRP). There are both differences and commonalities concerning what type(s) of research are regulated by either the FDA, OHRP, or both.

Drug Regulation and Oversight

The modern-day FDA is the most powerful regulatory agency in the world. However, it attained this status from humble beginnings as a single chemist in the U.S. Department of

Agriculture in 1862. Today, the FDA employs chemists, pharmacologists, physicians, microbiologists, veterinarians, pharmacists, lawyers, and many others. About one-third of the agency's employees are stationed outside of the Washington, D. C. area, staffing over 150 field offices and laboratories, including five regional offices and 20 district offices. FDA scientists evaluate applications for new human drugs and biologics, medical devices, food and color additives, infant formulas, and animal drugs (FDA History I, 2009).

The FDA's authority began with a key piece of legislation known as the 1906 Food and Drugs Act, also commonly known as the Wiley Act[2] (FDA History I, 2009). The act, under the operational oversight of the Bureau of Chemistry, prohibited the interstate transport of unlawful food and drugs and allowed seizure of the questionable products and/or prosecution of the responsible parties (FDA History I, 2009). Unlike current practices, the basis of the law rested on the regulation of product labeling rather than pre-market approval. Drugs had to adhere to standards of the time and plainly state dosage and indications on the label (Federal Food and Drugs Act of 1906, 2009) (FDA History I, 2009).

Much of the focus of the Wiley Act centered on food regulation, even though foods were not defined according to standards in the same manner as drugs (FDA History I, 2009). Nonetheless, the law prohibited the addition of any ingredients that would substitute for the food, conceal damage, pose a health hazard, or constitute a filthy or decomposed substance. Interpretations of the food provisions in the law led to many, sometimes

[2] . The term "Wiley Act" was established after Dr. Harvey Wiley, head of the Bureau of Chemistry and whose persistence is largely credited with the passage of this law.

protracted, court battles (FDA History I, 2009). If the manufacturer opted to list the weight or measure of a food, this had to be done accurately. Also, the food or drug label could not be false or misleading in any particular, and the presence and amount of eleven dangerous ingredients, including alcohol, heroin, and cocaine, had to be listed (Federal Food and Drugs Act of 1906, 2009).

After Wiley's resignation in 1912, the bureau devoted more effort to drug regulation, with some emphasis on the so-called patent medicines (FDA History II, 2009). After the election of Franklin Roosevelt and the death of Wiley in 1930, the FDA could pursue needed changes to the law. Congress responded by passing the 1938 Food, Drug, and Cosmetic Act. The new law brought cosmetics and medical devices under control, and required that drugs be labeled with adequate directions for safe use. The law also mandated pre-market approval of all new drugs, requiring a manufacturer to prove to the FDA that a drug were safe before it could be sold. It prohibited false therapeutic claims for drugs, corrected abuses in food packaging and quality, and mandated legally enforceable food standards. According to the FDA's historical account, the law formally authorized factory inspections, and it added injunctions to the enforcement tools at the agency's disposal (2012). Within two months of the passage of the act, the FDA began to identify drugs that could not be labeled for safe use directly by the patient, requiring a prescription from a physician (FDA History II, 2012).

In 1962, the Kefauver-Harris Amendment[3] to the 1938 Food, Drug and Cosmetic Act was approved, representing a significant change in FDA regulatory authority. The legislation gave the FDA the ability to demand that drug makers prove their products were safe and effective before receiving approval to market them in the United States (Kefauver-Harris Amendments Revolutionized Drug Development, 2012). As a result of the amendment, the following changes were enacted (Kefauver-Harris Amendments Revolutionized Drug Development, 2012):

- Manufacturers had to provide evidence that proposed drugs were both safe and effective, demonstrated by adequate and well-controlled clinical investigations conducted by qualified experts.
- FDA was given 180 days to evaluate a new drug application, and the application would no longer become automatically effective.
- New drugs required an affirmative decision by the agency before marketing.
- Manufacturers had to maintain records of adverse events associated with drugs and report these promptly to FDA.

Kefauver considered the amendment his "finest achievement" in consumer protection (Kefauver-Harris Amendments Revolutionized Drug Development, 2012). It laid the groundwork for modern drug approvals and ultimately led to an evidence-based model for drug evaluation decisions that today stands as the global standard (Kefauver-Harris Amendments Revolutionized Drug Development, 2012). This model is largely contingent

[3] Named after U.S. Senator Estes Kefauver, of Tennessee, and U.S. Representative Oren Harris of Arkansas, who proposed the amendment.

upon standardization of process, disease characterization, and the products for which the FDA is seeking to evaluate. Such standards require risk-benefit analyses through which products are assessed for safety and efficacy, oftentimes relative to existing standards of care. That is, the FDA seeks to determine whether a novel therapeutic is superior to existing treatments in clinical outcomes and/or equivalent with a better safety profile regarding expected adverse events. The model relies upon extensive data collected via pre-clinical studies and clinical trials enrolling thousands of subjects such that treatment outcomes can be satisfactorily attributable to the test article administration. In contrast to traditional medical therapeutics, precision medical products dislodge this quantitative standards model due to the minimal number of patients whose disease is characterized by targeted genetic variants. As a result, precision medical products are intentionally de-stabilizing historical models of standardization for regulators, which I will discuss in greater detail later in this chapter.

*Human Subjects' Protection*s

The history of contemporary human subjects' protections began in 1947 with the Nuremberg Code, developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis (45 CFR 46 FAQ's, 2012). The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects.

Basic regulations governing the protection of human subjects in research supported or conducted by HHS (then the Department of Health, Education and Welfare) were first published in 1974. In the United States, a series of highly publicized abuses in research led to the enactment of the 1974 National Research Act, which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the National Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines to assure that such research is conducted in accordance with those principles (45 CFR 46 FAQ's, 2012). In 1978, the Commission published "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," also known as the Belmont Report, named after the Belmont Conference Center where the Commission met when drafting the report (45 CFR 46-FAQ's, 2012). The Belmont Report identifies three fundamental ethical principles for all human subjects' research: respect for persons, beneficence, and justice. Largely based upon the elements of the Belmont Report, HHS regulations are codified at 45 CFR Part 46, subparts A through E, which are upheld by the OHRP.

The FDA was involved early and often in human subjects' protection (Carpenter, 2004). The FDA's Investigational New Drug Regulations of 1963 included requirements for informed consent and human subjects' protections in clinical trials with investigational new drugs. The FDA's formal capacity in regulating clinical research is augmented by the day-to-day field and enforcement activities that the agency devotes to human subjects' protection. The FDA launched its Bioresearch Monitoring Program in 1977, which

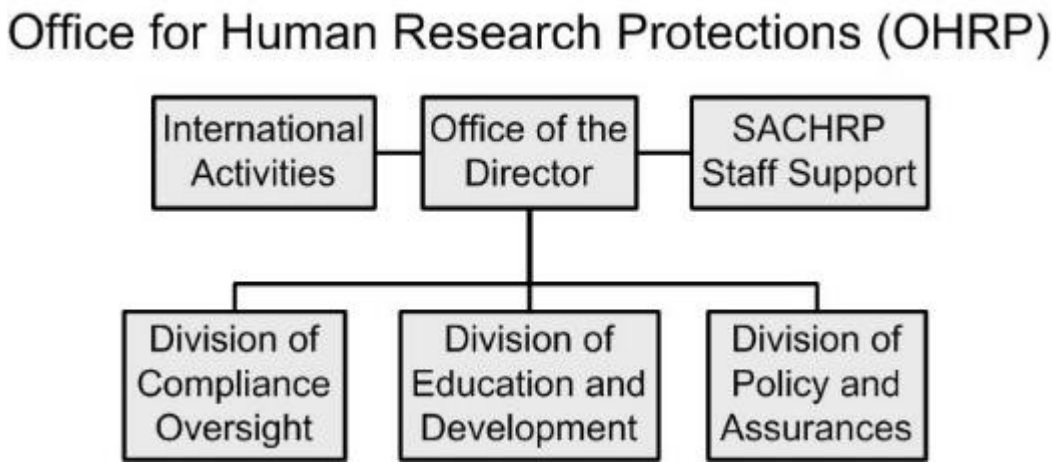
included inspection of clinical investigators, biopharmaceutical laboratories, toxicology laboratories, and IRBs. When deficiencies are found, the FDA may issue a warning letter to institutions detailing "significant deficiencies" in IRB oversight. If the deficiencies are serious enough, the FDA can disqualify both the IRB and the clinical investigator (Carpenter, 2004).

The FDA cannot disqualify physicians from medical practice, nor can it prohibit universities from engaging in research. What backs up the FDA's human subjects' regulations is its authoritative gatekeeping role in the pharmaceutical and medical device marketplaces (Carpenter, 2004). In addition, since research funding is the lifeblood of any research endeavor, FDA sanctions can do enormous implicit and explicit damage to the careers and livelihoods of researchers and research organizations that violate federal law (Carpenter, 2004).

The National Institutes of Health's Office for Human Research Protections (OHRP), part of the U.S. Department of Health and Human Services (HHS), provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS) (OHRP Fact Sheet, 2012). OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.

The OHRP is organized into three primary divisions – the Division of Compliance Oversight, the Division of Education and Development, and the Division of Policy and Assurances (see Figure 3 below).

Figure 3: OHRP Organization Chart



According to OHRP's Fact Sheet, OHRP's Division of Compliance Oversight (DCO) evaluates written substantive indications of noncompliance with 45 CFR 46 (2012). OHRP asks the institution involved to investigate the allegations and to provide OHRP with a written report of its investigation. The Office then determines what, if any, regulatory action needs to be taken to protect human research subjects. The DCO also conducts a program of not-for-cause surveillance evaluations of institutions, and receives, reviews, and responds to incident reports from Assured institutions (OHRP Fact Sheet, 2012).

OHRP's Division of Education and Development provides guidance to individuals and institutions conducting federally funded human subject research and holds national and regional conferences. They also participate in professional, academic, and association conferences and develop/distribute resource materials in an effort to improve protections for human research subjects (OHRP Fact Sheet, 2012).

OHRP's Division of Policy and Assurances prepares policies and guidance documents and interpretations of requirements for human subject protections and disseminates this information to the research community, as stated on OHRP's Fact Sheet (2012). The Division also administers the Federalwide Assurances of Compliance and registration of institutional review boards.

In terms of the relevant areas of regulatory oversight for OHRP and the FDA, OHRP requirements apply to all types of human subjects' research (e.g. greater that minimal risk, minimal risk, drugs, questionnaires, etc.). In contrast, FDA oversight is strictly limited to research involving the use of FDA-regulated articles, such as drugs, medical devices, biological agents, and radiation-emitting products. If a particular research project does not involve such a test article, the oversight does not fall under the purview of the FDA. OHRP derives its regulatory authority from 45 CFR 46, Subparts A-E (also known as the Common Rule because of its applicability to many federal agencies…including the FDA). For the FDA, applicable regulations are much more applicable to the type(s) of products being regulated, including 21 CFR 50 (human subjects protection), 21 CFR 56 (IRBs), 21 CFR 312 (IND's), 21 CFR 812 (IDE's), 21 CFR 58 (GLP), 21 CFR 4 (Combination Products),

21 CFR 600 (Biologics) and others. A comprehensive listing of the comparative regulatory requirements between the FDA and OHRP are provided in Attachment A (Comparison of FDA and HHS Human Subject Protection Regulations, 2009).

Both the OHRP and FDA play significant roles in the governance and regulation of human subjects' research in the U.S. There are many similarities in their respective regulatory requirements, as well as some key differences. One area of divergence for the FDA and OHRP is their applicable source(s) of power in regulating research activities.

OHRP typically derives its authority from its ties to federal research funding. Specifically, if an individual or organization wishes to engage in human subjects research activities funded whole or in part by federal dollars (e.g. NIH or NSF grants), they must first agree to abide by the regulations set forth by OHRP and, in particular, the Common Rule. This requirement is codified through the execution of a document known as a Federalwide Assurance (FWA) between OHRP and the grantee organization. Within the FWA, the grantee provides information about their organization, including the type(s) and volumes of research they perform and they are required to ensure, in writing, that they will abide by all federal regulatory requirements and ethical doctrine for any/all research activities funded by federal dollars. Of note is the fact that the FWA also allows a grantee organization to elect that they will abide by the same regulatory and ethical standard for all research activities, regardless of funding source. This is usually not elected by organizations due to a fear of audits/reprisal if there are compliance or research integrity issues surrounding research activities that aren't federally funded.

The FDA derives its authority in a much different manner than that of OHRP. For the FDA, the ability to influence is less about federal funding ties and more about power, reputation, and its ability to impact access to markets. According to Carpenter, from one vantage, the agency's formal authority is limited to the jurisdictions and territories of the United States (2010). It legally tends the boundaries of only one nation. From another vantage, however, the FDA rules the entire global pharmaceutical market (Carpenter, 2010). This is to say that, because the FDA is the regulatory authority for the world's largest pharmaceutical market, the agency is able to wield power globally via regulatory acts, requiring that pharmaceutical companies that wish to market regulated products in the U.S. adhere to the standards set forth by the FDA, regardless of the site(s) of clinical trial performance.

Another method through which the FDA exerts influence is through the development of perceived power and reputation, primarily as it relates to drug safety for the American public. Perhaps the best example of this is the thalidomide tragedy of the late 1950s and early 1960s, during which more than 10,000 children in 46 countries were born with deformities as a consequence of thalidomide use by pregnant mothers. According to Carpenter (2010), the visible and evocative horror of the thalidomide tragedy—babies born limbless, their pictures scattered across front pages of newspapers and magazines, their horrific deformities and stories of agony repeatedly narrated on television and over radio—created the substrate for a powerful historical lesson. Drugs were inherently dangerous, and the Administration could protect the unaware American family from them, not merely through police-like enforcement but through regulatory gatekeeping (Carpenter, 2010).

Despite being etiologically divergent, the power held by both the OHRP and FDA are both examples of the Foucauldian concept of "biopolitics". Biopolitics is the strategic coordination of these power relations in order to extract a surplus of power from living beings. Biopolitics is a strategic relation, not the pure and simple capacity to legislate or legitimize sovereignty. Biopolitical functions of coordination and determination concede that biopower, from the moment it begins to operate in this particular manner, is not the true source of power. It can be said that biopower is always born of something other than itself (What is biopower, 2012). In the cases of the OHRP and the FDA, the pursuit of federal research funds or the desire to access the American pharmaceutical market provide adherence to, and legitimacy of, their influence. [fine to introduce biopolitics/biopower, but what analytic work is it doing for you here? Connect to the regulatory role of FDA in the previous chapter as an agency that positions itself as protecting human lives? What are the (bio)politics of its conceptions and modes of protection vis-à-vis precision medicine?

Impact of Precision Medicine on Regulatory Structures

The impact of precision medicine on regulatory oversight mechanisms and processes cannot be over-stated. In 2019, the FDA's Center for Drug Evaluation and Research (CDER) approved 48 novel drugs (Nature, 2020). "Among these approved drugs, were targeted drugs, including 27 small molecules, 3 antibody-drug conjugates (ADCs), 1 RNA interference (RNAi) therapy, 1 antisense oligonucleotide, 4 monoclonal antibodies (mAbs), 1 recombinant fusion protein, and 2 synthetic peptide analogs" (Nature, 2020). Applicable targets were kinases, ion channels, exons, enzymes, and receptors. Oncology

remained the most important drug discovery area, accounting for 23% (9/39) of the targeted drug approvals (Nature, 2020). This dynamic by regulators is directly attributable to aforementioned advances in sequencing technologies and the subsequent delineation of genetic variants associated with disease.

Assimilations and adaptations by the FDA, and the federal government, have occurred through the co-development of strategic, tactical, and policy-related doctrine, as well as evolving regulatory review and approval practices when considering marketing applications for precision medical products.

In 2013, the FDA published a report entitled *Paving the Way for Precision Medicine-FDA's Role in a New Era of Medical Product Development.* The report sought to shed light on the concept of precision medicine. In the report, the FDA stated that "what is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects" (2013, p. 4). To be clear, these are lofty aspirations with many overlapping components. As a result, by the time President Obama presented his vision to the nation, several key policy decisions had either already occurred or would be taken by the federal government, as follow:

In August 2011, the FDA released its *Advancing Regulatory Science at FDA* strategic plan, which included provisions for stimulating innovation in clinical evaluations and precision

medicine and others to ensure the FDA's readiness to evaluate innovative emerging technologies (FDA, 2011). In October 2013, the FDA released another publication entitled *Paving the Way for Precision Medicine – FDA's Role in a New Era of Medical Product Development* (FDA, 2013). In the report, the FDA stated their "responsibility for ensuring that drugs, devices, and biologics are safe and effective provides the agency with a unique perspective on both the successes and failures that occur in medical product development and special insight into the emergence and direction of the field of precision medicine" (FDA, 2013, p. 11). In August 2014, the National Institutes of Health (NIH) released its Genomic Data Sharing Policy that required all federal funding grant applications submitted for the January 25, 2015 deadline and thereafter, that were intended to generate large-scale human or non-human genomic data (as well as the use of these data for subsequent research), to include a plan for sharing of those data via approved digital repositories accessible to the scientific community (NIH, 2014). The policy defined large-scale data as including genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data, irrespective of funding level and funding mechanism (e.g., grant, contract, cooperative agreement, or intramural support) (NIH, 2014). Lastly, ten days following President Obama's 2015 speech, at a meeting with patients, advocates, scientists, and industry leaders, he "shared his vision of moving the U.S. into an era where medical treatment can be tailored to each individual patient" (NIH, 2015, p. 1). Afterward, the NIH developed the PMI Cohort Program (PMI-CP) to develop a plan for public engagement through the genomic sequencing of at least one million participants over four years to

facilitate the analysis of the genetic profiles of the most challenging diseases of our time (NIH, 2015). This program became known as the *All of Us* research program.

In response to such advancements, the FDA issued a 2011 *Strategic Plan for Regulatory Science*, outlining eight priority areas within the realm of regulatory science which were determined to be essential to the advancement of their regulatory mission, with a ninth being added in 2013 (FDA, 2011).

One such priority area for the FDA is Increasing Choice and Competition through Innovation. According to the FDA, individualized therapies have become increasingly feasible due to improved understanding of individual variability and identifying new ultrarare genetic diseases with next generation sequencing (NGS) technologies. The challenges and opportunities for utilizing FDA-regulated products as individualized therapeutics span the product lifecycle: the development of robust manufacturing and assurance of product quality, extent of preclinical testing to support regulatory evaluation, the collection of clinical evidence with a very small number of patients worldwide (e.g., populations as small as one patient). These issues impact safety and effectiveness evaluation, and sustainability.

To realize the promise of precision medicine and individualized therapeutics, FDA sees a critical need for more mechanistic understanding, improved manufacturing capabilities, and additional tools. FDA is exploring new technologies (omics) to advance major

breakthroughs in thinking about diagnosis, prognosis, and treatment of disease. The FDA created precisionFDA, a cloud-based community research and development portal that engages users across the world to share data and tools to test, pilot, and validate existing and new bioinformatics approaches to NGS processing. Pharmacogenetics studies how individuals respond differently to drug therapies based on their genetic make-up or genes using technology such as NGS which allows sequencing of a human's entire genome in a short period of time (as short as one day). This technology combined with others enables researchers to identify precise genetic, mechanistic, or lifestyle reasons to understand why certain individuals or subpopulations respond positively or negatively when treated for the same disease with the same drug. Being able to more precisely classify the genetic basis of diseases and drug responses through diagnostic tests and devices enables the development of mechanistically targeted therapeutics.

In addition to such publications and policy-related steps, the FDA is concurrently taking measures to assimilate precision medical products into its evaluative processes in determining whether to approve a product's marketing application to the FDA. However, such prioritization does not suggest that advancement of regulatory science is without challenges.

To explore this process further, I spoke with a senior official in the FDA's Center for Biologics Evaluation and Research (CBER) who was directly involved in the review and approval process for tisagenlecleucel. During our conversation, he reported that precision

medical technologies, while holding tremendous promise for the treatment and/or eradication of disease, present challenges to the regulatory community. Specifically, traditional medical products are designed to act upon certain attributes of a disease or medical condition, whereas precision medical products recontextualize clinical disorders based upon genetic variants or mutations, thereby challenging the classification of disease.

One of the most salient challenges discussed was the ability, or rather the inability, to gather much evidence in support of a product's claim to evoke a medical impact on a clinical condition. This is to say that the ability to target therapeutic compounds to a single or small group of genetic variants or mutations reduces the overall number of subjects that can be evaluated in the course of clinical trials. This scenario presents a challenge to regulatory personnel and their ability to characterize or quantify effect. This is to say that the standardization of disease allows the standardization of tests of efficacy and measures of what counts as efficacy. So, measuring effect in the old paradigm is predicated on disease being standard(izable). He continued to report that, within the new paradigm of precision medical products, when the effect is dramatic, this does not impede the regulatory approval process. However, when the clinical effect is small or non-existent on average across all cases presented as part of a marketing application, then the problem has not been solved. While this approach may support the rejection of a product's marketing application, it may also be confounded by the limited evidence available for consideration.

When the FDA evaluates a marketing application for a medical product, the goal is to meet a statutory standard that demonstrates that a drug is safe and effective for its labeled indications under its labeled conditions of use (FDA, 2016). To evaluate a drug's application against this standard, an entire series of events ensues, involving dozens of people who evaluate specific aspects of the application. These include safety/effectiveness, analysis of pre-clinical studies, manufacturing processes, labeling, potency, sterility, statistics, and epidemiological concerns. As a result of limited evidence, it is often the case that approval or disapproval outcomes are subject to individual interpretation, resulting in a lack of consensus. Within the Administration, precision medical products are presenting challenges to the historical standards through which the FDA evaluates the targeted condition and available treatments, risks and benefits presented from clinical data, and potential strategies for managing risks (FDA, 2019 b). This is largely due to the fact that precision medical practice is, in some ways, at odds with historical disease standardization models, built upon clinical presentation and phenotypical symptomatology, due to their targeted variant specificity that may not align with traditional diagnostics. As such, precision medicine is introducing a new epistemology that de-standardizes modes of standardization and, concurrently, existing regulatory standards. Consequently, there is much more uncertainty in terms of product safety and effectiveness and the tolerance level of regulatory personnel.

This scenario is representative of *bounded rationality,* a way of thinking about decisions made by individuals and institutions that incorporates constraints on time, information, and

cognitive resources (Lewallen, et al, 2016). According to Lewallen, "Herbert Simon, James March, and other scholars in the social sciences developed the concept of *bounded rationality* in the mid-twentieth century as a response to the rational, comprehensive decision-making model. In a comprehensive rationality model, decision makers' priorities do not change (they have stable preferences), and they seek out as much information as they need to make a decision that yields their most preferred feasible outcome (they "maximize" their utilities)" (2016). Further, in his 2020 article entitled Unknown Knowns, Sarewitz states that "because the world is far too rich and complex for full comprehension by anyone, unknown knowns are a necessary cognitive strategy for allowing each of us to maintain a view of things coherent enough to allow us to act in the world" (2020). For the FDA regulatory scientist, this requires the assimilation and understanding of a limit set of information in order to render a decision regarding the approvability of a drug.

According to the FDA, in its marketing application review of Kymriah, one single-arm trial supported the BLA application, CCTL019B2202 (B2202). Two additional studies that utilized the University of Pennsylvania CTL019 product were provided for safety and efficacy comparison (CCTL019B2205J [B2205J] and CCLT019B2101J [B2101J]) (n.d.). They were both conducted at the University of Pennsylvania. CCTL019B2101J (UPCC04409) which was a pilot study of anti-CD19 CAR T cells in CD19+ leukemia and lymphoma. Six patients with acute lymphoblastic leukemia (n=6) were treated. The mean age of the adult ALL patients was 50 years (SD 15.77) and one was under 40 years of age (26 years, diagnosed at age 18). CCTL019A2201 was a dose optimization trial for patients

with CD19+ CLL. No formal comparability study of tisagenlecleucel and the University of Pennsylvania and Children's Hospital of Philadelphia CTL019 was conducted, and there were differences in manufacturing processes that precludes comparability without appropriate analysis. Therefore, this review is limited to B2202 for safety and efficacy. The primary efficacy and safety analyses for the BLA were based on data from Study B2202. Eighty-eight patients were enrolled. Sixty-eight patients received tisagenlecleucel from the U.S. (n=63) or the German (n=5) manufacturing sites. This clinical review for efficacy focused on the 63 patients treated with tisagenlecleucel from the U.S. manufacturing plant in Morris Plains, New Jersey and focused on the confirmation of the primary endpoint of best overall remission rate (ORR, equals complete remission [CR] plus CR with incomplete hematologic recovery]) within 3 months of the infusion of tisagenlecleucel as determined by an independent review committee (IRC), secondary endpoints of status of minimal residual disease at time of best overall response (BOR), duration of response, overall survival, and relapse-free survival.

The FDA was confronted with a risk/benefit analysis that required them to consider both the citizen consumer (i.e., patients) and their collective need for access to potentially life-saving treatment along with the potential for serious clinical side effects as a result of such treatment. Within this framework, the FDA opted for a conservative approach to its approval of Kymriah by approving the product for market entry by Novartis while requiring significant post-market measures to be taken on the part of Novartis and clinical sites in terms of patient and staff education, as well as the requirement to collect additional post-

market surveillance data. This decision was, in my opinion, a result of limited clinical data that was also characterized by a significant treatment effect. That is, although the data was limited relative to traditional marketing applications for traditional drug products, the treatment outcomes for clinical trial participants were profound in their support of Kymriah as a promising treatment for ALL patients.

During its review of Foundation Medicine's F1CDx test, the FDA characterized the test as "a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens" (FDA, 2017c). For the FDA, the F1CDx test represented a more comprehensive companion diagnostic than they had previously considered for market approval due to the extensive number of genetic mutations and genomic signatures it claimed to identify, as well as its ability to align such findings with existing targeted therapeutics in a single comprehensive report. F1CDx was designed to serve as a companion diagnostic for medical practitioners to help with the identification of patients who may benefit from treatment with targeted therapies in accordance with their product labeling (FDA, 2017c). The list of targeted therapies and clinical indications associated with the F1CDx test are shown in Table 2 below.

Table 2. F1CDx Test Indications and Targeted Therapies (FDA, 2017c).

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and EGFR exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations T	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	BRAF V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	ERBB2 (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), or Perjeta® (pertuzumab)
Colorectal cancer	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	BRCA1/2 alterations	Rubraca® (rucaparib)

The FDA also evaluated F1CDx's probable risk associated with analytical performance of the device, representation of variants, additional and ongoing analytical testing (FDA, 2017c). In considering the risk/benefit determination of the assay in terms of the potential collective benefit for patients, the FDA reported that, given the data provided, their analyses supported the marketing approval of the F1CDx test, noting that its probable benefits outweighed its probable risks (FDA, 2017c). This is to say that the FDA, in its review of F1CDx, essentially distilled its marketing approval decision down to a risk-

benefit ratio for patients and their medical care. They ultimately determined that the information revealed by the test for medical practitioners was adequate to offset any potential risk to patients and carried the potential to provide actionable information in a medical setting that could potentially augment clinical decision-making and benefit patients by aligning targeted therapeutics to their individual instances of disease and, concurrently, eliminating or minimizing undue risk to patients.

To interrogate this process, I spoke with a representative from the FDA's Center for Devices and Radiological Health's Office of In Vitro Diagnostics and Radiological Health, who informed me that considerations of uncertainty in making risk/benefit determinations are subject to a statutory standard in their efforts to demonstrate safety and efficacy for applicable product(s). In the case of precision medical devices, such as companion diagnostics like the F1CDx test, they reported that the FDA maintains a standardized approach via its statutory standards to navigate issues such as risk, but the specific decisions surrounding individual products can vary based upon the contextual details surrounding a specific device. The statutory standard for medical devices, including for certain marketing authorizations, reflects this reality by requiring devices to have a "reasonable" assurance, rather than an absolute assurance, of safety and effectiveness (FDA, 2019a). The extent of uncertainty is contingent on the type of premarket decision and its context. As a result, the appropriate uncertainty in a benefit-risk determination to support a device premarket decision would depend on the circumstances, including the totality of information about the device. In considering uncertainty in benefit-risk

determinations, the FDA considers several factors, as appropriate to the circumstances, including (FDA, 2019a):

- The extent of the probable benefits of the device, taking into account the type, magnitude, probability, duration, and frequency of those benefits, including if the probable benefits are greater than those of approved or cleared alternative treatments or diagnostics or the standard of care;
- The extent of the probable risks of the device, taking into account the severity, type, number, rates, probability, and duration of those risks, including if the probable risks are less than those of approved or cleared alternative treatments or diagnostics or the standard of care;
- The extent of uncertainty regarding the benefit-risk profile of approved or cleared alternative treatments or diagnostics or the standard of care (e.g., the strength of the evidence supporting the alternative treatment or diagnostic);
- Patients' perspective on appropriate uncertainty about the probable benefits and risks of the device, if available.
- The extent of the public health need (e.g., seriousness of the illness; benefit-risk profile of other available therapeutics or diagnostics, if any, including the current standard of care; the portion of the target population for whom there would be a positive benefit-risk profile); The feasibility of generating extensive clinical evidence premarket based on appropriate considerations, e.g., taking into account the prevalence of the disease or condition;

- The ability to reduce or resolve remaining uncertainty of a device's benefit-risk profile postmarket (e.g., consideration of FDA's authority to require postmarket data collection and the likelihood that the necessary postmarket data collection will be completed within reasonable timeframes);
- The likely effectiveness of mitigations, such as labeling, and other tools to help provide a reasonable assurance of safety and effectiveness of the device, as applicable;
- The type of decision being made (e.g., there is generally likely to be more uncertainty surrounding a device's benefit-risk profile based on the evidence submitted in an HDE application, as compared to a PMA, because the standards for approval are different); and
- The probable benefits of earlier patient access to the device (FDA, 2019, p. 10).

From a regulatory classification perspective, the FDA determined that the F1CDx test met the definition of a Class III device due to its intended use of diagnosing or mitigating life or disease. However, it was also determined that, despite the existence of commercially available genetic sequencing tests, the novel nature of the assay due to its extensiveness and ability to align existing targeted therapeutics to a series of genetic mutations or variants would not qualify the test as a 510(k) product. That is, there was no existing predicate device on the market at the time of submission to the FDA. As a result, Foundation Medicine was required to submit a Premarket Application (PMA) to the FDA, requiring demonstration of safety and efficacy. Such novel products present challenges to regulators

in that there is both uncertainty and risk associated with potential marketing approval decision-making.

In their risk analysis of the F1Cdx test, the FDA reported that risk associated with the test "included the possibility of inaccurate results that may lead to mismanagement of patients" (2017, c). However, F1CDx demonstrated noninferiority to other companion diagnostics and did not introduce additional risks above or beyond other approved devices. In addition, at the pre-marketing stage, the test demonstrated accuracy in detecting biomarkers associated with applicable types of cancer (FDA, 2017c). Despite any potential concerns regarding the extensiveness of the F1CDx product, the FDA was able to determine that the test satisfactorily performed in a manner consistent with its intended use. As a result, the FDA was able to render a decision to approve Foundation Medicine's marketing application for the F1CDx test that, from my perspective, was based on their validation of the test's accuracy and its potential to provide guidance to medical practitioners regarding potential treatment options for patients, while concurrently requiring a post-market risk-mitigation strategy to remain informed of any potential risks or concerns not fully identified or quantified during the premarket phase.

The Kymriah and F1CDx cases are good examples of the impacts and adaptations occurring within the premarket phase for precision medical products. Capital investors are responding by broadening their investment portfolios in response to such technologies by adopting a stance to avoid errors of omission such that they fail to invest in a promising

technology. Pharmaceutical and medical device companies are assimilating such technologies into their portfolios while applying lessons learned during the biotechnology boom of the 1990's and 2000's. That is, they are explicitly aware that precision medical products are advancing rapidly. As such, there is market pressure to try and gain a competitive advantage, which may prove short lived. However, there is increasing momentum within the pharmaceutical industry to establish public/private collaborations in an attempt to mitigate market risk by seeking to delineate future clinical applications for their products with minimal additional investment. Regulators are grappling with the destabilization of historical regulatory science models that are heavily reliant on extensive clinical data in support of a product's marketing application. Further, those models are enabled and reliant upon process and disease standardization, which is being perturbed by the sheer nature of the emerging new taxonomy of disease and lack of data upon which market approval decisions were based. As a result, new metrics such as effect size are emerging, through which regulators are adapting market approval decisions to an evolving patient-consumer in order to provide them with access to potentially life-saving therapeutics.

When considering the entire ecosystem of stakeholders associated with precision medical products, it is interesting to note that what is occurring is the disruption of traditional processes in lieu of accompanying innovation by sacrificing traditional elements of the premarket phase. Specifically, regulators are opting to approve such products for marketing despite lacking comprehensive expert validation. That is, the medicalization of

such products is being prioritized over comprehensive safety and efficacy data characteristic of historical marketing application review models. Rather, the FDA is responding to market pressures from clinicians and patients to provide access to advanced therapeutics despite lacking comprehensive safety and efficacy data. The FDA is able to adopt such a position through the requirement of post-market surveillance measures which, in effect, position such products into Phase IV trials prior to the completion of Phase III data. Lastly, although all of these adaptations and impacts are occurring within the premarket phase of precision medical products, the impact of precision medical technologies is not limited to premarket development, investment, and review mechanisms. There are also significant impacts occurring during the post-market phase of a product's life cycle, which I will discuss further in Chapter 4.

Chapter 4 – Post-Market Impacts, Adaptations, and the Assimilation of Precision Medical Products

At this point, I will transition to the post-market phase for precision medical products approved for entry into the U.S. market. During the FDA's review of Kymriah, perhaps the most concerning of potential side effects was Cytokine Release Syndrome (CRS), which the FDA determined warranted attention on the part of the manufacturer. CRS is a systemic response to the activation and proliferation of CAR T cells. CRS includes a spectrum of clinical events, including high fevers, hypozia, hypotension, and malaise. CRS generally occurs within 1 to 14 days following anti-CD19 CAR T cell therapy. Duration is variable and dependent upon the severity of clinical events.

As mentioned in Chapter 3, during the regulatory review process of tisagenlecleucel, the potential for CRS was a significant concern in terms of risk to patients. In a Clinical Information Request to Novartis dated August 7, 2017, the FDA requested that they provide information on all subjects intubated for CRS to include subject ID number, duration, median and mean time of intubation, and study start/end dates for such intubations (FDA, 2017d).

As a result, the FDA determined that the life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and neurotoxicity (See Appendix F - Kymriah Boxed Warning and Package Insert), and a Risk Evaluation and Mitigation Strategy (REMS) (see Appendix G – Kymriah Risk Evaluation and Mitigation Strategy

(REMS) Document: Kymriak (tisagenlecleucel) REMS Program). According to the FDA's draft guidance entitled *FDA's Application of Statutory Factors in Determining When a REMS is Necessary*, "the Food and Drug Administrative Amendments Act of 2007 created section 505-1 of the FD & C Act, which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks" (2016). For Kymriah, the FDA determined that the Communication Plan as proposed by Novartis would not be sufficient; instead, a REMS with elements to assure safe use (ETASU) was the appropriate approach. The focus of the REMS ETASU was site preparation, patient education, and risk mitigation strategies with emphasis on recognition and treatment of CRS and neurotoxicity (FDA Draft Guidance, 2016).

Given that the available safety data suggested that a Risk Evaluation and Mitigation Strategy (REMS) was indicated, Novartis was sent a Risk Evaluation and Mitigation Strategy (REMS) Memorandum on August 2, 2017. The FDA required the submission of a REMS to ensure that the benefits of tisagenlecleucel outweigh the risks (see Appendix H – Risk Evaluation and Mitigation Strategy (REMS) Memorandum).

As detailed in Appendix G – Kymriah Risk Evaluation and Mitigation Strategy (REMS) Document: Kymriah (tisagenlecleucel) REMS Program, the REMS also required an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU that require health care settings that dispense the drug be specially certified

and the drug be dispensed to patients only in certain health care settings, specifically, certified hospitals and affiliated clinics with appropriate access to tocilizumab (FDA, 2017f). Novartis was asked to include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.

Existing procedures for the training and certification of the investigational sites (e.g., affiliated outpatient clinics and hospitals) should be included in the REMS. Novartis was asked to incorporate the components of their REMS Communication Plan into the ETASU, as follow (FDA, 2017f).

For Hospitals:

1. To become certified to dispense tisagenlecleucel, hospitals and associated clinics must: a. Designate an authorized representative on behalf of the hospital.

b. Ensure the authorized representative is assigned to the program for tisagenlecleucel and oversees implementation and compliance with the Tisagenlecleucel REMS Program requirements by the following:

i. Complete the training and successfully complete the Tisagenlecleucel REMS Program Knowledge Assessment.

ii. Ensure all relevant staff involved in the prescribing, dispensing or administering of tisagenlecleucel are trained on the REMS Program requirements per the training

materials and successfully complete the Tisagenlecleucel REMS Program Knowledge Assessment, and maintain a record of training.

iii. Goals of the training include: Informing prescribers and other staff about the risks, clinical manifestations, and management of cytokine release syndrome (CRS) and neurotoxicity with tisagenlecleucel.

c. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing and administering tisagenlecleucel:

i. Verify tocilizumab (two doses) is ordered and available for administration before a dose of tisagenlecleucel is administered.

ii. Instruct families and patients that, they must remain within 2 hours of the hospital that administered the tisagenlecleucel for 3-4 weeks, so that if they develop CRS or neurotoxicity, they can return.

iii. The patient and family: wallet cards to remind them of the signs and symptoms of CRS and neurotoxicity that require medical attention.

2. As a condition of certification:

a. The certified hospital must recertify if the hospital designates a new authorized representative or if additional healthcare personnel are added to their staff. Routine re-education of all staff by the certified hospital representative should be included in the REMS plan.

b. Report any adverse events suggestive of cytokine release syndrome, neurotoxicity, or suspected unexpected serious adverse reactions (SUSARS) to the tisagenlecleucel.

c. Maintain documentation for the Tisagenlecleucel REMS Program, and provide this documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis or FDA.

d. Comply with audits by the applicant, FDA, or a third party acting on behalf of the applicant or FDA to ensure that all processes and procedures are in place and are being followed for the Tisagenlecleucel REMS Program.

e. Dispense tisagenlecleucel to patients only after verifying tocilizumab is ordered and ready for administration within 2 hours of the order. A second dose must also be available.

For Novartis:

To implement the Tisagenlecleucel REMS Program in hospitals, Novartis must:

a. Ensure that hospitals that dispense tisagenlecleucel are certified, see above.

b. Provide initial live training for healthcare providers who prescribe, dispense, or administer tisagenlecleucel to ensure that the hospital can complete the certification process for the Tisagenlecleucel REMS Program for new dispensing institutions. For recertification for the Tisagenlecleucel REMS Program, the training should be placed on a website accessible to treatment sites for tisagenlecleucel.

c. Ensure that hospitals are notified when they have been certified by the Tisagenlecleucel REMS Program.

d. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital.

e. Provide the REMS materials listed below to all healthcare providers at new sites who: (1) attempt to order tisagenlecleucel and are not yet certified or (2) inquire about how to become certified.

• Tisagenlecleucel REMS Program Knowledge Assessment • Slides for Live Training/Hospital Training material(s)

• Tisagenlecleucel REMS Program Hospital Enrollment Form

• Tisagenlecleucel REMS Program website

• Tisagenlecleucel Patient Wallet Card

4. To further implement the Tisagenlecleucel REMS Program. Novartis must:

a. Ensure that tisagenlecleucel is only distributed to certified hospitals.

b. Maintain a validated secure database of hospitals that are certified to dispense tisagenlecleucel in the tisagenlecleucel REMS Program.

c. Maintain records of tisagenlecleucel distribution and dispensing to certified hospitals to meet the REMS requirements.

d. Maintain a Tisagenlecleucel REMS Program Call Center and a REMS Program Website. The REMS Program Website must include the option to print the Package Insert, the Medication Guide, and tisagenlecleucel REMS materials. The tisagenlecleucel product website must include a prominent REMS-specific link to the tisagenlecleucel REMS Program Website (not the reverse).

e. Ensure that Tisagenlecleucel REMS Program website is fully operational and the REMS materials listed in or appended to the tisagenlecleucel REMS document are available through the tisagenlecleucel REMS Program Website and by calling the tisagenlecleucel REMS Program Call Center.

f. Monitor that the certified hospitals are evaluating their training program on a regular basis to ensure the requirements of the tisagenlecleucel REMS Program are being met; institute corrective action if noncompliant, and decertify hosptials that do not maintain compliance with the REMS.

g. Maintain an ongoing annual audit plan that involves hospitals and audit all newly certified hospitals within 180 calendar days after the hospital places its first order for tisagenlecleucel to ensure that all processes and procedures are in place and functioning to support the requirements of the Tisagenlecleucel REMS Program.

h. Take reasonable steps to improve implementation of and compliance with the requirements in the Tisagenlecleucel REMS Program.

The Pharmacovigilance Reviewer also concluded that long-term safety in patients treated with tisagenlecleucel needs to be confirmed as a postmarketing requirement (PMR). The applicant has submitted a postmarketing Study CCTL019B2401 (B2401) as the means to address the PMR.

The study was to be a multicenter, prospective, observational, non-interventional, planned safety study. The intent is to follow the recipients of tisagenlecleucel for 15 years to assess RCR, persistence, and the potential for insertional mutagenesis with tisagenlecleucel that is transduced with a lentivirus. The planned enrollment

to be recommended by FDA is 1000 patients enrolled within 3 months of tisagenlecleucel infusion (enrollment period of 5 years). All enrolled patients will be followed for 15 years from their tisagenlecleucel infusion. Standard of care follow-up for pediatric and young adult ALL patients will be done. The FDA recommended endpoint will be evaluation for second malignancy which will include tissue work-up by the applicant for these events. Secondary endpoint will be adverse events and laboratory abnormalities, adverse events of special interest (CRS, neurotoxicity, infections, prolonged cytopenias), growth and development, reproductive status and pregnancy outcomes, and disease outcomes (ORR, OS).

At the completion of its review and, upon requiring all of the aforementioned precautionary components, the FDA ultimately approved the Kymriah BLA, authorizing Novartis to introduce tisagenlecleucel into interstate commerce with post-market surveillance requirements designed to mitigate against undue risk for patients. These included required adverse event reporting in accordance with regulatory requirements for licensed biological products found within 21 CFR 600.81; the requirement to conduct a post-marketing, prospective, multi-center, observational study to assess the long-term safety of tisagenlecleucel and the risk of all secondary malignancies occurring after treatment with tisagenlecleucel (FDA, 2017e). The study is required to include at least 1000 pediatric and young adult patients with relapsed / refractory B cell acute lymphoblastic leukemia; the enrolled patients will be followed for 15 years after the product administration (FDA, 2017e). The rationale for the FDA's decision to bring Kymriah to market while,

concurrently, requiring extensive post-market surveillance measures was, in my opinion, twofold. That is, by approving Kymriah, the FDA was able to provide a service to patients through a bioconstitutional imaginary of the patient-consumer. In doing so, the FDA was able to position themselves as an imaginary of being a positive steward of the collective well-being of patients and provided clinicians with additional resources in their treatment arsenal for a targeted patient population. Given these approaches and governance perspectives, I believe this was an easy decision for the FDA in that, considered the small patient population for whom Kymriah would be prescribed, the potential for undue risk to patients was low, while the likelihood of a positive public perception of providing clinicians and patients with access to this potentially curative precision medical therapeutic was high. As such, the approval of Kymriah was, for the FDA, a low-risk high-reward scenario through which they could reconfigure and sacrifice certain aspects of the premarket approval review and collect additional safety and efficacy information via post-market surveillance requirements and studies.

In addition to the above-mentioned post-market requirements, the FDA also required the submission of a risk evaluation and mitigation strategy (REMS) with the following requirements (FDA, 2017e):

(1) For the first (6 month) assessment only:

Provide the following information on Kymriah REMS Program Implementation:

a. Date Kymriah REMS website went live

b. Date REMS Call Center operational

c. Date hospitals were able to complete REMS certification process

d. Date of first notification of hospital certification

e. Number of hospitals that were trained by Novartis prior to August 1, 2017.

(2) For the 12-month and subsequent annual assessments:

Kymriah REMS Program Infrastructure and Performance

a. Hospital enrollment and education statistics

i. List of all enrolled hospital sites, location, date of enrollment, and method (e.g., online, fax) of enrollment and date of certification notification

ii. Number of incomplete enrollments at the time of assessment data lock

iii. Number and date and format (live, webcast) of training on Kymriah REMS

iv. Number of knowledge assessments completed by hospital personnel other than the authorized representative, by certified hospital.

v. Mean and range of attempts to successfully complete knowledge assessment

vi. Summary of most frequently missed questions

b. Utilization

i. Number and age of patients treated with Kymriah; provide number treated at each certified hospital

ii. Number and age of patients for which Kymriah was ordered but never infused and the reason(s) that the patient was not treated; provide number

of occurrences at each certified hospital for each reporting period and cumulatively

iii. Time between certification and first order for Kymriah for each hospital

c. Compliance with Kymriah REMS program

i. Number and name of non-certified hospitals that have treated a patient with Kymriah and any corrective actions taken to prevent future occurrences (e.g., provision of REMS Training slides, REMS Hospital Certification form) and the number of these that subsequently became certified.

ii. Audits

1. A summary of findings from first order audits and annual audits and any action taken and outcome of actions to prevent future occurrences

iii. Summary of monitoring findings for monitoring conducted during the reporting period by hospital, including any corrective and preventative actions (CAPA)

iv. Any additional non-compliance, source of report, resulting corrective and preventative actions.

d. Kymriah REMS Program Call center

i. Number of contacts by stakeholder type (patient/parent/legal guardian, prescriber, hospital authorized representative, other HCP, other)

ii. Summary of frequently asked questions (FAQ) by stakeholder type.

iii. Summary of any non-compliance that is identified through call center contacts, source of report and resulting corrective and preventative actions.

Lastly, the approval required the implementation of Knowledge, Attitudes, and Behavior (KAB) surveys will be conducted with those who prescribe, dispense, or administer Kymriah as well as hospital authorized representatives, in order to assess their awareness and understanding of the risks of Kymriah and the mitigation strategies as outlined in the REMS goals and objectives (FDA, 2017e).

For the F1CDx test, data provided in its PMA supported the reasonable assurance of safety and effectiveness of the device when used in accordance with the indication for use. As a result, the FDA's Center for Devices and Radiological Health (CDRH) issued an approval order on November 30, 3017, with the following final conditions (FDA, 2017c):

1. Foundation Medicine would provide additional clinical concordance data to support the performance of your device within the appropriate clinical contexts. Please perform concordance testing against additional approved CDx devices for their respective approved clinical indications. In requiring this step, the FDA was able to facilitate F1CDx's market entry while concurrently continuing to have Foundation collect efficacy data for the test to ensure its accuracy

2. Provide clinical response data for NSCLC patients with an EGFR T790M mutation detected with mutant allele frequency (MAF) < 5% who were subsequently treated with Tagrisso® (osimertinib). This will support the clinical performance of your device for patients detected as positive by F1CDx (with MAF < 5%) who were considered negative by another approved CDx.

3. Provide results from additional testing of clinical samples to establish the analytical performance characteristics of your device for all variant types and genomic signatures that may be detected. Please ensure that the samples adequately represent the ranges of CNAs, rearrangements, MSI and TMB that are detected by your device, with consideration given to the fusion partners (for rearrangements) and the reportable ranges (for MSI and TMB).

4. Provide software documentation for validating and implementing software changes required to generate the test report. The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

FDA's consideration of these factors is individualized toward a given device and intended to be pragmatic, context-dependent, and consistent with FDA's statutory and regulatory authorities and requirements (FDA, 2019a). According to the FDA, "when considering a de novo request, FDA expects that the risks associated with the device would contribute to its analysis of uncertainty and the overall benefit-risk profile, recognizing that the FDA may be able to accept greater uncertainty due to factors such as whether the device presents minimal risks or whether the imposition of special controls can mitigate the risks" (2019, p. 12).

Putting all of this into perspective, approaches taken for the approval of Kymriah and F1CDx demonstrate that the FDA is adapting to marketing requests for precision medical products by subscribing to two approaches, or imaginaries, regarding patients and their access to genetic testing. The first is, as Hurlbut et al. report, affirming "an imaginary of the state as facilitator of the liberal agency of the knowledge-able consumer citizen, and the right of the consumer to choose for herself what is a good future and how best to achieve it", while the second is similar to that of the United Kingdom, in its governance of Alzheimer's disease and direct-to-consumer genetic testing products, "in keeping with an imaginary of the state as responsible for maximizing collective health, (by determining) which tests should be made publicly available to individuals (clinical treatment)" (2020).

This is to say that the emerging era of precision medicine is impacting the bioconstitutional imaginaries of patients, characterizing them as both patient-consumers whose rights and protections need to be considered and as downstream beneficiaries of technologies that can contribute to the collective health of society. The regulatory review and approval processes for both F1CDx and Kymriah substantiate their position as precision medical products that challenged existing review standards and practices. Nonetheless, the FDA, through its determination of an acceptable risk-benefit profile despite limited data relative to traditional drug products and the lack of a predicate device vis-à-vis accuracy of its results, was able to issue market approval for both products with the inclusion of post-market surveillance. By adopting this approach, the FDA is opting to respond to technical innovation characteristic of precision medical products by, in some ways, re-establishing and routinizing the practical application through which such products are evaluated for market approval by placing greater priority on the creation of precision medicine than adhering to historical linear models inherent to the marketing review processes for drugs and significant risk devices.

Medicalization

The ultimate proving ground for precision medicine lies within the practice of medicine and is facilitated by the doctor-patient relationship. It is precisely this location through which all stakeholders of precision medicine converge, including physician scientists, patients, biotechnology companies, big pharma, insurance providers, regulatory agencies, investors, and the public. In doing so, the emergence and evolution is perturbing the

manner in which physicians are approach the concept of disease, their approaches to clinical care, and the long-term management of patients post-intervention.

The practice of medicine is characterized by such a social context of cognition. That is, medical practice in the United States applies the dynamic concept of "standards of care", which takes into consideration current collective knowledge regarding disease, its diagnostic and prognostic characteristics, and cultural dynamics inherent to the practice of medicine to provide patients with (hopefully) ethical medical advice, prescriptive interventions, and healthcare recommendations. In this framework, medical communities establish thought styles and beliefs within the construct of standards of care. Similar to Fleck's evolution of knowledge as a result of thought collectives, "standards of care should not be thought of as a single, uniform whole" (Kinney, 2004, p. 574). According to Kinney, "the development of medical standards of care took off in the 1980s. Medical professional associations, specialty societies, and voluntary health organizations became involved in developing standards of care in an increasingly rigorous fashion. By the late 1980s, Kinney reports that the American Medical Association, working with medical specialty societies, launched a major initiative that signaled the endorsement of medical standard-setting by the organized medical profession" (2004, p. 574). Such standards are the result of a complex socio-technical network of biomedical researchers, physician-scientists, patients, pharmaceutical and biotechnology companies, and regulatory agencies that ultimately impact and guide third-party payers as to what specific treatment(s) for which they will provide coverage.

The concept of a thought collective directly supports the emergence and validation of a new taxonomy of disease as a result of the intellectual exchange associated with techno-scientific advancements surrounding the field of precision medicine. Physicians, regulators, patients, and third-party payers are increasingly subscribing to the value of the molecular basis of disease. From a thought collective perspective, the emergence and continued galvanization of such an approach is both the product of such technological advancement and the mobilization of knowledge throughout the medical and patient communities. From a research perspective, the validation of precision medicine and a new taxonomy of disease is only possible through the scientific community's contribution to generalizable knowledge. For the individual investigator, stand-alone discoveries are not considered valid without engagement and intellectual exchange with the knowledge base of the collective whole. It is this exchange of ideas and agreement among members of our present-day medical thought collective that is allowing precision medicine and its new definition of disease to transition from discovery to standard of care.

The Center for Cancer and Blood Disorders (CCBD) at Phoenix Children's Hospital (PCH) in Phoenix, Arizona, like other prominent academic medical centers, is front and center when evaluating the impact of precision medical technologies on medical practice. For patients and their families, the environment is both ominous and promising. Long patient corridors contain infusion bays splashed with vibrant colors and animated pictures to, hopefully, diminish the gravity of the situations patients and families are facing. The

CCBD faculty are among the most respected clinicians in the pediatric oncology community and they are committed to providing both exceptional patient care and knowledge development through an extensive portfolio of clinical trials. PCH is a destination facility for pediatric care and it sees patients from all fifty states and multiple international locations.

In an effort to gauge the impact of precision medicine on medical practitioners, I met with physician members of the CCBD hematologic oncology medical staff. During our interviews, they reported that precision medicine, while being an immature and evolving approach toward medical practice, has been a "game changer" for patients and families. That is, they reported that "the entire conversation has changed in recent years due to advancements in both genetic-based diagnostic tests and the availability of treatment options for some patients". This dynamic suggests the de-standardization of physicians' approaches toward clinical care secondary to clinical technical innovation inherent to precision medical products.

Hearing such feedback, I inquired how their approach toward medical practice has changed due to the emergence of precision medical technologies and diagnostics. They reported that for patients suffering from Acute Lymphoblastic Leukemia (ALL), they require up-front genetic testing to delineate genetic mutations and variants associated with an individual patient's instance of disease. For many of their patients, they are able to offer advanced precision medical diagnostics and therapies, such as Foundation Medicine's

F1CDx test and Novartis' Kymriah CAR T cell therapy. Such resources have "transformed the conversation from survival rates and probability of remission to the potential for a curative effect" based upon a single treatment.

The physicians reported to me that they have integrated both F1CDx and Kymriah into their practice. Specifically, they are having all of their leukemia patients complete the F1CDx test upon presenting to their clinic as new patients. The information yielded by the test provides them with succinct information that allows them to make medical decisions for patients in a more efficient manner than in the past. For the subset of patients whose genetic profiles and clinical parameters meet the criteria for CAR T cell therapy, they offer Kymriah as a treatment option. This scenario exists for newly diagnosed, refractory, and relapsed patients.

They also reported that they have worked with Novartis to create an Expanded Access Program, within which they are able to enroll patients on a clinical study of Kymriah that diverges from the clinical indications and parameters set forth in the product labeling. They reported that the goal of this program is to determine whether this therapeutic approach can prove safe and effective for more patients. For Novartis, this is a win-win scenario in that they are able to collect additional outcomes and safety data that may ultimately be supportive of a change in labeling via the FDA's IND process.

Such advancements are also beginning to change the way in which they, as practitioners, identify with diseases such as ALL. That is, concurrent with advancements in the genetic analysis of disease, there is an emerging co-production among practitioners to think of a disease in terms of its genetic profile, rather than blanket terms such as "cancer" or "ALL". I inquired whether this dynamic is beginning to occur within patient populations and their family members, to which they stated "not really as of yet", especially for "newly diagnosed patients". According to the physicians, newly diagnosed patients and their families are still confronted with a grave diagnosis and still have difficulty processing nuanced information beyond the scope of "cancer". This is to say that biological citizenship among newly diagnosed cancer patients has not yet permeated the evolving new taxonomy of disease. In other words, patients are not yet identifying with their disease as having a particular genetic variant or molecular profile. Rather, the manner in which they identify with their instance of disease remains limited to a patient's initial diagnosis (i.e. cancer type. In contrast, for patients who have been previously diagnosed and failed prior therapies, there is a "much greater understanding of things like genetic variants and profiles associated with their diagnosis". This being said, there is a common characteristic between newly diagnosed and previously treated patients that is attributable to precision medical advancements. Specifically, both groups are increasingly seeking out such therapies, such as Kymriah, due to the curative potential associated with the approach. This dynamic is suggestive of Latourian Actor Network Theory, through which both practitioners and patients are interacting with emergent precision medical technologies in both educational and applied practice as a means of diagnosing and treating disease.

Despite these positive impacts on medical practice and the efficacy rates among patients, precision medicine has begun to confront standards of care within the oncology community, at times leaving physicians unsure of how to provide follow-up care to patients. Specifically, in the case of ALL patients successfully treated with CAR T cell therapeutic interventions, physicians are unsure whether to follow such outcomes with bone marrow transplantation procedures, which would be the standard of care for traditional chemotherapeutic interventions, or to simply observe the patients long-term. Inquiring about how they are processing such information and how the medical community can arrive at a standardized approach to this dilemma, they informed me that future trials are warranted to determine the best approach in terms of long-term survival and quality of life.

My research revealed that advancements in precision medical technologies is having a downstream impact on clinical practice and the manner in which physicians approach both their understanding of disease and their approach toward medical interventions. In the oncology community, there is an evolving co-production of knowledge concerning the new taxonomy of disease and the practical application of such knowledge. This scenario is not necessarily suggestive of a paradigm shift in the epistemological systems associated with the practice of medicine. Physicians still maintain their reliance on standards of care adopted via local application of generalizable knowledge secondary to literature reports or revelations of findings at conferences such as ASCO. What is changing as a result of

precision medical advancements is the sources of knowledge production, such as genomic data generated from clinical trials and specimen donations, which is facilitating the assimilation of the new taxonomy of disease. Further, the adoption of individual treatment advancements such as Kymriah are becoming increasingly the standard within settings such as CCBD. For the medical practitioner, precision medicine is changing the ways in which they classify and relate to disease. Historical, symptomology-based disease classification models are increasing being challenged and replaced by an emerging new taxonomy of disease based upon molecular markers and genetic variants. Precision medicine is also, in some settings, changing the entire conversation that physicians are having with their patients in terms of prognosis and treatment options. For some patients, products such as Kymriah are allowing for the discussion of a curative outcome that was previously not achievable. Also, precision medicine is serving to destabilize existing standards of care for medical practitioners, as described earlier in this chapter, by creating a level of uncertainty concerning steps for long-term follow-up or next steps for patients who attain a level of metabolic remission secondary to treatment with products such as Kymriah. For patients, precision medical products are increasingly being sought out as treatment options due to their immense clinical potential. However, unlike physicians, patients are yet to exemplify a level of biosociality as it relates to their individual instances of disease. That is, patients largely continue to relate to their instance of disease via traditional disease classification models despite the concurrent advancement of knowledge regarding the genetic bases of disease.

In summary, precision medical products are having a significant impact on the entire pre- and post-market continuum of drug and device development in the United States. From an FDA perspective, to bring a drug or therapeutic to market in the United States, as Carpenter states, "it is fair to say that the basic terms, standards, schedules, and rules of modern-day drug development have been fashioned by the Administration as much as any other global entity" (2010, p. 17). In doing so, the FDA has shaped the entire narrative surrounding drug and device approvals, as well as the perception of well-being for the public as a result of such regulatory structures. Precision medical products have served to destabilize historical models of standardization of both process and disease. In doing so, the FDA is, as my research revealed, invoking two bioconstitutional imaginaries, one of a citizen-consumer who has the right to access novel therapeutics and diagnostics, such as Kymriah and F1CDx, and another as a steward of collective public health. These approaches are illustrated by the market approvals of Kymriah and F1CDx as a result of treatment effect size and validation of results, despite not having significant amounts of data that would be required in historical models of market approval, as well as the requirement of significant post-market surveillance measures for both products, allowing the FDA to remain informed of any unforeseen or undue risks that may not have been significant in nature or volume during the pre-market phase of both products. Within this paradigm, precision medical products have dislodged and destabilized the entire linear drug and medical device continuum by having the FDA enact adaptations, occlusions, and priorities within the review and approval processes such that the desire to actualize precision medicine as a practice is supplanting their traditional models for comprehensive validation via extensive

premarket safety and efficacy data in favor of post-market surveillance mechanisms through which the FDA can attain such information which concurrently providing patients and practitioners with access to novel products such as F1CDx and Kymriah.

Chapter 5 – Conclusion

At the beginning of this dissertation, I mentioned the 2000 announcement by President Clinton, along with NIH Director Dr. Francis Collins, that the human genome had been successfully sequenced, indicating the successful culmination of the Human Genome Project (HGP). During their speech, they spoke to the enormous promise such advancements held for the treatment and potential eradication of the most devastating diseases of our time. This event served as an inflection point for the medical and biomedical research communities and has led to unprecedented advancements in the areas of next generation DNA high throughput sequencing, making it possible to delineate genetic variances and molecular aberrations consistent with the presence of and susceptibility to diseases. What has transpired since that announcement is nothing short of breathtaking in terms of knowledge development, data generation, and therapeutic potential for patients. The emerging era has become known as "precision medicine" and carries the promise that a person's medical care can one day be tailored to their individual needs based upon data gathered through the sequencing of their genetic information and the subsequent delineation of molecular aberrations consistent with their individual instance of illness or disease.

During their speech, Collins went on to say that "the challenge is to deliver the benefits of this work to patients" (Hamburg and Collins 2010). According to the FDA (2019), precision medicine involves aligning the right drugs or treatments with the right patient, based on a genetic or molecular understanding of their disease, which is based upon the

concept that one person's disease isn't exactly the same in someone else who seemingly has the same disease. For this to occur successfully for the individual patient, as well as the long-term aggregation of "individual patients" who may present with N=1 disease-specific genetic profiles, there is a necessary engagement and interplay of individual actors. Specifically, patients must contribute high quality biospecimens for both targeted and unknown future research; basic scientists in universities, private research institutes, and academic medical centers must perform sequencing studies and advanced analytics on the data yielded by such studies in order to delineate genetic variants associated with disease; investors must provide promising technologies with funding mechanisms to advance the products from conceptualization and development into the drug and device development life-cycle; pharmaceutical, medical device, and biotechnology companies must develop novel diagnostics and therapeutics designed to act upon identified genetic targets and test those products in pre-clinical and clinical trial settings to demonstrate safety and efficacy, the FDA must continue to evolve in adapting and applying regulatory science methodologies to evaluate such products for market approval, and medical practitioners must embrace such advancements through existing epistemology channels to enhance their understanding of a new taxonomy of disease, as well as the occlusion of prior standards of care to assimilate precision medical products into practice for applicable patient populations. This is to say that there is an entire ecosystem built around the development, advancement, approval, and implementation of precision medical products. I have described these actors throughout this dissertation, but it is important to understand that, without their concurrent engagement and evolution, precision medicine as a practice does

not happen. That is, none of these stakeholders is independent or mutually exclusive of the others. Within this framework, and considering the findings from this research, it is evident that the pathway from development to medicalization of precision medical products is evolved, rather than created, and is being driven by a multitude of factors, depending on the specific area within the precision medical ecosystem. From a capital investment perspective, investors are seeking to advance innovation with the hopes of a downstream return on investment by licensing or selling intellectual property interests in a promising precision medical technology, a stance that is largely driven by market potential and speculative value associated with precision medical products. Pharmaceutical, biotechnology, and medical device companies are seeking to gain a competitive advantage over competitors through the identification of specific molecular targets associated with various diseases that are delineated via the collection and sequencing of specimens from patient donors and clinical trial participants. Further, such companies are increasingly embracing public-private partnerships through which they can identify additional diseases carrying the same genetic variants as a means of long-term financial risk mitigation relative to their product development investments. Regulators are opting to prioritize the medicalization of precision medical products through the amendment of historical linear standardized models of regulatory science and definitive premarket validation based upon, in my opinion, market pressures resulting from patient populations seeking effective treatments to the most significant diseases of our time, such as ALL. In doing so, the FDA is maintaining its role as gatekeeper and protector of citizen consumers and collective public health. Medical practitioners are increasingly integrating precision medical

products into their practice in response to similar patient-centric market pressures and in an effort to provide patients with the right treatment at the right time.

The precision medical movement is not only having a profound impact on the manner in which products are developed, evaluated, and approved for marketing, but also what it means to be a patient. That is, patients are no longer merely a set of acute symptomotology for which medical interventions are prescribed. Rather, precision medicine concurrently re-characterizes patients as subjects of intervention and objects of information. That is, disease risk equates to a method of self-identification and, in addition to being biosocial, also subjects individuals to potentially perpetual therapeutic consumption, turning them into almost always already patients-in-waiting (Sunder-Rajan, 2007). I would offer a concept of citizen-patients to accurately portray this scenario, which is continuing to evolve as more data are gathered and analyzed to elucidate the genetics bases of our human condition.

This is to say that, unlike traditional medical practice, the role that the citizen-patient (or human subject in the context of research) plays in the development of therapeutic compounds through their contribution of tissue and biological samples, under the auspices of research, is co-producing both the advancement of the practice of precision medicine and the classification of humans in terms of immediate or eventual susceptibility to symptomatic presentation. Historically, translational science has adhered to the model of developing a compound, performing *in vitro, in vivo*, and human subjects' research in an

effort to translate those technologies into human medical application. In the realm of precision medicine, this 'bench to bedside' approach is supplanted by a new paradigm in which bioinformatic data are generated from patients (via biospecimens) and novel therapeutic compounds are developed based upon the information gathered, then subjected to analysis and provided back to patients in the form of pharmaceutical or biological agents. This scenario validates patients as both subjects of therapeutic intervention and objects of knowledge consumption and the continued evolution of this techno-scientific medical revolution is affecting all aspects of the drug life cycle continuum, from laboratory discovery to the physician-patient relationship.

This dissertation was focused on the complex sociotechnical intersection of precision medical technologies, regulatory processes, capital structures, methods of governance, and patient-consumers. Specifically, how are decisions regarding investment, risk, and governance of precision medical technologies deliberated and approved for release into the U.S. market and what has been the self-actualizing impact of such technologies on regulatory oversight mechanisms, medicalization, capital structures, and patient regimes.

One of the most salient findings of this research was the destabilization of a historical linear process through which drugs and medical devices are developed, researched, reviewed for market approval, and implemented into medical practice. Specifically, the manner in which the FDA has, thus far, chosen to consider precision medical technologies for market is to prioritize medicalization over pre-market safety and efficacy certitude in an effort to provide patients with access to such treatments without additional delay that would

normally occur within the context of Phase III trials designed to provide the FDA with extensive safety and efficacy data. Instead, the FDA has adopted the construct of effect size in conjunction with subjective risk tolerance to allow market entry with a host of post-market medical surveillance requirements. Such decision-making presents a downstream effect for medical practitioners through which, by implementing precision medical technologies such as Kymriah and the F1CDx test into their medical practice, they are, in fact, assisting with the collection of safety and efficacy data that would have historically occurred within the premarket phase of the drug development life cycle.

This non-linear approach is not limited to regulators and medical practitioners. As mentioned in earlier chapters, pharmaceutical, biotechnology, and medical device companies are advancing the practice of precision medicine by positioning patients as subjects of intervention and objects of information. This approach dislodges the traditional linear bench-to-bedside process inherent to translational research in that post-market medical interventions are increasingly accompanied by specimen collection and processing studies for either targeted analyses or future unspecified research. These actions provide a feedback loop to the premarket phase for drug developers, investors, and companies through which sequencing outcomes can assist in the further identification of genetic variants for which additional novel therapeutics can be developed.

Methodology for this project involved qualitative methods including the accession and analysis of both primary and secondary sources as a means of describing and analyzing regulatory, ethical, and scientific policy aspects of the evolving field of precision

medicine. Primary sources will include archived regulatory submissions, correspondence, documentation of deliberations, press releases, and approval documents. In addition, documentation of interviews with representatives from the FDA, medical practitioners, industry representatives, and capital investment firms were included as primary sources.

The central aim of my dissertation was to illuminate, understand and offer novel insight into the impacts of precision medical technologies as they relate to the co-production of governance structures, the practice of medicine, investment mechanisms, and the resulting biosocial, bioconstitutional, and biocapital frameworks through which patients, practitioners, regulators, and investors interact with such technologies. The overarching question for this project was summarized as the following: **What assimilations, occlusions, or adaptations have been co-produced or occurred secondary to the emergence of precision medical technologies with respect to patients, medicalization, regulatory processes, and investors (e.g. venture capitalists)?** This is to say that there are challenges to the advancement of precision medical products into mainstream medical practice and this dissertation highlighted an existing disjunction between precision medicine and historical governance, oversight, and medical practice mechanisms. As a result, and as a means of illumination, I used theoretical concepts/frameworks as necessary and appropriate to describe the different elements at work in the effort to navigate this disjunction to characterize the challenges and ongoing adaptations inherent to the drug and medical device development and approval processes.

I designed my project around two case studies for precision medical technologies and their journeys from pre-market application to post-market approval, Foundation One's F1CDx test and Novartis' Kymriah (tisagenlecleucel) gene therapy treatment. Both F1CDx and Kymriah, and their approvals by the FDA, represent significant milestones in modern medicine and, more specifically, the advancement of precision medical technologies in the U.S. market. In framing my analysis of these products and their sociotechnical implications for patients, investors, regulators and the medical community, I sought to determine how these products differed from a regulatory perspective due to their *de novo* status and unique characteristics, if at all. Within this vein, my findings revealed that their transition from pre-market application to post-market approval required the co-production and adaptation of approaches toward risk analysis and, which differed from traditional non-molecular therapeutic and diagnostic products.

As I embarked upon this research, I was unsure of the exact outcomes or reports that I would receive. Given my many years spent in the regulatory and ethical aspects of the clinical and translational research sector, I had some notions of the types of impacts that precision medical technologies may have on cultural artifacts inherent to regulatory structures and physician-patient relations, or at least the challenges such technologies and their informational baggage could present to regulators and practitioners. Nonetheless, I was surprised at certain times during my research by the candor and matter-of-fact reports provided in terms of the impacts of current and ongoing impacts of such technologies. Key

assimilations, adaptations, accommodations, and occlusions occurring within and across the various components of the drug development process are as follow:

Capital

From a capital perspective, precision medicine has introduced an unprecedented biocapitalist market driven by genomic data secondary to the sequencing of biospecimens collected from patient-consumers, research subjects, and patients. The information resulting from such data are comprised of genetic variants associated with disease, representing potential targets for novel compounds *vis a vis* a patient's clinical presentation. Both technology transfer and venture capital firms are embracing this biocapitalist economy in an effort to gain equity in products that may prove non-inferior to current standards of care and offer curative effects to current and future patients. Interestingly, the co-production of strategic and tactical policies of technology transfer firms and venture capitalists toward this biocapitalist economy diverge in that technology transfer firms are accommodating precision medical products into their investment portfolios via a stance of error of omission avoidance, whereas venture capital firms are more likely to ensure a potential return on investment through promised cost savings by established companies, rather than speculative ideas. In addition, within the precision medical arena, technology transfer firms are occluding some of the traditional rigorous steps through which they evaluate inventions and novel technologies due to rapid techno-scientific advancements. In other words, technology transfer firms recognize their inability to keep pace with the rapid advancements in the precision medical innovation

arena and are, therefore, likely to invest time and effort based upon mere speculative value, whereas venture capital firms are seeking to maintain financial metrics before opting to invest in such technologies.

Industry

Pharmaceutical companies have also incurred significant impacts at the hands of precision medical advancements, some of which have invoked the need to alter or divest of certain aspects of their historical business models. More specifically, pharmaceutical companies are assimilating precision medical products into their product portfolios by placing increased emphasis on the collection and analysis of biological specimens from research subjects, such as those participating in clinical trials, in order to perform genomic sequencing and analysis with a goal of delineating genetic variants associated with a given disease. Similar to capital investment firms, this scenario represents a strategic decision to embrace a biocapital economy fostered by data-driven currency. In doing so, pharmaceutical manufacturers are seeking to develop novel targeted therapeutics to advance along the drug development life cycle and ultimately submit a New Drug Application (NDA) to the FDA for review and marketing approval. This position, however, has not necessarily been an easy one to assimilate by pharmaceutical companies. That is, big pharma has historically constructed its industry and success around blockbuster drugs designed to treat masses of patients with the same exact drug and dosage. Precision medicine, in contrast, requires that companies re-think this model due to the small number of patients for which a given drug can be prescribed. As such, the emergence of the

precision medical biocapital economy has evoked adaptations and occlusions among pharmaceutical companies, such as the divesting of non-core business units (e.g. imaging operations), in order to save money and focus more on their core business of drug development.

Regulatory Oversight and Governance

U.S. drug regulators and governance structures are also implementing profound adaptations and occlusions into their market review processes as a result of precision medical advancements. This is to say that, for the FDA, its architectures of governance, speaking specifically of the drug regulatory review and approval process, have historically utilized a quantitative-driven model through which applicants (i.e. pharmaceutical companies) conduct multiple clinical trials including tens of thousands of patients in order to determine whether a metabolic effect can be attributed to their investigational test article. While this model has proven effective for traditional medical approaches, it is in direct contrast to the individualized treatment goals of precision medicine. As such, the FDA is accommodation precision medical products into their review processes by amending the metrics through which products are determined to be approvable for market. While the goal of consumer protections remains the same, their procedural adaptations and occlusions are largely due to the fact that the types and volumes of information available to regulators for precision medical product marketing applications is not equal to that of traditional medical products. As a result, regulators must adhere to a destandardized *bounded rationality* model to form approval recommendations for precision medical products. In

doing so, the predominant metric that has emerged is effect size, rather than a volume-driven P-value, to determine whether a metabolic treatment effect can be attributed to the applicable test article. However, efficacy is only one aspect of concern for the regulatory community. They also need to consider safety because, from a bioconstitutionality perspective, patients are placed as citizen consumers who are afforded all rights of freedom of choice and protections. Within this framework, the FDA considers challenges of public welfare as best addressed by a conservative regulatory approval approach designed to gather more information while providing access to the consumer citizen. For precision medical products, such as Kymriah, this stance equates to market approval with post-marketing stipulations, such as Risk Evaluation and Mitigation Strategies (REMS). As a result, the FDA is engaging in the co-production of advancing precision medicine while concurrently migrating toward re-standardization of a process to both protect citizen consumers while providing them with access to a service in the form of novel targeted therapeutics. Precision medical products are serving to de-stabilize the previous standards and linear nature of product evaluations such that two bioconstitutional imaginaries are emerging, that of the above-mentioned consumer citizen and another as a steward of the collective public health. The FDA is able to adopt such positions through the occlusion of extensive pre-market safety and efficacy data and certitude via the enactment of post-approval surveillance mechanisms for precision medical products. For the FDA, this process concurrently limits potential undue risk for patients secondary to limited labeling requirements based upon the genetic bases of disease and also presents the FDA with opportunities to advance such products to market approval as a means of equipping

clinicians and patients with technologically-advanced therapeutics with curative potential. As mentioned earlier in this chapter, this approach by the FDA places priority of medicalization over validation, in effect creating a reality of precision medical practice while seeking to co-produce a re-stabilization of the regulatory review processes.

Medicalization

For medical practitioners, the practice of medicine is characterized by a social context of cognition. Modern medicine is built upon a dynamic concept of "standards of care", which takes into consideration current knowledge regarding disease, its diagnostic and prognostic characteristics, and cultural dynamics inherent to the practice of medicine to provide patients with (hopefully) ethical medical advice, prescriptive interventions, and healthcare recommendations. This approach is representative of Fleck's concept of a "thought collective", through which the emergence and continued galvanization of such an approach is both the product of such technological advancement and the mobilization of knowledge throughout the medical and patient communities. From a research perspective, the validation of precision medicine and a new taxonomy of disease is only possible through the scientific community's contribution to generalizable knowledge. For the individual investigator, stand-alone discoveries are not considered valid without engagement and intellectual exchange with the knowledge base of the collective whole. It is this exchange of ideas and agreement among members of our present-day medical thought collective that is allowing precision medicine and its new definition of disease to transition from discovery to standard of care.

As a result of this process, the individual physician-patient relationship is being significantly impacted by the emergence of precision medicine. This is to say that medical practitioners are accommodating and assimilating precision medical products into their practice and presenting patients with potentially positive treatment outcomes in a manner that was previously un-attainable through the use of traditional medical products. However, this dynamic remains limited at this time to certain clinical areas, such as oncology, and is most predominant in academic medical settings, rather than community-level providers. That being said, for such settings the impact is profound and has directly impacted the types of conversations between physicians and their patients, as well as the prognoses of medical outcomes. Precision medical advancements are facilitating a shift toward curative outcomes, rather than disease mitigation. Physicians are beginning to identify with a new taxonomy of disease characterized by genetic profiles, rather than symptomatic presentation and histological results. Within this framework, an interesting phenomenon is beginning to emerge as a challenge to the standards of care model, in which physicians are increasingly confronted with a lack of consensus regarding how to provide follow-up treatment once a desired clinical outcome has been achieved. As an example, for an Acute Lymphocytic Leukemia patient, historically-speaking if he or she had reached a clinical outcome of metabolic remission, they would oftentimes be prescribed a bone marrow transplantation in an effort to provide a "curative" effect. In the era of precision medicine, that outcome is increasingly being achieved through a single treatment via therapeutic intervention by products such as Kymriah. While this outcome is desirable, it

leaves the clinician unsure of next steps in the continued care of the patient and there is a lack of community consensus whether to refer such patients for a bone marrow transplant procedure or to simply take an observational follow-up approach. This paradigm represents an occlusive step on the part of the medical practitioner through the removal of traditional follow-up care and disease management strategies. Undoubtedly, these and other issues will be sorted out over time through clinical trial outcome reports at various venues such as the ASCO conference, fostering in the co-production of knowledge and practice.

Impacts Within and Across the Precision Medicine Development Ecosystem

Impacts, adaptations, assimilations, and occlusions secondary to advances in precision medicine are not only occurring within the individual components of the evolving precision medicine development ecosystem, but also occurring within and across the ecological relations and interactions of member components of the ecosystem itself. The most salient of these findings were in the regulatory oversight and medicalization areas.

From a regulatory perspective, the re-prioritization of regulatory review and approval processes from extensive and certitude-based pre-market safety and efficacy data to rapid market entry and medicalization of precision medical products represents an occlusion of historical standards and processes. This is to say that, for precision medical products, the accommodation of such technologies via the development and introduction of novel metrics, such as effect size, and review outcomes such as those invoked for F1CDx and

Kymriah, allowing their market entry while concurrently requiring post-market surveillance places patient access ahead of public safety. This position diverges from the historical role of the FDA as a steward of public health and safety, through which they sought to protect patients and the public from dangerous products, such as Thalidomide, which was prevented market entry in the U.S. due to its potential for serious adverse events. The occlusion of this role in lieu of expeditious market entry for precision medical products, if continued, may represent undue risk for patients and render healthcare organizations liable in the event of litigation secondary to serious adverse events or death following treatment with a precision medical product. In other words, by expediting the market approval of precision medical products the FDA is, in effect, transferring safety responsibility and liability to healthcare organizations by diverging from the traditional linear process of extensive and certitude-based safety and efficacy analysis prior to market entry. The current approach destabilizes this process and re-characterizes the FDA from a protector of public safety to a formal pass-through mechanism which concurrently provides patient access to novel treatments and re-allocates risk assumption and potential liability to healthcare organizations.

In addition, macro-level occlusions are occurring within the area of potential improvements to the healthcare system in the United States. Specifically, the U.S. healthcare system is characterized by both exceptional medical care in elite academic medical organizations and a lack of effective and affordable healthcare in rural and financially challenged communities. Precision medical products carry the potential to facilitate safe and effective

healthcare policies, provide effective and cost-efficient care to all patients due to the accuracy of their diagnostics and the known outcomes for specific patient populations. However, such treatment options remain largely limited to academic medical settings in America's urban centers, perpetuating the healthcare gap in the United States. From a policy perspective, it is concerning to note that products with such vast clinical potential are being limited in terms of their equitable distribution to certain patients with specialized treatment centers. Such a paradigm requires that citizen patients adapt to the policies and practices of the current and evolving precision medicine development ecosystem in order to gain access to novel targeted therapeutics, rather than adapting the ecosystem in response to societal healthcare needs. Until such time that the precision medicine regulatory and medicalization complex is able to use such technologies to address such disparities at the societal level, the actual value of such products for the public will remain in the realm of speculation.

Considering that the ecological relations of the various components of the precision medical ecosystem are being altered and impacted by the emergence and continued evolution of precision medical products, it is important to identify and understand their dynamics of unification. That is, what common factors or interests are characteristic of each component such that they continue to concurrently advance precision medical products from development to market? Within this framework, my research revealed that there are two primary narratives concerning unifying variables for the individual components of the precision medicine development ecosystem, public policy and speculative value.

As mentioned in Chapter 3, from a public policy perspective, the development of strategic, tactical, and policy-related doctrine are helping to facilitate the advancement of precision medicine. In doing so, such policy are also serving as unifying factors for the components of the precision medicine development ecosystem. Specifically, the 2011 FDA strategic plan entitled *Advancing Regulatory Science at FDA* included provisions for stimulating innovation in clinical evaluations and precision medicine and others to ensure the FDA's readiness to evaluate innovative emerging technologies (FDA, 2011). This was followed by the October 2013 FDA publication entitled *Paving the Way for Precision Medicine – FDA's Role in a New Era of Medical Product Development* (FDA, 2013). In the report, the FDA stated their "responsibility for ensuring that drugs, devices, and biologics are safe and effective provides the agency with a unique perspective on both the successes and failures that occur in medical product development and special insight into the emergence and direction of the field of precision medicine" (FDA, 2013, p. 11). That same year, the FDA released a report entitled *Paving the Way for Precision Medicine-FDA's Role in a New Era of Medical Product Development,* which sought to shed light on the concept of precision medicine. In the report, the FDA stated that "what is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects" (2013, p. 4). Further, in August 2014, the National Institutes of Health (NIH) released its Genomic Data Sharing Policy that required all federal funding grant applications submitted for the January 25, 2015 deadline and thereafter, that were intended to generate large-scale human or non-human genomic data (as well as the use of these data

for subsequent research), to include a plan for sharing of those data via approved digital repositories accessible to the scientific community (NIH, 2014). Lastly, in 2015 the NIH developed the PMI Cohort Program (PMI-CP) to develop a plan for public engagement through the genomic sequencing of at least one million participants over four years to facilitate the analysis of the genetic profiles of the most challenging diseases of our time (NIH, 2015).

The second narrative concerning unifying factors for the components of the precision medicine development ecosystem is speculative value. According to Faulkner, et al, "There is a need for concerted effort in defining and applying a relevant and consistent value assessment approach to precision medicine" (2020, p. 537). This is to say that much of the momentum associated with the continued advances in precision medicine are driven by speculative value. However, the exact nature of such speculative value can differ from one stakeholder to another.

For capital investors, the speculative value of precision medical products represents opportunities to align investment decisions with specific downstream patient populations with greater certitude that traditional medical products. As a result, investment strategies can benefit from potential financial risk mitigation, minimizing financial loss as a result of more precise forecasting models for medical products seeking market entry in the United States. Pharmaceutical, medical device, and biotechnology companies identify speculative value as the "ability to identify certain patients as candidates for/better responders to certain therapeutic applications based on genetic or other biomarker status, the ability to enable

stronger outcomes in patient subsets based on patient genetics or other biomarker status, and improved potential ability to gain acceptance versus broader population strategies with more dilute outcomes" (Faulkner, et al, 2020, p. 532). From a regulatory perspective, precision medicine carries speculative value in its ability to provide patients and the public with greater certainty of outcomes for a known subset of patients, provide practitioners with a value of knowing clinical specifics associated with rare diseases, and providing practitioners with improved decision-making for their patients. Similar to regulators, medical practitioners associate value in precision medical products in their ability to improve patient outcomes, accurate diagnostics, and apply greater certainty in their medical decision-making for patient care and management.

On the surface, these narratives seem reasonable as unifying factors driving continued development and advances in precision medicine. However, my findings regarding the implications of precision medical products at both the individual component and broader precision medical ecosystem levels reveal the characterization of the narratives of public policy and speculative value as the unifying and driving factors of the advancement of precision medicine as merely aspirational, rather than actual. Within this framework, I would like to draw the reader's attention to what I believe are the actual drivers and unifying factors to accurately reflecting the current state of precision medicine investment, strategy, governance, and medicalization.

According to Marks, "throughout the twentieth century, therapeutic reformers have worked toward a common end: ensuring that physicians' therapeutic practices are governed by

science and not by the "idols of the marketplace" or vagaries of clinical opinion" (1997, p. 230). Contextually speaking, while the spirit reflected in Marks' statement is omnipresent within and across the precision medicine development ecosystem, the application of such spirit, in my opinion, falls short of actualization for precision medicine in its current form. Specifically, my findings revealed that investors are currently ill-equipped to evaluate such technologies from a scientific-driven perspective and are, rather, haphazardly seeking to advance early-stage diagnostics and therapeutics with the hope that downstream clinical utility can validate their errors of omission advancement strategy. Similarly, pharmaceutical, medical device, and biotechnology companies are yet to approach compound development with a degree of certitude and standardization. Rather, through the overt collection of biospecimens from patient donors, companies aspire to delineate patterns of novel variants associated with disease and seeking to develop novel therapeutics or retrofit existing compounds to target such variants, with the hope of delineating clinical utility at a level that would justify market entry. Regulators have occluded historical practices of pre-market extensive and certitude-based safety and efficacy analyses in lieu of exploratory governance practices characterized by the creation and adoption of *ad hoc* clinical metrics as a medium through which they are able to rationalize market approval for precision medical compounds vis-à-vis profound risk to patients in some instances. Further, medical practitioners are engaging in what amounts to experimental medicalization through the navigation of post-market surveillance requirements and a current lack of comprehensive knowledge regarding how to implement and manage precision medical therapeutics into standards of care and clinical practice. None of these

scenarios, in my opinion, speak to the current realization of the speculative value assigned to precision medicine and the existence of public policy doctrine are not yielding the field of precision medicine as proficient or optimized in any way commensurate with its aspirational envisioned manifestation.

Despite all of these challenges, precision medicine continues to advance as an emerging practice. This is, in my opinion, the direct result of what I believe to be the actual current driving and unifying factors within and across the precision medicine development ecosystem, early-stage end user engagement, regulatory invocation, and early uptake/adoption of precision medical products.

In terms of early-stage end user engagement, clinicians are not merely downstream recipients of precision medical technologies they can offer to patients as advanced diagnostic or targeted therapeutic options. Rather, practitioners and patients are being engaged at the pre-clinical and clinical testing stages, which are operationalized through the collection of biospecimens that directly lead to advances in knowledge development of genetic variant identification and the oversight of clinical trials through which the clinical utility of novel therapeutics is validated, makes the medical community an active player in the advancement of precision medicine as an emerging medical practice.

Complimentary to the engagement of end users in the pre-clinical and clinical testing stages, the FDA is, in-fact, creating a precision medical market through its adaptive regulatory review and approval processes. As mentioned, much of this is being conducted

through the lessening or lowering of pre-market safety and efficacy evaluation thresholds in order to advance products to market for patients and practitioners.

In a similar vein and, from an early uptake/adoption perspective, the stance taken by the FDA to prioritize medicalization of precision medical products, rather than prolong extensive pre-market safety and efficacy data collection, has led to the successful treatment with curative outcomes for patients with products such as Kymriah. As a result, these outcomes transcend the speculative value assigned to precision medicine though the actual demonstrated efficacy of such products in a clinical setting.

By engaging medical practitioners and patients into earlier stages of the development process, they become part of the precision medical development process itself and directly contribute to its advancement as a field and, as a result, they themselves become active stakeholders in the furtherance of precision medicine itself. It is my opinion that this paradigm will continue to unify the components of the precision medical ecosystem and drive precision medicine forward through the co-production of knowledge and process development, and improved clinical outcomes, to the eventual realization of precision medicine as a remarkable advancement in American medicine.

Having revealed all of the above-mentioned findings within my research, I would like to leave the reader with an encapsulation of the implications of the aforementioned impacts, assimilations, and occlusions occurring within and among the components of the current precision medicine development ecosystem, as well as the narratives and unifying factors and drivers advancing precision medicine in its current state. I believe it is appropriate to

characterize the individual components of the precision medical ecosystem as actors in a network built around an emerging and evolving technology and driven by knowledge development and technological innovation. This network is currently in a state of disequilibrium due to the dynamic interactions within each member component, as well as the ecological relations between and among the components. This is to say that precision medical products are facilitating a paradigm shift in not only the form(s) of medicine being implemented, but also the inputs and processes that bring precision medicine itself into fruition. Findings from this research support my initial assumption that there exists a disjunction between precision medicine and historical governance, oversight, and medical practice mechanisms. However, I believe the current state of disequilibrium is temporary in nature. Each of the ecosystem components is committed to the advancement of precision medicine based upon their individual definitions of speculative value. Also, dovetailing with the current practices and interactions among member components, there is a concurrent knowledge base emerging through which practitioners, investors, regulators, and corporations will, over time, learn to proficiently implement and manage precision medical technologies within their portfolios, regulatory queues, and medical practices. In doing so, it is my belief that the ecosystem will stabilize and re-standardize itself into a state of equilibrium.

Limitations

While the findings from this research are truthful and real, there are some limitations that should be acknowledged. First, my interactions with physician-scientists was limited to a single academic medical center. I do believe the reports and information are generalizable to other similar settings, but the scenario likely diverges significantly among rural and community-based clinics and healthcare facilities. This is primarily due to human capital and technological resources available within academic medical settings. This is to say that, for the physician-scientist in an academic medical center, they are likely engaged in a comprehensive care environment with access to laboratory facilities, informaticians, on-site pharmacists, clinical and translational research programs, medical school affiliations, and a collection of specialized medical personnel from whom to draw upon expertise in the treatment planning for patients. By comparison, rural and community-based healthcare facilities are oftentimes limited to a few providers who rely on traditional outsourced imaging and laboratory tests. To effectively adapt to the precision medical era, it is incumbent upon practitioners to have access to resources and colleagues in the interest of knowledge development that is translatable to the physician-patient relationship.

Another limitation is that my findings are limited to a moment in time in the continued advancement of precision medicine. It is likely that regulators will, over time, develop evaluation standards and clinicians will be better educated as part of their medical school and residency programs to implement precision medicine into their practice. This limitation supports the position that both knowledge and practice are being concurrently

co-produced at such a rate that any specific impacts, assimilations, adaptations, and occlusions are momentary in nature.

Closure

I opened this dissertation with a reference to the oil boom that started at Spindletop Hill outside of Beaumont, Texas in the early 1900's. Much time has passed since that seminal event in the energy industry. The original geyser site is now merely a roadside destination and museum dedicated to an earlier time (see Figure 4).

Figure 4: Spindletop Museum

The era of precision medicine that was famously ushered in by President Clinton and Dr. Collins in 2000 will, in my opinion, serve as a similar seminal moment for the practice of medicine in the U.S. Drug regulators, pharmaceutical companies, investors, and medical practitioners are acutely aware that they are navigating an inflection point in the history of medicine and knowledge of the human condition, including the understanding and confrontation of the most prevalent diseases of our time. In my opinion, the continued emphasis on the advancement of precision medicine by medical practitioners, federal regulators, and capital investors is tantamount to our ability to realize the vast espoused potential of precision medicine. In a similar vein, regulatory bodies need to apply continued and steady pressure on the advancement and re-standardization of the regulatory science field so that regulatory specialists are not incessantly seeking to keep up with technological advancement. Ethically-speaking, much attention has been placed upon the risk associated with breaches in confidentiality and risks associated with the sharing of genetic information that may or may not hold any clinical utility for a patient and their family. I believe the NIH Office of Human Research Protections and Institutional Review Boards should embrace ethics-based research and exploratory governance initiatives with a goal of protecting citizen-patients while facilitating a service to the same individuals in their role of citizen consumer.

If these measures are taken and embraced at a level commensurate with the speculative value applied to the field of precision medicine, it is then that the true and long-lasting

impacts, assimilations, and adaptations of this exciting era of medicine and human health can be fully realized.

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APPENDIX A

F1CDX APPROVAL LETTER

November 30, 2017

Foundation Medicine, Inc.
Christine Vietz, PhD, RAC
Sr. Director Regulatory Affairs
150 Second Street, 1st Floor
Cambridge, MA 02141

Re: P170019
Trade/Device Name: FoundationOne CDx™
Filed: June 6, 2017
Amended: November 22, 2017
Product Code: PQP

Dear Dr. Vietz:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the FoundationOne CDx™. This device is indicated for the following:

> FoundationOne CDx™ (F1CDx) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)

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	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the device is to be distributed only with serial number-controlled instruments and only to Foundation Medicine, Inc., a single laboratory site located at 150 Second Street, Cambridge, MA 02141. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved as follows: library construction reagents, hybrid capture reagents and sequencing reagents may be stored between 4°C and -20°C for up to 90 days; DNA samples may be stored at 4°C for up to 6 weeks; and -20°C for up to 3 months. This is to advise you that the protocols you used to establish this expiration dating are considered approved protocols for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of

the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to provide the following information in a report(s) which may be followed by a PMA supplement(s) when applicable.

1. Provide additional clinical concordance data to support the performance of your device within the appropriate clinical contexts. Please perform concordance testing against additional approved CDx devices for their respective approved clinical indications.

2. Provide clinical response data for NSCLC patients with an EGFR T790M mutation detected with mutant allele frequency (MAF) < 5% who were subsequently treated with Tagrisso® (osimertinib). This will support the clinical performance of your device for patients detected as positive by F1CDx (with MAF <5%) who were considered negative by another approved CDx.

3. Provide results from additional testing of clinical samples to establish the analytical performance characteristics of your device for all variant types and genomic signatures that may be detected. Please ensure that the samples adequately represent the ranges of CNAs, rearrangements, MSI and TMB that are detected by your device, with consideration given to the fusion partners (for rearrangements) and the reportable ranges (for MSI and TMB).

4. Provide software documentation for validating and implementing software changes required to generate the test report.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50

and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at
http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Hisani Madison, Ph.D., MPH at 301-796-6162 or Hisani.Madison@fda.hhs.gov.

Sincerely,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of *In Vitro* Diagnostics and
Radiological Health
Center for Devices and Radiological Health

APPENDIX B

F1CDX LABEL DOCUMENT

FOUNDATIONONE CDx™

FoundationOne CDx™
Technical Information

Foundation Medicine, Inc.
150 Second Street, Cambridge, MA 02141
Phone: 617.418.2200

Intended Use

FoundationOne CDx™ (F1CDx™) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), *XALKori*® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

Contraindication

There are no known contraindications.

Warnings and Precautions

- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
- Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
- Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by F1CDx, in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%[1].

[1]Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/*ERBB2*/238/) report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

Limitations

- For *in vitro* diagnostic use.
- For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
- Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
- A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
- Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
- Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
- Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
- The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer <insert link to SSED> for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.
- TMB by F1CDx is defined based on counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. The clinical validity of TMB defined by this panel has not been established.
- Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
- The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.

Test Principle

FoundationOne CDx™ (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome

shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons (refer to Table 2 and Table 3 for complete list of genes included in F1CDx. In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture–selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) are reported.

Table 2. Genes with full coding exonic regions included in FoundationOne CDx™ for the detection of substitutions, insertions and deletions (indels), and copy number alterations (CNAs).

ABL1	*BRAF*	*CDKN1A*	*EPHA3*	*FGFR4*	*IKZF1*	*MCL1*	*NKX2-1*	*PMS2*	*RNF43*	*TET2*
ACVR1B	*BRCA1*	*CDKN1B*	*EPHB1*	*FH*	*INPP4B*	*MDM2*	*NOTCH1*	*POLD1*	*ROS1*	*TGFBR2*
AKT1	*BRCA2*	*CDKN2A*	*EPHB4*	*FLCN*	*IRF2*	*MDM4*	*NOTCH2*	*POLE*	*RPTOR*	*TIPARP*
AKT2	*BRD4*	*CDKN2B*	*ERBB2*	*FLT1*	*IRF4*	*MED12*	*NOTCH3*	*PPARG*	*SDHA*	*TNFAIP3*
AKT3	*BRIP1*	*CDKN2C*	*ERBB3*	*FLT3*	*IRS2*	*MEF2B*	*NPM1*	*PPP2R1A*	*SDHB*	*TNFRSF14*
ALK	*BTG1*	*CEBPA*	*ERBB4*	*FOXL2*	*JAK1*	*MEN1*	*NRAS*	*PPP2R2A*	*SDHC*	*TP53*
ALOX12B	*BTG2*	*CHEK1*	*ERCC4*	*FUBP1*	*JAK2*	*MERTK*	*NT5C2*	*PRDM1*	*SDHD*	*TSC1*
AMER1	*BTK*	*CHEK2*	*ERG*	*GABRA6*	*JAK3*	*MET*	*NTRK1*	*PRKAR1A*	*SETD2*	*TSC2*
APC	*C11orf30*	*CIC*	*ERRFI1*	*GATA3*	*JUN*	*MITF*	*NTRK2*	*PRKCI*	*SF3B1*	*TYRO3*
AR	*CALR*	*CREBBP*	*ESR1*	*GATA4*	*KDM5A*	*MKNK1*	*NTRK3*	*PTCH1*	*SGK1*	*U2AF1*
ARAF	*CARD11*	*CRKL*	*EZH2*	*GATA6*	*KDM5C*	*MLH1*	*P2RY8*	*PTEN*	*SMAD2*	*VEGFA*
ARFRP1	*CASP8*	*CSF1R*	*FAM46C*	*GID4 (C17orf39)*	*KDM6A*	*MPL*	*PALB2*	*PTPN11*	*SMAD4*	*VHL*
ARID1A	*CBFB*	*CSF3R*	*FANCA*	*GNA11*	*KDR*	*MRE11A*	*PARK2*	*PTPRO*	*SMARCA4*	*WHSC1*
ASXL1	*CBL*	*CTCF*	*FANCC*	*GNA13*	*KEAP1*	*MSH2*	*PARP1*	*QKI*	*SMARCB1*	*WHSC1L1*
ATM	*CCND1*	*CTNNA1*	*FANCG*	*GNAQ*	*KEL*	*MSH3*	*PARP2*	*RAC1*	*SMO*	*WT1*
ATR	*CCND2*	*CTNNB1*	*FANCL*	*GNAS*	*KIT*	*MSH6*	*PARP3*	*RAD21*	*SNCAIP*	*XPO1*
ATRX	*CCND3*	*CUL3*	*FAS*	*GRM3*	*KLHL6*	*MST1R*	*PAX5*	*RAD51*	*SOCS1*	*XRCC2*
AURKA	*CCNE1*	*CUL4A*	*FBXW7*	*GSK3B*	*KMT2A (MLL)*	*MTAP*	*PBRM1*	*RAD51B*	*SOX2*	*ZNF217*
AURKB	*CD22*	*CXCR4*	*FGF10*	*H3F3A*	*KMT2D (MLL2)*	*MTOR*	*PDCD1*	*RAD51C*	*SOX9*	*ZNF703*
AXIN1	*CD274*	*CYP17A1*	*FGF12*	*HDAC1*	*KRAS*	*MUTYH*	*PDCD1LG2*	*RAD51D*	*SPEN*	
AXL	*CD70*	*DAXX*	*FGF14*	*HGF*	*LTK*	*MYC*	*PDGFRA*	*RAD52*	*SPOP*	
BAP1	*CD79A*	*DDR1*	*FGF19*	*HNF1A*	*LYN*	*MYCL*	*PDGFRB*	*RAD54L*	*SRC*	
BARD1	*CD79B*	*DDR2*	*FGF23*	*HRAS*	*MAF*	*MYCN*	*PDK1*	*RAF1*	*STAG2*	
BCL2	*CDC73*	*DIS3*	*FGF3*	*HSD3B1*	*MAP2K1*	*MYD88*	*PIK3C2B*	*RARA*	*STAT3*	
BCL2L1	*CDH1*	*DNMT3A*	*FGF4*	*ID3*	*MAP2K2*	*NBN*	*PIK3C2G*	*RB1*	*STK11*	

BCL2L2	*CDK12*	*DOT1L*	*FGF6*	*IDH1*	*MAP2K4*	*NF1*	*PIK3CA*	*RBM10*	*SUFU*	
BCL6	*CDK4*	*EED*	*FGFR1*	*IDH2*	*MAP3K1*	*NF2*	*PIK3CB*	*REL*	*SYK*	
BCOR	*CDK6*	*EGFR*	*FGFR2*	*IGF1R*	*MAP3K13*	*NFE2L2*	*PIK3R1*	*RET*	*TBX3*	
BCORL1	*CDK8*	*EP300*	*FGFR3*	*IKBKE*	*MAPK1*	*NFKBIA*	*PIM1*	*RICTOR*	*TEK*	

Table 3. Genes with select intronic regions for the detection of gene rearrangements, one with 3'UTR, one gene with a promoter region and one ncRNA gene.

ALK *introns 18, 19*	*BRCA1* *introns 2, 7, 8, 12, 15, 19, 20*	*ETV4* *introns 5, 6*	*EZR* *introns 9- 11*	*KIT* *intron 16*	*MYC* *intron 1*	*NUTM1* *intron 1*	*RET* *introns 7-11*	*SLC34A2* *intron 4*
BCL2 *3'UTR*	*BRCA2* *intron 2*	*ETV5* *introns 6, 7*	*FGFR1* *intron 1, 5, 17*	*KMT2A (MLL)* *introns 6-11*	*NOTCH2* *intron 26*	*PDGFRA* *introns 7, 9, 11*	*ROS1* *introns 31-35*	*TERC* *ncRNA*
BCR *introns 8, 13, 14*	*CD74* *introns 6- 8*	*ETV6* *introns 5, 6*	*FGFR2* *intron 1, 17*	*MSH2* *intron 5*	*NTRK1* *introns 8-10*	*RAF1* *introns 4-8*	*RSPO2* *intron 1*	*TERT* Promoter
BRAF *introns 7- 10*	*EGFR* *introns 7, 15, 24-27*	*EWSR1* *introns 7-13*	*FGFR3* *intron 17*	*MYB* *intron 14*	*NTRK2* *intron 12*	*RARA* *intron 2*	*SDC4* *intron 2*	*TMPRSS2* *introns 1- 3*

Summary and Explanation

FoundationOne CDx™ is a broad companion diagnostic (CDx) test for five tumor indications. In addition to use as a companion diagnostic, F1CDx provides cancer relevant alterations that may inform patient management in accordance with professional guidelines. Information generated by this test is an aid in the identification of patients who are most likely to benefit from associated therapeutic products as noted in Table 1 of the Intended Use.

The F1CDx platform employs whole-genome shotgun library construction and hybridization-based capture of DNA extracted from FFPE tumor tissue prior to uniform and deep sequencing on the Illumina® HiSeq 4000. Following sequencing, custom software is used to determine genomic variants including substitutions, insertion and deletion variants (indels), copy number alterations (CNAs), genomic rearrangements, microsatellite instability (MSI) and tumor mutational burden (TMB). The output of the test includes:

Category 1: Companion Diagnostic (CDx) Claims noted in Table 1 of the Intended Use

Category 2: Cancer Mutations with Evidence of Clinical Significance

Category 3: Cancer Mutations with Potential Clinical Significance

Genomic findings other than those listed in Table 1 of the intended use statement (i.e., Categories 2 and 3) are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Test Kit Contents

The FoundationOne CDx™ (F1CDx) test includes a sample shipping kit, which is sent to ordering laboratories. The shipping kit contains the following components:

- Specimen Preparation Instructions and Shipping Instructions
- Return Shipping Label

All other reagents, materials and equipment needed to perform the assay are used exclusively in the Foundation Medicine laboratory. The F1CDx assay is intended to be performed with serial number-controlled instruments.

Sample Collection and Test Ordering

To order FoundationOne CDx™, the Test Requisition Form (TRF) included in the test kit must be fully completed and signed by the ordering physician or other authorized medical professional. Please refer to Specimen

Preparation Instructions and mailing instructions included in the test kit.

For more detailed information, including Performance Characteristics, please find the FDA Summary of Safety and Effectiveness Data at: [Insert link to SSED upon approval here]

1. **Instruments**

   The FoundationOne CDx™ device is intended to be performed with the following instruments, as identified by specific serial numbers:

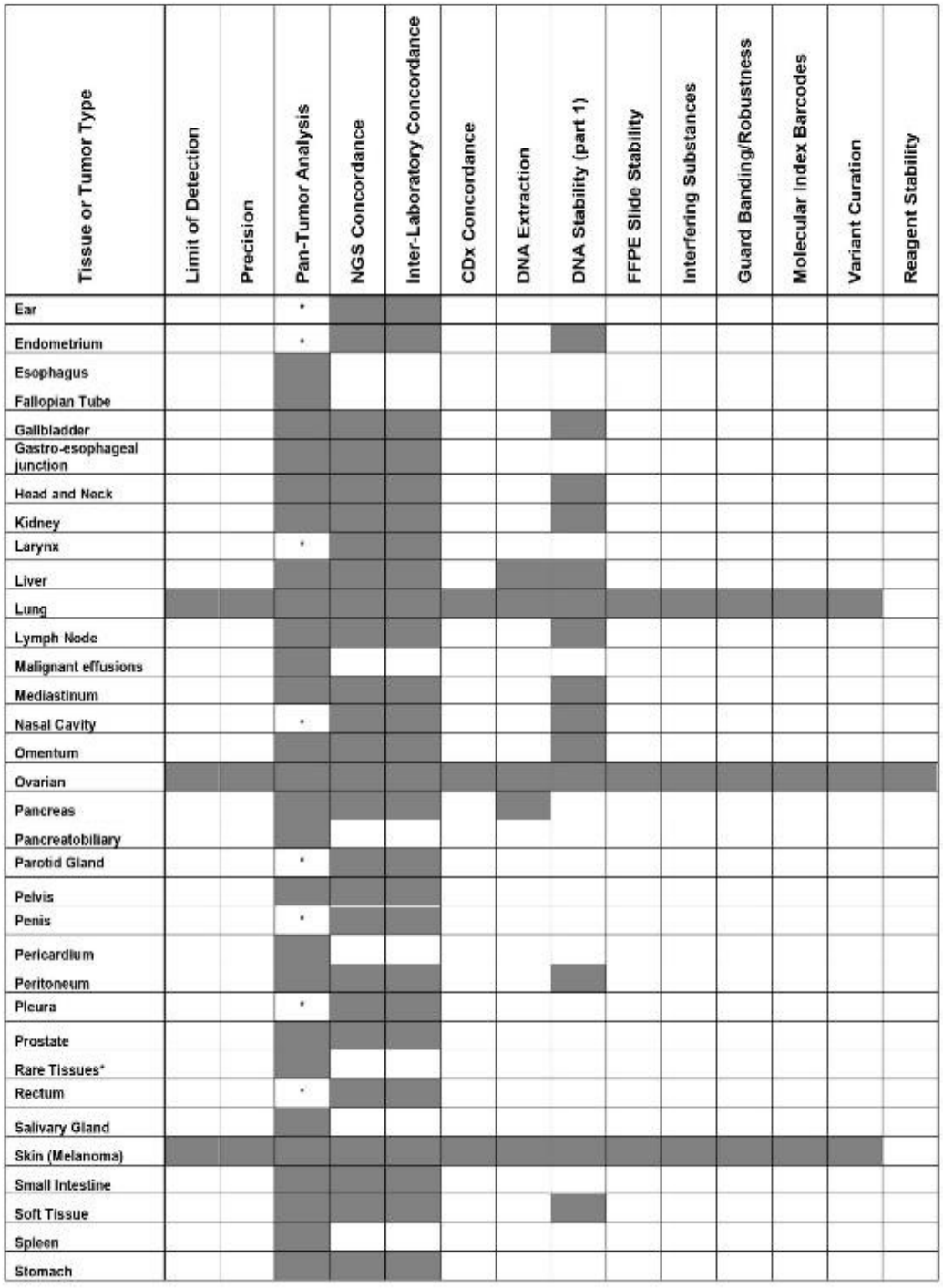
   - Agilent Technologies Benchbot Workstation with Integrated Bravo Automated Liquid Handler
   - Beckman Biomek NX^{P} Span-8 Liquid Handler
   - Covaris LE220 Focused ultrasonicator
   - Thermo Fisher Scientific KingFisher™ Flex with 96 Deep-well Head
   - Illumina® cBot System
   - Illumina® HiSeq 4000 System

2. **Performance Characteristics**

   Performance characteristics were established using DNA derived from a wide range of FFPE tissue types; tissue types associated with CDx indications were included in each study. Table 4 below provides a summary of tissue types included in each study. Each study also included a broad range of representative alteration types for each class of alteration (substitution, insertion-deletion, copy number alterations, and rearrangements) in various genomic contexts across a broad selection of genes as well as analysis of genomic signatures including MSI and TMB. Table 5 provides a summary of genes and alteration types associated with validation studies.

Table 4. Summary of Tissue Types Included in Validation Studies.

Tissue or Tumor Type	Limit of Detection	Precision	Pan-Tumor Analysis	NGS Concordance	Inter-Laboratory Concordance	CDx Concordance	DNA Extraction	DNA Stability (part 1)	FFPE Slide Stability	Interfering Substances	Guard Banding/Robustness	Molecular Index Barcodes	Variant Curation	Reagent Stability
Abdomen or Abdominal wall			■	■	■			■						
Adrenal Gland			■	■	■									
Anus			■	■	■									
Appendix			■	■	■									
Bladder			■	■	■		■							
Bone			■	■	■									
Brain			■	■	■		■	■						
Breast	■	■	■	■		■	■	■	■	■	■	■	■	
Cervix			■	■	■			■						
Chest wall			■	■	■			■						
Colon	■		■	■	■	■	■	■	■	■	■	■	■	
Diaphragm			■	■	■			■						
Duodenum			*	■	■									

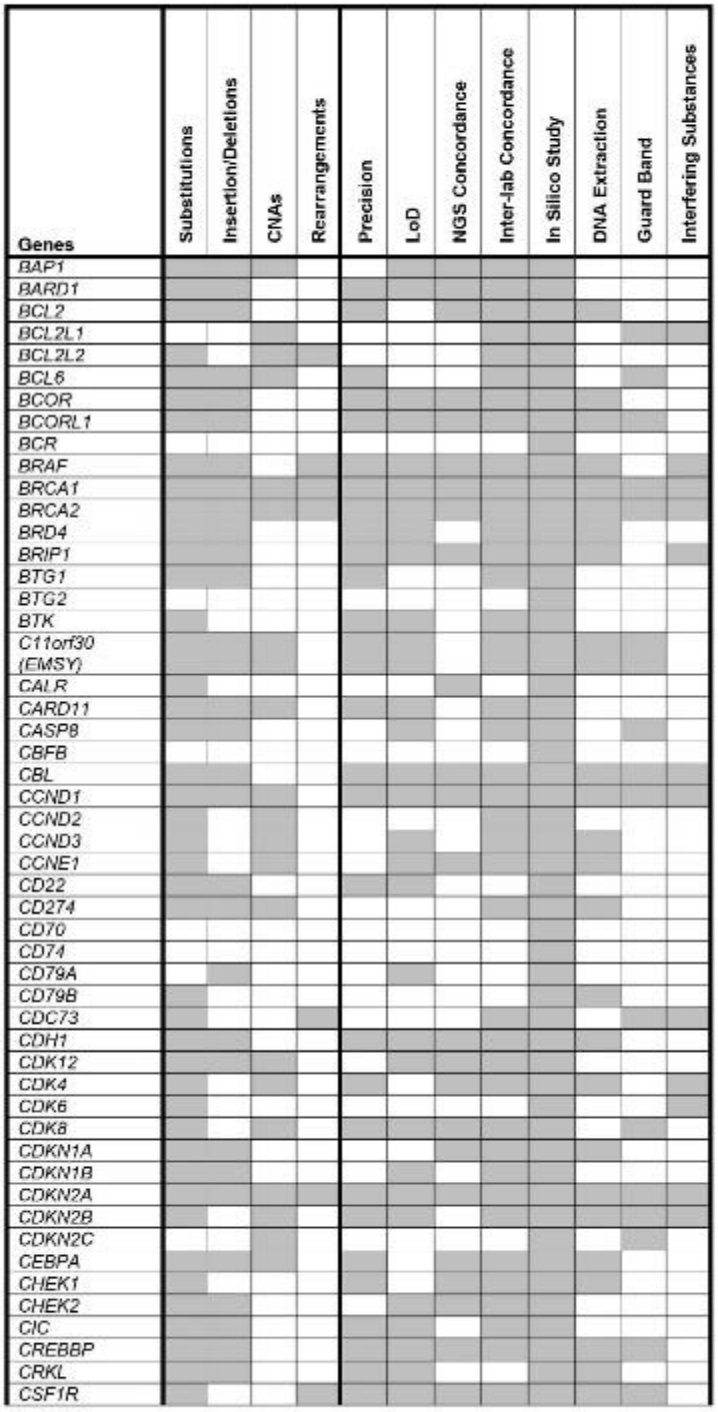

Tissue or Tumor Type
Limit of Detection
Precision
Pan-Tumor Analysis
NGS Concordance
Inter-Laboratory Concordance
CDx Concordance
DNA Extraction
DNA Stability (part 1)
FFPE Slide Stability
Interfering Substances
Guard Banding/Robustness
Molecular Index Barcodes
Variant Curation
Reagent Stability
Ear
Endometrium
Esophagus
Fallopian Tube
Gallbladder
Gastro-esophageal junction
Head and Neck
Kidney
Larynx
Liver
Lung
Lymph Node
Malignant effusions
Mediastinum
Nasal Cavity
Omentum
Ovarian
Pancreas
Pancreatobiliary
Parotid Gland
Pelvis
Penis
Pericardium
Peritoneum
Pleura
Prostate
Rare Tissues*
Rectum
Salivary Gland
Skin (Melanoma)
Small Intestine
Soft Tissue
Spleen
Stomach

Tissue or Tumor Type	Limit of Detection	Precision	Pan-Tumor Analysis	NGS Concordance	Inter-Laboratory Concordance	CDx Concordance	DNA Extraction	DNA Stability (part 1)	FFPE Slide Stability	Interfering Substances	Guard Banding/Robustness	Molecular Index Barcodes	Variant Curation	Reagent Stability
Thyroid														
Tongue			*											
Trachea			*											
Ureter														
Uterus														
Vagina														
Vulva														
Whipple Resection														

*Included as "Rare Tissues" in Pan-Tumor Analysis

Table 5. Summary of Genes and Alteration Types Included in Validation Studies.

Genes	Substitutions	Insertion/Deletions	CNAs	Rearrangements	Precision	LoD	NGS Concordance	Inter-lab Concordance	In Silico Study	DNA Extraction	Guard Band	Interfering Substances
ABL1												
ACVR1B												
AKT1												
AKT2												
AKT3												
*ALK**												
ALOX12B												
AMER1 (FAM123B)												
APC												
AR												
ARAF												
ARFRP1												
ARID1A												
ASXL1												
ATM												
ATR												
ATRX												
AURKA												
AURKB												
AXIN1												
AXL												


Genes
Substitutions
Insertion/Deletions
CNAs
Rearrangements
Precision
LoD
NGS Concordance
Inter-lab Concordance
In Silico Study
DNA Extraction
Guard Band
Interfering Substances
BAP1
BARD1
BCL2
BCL2L1
BCL2L2
BCL6
BCOR
BCORL1
BCR
BRAF
BRCA1
BRCA2
BRD4
BRIP1
BTG1
BTG2
BTK
C11orf30 (EMSY)
CALR
CARD11
CASP8
CBFB
CBL
CCND1
CCND2
CCND3
CCNE1
CD22
CD274
CD70
CD74
CD79A
CD79B
CDC73
CDH1
CDK12
CDK4
CDK6
CDK8
CDKN1A
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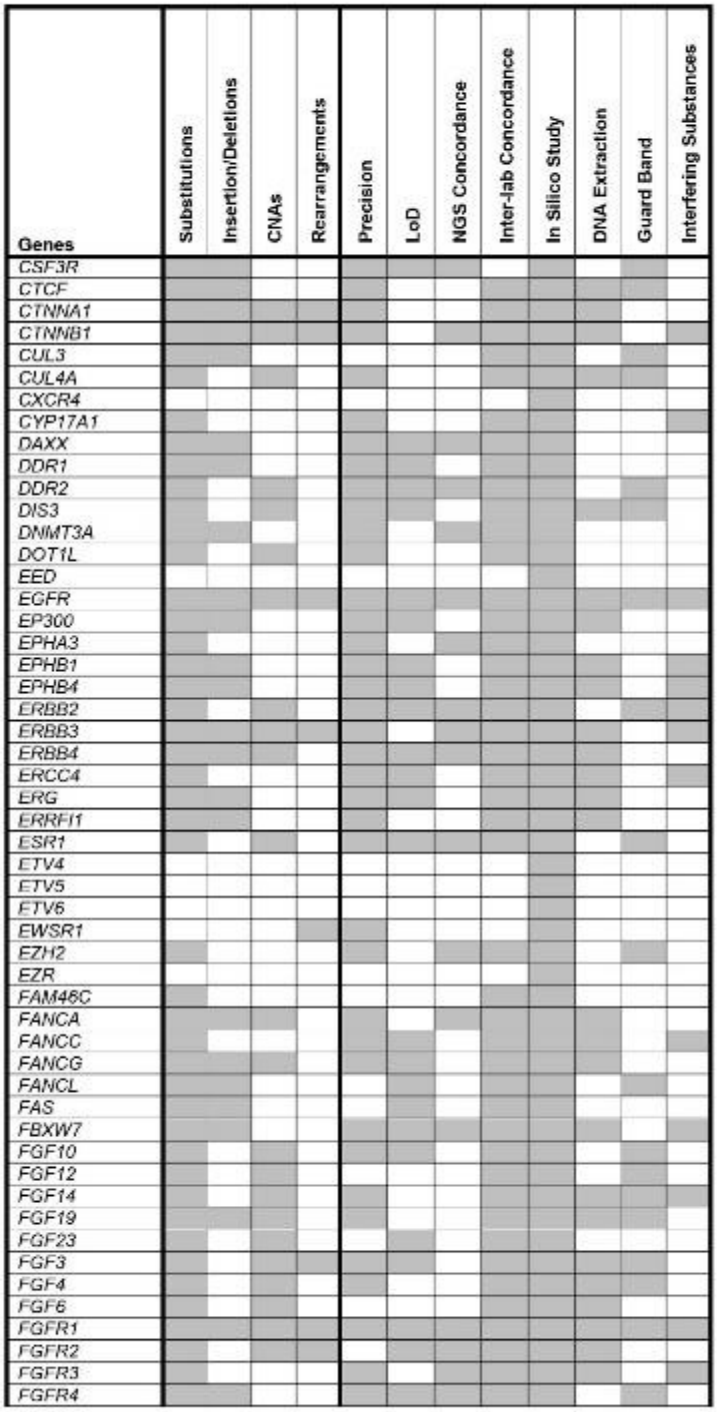
CDKN2B
CDKN2C
CEBPA
CHEK1
CHEK2
CIC
CREBBP
CRKL
CSF1R


Genes
Substitutions
Insertion/Deletions
CNAs
Rearrangements
Precision
LoD
NGS Concordance
Inter-lab Concordance
In Silico Study
DNA Extraction
Guard Band
Interfering Substances
CSF3R
CTCF
CTNNA1
CTNNB1
CUL3
CUL4A
CXCR4
CYP17A1
DAXX
DDR1
DDR2
DIS3
DNMT3A
DOT1L
EED
EGFR
EP300
EPHA3
EPHB1
EPHB4
ERBB2
ERBB3
ERBB4
ERCC4
ERG
ERRFI1
ESR1
ETV4
ETV5
ETV6
EWSR1
EZH2
EZR
FAM46C
FANCA
FANCC
FANCG
FANCL
FAS
FBXW7
FGF10
FGF12
FGF14
FGF19
FGF23
FGF3
FGF4
FGF6
FGFR1
FGFR2
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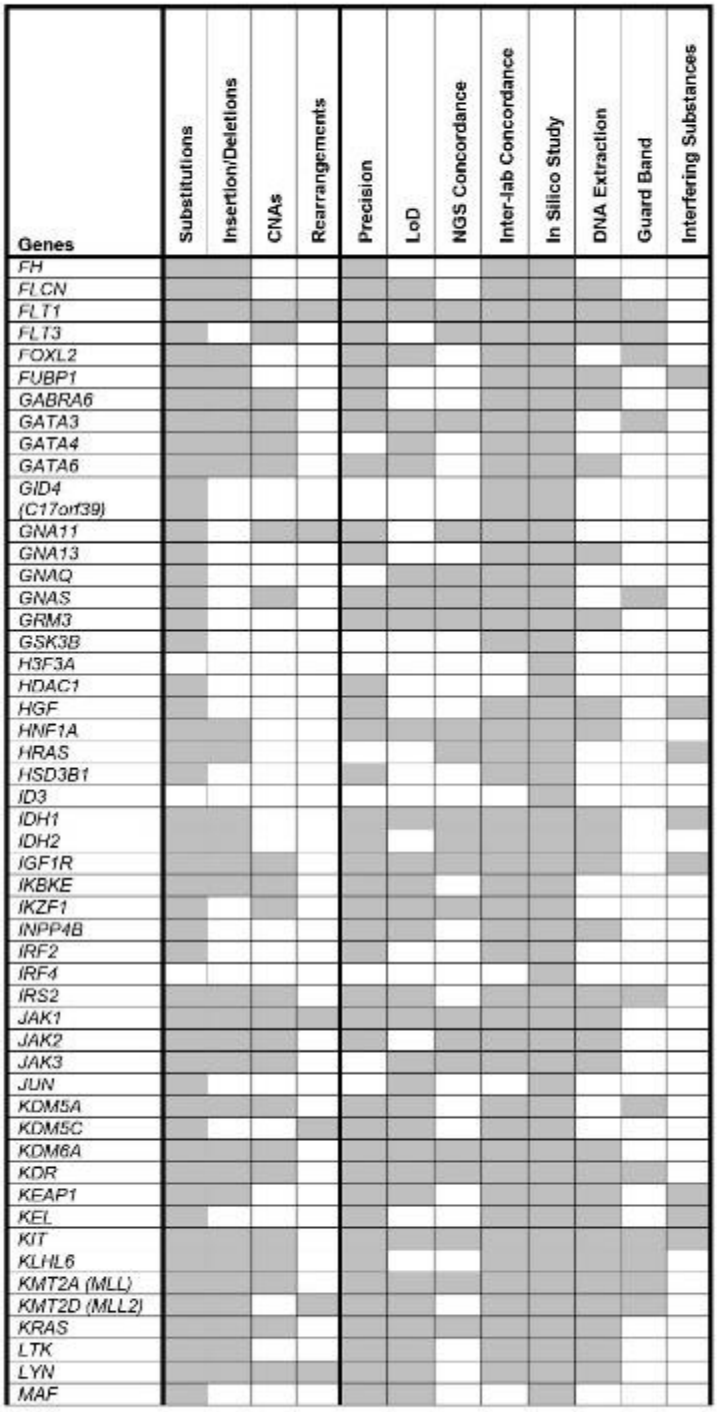
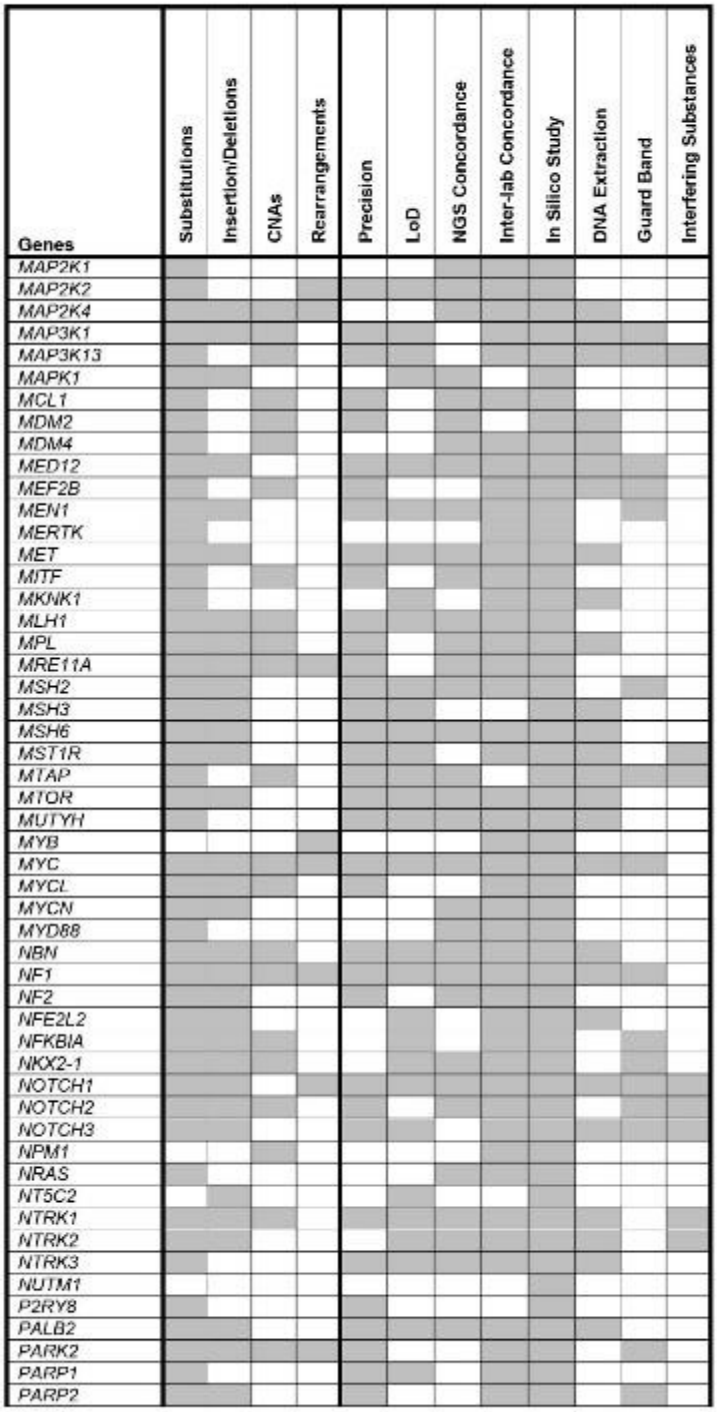

Genes
Substitutions
Insertion/Deletions
CNAs
Rearrangements
Precision
LoD
NGS Concordance
Inter-lab Concordance
In Silico Study
DNA Extraction
Guard Band
Interfering Substances
FH
FLCN
FLT1
FLT3
FOXL2
FUBP1
GABRA6
GATA3
GATA4
GATA6
GID4 (C17orf39)
GNA11
GNA13
GNAQ
GNAS
GRM3
GSK3B
H3F3A
HDAC1
HGF
HNF1A
HRAS
HSD3B1
ID3
IDH1
IDH2
IGF1R
IKBKE
IKZF1
INPP4B
IRF2
IRF4
IRS2
JAK1
JAK2
JAK3
JUN
KDM5A
KDM5C
KDM6A
KDR
KEAP1
KEL
KIT
KLHL6
KMT2A (MLL)
KMT2D (MLL2)
KRAS
LTK
LYN
MAF


Genes
Substitutions
Insertion/Deletions
CNAs
Rearrangements
Precision
LoD
NGS Concordance
Inter-lab Concordance
In Silico Study
DNA Extraction
Guard Band
Interfering Substances
MAP2K1
MAP2K2
MAP2K4
MAP3K1
MAP3K13
MAPK1
MCL1
MDM2
MDM4
MED12
MEF2B
MEN1
MERTK
MET
MITF
MKNK1
MLH1
MPL
MRE11A
MSH2
MSH3
MSH6
MST1R
MTAP
MTOR
MUTYH
MYB
MYC
MYCL
MYCN
MYD88
NBN
NF1
NF2
NFE2L2
NFKBIA
NKX2-1
NOTCH1
NOTCH2
NOTCH3
NPM1
NRAS
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NUTM1
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PALB2
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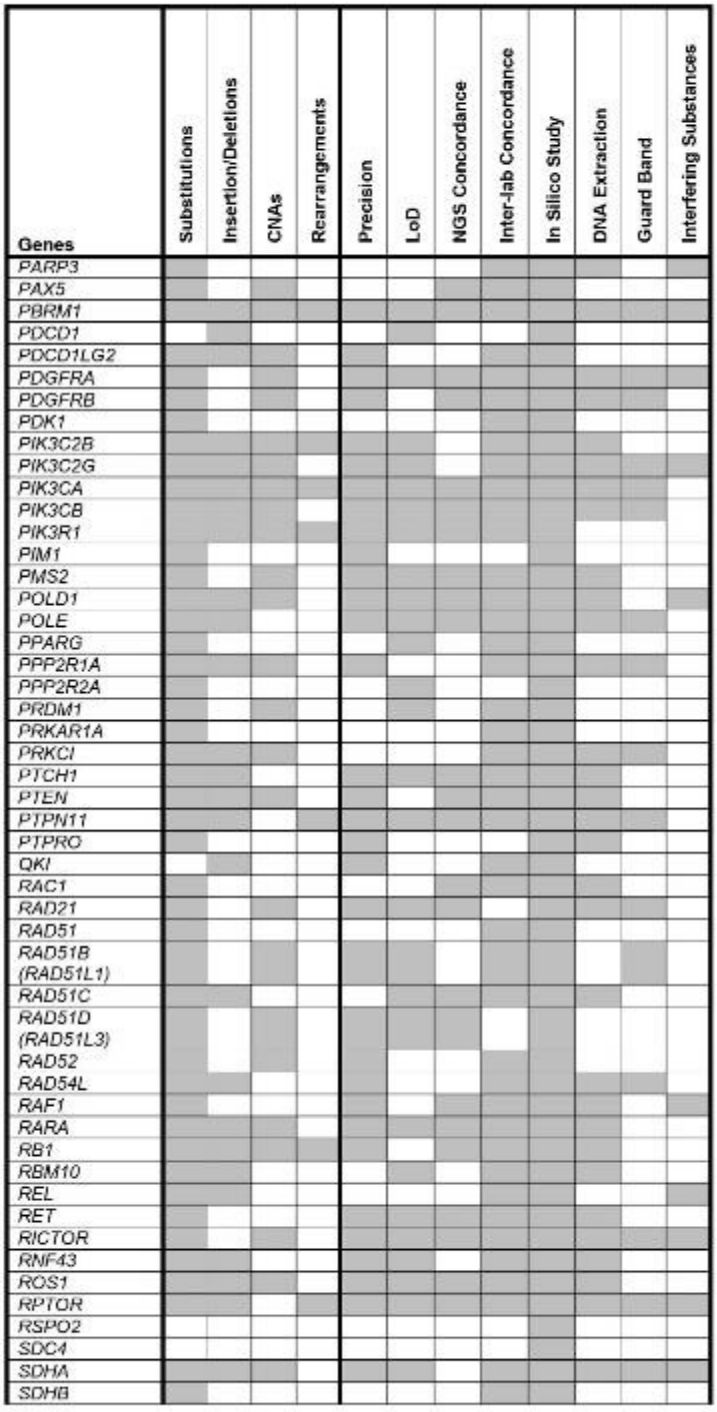
Genes
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Inter-lab Concordance
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DNA Extraction
Guard Band
Interfering Substances
PARP3
PAX5
PBRM1
PDCD1
PDCD1LG2
PDGFRA
PDGFRB
PDK1
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PIK3C2G
PIK3CA
PIK3CB
PIK3R1
PIM1
PMS2
POLD1
POLE
PPARG
PPP2R1A
PPP2R2A
PRDM1
PRKAR1A
PRKCI
PTCH1
PTEN
PTPN11
PTPRO
QKI
RAC1
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RAD51C
RAD51D (RAD51L3)
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RAD54L
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RICTOR
RNF43
ROS1
RPTOR
RSPO2
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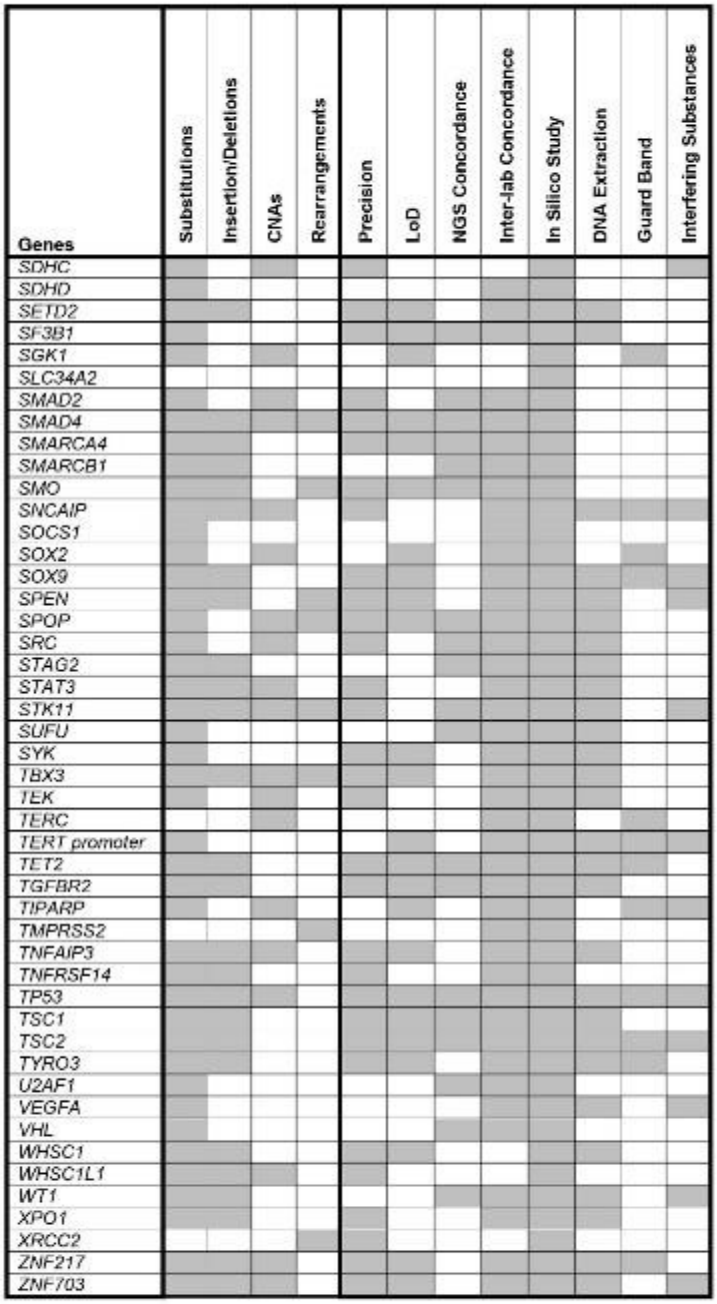

2.1 Concordance – Comparison to an Orthogonal Method

The detection of alterations by FoundationOne CDx™ (F1CDx) assay was compared to results of an externally validated NGS assay (evNGS). Overall there were 157 overlapping genes between the two assays. The comparison between short alterations, including base substitutions and short indels, detected by F1CDx and the orthogonal method included 188 samples from 46 different tumors. A summary of Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) is provided in Table 6 below. Differences in variants of unknown significance (VUS) alteration calls between the platform were noted, and are expected based on differences in filtering employed by F1CDx and evNGS. Negative predictive value and positive predictive value were also calculated and were found to be different than percent agreement because the two platforms filter VUS differently. Discordant alterations not related to VUS filtering were primarily caused by deletions with low allelic fraction in homopolymer regions. The F1CDx variant calling pipeline imposes a filter based on MAF of ≥0.10 for indels in homopolymer regions to reduce the likelihood of calling false positives resulting from artifacts introduced by the technology. As such, the difference observed was due to varying filter thresholds between the two platforms. For additional concordance results for the CDx-associated variants, refer to the Summary of Clinical Studies in Section 4.

Table 6. Concordance Summary for short variants inclusive of both substitutions and indels.

	F1CDx+ /evNGS+	F1CDx- /evNGS+	F1CDx+ /evNGS-	F1CDx- /evNGS-	PPA [95% CI]*	NPA [95% CI]*
All short variants	1282	73	375	284218	94.6% [93.3%-95.8%]	99.9% [99.9%-99.9%]
Substitutions	1111	39	334	242540	96.6% [95.4%-97.6%]	99.9% [99.8%-99.9%]
Indels	171	34	41	41678	83.4% [77.6%-88.2%]	99.9% [99.9%-99.9%]

*The PPA and NPA were calculated without adjusting for the distribution of samples enrolled using the FoundationOne Laboratory Developed Test (F1 LDT), therefore these estimates may be biased upward.

2.2 Concordance – Comparison to FoundationOne®

To support the use of retrospective data generated using the FoundationOne® (F1 LDT), a concordance study was conducted with FoundationOne CDx™ (F1CDx). This study evaluated a test set of 165 specimens. PPA and NPA between the F1CDx and F1 LDT, using the F1 assay as the reference method, was calculated for all alterations, as well as for alterations binned by type: short variants, copy number alterations (CNAs) and rearrangements. A total of 2325 variants, including 2026 short variants, 266 copy number alterations and 33 rearrangements were included in the study. The study results are summarized in Table 7 below.

Table 7. Summary of Inter-Laboratory Concordance Comparing FoundationOne CDx™ to the FoundationOne LDT (F1).

	F1CDx+/F1 LDT+	F1CDx-/F1 LDT+	F1CDx+/F1 LDT-	F1CDx-/F1 LDT-	PPA	NPA
All variants	2246	33	46	322890	98.6%	99.99%
All short variants	1984	19	23	299099	99.1%	99.99%
Substitutions	1692	10	19	254854	99.4%	99.99%
Indels	292	9	4	44245	97.0%	99.99%
All CNA	230	14	22	19204	94.3%	99.9%
Amplifications	157	10	12	14671	94.0%	99.9%
Losses	73	4	10	4533	94.8%	99.8%
Rearrangements	32	0	1	4587	100.0%	99.98%

The qualitative output for MSI (MSI-H vs. MSS) in the F1 LDT and F1CDx were evaluated. PPA, NPA and Overall Percent Agreement (OPA) of MSI status between the two assays was calculated for all 165

samples. Of the 165 samples, 5 were MSI-H by F1 LDT and 160 were MSS by F1 LDT; there was one discordant sample observed. The discordant sample was called MSS by F1 LDT and MSI-H by F1CDx. After manual review, the discordant case had an MSI score close to the threshold used to classify MSI status. PPA was 100% with a 95% confidence interval (95% CI) of 47.8-100%, NPA was 99.5% with a 95% CI of 96.6%-99.98% and OPA was 99.4% with a 95% CI of 96.7%-99.98%.

TMB concordance was evaluated by comparing the TMB output in terms of mutations per Mb. Analyses were conducted to examine the 21 samples with TMB score of ≥10, as well as all 153 samples with a non-zero TMB scores. The concordance of TMB score between the F1CDx and FoundationOne LDT assays was defined as the ratio of the two scores at log scale, ratio log (ϑDX1 / ϑT7). The 90% bootstrap CI of the ratio is within the equivalence interval (-0.5, +0.5), thus the TMB scores are considered equivalent. The details are summarized in Table 8 below. From linear regression analysis using F1 LDT TMB as the predictor and F1CDx TMB as the outcome, the intercept is - 0.27782[95%CI: -0.662, 0.106], and the slope is 0.94064[%95 CI: 0.919, 0.963]. A graphical representation of the data is presented in Figure 1 below.

Table 8. Summary of TMB Score Concordance Data.

Analysis	Number of samples	90% bootstrap CI of ratio *log* (ϑ_{DX1} / ϑ_{T7})	Acceptance Criteria
F1 LDT TMB Score≥10	21	(-0.246, -0.047)	90% CI is within (-0.5, 0.5)
Non-zero TMB score from F1 LDT or F1CDx	153	(-0.237, -0.120)	

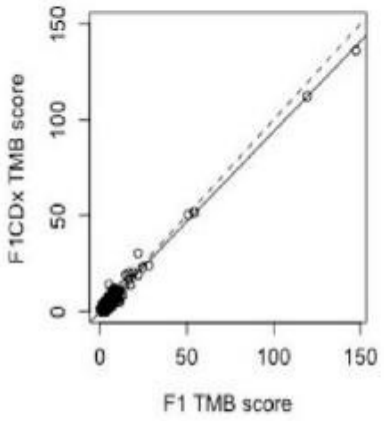

Figure 1. Comparison of F1CDx TMB scores with F1 LDT TMB scores. The solid black line represents the linear regression F1CDx TMB score ~ F1 LDT TMB, and the dash line is the diagonal plot denoting y=x.

2.3 Tissue Comparability

A large-scale retrospective analysis was conducted, using 80,715 specimens from 43 tissue types, in order to establish the comparability of assay performance across tumor tissue types. The goal of the study was to establish that assay performance after DNA extraction is independent of the tissue type from which the DNA was extracted. The retrospective analysis of data included specimens assayed using the F1 LDT assay. DNA extraction, and post-DNA extraction data were assessed for comparability of performance across tissue types. The dataset for analysis consisted of routine clinical samples analyzed using F1 LDT from March 25, 2015 to March 13, 2017.

Thirty-nine of the 43 tissue types had ≥90% of specimens passing DNA extraction QC. Specimen DNA extraction pass rates for the remaining four tissue types, lung, pancreas, pelvis and prostate, were 89.6%, 89%, 89%, and 79.7%, respectively. Each of these four tissue types have characteristically small biopsies and may also be more likely to require macro-dissection.

Of specimens entering the assay at Library Construction (LC), 39 of 43 tissue types had ≥90% of specimens resulting in a successful patient report being issued. The four tissue types below 90% include pancreatobiliary, appendix, pericardium, and prostate, and had pass rates of 83%, 88%, 79%, and 84%, respectively. For these four tissue types, the most frequent cause of failure was low tumor purity with no alterations detected. The mean LC yields across tissue types were 7,050 ng to 8,643 ng compared to the minimum required 545 ng. The percent of specimens passing the LC QC for each tissue type ranged from 98%-100%. After Hybrid Capture (HC), the mean yields across tissue types ranged from 434 ng to 576 ng, well above the minimum requirement of 140 ng. The percent of specimens passing HC across tissue types ranged from ranged from 97%-100%. The average median exon coverage assessed across tissue types ranged from 702X-793X, with percent of specimens passing QC for median coverage across tissue types ranging from 96%-100%. Uniformity of coverage was assessed by calculating the average percent of targets with >100X coverage across tissue types, and ranged from 99.0%-99.8%. The percentage of specimens passing this QC metric ranged from 98%-100%. The average sequencing error rate, assessed across tissue types, is 0.0028-0.0031, well below the required error rate (0.01) for assay acceptance. The pass rate for all tissue types was 100% for error rate. Performance data for this study is summarized in Table 9 below.

Table 9. Summary of post-DNA Extraction Analysis.

QC Metric Name	F1CDx QC Specification	Mean QC Performance Across Tissue Types	QC Pass Rate Across Tissue Types	Tissue types with ≥90% QC Pass Rate
Overall report Pass/Qualified rate	Pass rate: ≥90% specimens	N/A	79%-98%	39/43 (90.6%)
LC Yield	≥545 ng	7050–8643 ng	98-100%	43/43 (100%)
Library Yield after HC	≥140 ng	434-576 ng	97-100%	43/43 (100%)
Median Exon Coverage	≥250X	702-793X	96-100%	43/43 (100%)
Percent of target >100X coverage	≥95% target at ≥100X coverage	99.0%-99.8% targets	98%-100%	43/43 (100%)
Sequencing error rate	<1%	0.0028-0.0031	100%	43/43 (100%)
Noisy copy number data	N/A*	N/A	93.8-100%	43/43 (100%)

*for information only, not a specification

2.4 Analytical Specificity

2.4.1 Interfering Substances

The robustness of the FoundationOne CDx™ (F1CDx) assay process was assessed while evaluating human formalin-fixed paraffin-embedded (FFPE) samples in the presence of exogenous and endogenous interfering substances. Five FFPE specimens representing five tumor types (ovary, lung, colorectal, breast and melanoma) including representative variant types (substitution, indel, amplification, homozygous deletion and rearrangement) were assessed in duplicate (Table 10). An additional 54 short alterations (substitutions and indels) were assessed. The addition of interfering substances including melanin (endogenous), ethanol (exogenous), proteinase K (exogenous), and molecular index barcodes (MIB) (exogenous) was evaluated to determine if they were impactful to F1CDx, and the results were compared to the control (no interferents) condition.

Table 10. Summary of tumor types and variant types included in study.

Tumor Type	Gene (and variant as relevant)	Variant type
CRC	*FGFR1*	Rearrangement
	BCL2L1	Amplification
	AXIN1 c.1058G>A (R353H)	Substitution
	SOX9 c.768_769insGG (R257fs*23)	Insertion
Breast cancer	*ERBB2*	Amplification
	AKT1	Amplification
	CCND1	Amplification
Lung cancer	*CDKN2A*	Homozygous Deletion
	CDKN2B	Homozygous Deletion
	EGFR	Amplification
Ovarian cancer	*BRCA1* c.5263_5264insC (Q1756fs*74)	Insertion
	ERCC4 c.2395C>T	Substitution
	TP53 c.779_779delC (S261fs*84)	Deletion
Melanoma	*BRAF* c.1799T>A (V600E)	Substitution
	TP53 c. 856G>A (E286K)	Substitution
	IGF1R	Amplification

Interfering substances included melanin, ethanol, proteinase K, and molecular index barcodes, as noted in Table 11 below. Each of the five FFPE specimens were tested in either two or four replicates each, resulting in a total of 170 data points across the five specimens (10 without interferent, 80 for evaluation of melanin, ethanol and proteinase K and 80 for molecular index barcodes) were assessed in this study.

Table 11. Interfering Substance Evaluated.

Substances	Level	# Samples	# Replicates/Sample
No Interferent	–	5	2
Melanin	0.025 µg/mL	5	2
Melanin	0.05 µg/mL	5	2
Melanin	0.1 µg/mL	5	2
Melanin	0.2 µg/mL	5	2
Proteinase K	0.04 mg/mL	5	2
Proteinase K	0.08 mg/mL	5	2
Ethanol	5%	5	2
Ethanol	2.5%	5	2
MIB	0	5	4
MIB	5%	5	4

MIB	15%	5	4
MIB	30%	5	4

Substances were considered as non-interfering if, when compared to no interferent, the DNA yield is sufficient to meet the standard processing requirements of DNA isolation (≥55 ng), if the quality was sufficient to create products per the specification of library construction (≥545 ng) and hybrid capture (≥140 ng), and the sample success rate (fraction of samples that met all process requirements and specifications), across all replicates in aggregate, is ≥90%. Sequence analysis was assessed as percent agreement for each sample and calculated as the number of replicates with the correct alteration call reported per the total number of replicates processed. Percent agreement (fraction of correct calls) was computed across all replicates. The acceptance for concordance required a minimum of 90% of correct calls within each treatment category.

All samples tested at all interfering substance levels met all process requirements and specifications; achieving the acceptance criterion of ≥90%, indicating that the sample quality was not impacted by the interfering substances at the levels evaluated. The concordance of variants for the melanin, proteinase K and MIB evaluations was 100%, and was 95.3% for the ethanol evaluation, each meeting the acceptance criterion of ≥90%, indicating that the performance was not affected by the tested interferents. In addition to the variants selected to represent specific alteration types summarized in Table 10, samples included in the study harbored 54 additional short alterations (substitutions and indels) and were 100% concordant across all replicates for each variant.

See Summary of Safety and Effectiveness Data for P160018 for additional interference studies, wherein the interference of necrotic tissue, triglycerides, hemoglobin, and xylene, in addition to ethanol, proteinase K, and MIBs, was evaluated in ovarian tissue and assessed *BRCA1/2* alterations.

2.4.2 *In silico* Analysis – Hybrid Capture Bait Specificity

Bait specificity was addressed through an assessment of coverage at the base level for targeted regions included in FoundationOne CDx™ (F1CDx). Lack of bait specificity and/or insufficient bait inclusion would result in regions of diminished high quality mapped reads due to the capture of off-target content. This analysis showed that all regions that may harbor alterations associated with companion diagnostic claims consistently have high quality (MQS ≥ 30), deep coverage ≥ 250X. When assessing the entire gene set, 99.45% of individual bases in targeted coding regions +/-2 bp of flanking intronic splice site are covered with ≥100X coverage, and 91.45% of individual bases within targeted introns platform-wide had ≥100X coverage.

2.4.3 Carryover/Cross-contamination

No carryover or cross-contamination was observed when alternating positive and negative samples for *BRCA1* and *BRCA2* variants, assessed in a checker-board pattern (see Summary of Safety and Effectiveness Data for P160018). In addition, data from plates with high-level confirmed *ERBB2* amplifications, *EGFR* T790M alterations or *ALK* fusions were examined for cross-contamination in adjacent wells containing confirmed negative samples. No contamination was observed.

2.5 Precision: Repeatability and Reproducibility

In this study, repeatability and reproducibility of alterations associated with CDx claims and platform-wide alterations, including agreement for MSI, TMB, and MAF of short variants, were evaluated. Repeatability between intra-run aliquots (run on the same plate under the same conditions) and reproducibility of inter-run aliquots (run on different plates under different conditions) were assessed and compared across three different sequencers and three different reagent lots, across multiple days of performance by multiple operators.

A total of 47 samples had alterations representative of CDx associated alterations as well as exemplar alterations in a variety of genomic contexts, as shown in Tables 12 and 13 below. Each sample also included additional

alterations that were included in the assessment for a total of 717 alterations assessed. The maximum insertion length in this study was 30 bp and the longest deletion was 263 bp.

Table 12. Sample set selection for CDx validation.

Gene	Number of Unique Samples	Alteration	Tumor Type
EGFR	3	Exon 19 Deletion	NSCLC
	2	Exon 21 L858R	
	2	Exon 20 T790M	
KRAS	3	Codons 12/13 substitution	CRC
ALK	3	Fusion	NSCLC
BRAF	3	V600E/V600K	Melanoma
ERBB2	3	Amplification	Breast cancer

Table 13. Sample set selection for platform validation.

Alteration Type	Number of Unique Samples	Alteration Size	Genomic Context
Substitution	3	-	-
Short Insertion	2	1-2bp	Homopolymer Repeats
Short Insertion	2	1-2bp	Dinucleotide Repeats
Short Insertion	2	3-5bp	-
Short Insertion	2	>5bp	-
Short Deletion	2	1-2bp	Homopolymer Repeats
Short Deletion	2	1-2bp	Dinucleotide Repeats
Short Deletion	2	3-5bp	-
Short Deletion	2	>5bp	-
Amplification	3	-	-
Homozygous Deletion	3	-	-
Rearrangement	3	-	-

The results demonstrated that the F1CDx is robust regarding the repeatability and reproducibility of calling genomic alterations. Across all samples, the pre-sequencing process failure is 1.5%, and the no call rate is 0.18% for MSI, 6.38% for TMB (all) and 0.22% for TMB (>10 mut/Mb). Within the assessment of repeatability and reproducibility for CDx variants, all variants from all samples were 100% concordant. Percent of negative calls at each CDx variant location for wild-type samples was 100%.

Similarly, the platform-level repeatability and reproducibility showed high overall agreement across alteration bins, and high sample-level positive and negative call rates as summarized in Tables 14 and 15

below. The platform-level study included a total of 443 substitutions, 188 indels, 55 copy number amplifications, 13 copy number loss, and 18 rearrangements in the variant set across the samples.

Table 14. Reproducibility across variant bins (copy number, rearrangement, substitution, indels).

Variant Bin	# of Variants	# of valid Comparisons	# of Agreements	Positive Percent Agreement	95% CI Lower Limit	95% CI Upper Limit
CNAs	68	67,524	67,300	99.67%	99.62%	99.71%
Rearrangements	18	17,874	17,851	99.87%	99.81%	99.92%
Substitutions	443	439,899	439,649	99.94%	99.94%	99.95%
Indels	188	186,684	186,319	99.80%	99.78%	99.82%
All Variants	717	711,981	711,119	99.88%	99.87%	99.89%

Table 15. Positive and negative call rates per sample for platform variants (N=717).

Alteration Type(s) Assessed		exact 95% CI			exact 95% CI	
	PC Rate*	Lower	Upper	NC Rate**	Lower	Upper
CNA/RE/SUB	100.00%	99.40%	100.00%	99.98%	99.95%	99.99%
CNA/ SUB/Indel	99.37%	98.38%	99.83%	99.96%	99.92%	99.98%
SUB/Indel	100.00%	99.10%	100.00%	99.97%	99.95%	99.99%
CNA/ SUB/Indel	97.84%	96.89%	98.56%	99.84%	99.78%	99.89%
SUB/Indel	99.81%	98.94%	100.00%	99.98%	99.95%	99.99%
SUB/Indel	99.60%	97.81%	99.99%	99.94%	99.90%	99.97%
CNA/ SUB/Indel	98.33%	97.11%	99.14%	99.98%	99.96%	100.00%
SUB/Indel	100.00%	99.83%	100.00%	99.97%	99.94%	99.99%
CNA/ SUB/Indel	100.00%	99.32%	100.00%	99.98%	99.96%	100.00%
RE/ SUB/Indel	96.46%	94.14%	98.05%	99.96%	99.92%	99.98%
CNA/ SUB	98.67%	97.27%	99.46%	99.98%	99.96%	100.00%
CNA/RE/SUB/Indel	96.27%	95.39%	97.02%	99.87%	99.82%	99.91%
RE/SUB/Indel	98.23%	97.48%	98.80%	99.66%	99.58%	99.73%
CNA/ SUB/Indel	98.32%	97.57%	98.89%	99.92%	99.88%	99.95%
SUB/Indel	99.30%	98.90%	99.58%	99.90%	99.86%	99.94%
CNA/RE/SUB/Indel	85.42%	82.27%	88.20%	99.89%	99.84%	99.93%
RE/SUB/Indel	97.75%	96.42%	98.68%	99.98%	99.95%	99.99%
RE/SUB/Indel	95.30%	92.97%	97.03%	99.96%	99.93%	99.98%
CNA/RE/SUB/Indel	100.00%	98.31%	100.00%	99.89%	99.84%	99.93%
CNA/RE/SUB/Indel	100.00%	99.25%	100.00%	99.96%	99.93%	99.98%
CNA /SUB	96.83%	94.90%	98.17%	99.94%	99.90%	99.97%
CNA/RE/SUB/Indel	95.97%	94.06%	97.40%	99.98%	99.96%	100.00%
CNA/ SUB/Indel	100.00%	99.42%	100.00%	99.93%	99.89%	99.96%
CNA/RE/SUB/Indel	100.00%	99.30%	100.00%	99.95%	99.91%	99.97%
RE/SUB	100.00%	99.05%	100.00%	100.00%	99.98%	100.00%
CNA /SUB	96.99%	95.39%	98.15%	99.84%	99.79%	99.89%
CNA/RE/SUB/Indel	100.00%	98.95%	100.00%	99.93%	99.89%	99.96%
CNA/RE/SUB/Indel	99.80%	99.29%	99.98%	99.98%	99.96%	100.00%

*Abbreviations: SUB=substitution, Indel=Insertion or Deletion, CNA=Copy Number Alteration, RE=Rearrangement

For the assessment of MSI, 100% agreement was observed, with a lower limit of 99.7% and upper limit of 100%. For TMB determination, thirteen samples met the inclusion criteria (TMB ≥ 10) for assessment of repeatability and reproducibility. Twelve of 13 samples (92.3%) met the ≤20% Coefficient of Variation (CV) requirements; one sample fell just outside this requirement with a repeatability CV of 21% and reproducibility CV of 23%. The putative source of variability was determined to be low depth of coverage for this sample.

2.5.1 Reagent Lot-to-Lot Reproducibility

Three lots of critical reagents were assessed for four replicates per sample in a full factorial design. Reagents were evaluated as internally prepared kits for each process step (LC, HC, sequencing). The use of three different lots of reagents did not impact performance. Twenty-seven of 28 samples (96.4%) had pairwise agreement estimates (APA and ANA) above 95%; one sample had APA estimates below 90% (85.9% to 88.7%). ANA estimates were greater than 99%. The putative source of variability was determined to be non-focal copy number amplifications with low copy number close to the calling threshold observed in one sample; no specific reagent lot performed differently among three lots for this sample.

2.5.2 Instrument-to-Instrument Reproducibility

Four replicates per sample were sequenced on each of three Illumina HiSeq4000 sequencers, serial numbers K00255, K00256, and K00257 in a full factorial design. The use of three different sequencers did not impact performance. Twenty-seven of 28 samples (96.4%) had pairwise agreement estimates (APA and ANA) at least 97%; one sample had APA estimates below 90% (86.6% to 89.2%). ANA estimates was greater than 99%. The putative source of variability was determined to be non-focal copy number amplifications with low copy number close to the calling threshold observed in one sample; no specific sequencer performed differently among three sequencers for this sample.

2.6 Analytical Sensitivity: Limit of Detection (LoD) and Limit of Blank (LoB)

The Limit of Detection (LoD) of alterations assessed by FoundationOne CDx™ (F1CDx) was evaluated. The LoDs of seven (7) CDx biomarkers are summarized in Table 16-1 and 16-2 below. An additional twelve (12) categories of alteration types were evaluated for the F1CDx assay platform validation. A single FFPE tumor sample was selected for each of the variant categories. For each sample, six levels of MAF, with 13 replicates per level, were evaluated for a total of 78 replicates per sample. For platform-wide LoD assessment, the indels were grouped together (other than homopolymer repeat context) as they are similar in LoD characteristics. The indels ranged from 1 bp up to 42 bp insertions and deletions up to 276 bp. Indels at homopolymer repeat context had higher LoD, with a dependency on the length of the repeat context. In addition, LoD of MSI-high and TMB was also evaluated. The LoD for representative alterations detected by the F1CDx platform is summarized in Table 17-1 and 17.2.

Table 16-1. Summary of LoD for alterations associated with CDx claims (short variants). LoD is based on Allele Fraction.

Alteration	LoD[1] Allele Fraction (%) (100% Hit Rate)	LoD[2] Allele Fraction (%) (Probit)
EGFR L858R	2.4%	< 2.4% (all detected)
EGFR Exon 19 deletion	5.1%	3.4%
EGFR T790M	2.5%	1.8%
KRAS G12/G13	2.3%	< 2.3% (all detected)
BRAF V600E/K	2.0%	< 2.0% (all detected)
BRCA1/2[3]		
Alteration in non-repetitive or homopolymer <4 bp	N/A	5.9%
Deletion in 8 bp homopolymer	N/A	15.3%

[1] LoD calculations for the CDx variants were based on the hit rate approach, as there were less than three levels with hit rate between 10% and 90% for all CDx variants (not including *BRCA1/2* variants). LoD from the hit rate approach is defined as the lowest level with 100% hit rate (worst scenario).
[2]LoD calculations for the CDx variants based on the probit approach with 95% probability of detection.
[3]See Summary of Safety and Effectiveness Data for P160018.

Table 16-2. Summary of analytical sensitivity for tumor purity for alterations associated with CDx claims (copy number alteration and rearrangement). LoD is based on tumor purity.

Alteration	Tumor Purity (%) (100% Hit Rate)[1]	Tumor Purity (%) (Probit)[2]

ALK fusion	2.6%[3]	1.8%
ERBB2 amplification	25.3%[4]	19.7%

[1]Sensitivity calculations for the CDx variants were based on the hit rate approach, as there were less than three levels with hit rate between 10% and 90%. LoD from the hit rate approach is defined as the lowest level with 100% hit rate (worst scenario).
[2]Sensitivity calculations for the CDx variants based on the probit approach with 95% probability of detection.
[3]The number of chimeric reads for the sample evaluated is 16 at the indicated tumor fraction.
[4]The number of copy number amplifications for the sample evaluated is 6 at the indicated tumor fraction.

Table 17-1. Summary of representative LoD for F1CDx platform (short variants)

Variant Category	Subcategory	N	Range LoD[1] Allele Fraction (%)
Base Substitutions	known[3]	21[2]	1.8-7.9[2]
	other[4]	166	5.9-11.8
Indels at non-homopolymer context, including insertions up to 42bp and deletions up to 276bp	known	3	4.5-6.5
	other	17	6.0-10.2
Indels at homopolymer context	5bp repeat	8	10.0-12.2
	6bp repeat	2	13.6-13.7
	7bp repeat	4	16.3-20.4
	8bp repeat	3	17.0-20.0

[1]LoD calculations for the platform variants were based on the hit rate approach for variants with less than three levels with hit rate between 10% and 90% and probit approach for variants with at least three levels with hit rate between 10% and 90%. LoD from the hit rate approach is defined as the lowest level with 100% hit rate (worst scenario).
[2]Data includes an alteration in the *TERT* promoter, 124C>T (LoD of 7.9%). *TERT* is the only promoter region interrogated and is highly enriched for repetitive context of poly-Gs, not present in coding regions.
[3]Alterations classified as" known" are defined as those that are listed in COSMIC
[4]Alterations classified as "other" include truncating events in tumor suppressor genes (splice, frameshift and nonsense) as well as variants that appear in hotspot locations but do not have a specific COSMIC association, or are considered variants of unknown significance (VUS) due to lack of reported evidence and conclusive change in function.

Table 17-2. Summary of representative analytical sensitivity for tumor purity for F1CDx platform alterations (copy number variants and rearrangements)

Variant Category	N	Range Tumor Purity (%)[1]
Copy Number Amplifications (CN>10)	8	9.6%-18.5%
Copy Number Amplifications (6≤CN≤10)	7	19.5%-58.3%[2]
Copy Number: Homozygous Deletions	3	33.4%-33.4%
Genomic Rearrangements	3	9.2%-14.9%
MSI-High	3	8.3%-15.8%

[1]Sensitivity calculations for the platform variants were based on the hit rate approach for variants with less than three levels with hit rate between 10% and 90% and probit approach for variants with at least three levels with hit rate between 10% and 90%. LoD from the hit rate approach is defined as the lowest level with 100% hit rate (worst scenario)
[2]Max represents VUS alteration at calling threshold.

The LoB of zero was confirmed through the assessment of alterations within the LoB samples, with a percentage of false-positive results less than 5% (type I error risk α=0.05). Seventy-five (75) samples were used for the assessment of LoB. For all the alterations evaluated for LoD, the LoB of zero was confirmed. A similar study was conducted for *BRCA* alterations (PMA P160018) with no false-positive *BRCA* calls observed, thus confirming the LoB of zero for *BRCA*.

2.7 Stability

2.7.1 Reagent Stability

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDx$_{BRCA}$ Assay and FoundationOne CDx™ (F1CDx). For reagent stability performance data, see the Summary of Safety and Effectiveness Data for P160018. The claimed reagent stability is 4 months for the library construction (LC) and hybrid capture (HC) kits, and 3 months for the sequencing kits.

2.7.2 DNA Stability

Stability of DNA was evaluated through a retrospective review of data generated using the FoundationOne LDT assay. Samples from 47 unique clinical specimens from 21 different tissues of origin were evaluated. The sample set covered 200 alterations inclusive of nucleotide changes, indels, copy number amplifications, copy number losses and rearrangements. Duration of DNA storage at time of testing ranged from 48 to 464 days, with a median of 184 days and a mean of 199 days. A total of 199 of 200 alteration calls were concordant. A 242-day old sample with a single alteration call that met inclusion criteria was discordant; however, this sample was classified as not meeting all QC criteria due to other data quality issues. DNA age for the sample with discordance was 242 days. Sixteen other samples had concordant calls with DNA age >242 days. Based on this data, DNA stored in accordance with internal procedures can be considered stable for up to six months. Further supporting this retrospective data is a prospective study conducted using ovarian cancer samples, see the Summary of Safety and Effectiveness Data for P160018. An additional prospective DNA stability study is underway.

2.7.3 FFPE Sample Stability

The FFPE Slide Stability Study is an ongoing study with data summarized for T_0, T_1 (30 days), and T_2 (6 months). This study evaluated the stability of FFPE tumor tissue prepared as slides prior to DNA extraction for use within the F1CDx Assay. Five tumor samples including ovarian, lung, colorectal cancer, melanoma and breast cancer that contained a variety of DNA alterations, as described in Table 18 below. The five samples were selected to include specific alteration types that were reflective of the CDx-alterations, but were found to contain additional alterations as well (13 CNAs, one rearrangement, 53 base substitutions and five indels; refer to Table 19). To assess stability of pre-cut FFPE tissue for genomic alterations, the agreement between results from the defined time points for each sample were calculated by comparing the alteration call reported at each follow-up time point to the alteration call at baseline (T_0). Alterations at the 30-day time point and the 6-month time point are in 100% agreement with the Day 0 baseline results (T_0). The FFPE slides are considered stable for at least 6 months. Further assessment at Months 12 and 15 will evaluate stability of FFPE slides beyond 6 months.

Table 18. Stability Results at baseline, 30 days and 6 months.

Tissue	Baseline Call (T_0)		Percent Agreement to T_0	Percent Agreement to T_0
	Gene	Variant Effect	30 days (T_1)	6 months (T_2)
Ovarian	*BRCA1*	c.1340_1341insG, p.H448fs*8	100% (2/2)	100% (2/2)
Lung	*KRAS*	c.34G>T, p.G12C	100% (2/2)	100% (2/2)
CRC	*PIK3CA*	c.3139C>T, p.H1047Y	100% (2/2)	100% (2/2)
Melanoma	*CDKN2A*	Homozygous Deletion	100% (2/2)	100% (2/2)
Melanoma	*CDKN2B*	Homozygous Deletion	100% (2/2)	100% (2/2)
Breast	*ERBB2*	Amplification	100% (1/1)	100% (2/2)

Table 19. Percent agreement for each variant type.

Variant type	Number of variants	30 days (T_1) Percent Agreement (# agreement/total)	95% 2-sided CI LB, UB*	6 months (T_2) Percent Agreement (# agreement/total)	95% 2-sided CI LB, UB*
Copy Number	13	100% (23/23)	85.2%, 100.0%	100% (26/26)	86.8%, 100.0%
Rearrangement	1	100% (2/2)	15.8%, 100.0%	100% (2/2)	15.8%, 100.0%

Variant type	Number of variants	30 days (T_1) Percent Agreement (# agreement/total)	95% 2-sided CI LB, UB*	6 months (T_2) Percent Agreement (# agreement/total)	95% 2-sided CI LB, UB*
Substitution	53	100% (98/98)	96.3%, 100.0%	100% (106/106)	96.6%, 100.0%
Insertion/Deletion	5	100% (7/7)	59.0%, 100.0%	100% (10/10)	69.2%, 100.0%

*LB: lower bound; UB: upper bound

2.8 Reagent Lot Interchangeability

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDx$_{BRCA}$ assay and FoundationOne CDx™. For reagent lot interchangeability performance data, see the Summary of Safety and Effectiveness Data for P160018.

2.9 General Lab Equipment and Reagent Evaluation

2.9.1 DNA Amplification

Identical reagents and equipment with the same specifications are used following the same protocols for both the FoundationFocus CDx$_{BRCA}$ Assay and FoundationOne CDx™. For DNA amplification performance data, see the Summary of Safety and Effectiveness Data for P160018.

2.9.2 DNA Extraction

The performance of DNA extraction from FFPE tumor specimens was evaluated. The DNA extraction procedure for the FoundationOne CDx™ (F1CDx) assay was assessed by testing FFPE specimens including two samples per tissue type for ten different tumor tissue types including lung, breast, ovarian, melanoma, colorectal, brain, hepatic, pancreatic, thyroid, and bladder with different representative types of alterations. Samples were run in duplicate for a total of 240 extractions, employing two different KingFisher Flex Magnetic Particle Processors (120 extractions per processor) and comparing across three extraction reagent lots (80 extractions per reagent lot). Average DNA yield was calculated across twelve (12) replicates for each sample. All average DNA yields were significantly above the minimum requirement of 55 ng, with the minimum being 758.3 ng. Only one sample aliquot of the 240 replicates failed the DNA yield specification, and the success rates based on the reagent lot and the equipment were 98.8% (79/80) and 99.2% (119/120), respectively, passing the acceptance criteria (≥90%). Concordance of all genomic alterations detected was also analyzed for all variants across 12 replicates for each sample. Table 20 provides a summary of concordance across replicates. A study with an additional ten samples will be completed post-market.

Table 20. Summary of Concordance Across Replicates of DNA Extraction Study.

Group	$N_{concordance}$	N_{total}	Concordance	95% CI
Substitutions (All MAF)	2700	2969	90.9%	[89.9% 91.9%]
Substitutions (MAF > 10%)	1631	1637	99.6%	[99.2% 99.9%]
Substitutions (All MAF, excluding hypermutated sample)*	1663	1685	98.7%	[98% 99.1%]
Indel (All)	465	476	97.7%	[95.9% 98.8%]
Copy Number: Amplification	307	314	97.8%	[95.4% 99%]
Copy Number: Loss	132	144	91.7%	[85.9% 95.3%]
Rearrangement	84	90	93.3%	[85.9% 97.2%]

*One sample included in the study was hypermutated, harboring many alterations near LoD and exhibited evidence of external contamination. Concordance of substitutions was 80.8% for this sample.

2.10 Guard banding/Robustness

Guard banding studies were performed to evaluate the impact of process variation with regard to the measurement of DNA concentration at various stages of the process. Guard bands were evaluated relative to observed and measured process variability for Library Construction (LC), Hybrid Capture (HC), and Sequencing. Each of the three guard banding experiments demonstrated reliable and robust performance at all DNA input levels evaluated.

A total of 255 samples were processed; ninety (90) to assess DNA input into LC, ninety (90) to assess DNA input into HC, and seventy-five (75) to assess DNA input into sequencing. For LC input, five samples were run in triplicate over six different DNA input levels representing -20% and -50% from the lower limit (50 ng) to +20% and +50% from the upper limit (1000 ng) needed for LC (n=90). Five samples were run in triplicate over six DNA input levels representing -25% and -50% from the lower limit (0.5 µg) to +25% and +50% from the upper limit (2.0 µg) for HC input. The third component of the guard banding study evaluated the captured DNA input into the sequencing reaction. Five samples were run in triplicate over five different DNA input levels representing ±10% and ±20% from the required amount needed for sequencing (1.75 nM; n=75). Concordance of detected alterations was calculated for each condition across successful replicates. Results from this study supports the robustness of the F1CDx process. The study design and results are shown below in Tables 21-1 through 21-4.

Table 21-1. Summary of the success rate per process and per input level, and concordance of substitutions (SUB) among successful replicates.

Process	Input Level	# of Sample Failures	Variant Type	# of Concordant Successes	# of Variant Comparisons	Success Rate (95% CI) (Number of Concordant comparisons)
LC	25 ng	1/15	SUB	184	184	100.0% (98.0%, 100.0%)
LC	40 ng	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
LC	50 ng	0/15	SUB	191	192	99.5% (97.1%, 100%)
LC	1000ng	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
LC	1200 ng	0/15	SUB	191	192	99.5% (97.1%, 100%)
LC	1500 ng	0/15	SUB	190	192	99.0% (96.3%, 99.9%)
HC	0.25 µg	15/15	SUB	0	0	NA* (no samples sequenced)
HC	0.375 µg	12/15	SUB	30	30	100.0% (88.4%, 100.0%)
HC	0.5 µg	1/15	SUB	166	166	100.0% (97.8%, 100.0%)
HC	2.0 µg	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
HC	2.5 µg	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
HC	3.0 µg	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
Seq	1.4 nM	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
Seq	1.575 nM	1/15	SUB	180	180	100.0% (98.0%, 100.0%)
Seq	1.75 nM	1/15	SUB	184	184	100.0% (98.0%, 100.0%)
Seq	1.925 nM	0/15	SUB	192	192	100.0% (98.1%, 100.0%)
Seq	2.1 nM	0/15	SUB	192	192	100.0% (98.1%, 100.0%)

* All samples failed at the input level of 0.25 µg and as a result, there is no data available to present for that level.

Table 21-2. Summary of the success rate per process and per input level, and concordance of insertions and deletions (INDEL) among successful replicates.

Process	Input Level	# of sample failures	Variant Type	# of concordant successes	# of variant comparisons	Success Rate (95% CI) (Number of Concordant comparisons)
LC	25 ng	1/15	INDEL	17	17	100.0% (80.5%, 100.0%)

Process	Input Level	# of sample failures	Variant Type	# of concordant successes	# of variant comparisons	Success Rate (95% CI) (Number of Concordant comparisons)
LC	40 ng	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
LC	50 ng	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
LC	1000ng	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
LC	1200 ng	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
LC	1500 ng	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
HC	0.25 µg	15/15	INDEL	0	0	NA* (no samples sequenced)
HC	0.375 µg	12/15	INDEL	4	4	100.0% (39.8%, 100.0%)
HC	0.5 µg	1/15	INDEL	18	18	100.0% (81.5%, 100.0%)
HC	2.0 µg	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
HC	2.5 µg	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
HC	3.0 µg	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
Seq	1.4 nM	0/15	INDEL	18	18	100.0% (81. 5%, 100.0%)
Seq	1.575 nM	1/15	INDEL	16	16	100.0% (79.4%, 100.0%)
Seq	1.75 nM	1/15	INDEL	17	17	100.0% (80.5%, 100.0%)
Seq	1.925 nM	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)
Seq	2.1 nM	0/15	INDEL	18	18	100.0% (81.5%, 100.0%)

* All samples failed at the input level of 0.25 µg and as a result, there is no data available to present for that level.

Table 21-3. Summary of the success rate per process and per input level, and concordance of rearrangements (RE) among successful replicates.

Process	Input Level	# of sample failures	Variant Type	# of concordant successes	# of variant comparisons	Success Rate (95% CI) (Number of Concordant comparisons)
LC	25 ng	1/15	RE	6	6	100.0% (54.1%, 100.0%)
LC	40 ng	0/15	RE	6	6	100.0% (54.1%, 100.0%)
LC	50 ng	0/15	RE	6	6	100.0% (54.1%, 100.0%)
LC	1000ng	0/15	RE	6	6	100.0% (54.1%, 100.0%)
LC	1200 ng	0/15	RE	6	6	100.0% (54.1%, 100.0%)
LC	1500 ng	0/15	RE	6	6	100.0% (54.1%, 100.0%)
HC	0.25 µg	15/15	RE	0	0	NA* (no samples sequenced)
HC	0.375 µg	12/15	RE	2	2	100.0% (15.8%, 100.0%)
HC	0.5 µg	1/15	RE	6	6	100.0% (54.1%, 100.0%)
HC	2.0 µg	0/15	RE	6	6	100.0% (54.1%, 100.0%)
HC	2.5 µg	0/15	RE	6	6	100.0% (54.1%, 100.0%)
HC	3.0 µg	0/15	RE	6	6	100.0% (54.1%, 100.0%)
Seq	1.4 nM	0/15	RE	8	9	88.9% (51.8%, 99.7%)
Seq	1.575 nM	1/15	RE	9	9	100.0% (66.4%, 100.0%)
Seq	1.75 nM	1/15	RE	8	8	100.0% (63.1%, 100.0%)
Seq	1.925 nM	0/15	RE	8	9	88.9% (51.8%, 99.7%)
Seq	2.1 nM	0/15	RE	7	9	77.8% (40.0%, 97.2%)

* All samples failed at the input level of 0.25 µg and as a result, there is no data available to present for that level.

Table 21-4. Summary of the success rate per process and per input level, and concordance of copy number alterations (CN) among successful replicates.

Process	Input Level	# of sample failures	Variant Type	# of concordant successes	# of variant comparisons	Success Rate (95% CI) (Number of Concordant comparisons)
LC	25 ng	1/15	CN	128	128	100.0% (97.2%, 100.0%)
LC	40 ng	0/15	CN	132	132	100.0% (97.2%, 100.0%)
LC	50 ng	0/15	CN	132	132	100.0% (97.2%, 100.0%)
LC	1000ng	0/15	CN	132	132	100.0% (97.2%, 100.0%)
LC	1200 ng	0/15	CN	132	132	100.0% (97.2%, 100.0%)
LC	1500 ng	0/15	CN	132	132	100.0% (97.2%, 100.0%)
HC	0.25 µg	15/15	CN	0	0	NA* (no samples sequenced)
HC	0.375 µg	12/15	CN	13	14	92.9% (66.1%, 99.8%)
HC	0.5 µg	1/15	CN	107	108	99.0% (95.0 %, 100.0%)
HC	2.0 µg	0/15	CN	129	132	97.7% (93.5%, 99.5%)
HC	2.5 µg	0/15	CN	129	132	97.7% (93.5%, 99.5%)
HC	3.0 µg	0/15	CN	130	132	98.5% (94.6%, 99.8%)
Seq	1.4 nM	0/15	CN	131	132	99.2% (95.9%, 100.0%)
Seq	1.575 nM	1/15	CN	122	128	95.3% (90.1%, 98.3%)
Seq	1.75 nM	1/15	CN	128	128	100.0% (97.2%, 100.0%)
Seq	1.925 nM	0/15	CN	130	132	98.5% (94.6%, 99.8%)
Seq	2.1 nM	0/15	CN	131	132	99.2% (95.9%, 100.0%)

* All samples failed at the input level of 0.25 µg and as a result, there is no data available to present for that level.

3. Clinical Studies

CDx claims were based on a non-inferiority (NI) statistical testing approach using the enrichment design presented in the paper by Li (2016)[1], when the concordance study sample is not a random sample from the companion diagnostic (F1CDx) intended use population and a reference standard is not available.

To assess clinical concordance, F1CDx was compared to FDA-approved CDxs (CCD). All studies based on NI passed the acceptance criteria specified in each study protocol. Clinical concordance studies, with the exception of *ALK* and *EGFR* T790M, were subject to pre-screening bias. Therefore, the concordance results may be over or under estimated and the failure rate may be underestimated.

3.1 FoundationOne CDx™ Concordance Study for *EGFR* Exon19del/L858R

Clinical validity of FoundationOne CDx™ (F1CDx) as a companion diagnostic used for identifying patients with advanced NSCLC who may be eligible for treatment with Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib) was established by retrospectively testing 282 samples from NSCLC patients. The *EGFR* diagnostic results from the F1CDx assay were compared against those obtained from the approved **cobas®** *EGFR* Mutation Test v2 (Roche Molecular Systems). Samples were tested using **cobas®** *EGFR* mutation test (CCD1) with an approximately equal number of mutation positive and negative samples, followed by testing with F1CDx and a second, replicate testing of **cobas®** *EGFR* mutation test (CCD2). NSCLC tumor samples used for this study were not obtained from a clinical trial and had limited demographic data available. For this study age and gender data were available and were found to be similar to the pivotal study EURTAC.

Two separate concordance analyses were performed: one with samples with complete records only (N = 267), and the other with all the 282 samples, where missing data was handled by multiple imputation. Data from concordance testing is summarized in Table 22 below.

Table 22. Concordance Table with CCD1, CCD2 and F1CDX results with eligible samples.

	CCD1+				CCD1-			
	CCD2+	CCD2-	CCD2 missing	Total	CCD2+	CCD2-	CCD2 missing	Total
F1CDx+	106	0	0	106	1	1*	0	2
F1CDx-	2**	1	0	3	3	153	0	156
F1CDx Missing	3	0	0	3	1	9	2	12
Total	111	1	0	112	5	163	2	170

* QRF006212 was the only sample where both replicates of the **cobas®** v2 assay reported negative results but F1CDx reported positive for L858R with AF 33%. Upon further review, F1CDx identified a second somatic mutation in-cis (on same allele) as that of L858R with identical AF only 17bp downstream: *EGFR* A864P. Therefore, it is suspected that this second mutation interfered with the allele-specific PCR primers of **cobas®** v2, and thus L858R went undetected.

** QRF005867 was reported as positive for both replicates of **cobas®** v2 for exon19 deletion, but negative by F1CDx. F1CDx detected the exon19 deletion, but incorrectly annotated the variant as 2 frameshift mutations. This would have been corrected by manual curation review, which was not part of this concordance study. QRF005883 was also reported as positive for both replicates of **cobas®** v2 for exon19 deletion, but negative by F1CDx. F1CDx identified an 18bp exon 19 insertion event, with protein effect K745_E746insIPVAIK. As **cobas®** v2 is not designed to detect insertion events at exon 19, it is likely an error by **cobas®** v2.

Fifteen (15) samples were assigned as missing data for F1CDX, two of which also had missing results for CCD2. Missing data was caused by process failures or samples not meeting assay specifications.

By defining the reference standard as the consensus calls between CCD1 and CCD2, F1CDx achieved a PPA of 98.1% (106/108) (95% CI [93.5%, 99.8%]) and NPA of 99.4% (153/154) (95% CI [96.4%, 100.0%]). These data are summarized in Table 23.

Table 23. Summary of concordance data using agreement between CCD1 and CCD2 as the reference.

	CCD1+/CCD2+	**CCD1-/CCD2-**
F1CDX+	106	1
F1CDX-	2	153

The mutations detected by **cobas®** *EGFR* mutation test include all the mutations detected by therascreen® *EGFR* RGQ PCR Kit, as well as a few additional exon19 deletions/L858R variants. Several concordance studies comparing the **cobas®** *EGFR* mutation test and therascreen® *EGFR* RGQ PCR Kit have been reported in literature[2,3,4], supporting that these two assays are concordant.

Additionally, a post-market concordance study will be completed comparing F1CDx to the therascreen® *EGFR* RGQ PCR Kit.

3.2 FoundationOne CDx™ Concordance Study for *EGFR* T790M

The study established the clinical validity of the FoundationOne CDx™ (F1CDx) as a companion diagnostics device used for identifying NSCLC patients harboring *EGFR* T790M that may be eligible for treatment with Tagrisso® (osimertinib). The patient samples and corresponding demographic information were obtained from AstraZeneca in connection with the clinical studies entitled AURA (NCT01802632), AURA2 (NCT02094261) and AURA3 (NCT02151981). The *EGFR* T790M diagnostic results from the F1CDx assay were compared against the consensus calls between the original T790M testing used in the AURA, AURA2 and AURA3 studies and a separate run of the FDA approved **cobas®** v2 *EGFR* Mutation

Test (Roche Molecular Systems, referred to as **cobas**® v2 assay below; designated as comparator companion diagnostic, CCD), using a NI approach.

Two separate concordance analyses were performed: one included samples with complete records only (N = 227), and the second analysis was with all the 312 samples, where missing data was handled by multiple imputation. A summary of concordance is presented in Table 24.

Table 24. Concordance Table with CCD1, CCD2 and F1CDX results with eligible samples.

	CCD1+				CCD1-			
	CCD2+	CCD2-	CCD2 missing	Total	CCD2+	CCD2-	CCD2 missing	Total
F1CDx+	87	19	1	107	8	15	0	23
F1CDx-	1	4	0	5	0	93	2	95
F1CDx Missing	21	4	8	33	1	37	11	49
Total	109	27	9	145	9	145	13	167

Eighty-two samples were assigned as missing data for F1CDx, which consisted of 78 samples with no sequencing results from F1CDx and four samples with QC status as "Fail" after curation. CCD2 had 22 samples with missing data in total, in which 19 samples also had missing values in F1CDx.

The concordance analysis above shows that for the results of PPA, F1CDx is more concordant with both CCD1 and CCD2 than CCD1 is with CCD2; the opposite is true for NPA results. See Venn Diagram below for the T790M-positive calls (Figure 2).

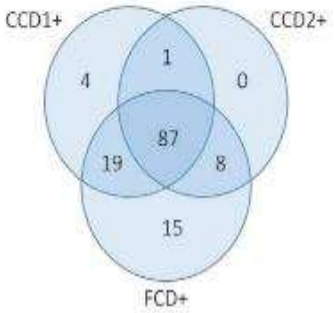

Figure 2. Venn Diagram for *EGFR* T790M-positive samples

A difference in detection sensitivity between CCD1 and CCD2 was observed, with CCD1 appearing to be more sensitive than CCD2. This could be attributed to the fact that CCD1 was run 2-3 years ago using freshly biopsied tissue, while CCD2 testing was recently performed using DNA extracted from archival FFPE sections. Figure 3 below illustrates the relationship between allele frequency and detection by F1CDx, CCD1 and CCD2. The results demonstrated that F1CDx detects mutations at allele frequency lower than 5% which are not detected by **cobas**® v2 assay. The clinical performance in this subset of patient population (patients with an *EGFR* T790M mutation detected with an allele fraction <5%) is ongoing and has not been established.

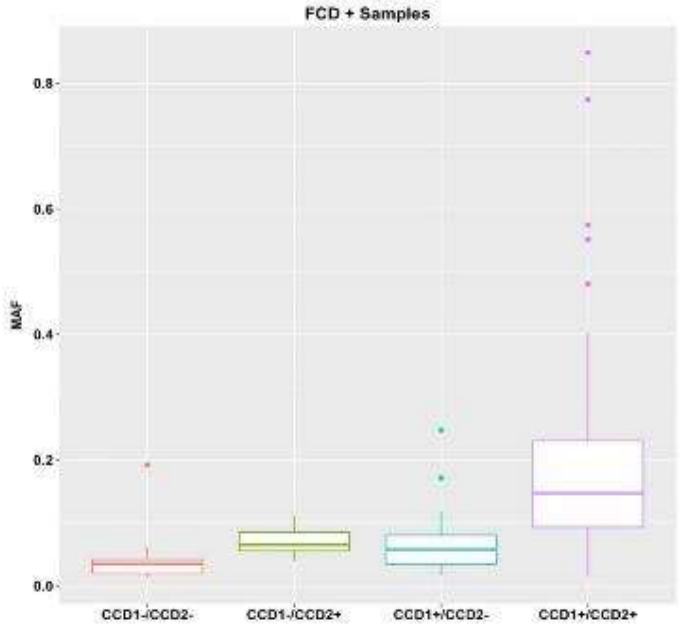

Figure 3. Distribution of MAF in F1CDx+ (FCD) samples

By defining the reference standard as the consensus calls between CCD1 and CCD2, F1CDx achieved a PPA of 98.9% (87/88) (95% CI [93.8%, 100.0%]) and NPA of 86.1% (93/108) (95% CI [78.1%, 92.0%]) as summarized in Table 25 below.

Table 25. Summary of concordance data using agreement between CCD1 and CCD2 as the reference.

	CCD1+/CCD2+	CCD1-/CCD2-
F1CDx+	87	15
F1CDx-	1	93

3.3 FoundationOne CDx™ Concordance Study for *ERBB2* (HER2)

Clinical validity of FoundationOne CDx (F1CDx) as a companion diagnostic device used to identify patients eligible for treatment with approved HER2-directed therapies including Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), and Perjeta® (pertuzumab) was established. A study was performed using 317 pre-screened retrospective samples obtained from patients with advanced breast cancer. The failure rate for pre-screening is not known, however, the sample set is enriched for samples with HER2+ samples with ratio between 2 and 3 representing 27% of samples compared to the expected range of 8-10% reported in literature[5,6]. The *ERBB2* amplification positive results from the F1CDx assay were compared against those obtained from the approved HER2 FISH PharmDx® Kit (Dako Denmark A/S). The samples used for this study were not obtained from a clinical trial and had limited demographic data available. For this study age and ethnicity data were available. Age data was compared to the Danish Study for the Danish Breast Cancer Group clinical trial 89-D in 1990 and was found to have a similar distribution, though the mean age was higher for the concordance samples.

Concordance data are summarized in Table 26 below.

Table 26. Concordance Table with CCD1, CCD2 and F1CDx results with eligible samples.

	CCD1+			CCD1-		
	CCD2+	CCD2-	Total	CCD2+	CCD2-	Total
F1CDx+	101	2	103	3	3	6
F1CDx-	12	10	22	6	180	186
Total	113	12	125	9	183	192

The prevalence of the *ERBB2*/HER2 amplification mutation in the IU population is based on the ASCO guideline and is estimated to be 17.5%. To assess the impact of prevalence for the main results of this study, a sensitivity analysis was performed using the lower and upper bound of the prevalence guideline of 15% and 20%. The sensitivity analysis also showed that there was no impact on the study conclusion. The distribution of age is similar to the IU population for all samples tested. However, there was missing demographic data from the sample population. For missing data analysis using multiple imputation, the results show that based on the MAR assumption, the invalid test results did not affect the conclusion of this study.

The Venn diagrams for samples tested positive or negative for *ERBB2*/HER2-amplification mutation in all three assays (F1CDx, CCD1 and CCD2) are presented in Figure 4.

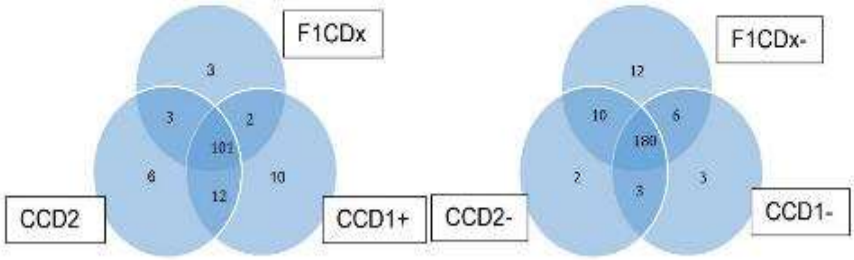

Figure 4. Venn Diagrams for *ERBB2*-amplification positive (left panel) and negative (right panel) samples.

These two Venn diagrams illustrate concordance among F1CDx, CCD1 and CCD2. For the F1CDx+ samples, concordance of F1CDx with CCD1 or CCD2 was better than concordance between the same platform tests CCD1 and CCD2; for the F1CDx- samples, F1CDx was more consistent in calling negative alterations than either CCD1 or CCD2.

Using the consensus calls between CCD1 and CCD2 as the reference standard, i.e. limiting analysis to only the samples in which CCD1 and CCD2 are in agreement, the results are shown below:

Table 27. Summary of concordance data using agreement between CCD1 and CCD2 as the reference.

	CCD1+/CCD2+	CCD1-/CCD2-
F1CDx+	101	3
F1CDx-	12	180

Based on these results, PPA is 89.4% (101/113) (95% CI [82.2%, 94.4%]) and NPA is 98.4% (180/183) (95% CI [95.3%, 99.7%]).

3.4 FoundationOne CDx™ Concordance Study for *ALK*

Clinical validity of FoundationOne CDx™ (F1CDx) as a companion diagnostic device used to identify non-small cell lung cancer (NSCLC) patients eligible for treatment with approved *ALK*-directed therapies including Alecensa® (alectinib), X*ALK*ori® (crizotinib), or Zykadia® (ceritinib) was established. The study was performed using 175 tumor samples from patients with histologically-confirmed NSCLC including enrolled patients as well as screen failures from the clinical trial NCT02075840, Roche study number BO28984 (also known as the ALEX study), which is a randomized, active controlled, multicenter phase III open-label study designed to evaluate the efficacy and safety of alectinib compared with crizotinib treatment in participants with treatment-naïve *ALK* rearrangement positive advanced NSCLC. The *ALK* diagnostic results from the F1CDx panel were compared against those obtained from the FDA approved Ventana *ALK* (D5F3) CDx Assay ("Ventana IHC", Ventana Medical Systems, Inc.) and Vysis *ALK* Break-Apart FISH Probe Kit ("Vysis FISH", Abbott Molecular). The Vysis FISH assay results used were obtained from the ALEX study. In this concordance study, the majority of the samples were from the IU population of the clinical trial NCT02075840. The concordance results are summarized in Table 28 below.

Table 28. Concordance Table with CCD1, CCD2 and F1CDx results with eligible samples

	CCD1 +			**CCD1 -**		
	CCD2 +	CCD2 -	Total	CCD2 +	CCD2 -	Total
F1CDx +	78	1	79	3	0	3
F1CDx -	6*	7	13	5	75	80
Total	84	8	92	8	75	83

*Two samples harbored *ALK* rearrangements that were detected by F1CDx but were classified as negative based on the study protocol.

The Venn diagrams for samples tested positive or negative for *ALK*-rearrangement mutation in all three assays (F1CDx, CCD1 and CCD2) are shown in Figure 5.

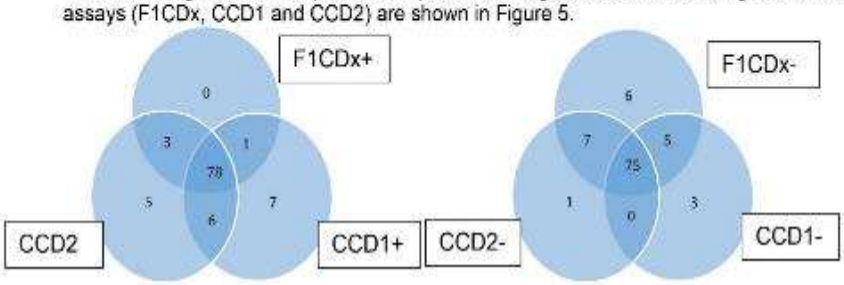

Figure 5. Venn Diagrams for *ALK*-rearrangement positive (left panel) and negative (right panel) samples.

These two Venn diagrams illustrate concordance among F1CDx, CCD1 and CCD2. A number of samples with discordant results between CCD1 and CCD2 were observed. This is expected because Vysis FISH Assay (CCD2) is a technology that probes at the DNA level while Ventana *ALK* IHC assay examines protein expression. When samples that were discordant between CCD1 and CCD2 were excluded, the concordance between F1CDx+ with CCD1+ and CCD2+ samples was superior to concordance between CCD1+ and CCD2+ samples. For the F1CDx- samples, F1CDx was more consistent in calling negative alterations than either CCD1 or CCD2.

Using the consensus calls between CCD1 and CCD2 as the reference standard, i.e. limiting analysis to only the samples in which CCD1 and CCD2 are in agreement, the results are shown below:

Table 29. Summary of concordance data using agreement between CCD1 and CCD2 as the reference.

	CCD1+/CCD2+	CCD1-/CCD2-
F1CDx+	78	0
F1CDx-	6*	75

*Two samples harbored *ALK* rearrangements that were detected by F1CDx but were classified as negative based on the study protocol.

Based on these results, PPA is 92.9% (78/84) (95% CI [85.1%, 97.3%]) and NPA is 100% (75/75) (95% CI [95.2%, 100.0%]).

3.5 FoundationOne CDx™ Concordance Study for *KRAS*

Clinical validity of FoundationOne CDx™ (F1CDx) as a companion diagnostic device used to identify colorectal cancer patients that may not benefit from certain *EGFR* inhibitor treatments, including Erbitux® (cetuximab) or Vectibix® (panitumumab), due to alterations in *KRAS*. The study was performed using 342 retrospective samples obtained from patients with advanced front-line or later-line colorectal cancer (CRC). Samples used in this study underwent pre-screening using the FoundationOne laboratory developed test (F1 LDT) or prescreening by an external vendor to enrich for positive samples. The prescreen failure rate using the F1 LDT was 3.7% and is unknown for the external vendor. The *KRAS* diagnostic results from the F1CDx assay were compared against those obtained from the approved therascreen® *KRAS* RGQ PCR Kit (Qiagen). The samples used for this study were not obtained from a clinical trial and had limited demographic data available. For this study age, gender and ethnicity data were available. Age and gender characteristics were found to be similar between the F1CDx concordance study and the pivotal studies, with the percentage of male samples in the concordance study being slightly lower compared to the pivotal studies (CRYSTAL and PRIME). Concordance data are summarized in Table 30 below.

Table 30. Concordance Table with CCD1, CCD2 and F1CDx results with eligible samples.

	CCD1+				CCD1-			
	CCD2+	CCD2-	CCD2 missing	Total	CCD2+	CCD2-	CCD2 missing	Total
F1CDx+	173	0	2	175	0	0	0	0
F1CDx-	0	2	0	2	1	154	7	162
F1CDx Missing	0	0	0	0	0	3	0	3
Total	173	2	2	177	1	157	7	165

Twelve (12) samples are assigned as missing data, including 3 samples with missing data in F1CDx and 9 samples with missing data in CCD2.

The prevalence of the *KRAS* mutation in the IU population is based on the CRYSTAL study for cetuximab (35.6%) and PRIME study for panitumumab (40%). The key statistics of PPA and NPA between F1CDx and the two replicates of the therascreen® assay (CCD1 and CCD2) were estimated based on the result in Table 31. Multiple imputation was used to impute the missing data and showed that missing data did not impact study conclusions. The summary statistics of age and sex were highly similar to the estimates from the pivotal trial CRYSTAL (for cetuximab) and PRIME (for panitumumab) studies.

By defining the reference standard as the consensus calls between CCD1 and CCD2, F1CDx achieved a PPA of 100% (173/173) (95% CI [97.9%, 100.0%]) and NPA of 100% (154/154) (95% CI [97.6%, 100.0%]).

Table 31. Summary of concordance data using agreement between CCD1 and CCD2 as the reference.

	CCD1+/CCD2+	CCD1-/CCD2-
F1CDx+	173	0
F1CDx-	0	154

3.6 FoundationOne CDx™ Concordance Study for *BRAF*

Clinical validity of the FoundationOne CDx™ (F1CDx) as a companion diagnostic device used to identify melanoma patients that may be eligible for treatment with approved *BRAF*-directed therapies was established. The study was performed using 305 retrospective samples obtained from patients with advanced melanoma. 157 samples used in this study underwent pre-screening using the FoundationOne laboratory developed test (F1 LDT) and 27 were prescreened by an external vendor to enrich for positive samples. The prescreen failure rate using the F1 LDT was 3.7% and is unknown for the external vendor. The *BRAF* diagnostic results from the F1CDx assay were compared against those obtained from the approved **cobas®** *BRAF* V600 mutation test (Roche Molecular Systems, Inc). These samples were not obtained from a clinical trial and had demographic data limited to age and gender. The distributions of age and gender to the intended use population (BRIM-3 trial) was found to be comparable.

Concordance analysis showed that the upper bounds of 95% one-sided Confidence Interval (CI) were below 20% for all four NI hypothesis tests. Thus, it can be concluded with 95% confidence that the differences of results between F1CDx and **cobas®** assays are less than 20%, the non-inferiority (NI) margin. Concordance results are summarized in Table 32 below.

Table 32. Concordance Table with CCD1, CCD2 and F1CDx results with eligible samples

	CCD1+			**CCD1-**		
	CCD2+	CCD2-	Total	CCD2+	CCD2-	Total
F1CDx+	166	0	166	3	14	17
F1CDx-	1	0	1	0	121	121
Total	167	0	167	3	135	138

Because the **cobas®** assay has lower sensitivity for detection of dinucleotide mutations, a separate analysis was conducted that included only eligible samples without dinucleotide mutations. A total of 273 (=305-32) samples were available for this analysis. The concordance results are summarized in Table 33.

Table 33. Concordance Table with CCD1, CCD2 and F1CDx results with eligible samples excluding samples with dinucleotide mutations detected by F1CDx

	CCD1+			**CCD1-**		
	CCD2+	CCD2-	Total	CCD2+	CCD2-	Total
F1CDx+	149	0	149	1	1*	2
F1CDx-	1**	0	1	0	121	121
Total	150	0	150	1	122	123

*QRF006472 was the only sample where both replicates of the **cobas®** assay reported negative results but F1CDx reported positive. The Allele Frequency of this sample was 3.45% with the computational tumor purity of 10%. According to Table 4 of the **cobas®** assay insert, the **cobas®** assay can correctly detect all *BRAF* V600E mutant specimens that have a minimum % mutant DNA above 5% and when the minimum tumor content is at least 15%. Thus, the discordance can be explained by F1CDx's high sensitivity in the lower % mutant DNA and low tumor purity condition.

QRF006374 was the only sample where both replicates of the **cobas® assay reported positive results but F1CDx reported negative. A mutation was recorded in the line data (Appendix 7) having protein effect V600_K601>E, which is a non-frameshift deletion of 3 nucleotides with CDS effect 1799_1801delTGA. This more complex mutation does result in V600E, but because of annotation differences to the canonical V600E, it was called negative by F1CDx.

PPA and NPA were calculated by defining the reference standard as the consensus calls between CCD1 and CCD2. The observed performance of **cobas®** has lower sensitivity for detection of dinucleotide V600 alterations (including V600K) than the single nucleotide V600E 1799T>A alteration, particularly at allele frequency below 40% detected by F1CDx, therefore, the data presented will include PPA/NPA results both with both alterations as the study was designed, as well as for V600E only in Table 34. A study using the THxID™ *BRAF* kit (bioMérieux) was conducted using 29 samples with *BRAF* V600 dinucleotide mutation detected by F1CDx and 29 negative samples to provide a better evaluation of V600 dinucleotide concordance. Out of the 51 samples with valid results from the THxID™ *BRAF* kit (Table 35), there was only one discordant result (F1CDx-/THxID+), achieving a PPA of 96.3% (26/27) (95% CI [81.0%, 99.9%]) and NPA of 100% (24/24) (95% CI [85.8%, 100.0%]).

Table 34. PPA and NPA for *BRAF* V600 detection with cobas®.

	PPA	NPA
All V600 alterations	99.4% (166/167)	89.6% (121/135)
Single nucleotide V600E (1799T>A)	99.3% (149/150)	99.2% (121/122)

Table 35. Concordance of *BRAF* dinucleotide samples with THxID™ *BRAF* kit.

Dinucleotide Samples	THxID+	THxID-	Total
F1CDx+	26	0	26
F1CDx-	1	24	25
Total	27	24	51

3.7 FoundationOne CDx™ Concordance with FoundationFocus CDx_{BRCA} for *BRCA1*and *BRCA2*.

FoundationOne CDx™ (F1CDx) and FoundationFocus CDx_{BRCA} use the same reagents, equipment and procedures with exception of the allowance for a broader range of DNA input into library construction and incremental enhancements to the analysis pipeline for F1CDx. The two changes were shown to have no impact on assay performance through the guard band study which included ovarian tissue and a comprehensive validation of the analysis pipeline which included robust regression testing and reanalysis of FoundationFocus CDx_{BRCA} clinical bridging sample data. As such, the assays were determined to be concordant. Details for the clinical study in which the assay was shown to be effective in identify patients with ovarian cancer that may benefit from rucaparib treatment can be found in the Summary of Safety and Effectiveness Data for PMA P160018.

3.8 Summary of Clinical Concordance Studies

A summary of clinical concordance study results is included in Table 36 below. The reference standard used to calculate positive percent agreement (PPA) and negative percent agreement (NPA) below is defined as the consensus calls between the two comparator methods or comparator runs. Agreement calculations solely using consensus calls may overestimate the performance of F1CDx.

Table 36. Summary of PPA and NPA for CDx Concordance Studies

Biomarker	PPA	NPA	Comparator Method
EGFR exon 19 deletions and L858R	98.1% (106/108)	99.4% (153/154)	**cobas®** *EGFR* Mutation Test v2
EGFR T790M	98.9% (87/88)	86.1% (93/108)	**cobas®** *EGFR* Mutation Test v1 **cobas®** *EGFR* Mutation Test v2
ALK rearrangements	92.9% (78/84)	100% (75/75)	Ventana *ALK* (D5F3) CDx Assay Vysis *ALK* Break-Apart FISH Probe Kit
KRAS	100% (173/173)	100% (154/154)	therascreen® KRAS RGQ PCR Kit

Biomarker	PPA	NPA	Comparator Method
ERBB2(HER2) Amplifications	89.4% (101/113)	98.4% (180/183)	Dako HER2 FISH PharmDx® Kit
BRAF V600	99.4% (166/167)	89.6% (121/135)*	**cobas**® *BRAF* V600 Mutation Test
BRAF V600E	99.3% (149/150)	99.2% (121/122)	**cobas**® *BRAF* V600 Mutation Test
BRAF V600 dinucleotide**	96.3% (26/27)	100% (24/24)	THxID™ *BRAF* kit

* Sensitivity of dinucleotide detection of *BRAF* V600K and V600E was found to be significantly reduced in **cobas**® test, in particular for samples in which F1CDx detected the dinucleotides to be of lower than 40% MAF, leading to low NPA values.

** A study using the THxID™ *BRAF* kit (bioMérieux) was conducted with samples with *BRAF* V600 dinucleotide mutation detected by F1CDx and *BRAF* V600 negative samples to provide a better evaluation of V600 dinucleotide concordance.

6. References

1. Li M. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External
2. Kimura H., Ohira T., Uchida O., et al. Analytical performance of the **cobas** *EGFR* mutation assay for Japanese non-small-cell lung cancer. Lung Cancer 83, 329-333 (2014).
3. Lopez-Rios F., Angulo B., Gomez B., et al. Comparison of molecular testing methods for the detection of *EGFR* mutations in formalin-fixed paraffin-embedded tissue specimens of non-small cell lung cancer. J Clin Pathol 66, 381–385 (2013).
4. Wong AT, To RM, Wong CL, et al. Evaluation of 2 Real-Time PCR Assays for In Vitro Diagnostic Use in the Rapid and Multiplex Detection of *EGFR* Gene Mutations in NSCLC. Diagn Mol Pathol 22, 138-43 (2013).
5. Press et al., HER2 Gene Amplification Testing by Fluorescent In Situ Hybridization (FISH): Comparison of the ASCO-College of American Pathologists Guidelines With FISH Scores Used for Enrollment in Breast Cancer International Research Group Clinical Trials, J Clin Oncol 34:3518-3528, 2016
6. Dowsett, M. et al, Disease-Free Survival According to Degree of HER2 Amplification for Patients Treated with Adjuvant Chemotherapy With or Without 1 Year of Trastuzumab: The HERA Trial, J Clin Oncol 27:2962-2969, 2009

Specimen Instructions

FOUNDATIONONE CDx™

FoundationOne CDx™ is a broad companion diagnostic (CDx) test for five tumor indications. In addition to use as a companion diagnostic, F1CDx provides cancer relevant alterations that may inform patient management in accordance with professional guidelines. Information generated by this test is an aid in the identification of patients who are most likely to benefit from associated therapeutic products as noted in Table 1 of the Intended Use.[1]

Acceptable Samples

- Formalin-fixed paraffin embedded (FFPE) specimens, including cut slide specimens are acceptable.
- Use standard fixation methods to preserve nucleic acid integrity. 10% neutral-buffered formalin for 6–72 hours is industry standard. DO NOT use other fixatives (Bouins, B5, AZF, Holland's).
- Do not decalcify.

☐ **SAMPLE SIZE**

1 When feasible, please send the block + 1 H&E slide.*

10 unstained slides (positively charged and unbaked at 4-5 microns thick) + 1 H&E slide.*

*For smaller samples, providing the original H&E will preserve material for testing.

☐ **SURFACE AREA**

2 **MINIMUM: 25 mm²**

If sending slides, provide 10 unstained slides cut at 4-5 microns thick to achieve a tissue volume of 1 mm³.**

**Specimens with a smaller surface area may meet volume requirements by submitting additional unstained slides (US) or block.

☐ **TUMOR CONTENT**

3 **OPTIMUM: 30% TN MINIMUM: 20% TN**

Percent tumor nuclei (%TN) = number of tumor cells divided by total number of all cells with nuclei

Note for liver specimens: higher tumor content may be required because hepatocyte nuclei have twice the DNA content of other somatic nuclei

Resection

Small Biopsy

Fine-Needle Aspiration (Cell Block)

Fluid Exfoliative Cytology (Cell Block)

Shipping Instructions

1. Place the samples, FoundationOne CDx™ requisition form, insurance information, and any other attachments into the FoundationOne CDx Specimen Shipping Kit.
2. Place the specimen shipping kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. blocks, slides) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack to:

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141
Phone: 888.988.3639

Intended Use

FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY*
Non-Small Cell Lung Cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast Cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab emtansine), or Perjeta® (pertuzumab)
Colorectal Cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3 and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix® (panitumumab)
Ovarian Cancer	*BRCA1/2* alterations	Rubraca® (rucaparib)

Reference

1. For full information on the intended use, assay descriptions, and for detailed performance specifications, refer to the complete FoundationOne CDx label at www.foundationmedicine.com/fdadx.

FOUNDATION MEDICINE®

www.foundationmedicine.com | Tel: 888.988.3639 | Fax: 617.418.2290 | MKT-0060-01

FOUNDATIONONE CDx™

PATIENT Helena Sample

TUMOR TYPE Breast invasive ductal carcinoma (IDC)

TRF# TRFXXXXXX

PATIENT

DISEASE: Breast invasive ductal carcinoma (IDC)
NAME: Not Given
DATE OF BIRTH: Not Given
SEX: Female
MEDICAL RECORD #: Not Given

PHYSICIAN

ORDERING PHYSICIAN: Not Given
MEDICAL FACILITY: Not Given
ADDITIONAL RECIPIENT: Not Given
MEDICAL FACILITY ID: Not Given
PATHOLOGIST: Not Given

SPECIMEN

SPECIMEN SITE: Not Given
SPECIMEN ID: Not Given
SPECIMEN TYPE: Not Given
DATE OF COLLECTION: Not Given
SPECIMEN RECEIVED: Not Given

CDx Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
Not detected [1]	

An ERBB2 amplification of copy number 4 was detected. While this result is considered negative by FoCDx, in a clinical concordance study with an FDA-approved FISH test, 70% (7 out of 10 samples) with copy number 4 were positive with an average ratio of 2.5, and 30% (3 out 10 samples) were negative by the FISH test. The frequency of ERBB2 with copy number 4 in breast cancer is estimated to be approximately 2%. Testing with an alternative FDA-approved companion diagnostic should be performed for confirmatory testing.

Other Alterations & Biomarkers Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for additional information.

GENOMIC FINDINGS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Clinical evidence consistent with clinical professional guidelines has been associated with biomarkers listed in this section.

MET amplification[3]

GENOMIC FINDINGS WITH POTENTIAL CLINICAL SIGNIFICANCE

Clinical significance has not been demonstrated in professional guidelines or with this test for alterations in this section.

Microsatellite status MS-Stable[3]
Tumor Mutation Burden 3 Muts/Mb[3]
C17orf39 amplification[3]
CDKN2A/B loss[3]
TOP2A amplification[3]
TP53 R248Q

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

FoundationOne CDx™ (F1CDx) is a next-generation sequencing based in vitro diagnostic device for detection of short variants, copy number alterations and select rearrangements, and genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) in targeted cancer genes and introns from formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling information for qualified cancer clinical investigations in accordance with institutional guidelines or oncology for patients with solid malignancies. The F1CDx assay is a comprehensive genomic profiling assay performed at Foundation Medicine, Inc.

TABLE 1

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exon 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exon 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib)

ABOUT THE TEST FoundationOne CDx™ is the first and only FDA approved broad companion diagnostic for solid tumors.

Electronically Signed by Julia A. Elvin, M.D., Ph.D. • Jeffrey S. Ross, M.D., Medical Director • ID November 2017
Foundation Medicine Inc. • 1-888-988-3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027331
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027331

FOUNDATIONONE CDx™

PATIENT Jane Sample

TUMOR TYPE Lung adenocarcinoma

TRF# TRFXXXXXX

PATIENT

DISEASE: Lung adenocarcinoma
NAME: Not Given
DATE OF BIRTH: Not Given
SEX: Female
MEDICAL RECORD #: Not Given

PHYSICIAN

ORDERING PHYSICIAN: Not Given
MEDICAL FACILITY: Not Given
ADDITIONAL RECIPIENT: Not Given
MEDICAL FACILITY ID: Not Given
PATHOLOGIST: Not Given

SPECIMEN

SPECIMEN SITE: Not Given
SPECIMEN ID: Not Given
SPECIMEN TYPE: Not Given
DATE OF COLLECTION: Not Given
SPECIMEN RECEIVED: Not Given

CDx Associated Findings

GENOMIC FINDINGS DETECTED		FDA-APPROVED THERAPEUTIC OPTIONS
EGFR	L858R	Gilotrif™ (Afatinib) Iressa™ (Gefitinib) Tarceva™ (Erlotinib)
	T790M[1]	Tagrisso™ (Osimertinib)

[1] *An EGFR T790M alteration was detected with an allele fraction of <5%. Clinical performance of Tagrisso® (Osimertinib) in this patient population is ongoing.*

Other Alterations & Biomarkers Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for additional information.

GENOMIC FINDINGS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Clinical evidence consistent with clinical professional guidelines has been associated with biomarkers listed in this section.

EGFR amplification[6]

KRAS G12R

GENOMIC FINDINGS WITH POTENTIAL CLINICAL SIGNIFICANCE

Clinical significance has not been demonstrated in professional guidelines or with this test for alterations in this section.

Microsatellite Status MS-Stable[2]

CDKN2A/B loss[3]

LRP1B C980*

PTCH1 T416S

RBM10 Q494*

TP53 amplification[6]

▲ POTENTIAL RESISTANCE

Individual patient response to listed therapies may vary based on genomic profile and other factors. See *professional services* section for additional information including alteration association with potential resistance.

[3] Refer to appendix for Evaluation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Examination of Clinical Significance Classification and for variants of unknown significance (VUS).

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Foundation Medicine Inc. • 1-888-988-3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531

FOUNDATIONONE CDx™

PATIENT Helena Sample

TUMOR TYPE Breast invasive ductal carcinoma (IDC)

TRF# TRFXXXXXX

PATIENT

DISEASE: Breast invasive ductal carcinoma (IDC)
NAME: Not Given
DATE OF BIRTH: Not Given
SEX: Female
MEDICAL RECORD #: Not Given

PHYSICIAN

ORDERING PHYSICIAN: Not Given
MEDICAL FACILITY: Not Given
ADDITIONAL RECIPIENT: Not Given
MEDICAL FACILITY ID: Not Given
PATHOLOGIST: Not Given

SPECIMEN

SPECIMEN SITE: Not Given
SPECIMEN ID: Not Given
SPECIMEN TYPE: Not Given
DATE OF COLLECTION: Not Given
SPECIMEN RECEIVED: Not Given

FoundationOne CDx® (F1CDx) is a next-generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion (indel), copy number alterations, and select gene rearrangements, and for genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling information for patients for whom clinical benefit is not established in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a qualitative assay performed at Foundation Medicine, Inc.

TABLE 1

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	ALK exon 19 insertions and EGFR exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	BRAF V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E or V600K	Mekinist® (trametinib) in combination with Zelboraf® (vemurafenib)
Breast cancer	ERBB2 (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab emtansine), or Perjeta® (pertuzumab)
Colorectal cancer	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild-type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	BRCA1/2 alterations	Lynparza® (olaparib)

ABOUT THE TEST FoundationOne CDx™ is the first and only FDA-approved broad companion diagnostic for solid tumors.

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Foundation Medicine Inc. • 1-888-988-3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027551
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027551

TEST PRINCIPLE

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50–1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MS) and tumor mutational burden (TMB) will be reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/fx1dx

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations
3. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
5. Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*
6. Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
7. Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
8. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer to the Summary of Safety of Effectiveness Data (SSED) for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established.
9. TMB by F1CDx is defined based on counting the total number of all synonymous and non synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. The clinical validity of TMB defined by this panel has not been established.
10. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.
11. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.

INTENDED USE

FoundationOne CDx™ (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.

INDICATION	GENOMIC FINDINGS	THERAPY
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
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	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E or V600K	**Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)**
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	***KRAS* wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild type (absence of mutations in exons 2, 3, and 4)**	Vectibix® (Panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Rubraca® (Rucaparib)

TABLE 1

The median exon coverage for this sample is 733X

APPENDIX C

KYMRIAH BLA APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125646/0

BLA APPROVAL
August 30, 2017

Novartis Pharmaceuticals Corporation
Attention: Manisha Patel, PharmD
One Health Plaza, Bldg 315, Office 3450B
East Hanover, NJ 07936

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) for tisagenlecleucel dated February 2, 2017, received February 2, 2017, submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have approved your BLA for tisagenlecleucel effective this date. You are hereby authorized to introduce, or deliver for introduction into interstate commerce, tisagenlecleucel under your existing Department of Health and Human Services U.S. License No. 1244. Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02435849, NCT02445248, NCT02228096, NCT02445222, NCT01626495, NCT01029366, NCT01747486, NCT02030847, NCT02030834 and NCT02135406.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tisagenlecleucel at your facility located at Morris Plains, New Jersey. The lentiviral vector (CTL019 (murine) HIV-1 vector) substance will be manufactured by (b) (4) and the lentiviral vector product will be manufactured by (b) (4)

You may label your product with the proprietary name KYMRIAH and market it in infusion bags containing 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight for patients 50 kg and below or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients above 50 kg, in a final volume of 10 to 50 mL.

DATING PERIOD

The dating period for tisagenlecleucel shall be 9 months from the date of manufacture when stored at ≤-120 °C in a vapor phase liquid nitrogen freezer. The date of

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

manufacture shall be defined as the date of final formulation of the drug product. The dating period for the lentiviral vector product shall be (b) (4) when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of tisagenlecleucel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of tisagenlecleucel, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft package insert labeling submitted under amendment 62, dated August 29, 2017, and the draft carton and container labeling submitted under amendment 61, dated August 28, 2017.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. All final labeling should be submitted as Product Correspondence to this BLA 125646 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm and FDA's Adverse Event Reporting System website http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125646. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "**Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher**."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

(see Section 908 of FDASIA on pages 1094-1098 which amends the FDCA by adding Section 529). Formal guidance about this program will be published in the future.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies associated with use of tisagenlecleucel.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

1. A post-marketing, prospective, multi-center, observational study to assess the long-term safety of tisagenlecleucel and the risk of all secondary malignancies occurring after treatment with tisagenlecleucel. The study will include at least 1000 pediatric and young adult patients with relapsed / refractory B cell acute lymphoblastic leukemia; the enrolled patients will be followed for 15 years after the product administration.

We acknowledge the timetable you submitted on August 28, 2017, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 8, 2017

Study Completion Date: December 31, 2037

Final Report Submission: December 31, 2038

Please submit the protocol to your IND 16130, with a cross-reference letter to this BLA 125646 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement to this BLA 125646. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIRMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of August 28, 2017 as outlined below:

2. Novartis commits to revalidate the (b) (4) test method for vector substance as specified in the validation protocol entitled "Validation of (b) (4) assay in the presence of CTL019 (DOCUMENT No: VP300808.DRAFT00)" submitted on July 19, 2017.

   Final Report Submission: June 30, 2018.

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA 125646. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our pre-approval REMS notification letter dated June 27, 2017.

Your proposed REMS, submitted on August 28, 2017, and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan for tisagenlecleucel must include, but is not limited to, the following:

REMS OPERATIONAL METRICS

(1) For the first (6 month) assessment only:

Provide the following information on KYMRIAH REMS Program Implementation

a. Date KYMRIAH REMS website went live
b. Date REMS Call Center operational
c. Date hospitals were able to complete REMS certification process
d. Date of first notification of hospital certification
e. Number of hospitals that were trained by Novartis prior to August 1, 2017.

(2) For the 12-month and subsequent annual assessments:

KYMRIAH REMS Program Infrastructure and Performance (provide in tabular format as appropriate)

a. Hospital enrollment and education statistics
    i. List of all enrolled hospital sites, location, date of enrollment, and method (e.g., online, fax) of enrollment and date of certification notification
    ii. Number of incomplete enrollments at the time of assessment data lock
    iii. Number and date and format (live, webcast) of training on KYMRIAH REMS
    iv. Number of knowledge assessments completed by hospital personnel other than the authorized representative, by certified hospital.

v. Mean and range of attempts to successfully complete knowledge assessment
vi. Summary of most frequently missed questions

b. Utilization
   i. Number and age of patients treated with KYMRIAH; provide number treated at each certified hospital
   ii. Number and age of patients for which KYMRIAH was ordered but never infused and the reason(s) that the patient was not treated; provide number of occurrences at each certified hospital for each reporting period and cumulatively
   iii. Time between certification and first order for KYMRIAH for each hospital

c. Compliance with KYMRIAH REMS program
   i. Number and name of non-certified hospitals that have treated a patient with KYMRIAH and any corrective actions taken to prevent future occurrences (e.g., provision of REMS Training slides, REMS Hospital Certification form) and the number of these that subsequently became certified.
   ii. Audits
      1. A summary of findings from first order audits and annual audits and any action taken and outcome of actions to prevent future occurrences
   iii. Summary of monitoring findings for monitoring conducted during the reporting period by hospital, including any corrective and preventative actions (CAPA)
   iv. Any additional non-compliance, source of report, resulting corrective and preventative actions.

d. KYMRIAH REMS Program Call center
   i. Number of contacts by stakeholder type (patient/parent/legal guardian, prescriber, hospital authorized representative, other HCP, other)
   ii. Summary of frequently asked questions (FAQ) by stakeholder type.
   iii. Summary of any non-compliance that is identified through call center contacts, source of report and resulting corrective and preventative actions.

KNOWLEDGE, ATTITUDES, AND BEHAVIOR SURVEYS

Knowledge, Attitudes, and Behavior (KAB) surveys will be conducted with those who prescribe, dispense, or administer KYMRIAH as well as hospital authorized representatives, in order to assess their awareness and understanding of the risks of KYMRIAH and the mitigation strategies as outlined in the REMS goals and objectives.

The methodology and the knowledge, attitudes, and behavior (KAB) protocols and survey instruments should be submitted to the Agency for review at least 90 days before the surveys are initially administered.

With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or

whether one or more such goals or such elements should be modified (Section 505-1(g)(3)).

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS.
g) *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at

least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125646 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125646 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125646
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125646
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125646
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT [125646/####]

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125646 REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 125646

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-APPROVAL FEEDBACK MEETING

New biological products qualify for a post-approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely yours,

Wilson W. Bryan, M.D.
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

ENCLOSURE:
REMS

APPENDIX D

KYMRIAH LABEL


tisagenlecleucel
KYMRIAH®
NDC 0078-0958-19
Human T cells Rx only
Suspension for IV infusion
Cultured, genetically modified
For autologous use only
Target Total Volume 10mL-50mL per bag
Dispense with Medication Guide
Dosage: See prescribing information. Dose may be suspended in 1 to 3 infusion bag(s)
Contains 0.6 x 10^8 to 6.0 x 10^8 CAR-positive viable T cells
Cryopreserved in: 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 20% (v/v) of 25% HSA, 10% (v/v) of 10% Dextran 40 (LMD)/5% Dextrose and 7.5% (v/v) DMSO
Store at ≤-120°C; see prescribing information
Properly identify intended recipient and product
Do not use leukocyte depleting filter
Do not irradiate
Not evaluated for infectious substances
Mfd. by: Novartis Pharmaceuticals Corporation
Morris Plains, NJ 07950
U.S. License # 1244 KYMRIAH.com
1-844-4KYMRIAH (1-844-459-6742)
NOVARTIS 92468US © Novartis
For Novartis use only

APPENDIX E

F1CDX SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Next generation sequencing oncology panel, somatic or germline variant detection system
Device Trade Name:	FoundationOne®CDx (F1CDx)
Device Procode:	PQP
Applicant's Name and Address:	Foundation Medicine, Inc. 150 Second Street Cambridge, MA 02141
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P170019/S016
Date of FDA Notice of Approval:	June 16, 2020

The original PMA (P170019) for FoundationOne®CDx (F1CDx) was approved on November 30, 2017 for the detection of genetic alterations in patients who may benefit from one of fifteen FDA-approved therapies for non-small cell lung cancer (NSCLC), melanoma, breast cancer, colorectal cancer, and ovarian cancer. Subsequently, eight PMA supplements were approved for expanding the indications for use of F1CDx since its original approval. PMA supplement (P170019/S005) for adding genomic loss of heterozygosity (LOH) was approved on April 10, 2019. PMA supplement (P170019/S004) for adding an indication for LYNPARZA® (olaparib) in ovarian cancer patients with *BRCA1/2* alterations was approved on July 1, 2019. PMA supplement (P170019/S008) for adding an indication for TAGRISSO® (osimertinib) in NSCLC patients with *EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations was approved on July 1, 2019. PMA supplement (P170019/S006) for adding an indication for PIQRAY® (alpelisib) in breast cancer patients with *PIK3CA* alterations was approved on December 3, 2019. PMA supplement (P170019/S010) for adding a second site in Research Triangle Park, NC, where the F1CDx assay will be performed, was approved on December 16, 2019. PMA supplement (P170019/S013) for adding an indication for PEMZYRE® (pemigatinib) in cholangiocarcinoma patients with *FGFR2* fusions was approved on April 17, 2020. PMA supplement (P170019/S011) for adding an indication for TABRECTA® (capmatinib) in NSCLC patients with *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping was approved on May 6, 2020. PMA supplement (P170019/S015) for adding an indication for LYNPARZA® (olaparib) in metastatic castration resistant prostate cancer (mCRPC) patients with mutations in homologous recombination repair (HRR) genes was approved on May 19, 2020.

The current supplement was submitted to expand the intended use of F1CDx to include a companion diagnostic indication for high tumor mutational burden (TMB) at the cut-off of 10 mutations per megabase (mut/Mb) in patients with solid tumors who may benefit from treatment with KEYTRUDA® (pembrolizumab).

II. INDICATIONS FOR USE

FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), Tagrisso® (osimertinib), or Tarceva® (erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (osimertinib)
	ALK rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	BRAF V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta™ (capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	BRAF V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib) in combination with Zelboraf® (vemurafenib)

Indication	Biomarker	Therapy
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab emtansine), or Perjeta® (pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3, and 4)	Vectibix® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (olaparib) or Rubraca® (rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (pemigatinib)
Prostate cancer	Homologous Recombination Repair (HRR) gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*) alterations	Lynparza® (olaparib)
Solid tumors	TMB ≥ 10 mutations per megabase	Keytruda® (pembrolizumab)

The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the Rubraca product label.

The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the FoundationOne®CDx assay labeling.

V. DEVICE DESCRIPTION

FoundationOne®CDx (F1CDx) is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC. The assay includes reagents, software, instruments and procedures for testing DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples.

The assay employs a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which undergoes whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, 1 promoter region, 1 non-coding RNA (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons (refer to Table 2 and Table 3, below, for the complete list of genes included in F1CDx). In total, the assay therefore detects alterations in 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid-capture selected libraries are sequenced to high uniform depth (targeting > 500X median coverage with > 99% of exons at coverage > 100X). Sequence data are processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) will be reported.

Table 2. Genes with full coding exonic regions included in F1CDx for the detection of substitutions, insertions and deletions (indels), and copy number alterations (CNAs)

ABL1	*BRAF*	*CDKN1A*	*EPHA3*	*FGFR4*	*IKZF1*	*MCL1*	*NKX2-1*	*PMS2*	*RNF43*	*TET2*
ACVR1B	*BRCA1*	*CDKN1B*	*EPHB1*	*FH*	*INPP4B*	*MDM2*	*NOTCH1*	*POLD1*	*ROS1*	*TGFBR2*
AKT1	*BRCA2*	*CDKN2A*	*EPHB4*	*FLCN*	*IRF2*	*MDM4*	*NOTCH2*	*POLE*	*RPTOR*	*TIPARP*
AKT2	*BRD4*	*CDKN2B*	*ERBB2*	*FLT1*	*IRF4*	*MED12*	*NOTCH3*	*PPARG*	*SDHA*	*TNFAIP3*
AKT3	*BRIP1*	*CDKN2C*	*ERBB3*	*FLT3*	*IRS2*	*MEF2B*	*NPM1*	*PPP2R1A*	*SDHB*	*TNFRSF14*
ALK	*BTG1*	*CEBPA*	*ERBB4*	*FOXL2*	*JAK1*	*MEN1*	*NRAS*	*PPP2R2A*	*SDHC*	*TP53*
ALOX12B	*BTG2*	*CHEK1*	*ERCC4*	*FUBP1*	*JAK2*	*MERTK*	*NT5C2*	*PRDM1*	*SDHD*	*TSC1*
AMER1	*BTK*	*CHEK2*	*ERG*	*GABRA6*	*JAK3*	*MET*	*NTRK1*	*PRKAR1A*	*SETD2*	*TSC2*
APC	*C11orf30*	*CIC*	*ERRFI1*	*GATA3*	*JUN*	*MITF*	*NTRK2*	*PRKCI*	*SF3B1*	*TYRO3*
AR	*CALR*	*CREBBP*	*ESR1*	*GATA4*	*KDM5A*	*MKNK1*	*NTRK3*	*PTCH1*	*SGK1*	*U2AF1*
ARAF	*CARD11*	*CRKL*	*EZH2*	*GATA6*	*KDM5C*	*MLH1*	*P2RY8*	*PTEN*	*SMAD2*	*VEGFA*
ARFRP1	*CASP8*	*CSF1R*	*FAM46C*	*GID4 (C17orf39)*	*KDM6A*	*MPL*	*PALB2*	*PTPN11*	*SMAD4*	*VHL*
ARID1A	*CBFB*	*CSF3R*	*FANCA*	*GNA11*	*KDR*	*MRE11A*	*PARK2*	*PTPRO*	*SMARCA4*	*WHSC1*
ASXL1	*CBL*	*CTCF*	*FANCC*	*GNA13*	*KEAP1*	*MSH2*	*PARP1*	*QKI*	*SMARCB1*	*WHSC1L1*
ATM	*CCND1*	*CTNNA1*	*FANCG*	*GNAQ*	*KEL*	*MSH3*	*PARP2*	*RAC1*	*SMO*	*WT1*
ATR	*CCND2*	*CTNNB1*	*FANCL*	*GNAS*	*KIT*	*MSH6*	*PARP3*	*RAD21*	*SNCAIP*	*XPO1*

ATRX	*CCND3*	*CUL3*	*FAS*	*GRM3*	*KLHL6*	*MST1R*	*PAX5*	*RAD51*	*SOCS1*	*XRCC2*
AURKA	*CCNE1*	*CUL4A*	*FBXW7*	*GSK3B*	*KMT2A (MLL)*	*MTAP*	*PBRM1*	*RAD51B*	*SOX2*	*ZNF217*
AURKB	*CD22*	*CXCR4*	*FGF10*	*H3F3A*	*KMT2D (MLL2)*	*MTOR*	*PDCD1*	*RAD51C*	*SOX9*	*ZNF703*
AXIN1	*CD274*	*CYP17A1*	*FGF12*	*HDAC1*	*KRAS*	*MUTYH*	*PDCD1LG2*	*RAD51D*	*SPEN*	
AXL	*CD70*	*DAXX*	*FGF14*	*HGF*	*LTK*	*MYC*	*PDGFRA*	*RAD52*	*SPOP*	
BAP1	*CD79A*	*DDR1*	*FGF19*	*HNF1A*	*LYN*	*MYCL*	*PDGFRB*	*RAD54L*	*SRC*	
BARD1	*CD79B*	*DDR2*	*FGF23*	*HRAS*	*MAF*	*MYCN*	*PDK1*	*RAF1*	*STAG2*	
BCL2	*CDC73*	*DIS3*	*FGF3*	*HSD3B1*	*MAP2K1*	*MYD88*	*PIK3C2B*	*RARA*	*STAT3*	
BCL2L1	*CDH1*	*DNMT3A*	*FGF4*	*ID3*	*MAP2K2*	*NBN*	*PIK3C2G*	*RB1*	*STK11*	
BCL2L2	*CDK12*	*DOT1L*	*FGF6*	*IDH1*	*MAP2K4*	*NF1*	*PIK3CA*	*RBM10*	*SUFU*	
BCL6	*CDK4*	*EED*	*FGFR1*	*IDH2*	*MAP3K1*	*NF2*	*PIK3CB*	*REL*	*SYK*	
BCOR	*CDK6*	*EGFR*	*FGFR2*	*IGF1R*	*MAP3K13*	*NFE2L2*	*PIK3R1*	*RET*	*TBX3*	
BCORL1	*CDK8*	*EP300*	*FGFR3*	*IKBKE*	*MAPK1*	*NFKBIA*	*PIM1*	*RICTOR*	*TEK*	

Table 3. Genes with select intronic regions for the detection of gene rearrangements, a promoter region, and an ncRNA gene

ALK introns 18, 19	*BRCA1 introns 2, 7, 8, 12, 16, 19, 20*	*ETV4 introns 5, 6*	*EZR introns 9-11*	*KIT intron 16*	*MYC intron 1*	*NUTM1 intron 1*	*RET introns 7-11*	*SLC34A2 intron 4*
BCL2 3'UTR	*BRCA2 intron 2*	*ETV5 introns 6, 7*	*FGFR1 intron 1, 5, 17*	*KMT2A (MLL) introns 6-11*	*NOTCH2 intron 26*	*PDGFRA introns 7, 9, 11*	*ROS1 introns 31-35*	*TERC ncRNA*
BCR introns 8, 13, 14	*CD74 introns 6-8*	*ETV6 introns 5, 6*	*FGFR2 intron 1, 17*	*MSH2 intron 5*	*NTRK1 introns 8-10*	*RAF1 introns 4-8*	*RSPO2 intron 1*	*TERT Promoter*
BRAF introns 7-10	*EGFR introns 7, 15, 24-27*	*EWSR1 introns 7-13*	*FGFR3 intron 17*	*MYB intron 14*	*NTRK2 Intron 12*	*RARA intron 2*	*SDC4 intron 2*	*TMPRSS2 introns 1-3*

Test Output

The output of the test includes:

Category 1: CDx Claims noted in Table 1 of the Intended Use

Category 2: Cancer Mutations with Evidence of Clinical Significance

Category 3: Cancer Mutations with Potential Clinical Significance

Genomic findings other than those listed in Table 1 of the intended use statement (i.e., Categories 2 and 3) are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Test Kit Contents

The test includes a sample shipping kit, which is sent to ordering laboratories. The shipping kit contains the following components:

- Specimen Preparation Instructions
- Shipping Instructions
- Return Shipping Label

Instruments

The F1CDx assay is intended to be performed with serial number-controlled instruments as indicated in Table 4, below. All instruments are qualified by Foundation Medicine, Inc. (FMI) under FMI's Quality System.

Table 4. Instruments for use with the F1CDx assay

Instrument
Illumina® HiSeq 4000
Illumina cBot® System
Agilent Technologies Benchbot Workstation with Integrated Bravo Automated Liquid Handler
Beckman Biomek NX^P Span-8 Liquid Handler
Hamilton Microlab STAR/STARlet Liquid Handling Workstation
Thermo Fisher Scientific KingFisher™ Flex with 96 Deep-well Head
Covaris LE220-Plus Focused-ultrasonicator

Test Process

All assay reagents included in the F1CDx assay process are qualified by FMI and are compliant with the medical device Quality System Regulation (QSR).

A. Specimen Collection and Preparation

Formalin-fixed, paraffin-embedded (FFPE) tumor specimens are collected and prepared following standard pathology practices. FFPE specimens may be received either as unstained slides or as an FFPE block.

Prior to starting the assay, a Hematoxylin and Eosin (H&E) stained slide is prepared, and then reviewed by a board-certified pathologist to confirm disease ontology and to ensure that adequate tissue (≥ 0.6 mm^3), tumor content (≥ 20% tumor), and sufficient nucleated cells are present to proceed with the assay.

B. DNA Extraction

Specimens passing pathology review are queued for DNA extraction which begins with lysis of cells from FFPE tissue by digestion with a proteinase K buffer followed by automated purification using the 96-well KingFisher™ Flex Magnetic Particle Processor.

After completion of DNA extraction, double-stranded DNA (dsDNA) is quantified by the Quant-iT™ PicoGreen® fluorescence assay using the provided lambda DNA standards (Invitrogen) prior to Library Construction (LC). The sample must yield a minimum of 55 ng of genomic DNA to ensure sufficient DNA for quality control (QC) and to proceed with LC.

C. Library Construction

Library Construction (LC) begins with normalization of DNA to 50-1000 ng. Normalized DNA samples are randomly sheared (fragmented) to ~200 bp by adaptive focused acoustic sonication using the Covaris LE220-Plus before purification with a 1.8X volume of AMPure® XP Beads (Agencourt®). Solid-phase reversible immobilization (SPRI) purification and subsequent library construction with the NEBNext® reagents (custom-filled kits by NEB), including mixes for end repair, dA addition and ligation, are performed in 96-well plates (Eppendorf) on the Bravo Benchbot (Agilent) or Microlab STAR (Hamilton) using the "with-bead" protocol[1] to maximize reproducibility and library yield. Indexed (6 bp barcodes) sequencing libraries are PCR amplified with HiFi™ (Kapa) for 10 cycles and subsequently 1.8X SPRI purified. Purification and dilution for QC are performed.

Following LC, a QC procedure is performed by quantifying single-stranded DNA (ssDNA) from purified libraries using the Quant-iT™ OliGreen® ssDNA Assay Kit (Life Technologies) read on a Molecular Devices Multimode SpectraMax M2 plate Reader. Libraries yielding insufficient sequencing library are failed.

D. Hybrid Capture

Hybrid Capture (HC) begins with normalization of each library to 500–2000 ng. Normalized samples then undergo solution hybridization which is performed using a > 50-fold molar excess of a pool of individually synthesized 5'-biotinylated DNA 120 bp oligonucleotides. The baits target ~1.8 Mb of the human genome including all coding exons of 309 cancer-related genes, introns or non-coding regions of 35 genes, plus > 3,500 single nucleotide polymorphisms (SNPs) located throughout the genome. Baits are designed by tiling overlapping 120 bp DNA sequence intervals covering target exons (60 bp overlap) and introns (20 bp overlap), with a minimum of three baits per target; SNP targets are allocated one bait each. Intronic baits are filtered for repetitive elements[2] as defined by the UCSC Genome RepeatMasker track.

After hybridization, the library-bait duplexes are captured on paramagnetic MyOne™ streptavidin beads (Invitrogen), and off-target material is removed by washing one time with 1X SSC at 25°C and four times with 0.25X SSC at 55°C. The PCR master mix is added to directly amplify (12 cycles) the captured library from the washed beads.[3] After 12 cycles of amplification, the samples are 1.8X SPRI purified. Purification and dilution for QC are performed.

QC for HC is performed by measuring dsDNA yield using the Quant-iT™ PicoGreen® dsDNA Assay Kit (Life Technologies) read on a Molecular Devices

Multimode SpectraMax M2 plate Reader. Captured libraries yielding less than 140 ng of sequencing library are failed.

E. Sequencing

Sequencing is performed using off-board clustering on the Illumina cBot with patterned flow cell technology to generate monoclonal clusters from a single DNA template followed by sequencing using sequencing by synthesis (SBS) chemistry on the Illumina HiSeq 4000. Fluorescently labeled 3'-blocked dNTPs along with a polymerase are incorporated through the flow cell to create a growing nucleotide chain that is excited by a laser. A camera captures the emission color of the incorporated base and then is cleaved off. The terminator is then removed to allow the nucleotide to revert to its natural form and to allow the polymerase to add another base to the growing chain. A new pool of fluorescently labeled 3'-blocked dNTPs are added with each new sequencing cycle. The color changes for each new cycle as a new base is added to the growing chain. This method allows for millions of discrete clusters of clonal copies of DNA to be sequenced in parallel.

F. Sequence Analysis

Sequence data are analyzed using proprietary software developed by FMI. Sequence data are mapped to the human genome (hg19) using Burrows-Wheeler Aligner (BWA) v0.5.9.[4] PCR duplicate read removal and sequence metric collection are performed using Picard 1.47 (http://picard.sourceforge.net) and SAMtools 0.1.12a.[5] Local alignment optimization is performed using Genome Analysis Toolkit (GATK) 1.0.4705.[6] Variant calling is performed only in genomic regions targeted by the test.

Base substitution detection is performed using a Bayesian methodology, which allows for the detection of novel somatic alterations at low mutant allele frequency (MAF) and increased sensitivity for alterations at hotspot sites through the incorporation of tissue-specific prior expectations.[7] Reads with low mapping (mapping quality < 25) or base calling quality (base calls with quality ≤ 2) are discarded. Final calls are made at MAF ≥ 5% (MAF ≥ 1% at hotspots).

To detect indels, *de novo* local assembly in each targeted exon is performed using the de-Bruijn approach.[8] Key steps are:

- Collecting all read-pairs for which at least one read maps to the target region.
- Decomposing each read into constituent k-mers and constructing an enumerable graph representation (de-Bruijn) of all candidate non-reference haplotypes present.
- Evaluating the support of each alternate haplotype with respect to the raw read data to generate mutational candidates. All reads are compared to each of the candidate haplotypes via ungapped alignment, and a read 'vote' for each read is assigned to the candidate with best match. Ties between candidates are resolved by splitting the read vote, weighted by the number of reads already supporting each haplotype. This process is iterated until a 'winning' haplotype is selected.
- Aligning candidates against the reference genome to report alteration calls.

Filtering of indel candidates is carried out similarly to base substitutions, with an empirically increased allele frequency threshold at repeats and adjacent sequence quality metrics as implemented in GATK: % of neighboring bases mismatches < 25%, average neighboring base quality > 25, average number of supporting read mismatches ≤ 2. Final calls are made at MAF ≥ 5% (MAF ≥ 3% at hotspots).

Copy number alterations (CNAs) are detected using a comparative genomic hybridization (CGH)-like method. First, a log-ratio profile of the sample is acquired by normalizing the sequence coverage obtained at all exons and genome-wide SNPs (~3,500) against a process-matched normal control. This profile is segmented and interpreted using allele frequencies of sequenced SNPs to estimate tumor purity and copy number at each segment. Amplifications are called at segments with ≥ 6 copies (or ≥ 7 for triploid/≥ 8 for tetraploid tumors) and homozygous deletions at 0 copies, in samples with tumor purity ≥ 20%. Amplifications in *ERBB2* are called positive at segments with ≥ 5 copies for diploid tumors.

Genomic rearrangements are identified by analyzing chimeric read pairs. Chimeric read pairs are defined as read pairs for which reads map to separate chromosomes, or at a distance of over 10 megabase (Mb). Pairs are clustered by genomic coordinate of the pairs, and clusters containing at least five chimeric pairs (three for known fusions) are identified as rearrangement candidates. Filtering of candidates is performed by mapping quality (average read mapping quality in the cluster must be 30 or above) and distribution of alignment positions. Rearrangements are annotated for predicted function (e.g., creation of fusion gene).

To determine microsatellite instability (MSI) status, 95 intronic homopolymer repeat loci (10-20 bp long in the human reference genome) with adequate coverage on the F1CDx assay are analyzed for length variability and compiled into an overall MSI score via principal components analysis (PCA). Using the 95 loci, for each sample the repeat length is calculated in each read that spans the locus. The means and variances of repeat lengths are recorded. PCA is used to project the 190-dimension data onto a single dimension (the first principal component) that maximizes the data separation, producing an MSI score. Each sample is assigned a qualitative status of MSI-High (MSI-H) or MSI-Stable (MSS); ranges of the MSI score are assigned MSI-H or MSS by manual unsupervised clustering. Samples with low coverage (< 250X median) are assigned a status of MSI-unknown.

Tumor mutational burden (TMB) is measured by counting all synonymous and non-synonymous substitution and indel variants present at 5% allele frequency or greater and filtering out potential germline variants according to published databases of known germline polymorphisms including Single Nucleotide Polymorphism database (dbSNP) and Exome Aggregation Consortium (ExAC). Additional germline alterations still present after database querying are assessed for potential germline status and filtered out using a somatic-germline/zygosity (SGZ) algorithm. Furthermore, known and likely driver mutations are filtered out to exclude bias of the data set. The resulting mutation number is then divided by the coding region

corresponding to the number of total variants counted, or 793 kb. The resulting number is communicated as mutations per Mb unit (mut/Mb).

After completion of the Analysis Pipeline, variant data are displayed in the FMI custom-developed CATi software applications with sequence QC metrics. As part of data analysis QC for every sample, the F1CDx assay assesses cross-contamination through the use of a SNP profile algorithm, reducing the risk of false-positive calls that could occur as a result of an unexpected contamination event. Sequence data are reviewed by trained bioinformatics personnel. Samples failing any QC metrics are automatically held and not released.

G. Report Generation

Approved results are annotated by automated software with CDx relevant information and are merged with patient demographic information and any additional information provided by FMI as a professional service prior to approval and release by the laboratory director or designee.

H. Internal Process Controls Related to the System

Positive Control

Each assay run includes a control sample run in duplicate. The control sample contains a pool of ten HapMap cell lines and is used as a positive mutation detection control. 100 different germline SNPs present across the entire targeted region are required to be detected by the analysis pipeline. If SNPs are not detected as expected, this results in a QC failure, as it indicates a potential processing error.

Sensitivity Control

The HapMap control pool used as the positive control is prepared to contain variants at 5%-10% MAF which must be detected by the analysis pipeline to ensure the expected sensitivity for each run.

Negative Control

Samples are barcoded molecularly at the LC stage. Only reads with a perfect molecular barcode sequence are incorporated into the analysis. The Analysis Pipeline includes an algorithm that analyzes the SNP profile of each specimen to identify potential contamination that may have occurred prior to molecular barcoding and can detect contamination lower than 1%.

I. Variant Classification

Biomarker Rules for SNVs and indels that lead to *MET* exon 14 skipping

An SNV or indel in *MET* shall be considered to result in skipping of exon 14 if one or more of the following criteria are met:

1. Deletions greater than or equal to 5 bp that affect positions -3 to -30 in the intronic region immediately adjacent to the splice acceptor site at the 5′ boundary of *MET* exon 14.

2. Indels affecting positions -1 or -2 at the splice acceptor site of the 5' boundary of *MET* exon 14.
3. Base substitutions and indels affecting positions 0, +1, +2, or +3 at the splice donor site of the 3' boundary of *MET* exon 14.

Homologous Recombination Repair (HRR) Genes

A clinical report is provided to the ordering physician for each F1CDx test performed at Foundation Medicine, Inc. Each report is generated and reviewed by an internal team consisting of clinical bioinformatics analysts, scientists, curators, and pathologists for mutations positive for the therapies identified. Each sample is assessed for mutations in the 14 HRR genes, *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L* (Table 5). For these genes, both deleterious and suspected deleterious mutations in short variant, copy number alteration, and rearrangement variant classes are determined by an in-house software pipeline. Alterations listed in the COSMIC database and homozygous deletions are considered deleterious. Suspected deleterious mutations include truncating events (i.e., splice, frameshift, and nonsense alterations), as well as large rearrangements that disrupt the coding sequence. The COSMIC check is a second layer of check for HRR positive suspected deleterious alterations. All splice, nonsense, and frameshift alterations in HRR genes are considered biomarker positive and would be considered as suspected deleterious mutations (or "likely" status in FMI reporting rules). If these mutations are additionally reported in COSMIC, they would be listed as deleterious mutations (or "known" status in FMI reporting).

The F1CDx assay is intended as an aid in selecting prostate cancer patients with deleterious or suspected deleterious HRR variants, identified by the rules below, and who may be eligible for treatment with Lynparza® (olaparib).

Table 5. Mutation types identified in the HRR genes

Variant Class	Alteration type	Description*
Short Variant	Nonsense, frameshift, or splice site	Any deleterious nonsense, frameshift, or splicing event that spans or occurs within ±2 bases of the intron/exon junction
	Missense or non-frameshift	Any of the mutations listed in Table 6 for *ATM*, *BRCA1*, and *BRCA2*
Copy Number Alteration	Homozygous copy number loss	Deleterious homozygous copy number loss of one or more exons
Rearrangement	Rearrangement	Any rearrangement that disrupts protein function

*For *BRCA2*, truncating mutations must occur upstream of bases encoding amino acid 3326. Additionally, the frameshift mutation T367fs*13 in *FANCL* is ineligible. All short variants must occur in the canonical transcript.

The specific deleterious mutation (DM) and suspected deleterious mutation (SDM) missense mutations or non-frameshift mutations for *BRCA1*, *BRCA2*, and *ATM* are shown in Table 6, below. However, any missense or non-frameshift mutations in the other 12 genes would not be considered HRR positive.

Table 6. Eligible deleterious mutations in the *ATM*, *BRCA1*, and *BRCA2* genes

ATM	*BRCA1*	*BRCA2*
M1T	M1V	M1R
R2032K	M1I	M1I
R2227C	C61G	V159M
R2547_S2549del	C64Y	V211L
G2765S	R71G	V211I
R2832C	R71K	R2336P
S2855_V2856delinsRI (annotated as S2855_V2856>RI)	R1495M	R2336H
R3008C	E1559K	
R3008H	D1692N	
8418+5_8418+8delGTGA or 8418+1_8418+4delGTGA	D1692H	
	R1699W	
	A1708E	
	G1788V	

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are FDA-approved companion diagnostic (CDx) alternatives for the detection of genetic alterations using FFPE tumor specimens, as listed in Table 1 of the F1CDx intended use statement. The approved CDx tests are listed in Table 7, below; for additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Each alternative has its own advantages and disadvantages. Physicians should consider the best method that suits their patients and that best meets their expectations.

Table 7. List of FDA approved CDx assays for genes targeted by F1CDx

	Device	Company	Technology	Therapy	Indication
HER2-Amplification	PathVysion HER-2 DNA Probe Kit	Abbott Molecular, Inc.	FISH	HERCEPTIN (trastuzumab)	Breast cancer
	PATHWAY Anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody	Ventana Medical Systems, Inc.	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	InSite HER-2/neu Kit	Biogenex Laboratories, Inc.	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	SPOT-Light HER2 CISH Kit	Life Technologies, Inc.	CISH	HERCEPTIN (trastuzumab)	Breast cancer
	Bond Oracle HER2 IHC System	Leica Biosystems	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	HER2 CISH pharmDx Kit	Dako Denmark A/S	CISH	HERCEPTIN (trastuzumab)	Breast cancer
	INFORM HER2 Dual ISH DNA Probe Cocktail	Ventana Medical Systems, Inc.	Dual ISH	HERCEPTIN (trastuzumab)	Breast cancer
	HercepTest	Dako Denmark A/S	IHC	HERCEPTIN (trastuzumab) PERJETA (pertuzumab) KADCYLA (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
	HER2 FISH pharmDx Kit	Dako Denmark A/S	FISH	HERCEPTIN (trastuzumab) PERJETA (pertuzumab) KADCYLA (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
BRAF-V600E and V600K	THxID BRAF Kit	bioMerieux	PCR	MEKINIST (tramatenib)	Melanoma
	cobas 4800 BRAF V600 Mutation Test	Roche Molecular Systems, Inc.	PCR	COTELLIC (cobimetinib) ZELBORAF (vemurafenib)	Melanoma
BRAF-V600E	cobas 4800 BRAF V600 Mutation Test	Roche Molecular Systems, Inc.	PCR	ZELBORAF (vemurafenib)	Melanoma
	THxID BRAF Kit	bioMerieux	PCR	TAFINLAR (dabrafenib)	Melanoma

	Device	Company	Technology	Therapy	Indication
BRAF-V600E	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	TAFINLAR (dabrafenib) MEKINIST (trametinib)	NSCLC
	therascreen BRAF V600E RGQ PCR Kit	QIAGEN	PCR	BRAFTOVI (encorafenib) Erbitux (cetuximab)	Colorectal cancer
NRAS	Praxis Extended RAS Panel	Illumina, Inc.	NGS	VECTIBIX (panitumumab)	Colorectal cancer
KRAS	**cobas** KRAS Mutation Test	Roche Molecular Systems, Inc.	PCR	ERBITUX (cetuximab) VECTIBIX (panitumumab)	Colorectal cancer
	therascreen KRAS RGQ PCR Kit	QIAGEN	PCR	ERBITUX (cetuximab) VECTIBIX (panitumumab)	Colorectal cancer
	Praxis Extended RAS Panel	Illumina, Inc.	NGS	VECTIBIX (panitumumab)	Colorectal cancer
ALK – fusion	Vysis ALK Break Apart FISH Probe Kit	Abbott Molecular, Inc.	FISH	XALKORI (crizotinib)	NSCLC
	ALK (D5F3) CDx Assay	Ventana Medical Systems, Inc.	IHC	XALKORI (crizotinib)	NSCLC
EGFR – Exon 19 deletions & L858R	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	TARCEVA (erlotinib) TAGRISSO (osimertinib) IRESSA (gefitinib)	NSCLC
	therascreen EGFR RGQ PCR Kit	QIAGEN	PCR	GILOTRIF (afatinib) IRESSA (gefitinib)	NSCLC
	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	IRESSA (gefitinib)	NSCLC
EGFR T790M	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	TAGRISSO (osimertinib)	NSCLC
BRCA1/2	FoundationFocus CDx$_{BRCA}$	Foundation Medicine, Inc.	NGS	RUBRACA (rucaparib)	Advanced ovarian cancer

	Device	Company	Technology	Therapy	Indication
PIK3CA	*therascreen* PIK3CA RGQ PCR Kit	QIAGEN	PCR	PIQRAY (alpelisib)	Breast cancer

Abbreviations: FISH – fluorescence *in situ* hybridization; IHC – immunohistochemistry; CISH – chromogenic *in situ* hybridization; ISH – *in situ* hybridization; PCR – polymerase chain reaction; NGS – next generation sequencing.

VII. MARKETING HISTORY

Foundation Medicine, Inc. initially designed and developed the FoundationOne® laboratory developed test (F1 LDT), and the first commercial sample was tested in 2012. The F1 LDT has been used to detect the presence of genomic alterations in FFPE tumor tissue specimens. The F1 LDT is not FDA-cleared or -approved.

The F1CDx Premarket Approval (PMA) was originally approved on November 30, 2017 by FDA (P170019) and is commercially available in the U.S. since March 30, 2018. The following PMA supplements affecting the Intended Use were approved by FDA.

- P170019/S005 was approved on April 10, 2019.
- P170019/S004 and P170019/S008 were approved on July 1, 2019.
- P170019/S009 was approved on August 21, 2019.
- P170019/S006 was approved on December 3, 2019.
- P170019/S010 was approved on December 16, 2019.
- P170019/S013 was approved on April 17, 2020.
- P170019/S011 was approved on May 6, 2020.
- P170019/S015 was approved on May 19, 2020.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results and, subsequently, inappropriate patient management decisions. Patients with false positive results may undergo treatment with one of the therapies listed in the above intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy. For the specific adverse events related to the approved therapeutics, please see the approved drug product labels.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The performance of F1CDx in detecting high TMB (TMB-H) as a qualitative pan tumor biomarker with respect to the 10 mut/Mb cut-off is supported by the data

presented using a broad range of tumor specimens across all validation studies. Over 400 unique samples comprising over 200 disease ontologies, including the rare cancers enrolled in the clinical validation study (please refer to Section X), were included in the analytical validation for TMB as a pan tumor biomarker. Samples had TMB scores ranging from 0 to 375 mut/Mb across a spectrum of tumor purities, from 4.8% to 99.9% (please refer to Section IX.A.2(a), below, for information on the detection limits of the TMB biomarker), as well as sufficient pre-analytical (e.g., percent tumor nuclei, DNA input) and post-sequencing (e.g., tumor purity, ≥ 100X coverage, median coverage) QC metrics to support robust F1CDx TMB calling across the intended use population. Analytical accuracy/concordance, limit of detection (LoD), and precision studies as well as analyses of DNA extraction and interfering substances data were conducted to support the indication for TMB as a pan tumor biomarker at the cut-off of ≥ 10 mut/Mb for TMB-H tumors.

For the F1CDx platform validation (P170019), device performance characteristics were established using DNA derived from a wide range of FFPE tissue types, and tissue types associated with CDx indications were included in each study. Each study included CDx variants as well as a broad range of representative alteration types, including substitution and insertion and deletion variants, in various genomic contexts across several genes. Analyses of genomic signatures including MSI and TMB were also conducted. TMB was previously analyzed as a score in mutations per megabase (mut/Mb) to support tumor profiling for the F1CDx platform (P170019). Results from the platform-level validation (P170019) have been leveraged, including precision, interfering substances, and DNA extraction studies, to support F1CDx detection of TMB as a qualitative biomarker with respect to the 10 mut/Mb cut-off for TMB-H samples. A post-market study will be conducted to support quantitative TMB score reporting for the CDx biomarker. For information regarding the F1CDx platform-level validation, please see Summary of Safety and Effectiveness Data P170019.

1. **Analytical Accuracy/Concordance**
   a. **Comparison to Whole Exome Sequencing for TMB Calling**

      An analytical accuracy study was performed to demonstrate the concordance between F1CDx and an externally validated whole exome sequencing (WES) assay for the detection of TMB-H as a qualitative biomarker. The WES assay sequenced matched tumor-normal samples to determine germline mutations in sample pairs, and germline mutations were filtered from the tumor sample results prior to the TMB calculation. The WES TMB algorithm included a variant calling threshold of 5% allele frequency or greater for SNVs and indels. Only mutations in coding regions were included in the TMB WES score. The final alteration count was converted to mut/Mb by dividing by 34.7 Mb, which was the total length of the coding regions in the WES assay.

      A total of 218 samples with valid F1CDx and WES TMB scores were evaluated that represented prevalent tumor types as well as the rare tumors from the clinical validation study. 64 samples obtained from rare tumors were assessed, including 45 samples that were screened for patient enrollment into

the KEYNOTE-158 clinical study, which supports the clinical validation of the F1CDx assay for TMB (please refer to Section X, below). 154 samples represented common tumor types including NSCLC, breast cancer, CRC, ovarian cancer, and melanoma. Of the 218 samples in the concordance analysis, 89 were selected by a non-FMI assay, and the remaining 129 samples were selected by F1CDx. TMB measurements were dichotomized using 10 mut/Mb as the TMB-H cut-off for both the F1CDx and WES assays. The positive percent agreements (PPA) and negative percent agreements (NPA) with 95% confidence intervals (CI) derived through bootstrapping are provided for the sample set selected by a non-FMI assay (unadjusted for prevalence) and samples selected by F1CDx (adjusted for prevalence of TMB-H estimated as 19%) in Tables 8 and 9, respectively.

Table 8. TMB concordance summary for samples selected by a non-FMI assay (unadjusted for prevalence)

TMB Cut-off	F1CDx+/ WES+	F1CDx-/ WES+	F1CDx+/ WES-	F1CDx-/ WES-	Unadjusted PPA (95% CI)	Unadjusted NPA (95% CI)
10 mut/Mb	28	7	4	50	80.0% (62.5%, 90.62%)	92.59% (82.62%, 98.04%)

Table 9. TMB concordance summary for samples selected by F1CDx (adjusted for prevalence)

TMB Cut-off	F1CDx+/ WES+	F1CDx-/ WES+	F1CDx+/ WES-	F1CDx-/ WES-	Adjusted PPA (95% CI)	Adjusted NPA (95% CI)
10 mut/Mb	23	1	17	88	92.31% (65.74%, 100%)	90.84% (87.76%, 93.99%)

The overall PPA and NPA based on a weighted average of the results (unadjusted and adjusted for TMB-H prevalence) in the TMB concordance analysis are provided in Table 10, below, with 95% bootstrap CI.

Table 10. Overall TMB concordance summary (weighted average)

TMB Cut-off	Overall PPA (95% CI)	Overall NPA (95% CI)
10 mut/Mb	87.28% (64.42%, 96.17%)	91.56% (85.66%, 95.64%)

Overall PPA was 87.28% with 95% CI (64.42%, 96.17%) and overall NPA was 91.56% with 95% CI (85.66%, 95.64%). Passing-Bablok regression was performed to assess the relationship between F1CDx and WES using the underlying continuous TMB score. The estimated slope was 0.93 with 95% CI (0.87, 1.03), and the estimated offset was -0.08 mut/Mb with 95% CI (-0.46, 0.2).

29 discordant results were observed in the TMB concordance analysis. An investigation of the discordances determined that 10 of the 29 discordant samples had F1CDx TMB scores that were close to the cut-off of 10 mut/Mb for TMB-H samples. Further, an analysis of the alteration level agreements was performed to explore the differences in the underlying component variants included in the TMB scores determined by the F1CDx and WES TMB algorithms. The alteration level assessment identified discordances in variant calls between the F1CDx and WES assays due to driver mutation exclusions, differences in germline variant designation, variants detected at low allele frequencies (i.e., below the F1CDx or WES TMB algorithm threshold of 5% MAF), and mutations in non-coding regions. The alteration level evaluation determined that exclusion of driver mutations by the F1CDx TMB algorithm and not by the WES TMB algorithm as well as differences in germline variant designation to be the greatest sources of TMB component variant discordances between F1CDx and WES.

2. **Analytical Sensitivity**

   a. **Limit of Detection (LoD)**

   The limit of detection (LoD) for TMB calling by F1CDx based on the cut-off of 10 mut/Mb was estimated with respect to computational tumor purity. Computational tumor purity is calculated by fitting the observed log-ratio and minor allele frequency data with statistical models that predict a genome-wide copy number profile, tumor ploidy, and tumor purity (i.e., computational tumor purity). The log-ratio profile is obtained by normalizing aligned tumor sequence reads by dividing read depth by that of a process-matched normal control, followed by a GC-content bias correction using Loess regression. The minor allele frequency profile is obtained from the heterozygous genome-wide SNPs.

   11 TMB-H (≥ 10 mut/Mb) FFPE samples were included in the analysis representing lung, colon, breast, bladder, and skin cancers as well as rare tumor types in the clinical validation study including anal and endometrial tissues. LoD was assessed at 5 levels of computational tumor purity, ranging from 2.5% to 50%, with 20 replicates per level, except for the highest tumor purity level at which 14 replicates were tested. The LoD for TMB calling based on computational tumor purity was determined empirically by the hit rate method, defined as the lowest level with 95% hit rate.

   The LoD for TMB calling based on computational tumor purity is 28.16%. The LoD may be driven by the proximity of the TMB score to the cut-off, as the sample with an average TMB score of 11.83 mut/Mb (at the highest level of tumor purity evaluated) had the highest hit rate LoD at 28.16% tumor purity for the cut-off of 10 mut/Mb.

   Several samples were tested at or near the TMB LoD based on computational tumor purity in the precision study (please see Section IX.A.5). Please also

refer to Section IX.A.2 of Summary of Safety and Effectiveness Data for P170019 for additional analytical sensitivity data.

b. Limit of Blank (LoB)

The limit of blank (LoB) of zero was confirmed by demonstrating that the percentage of false positive results did not exceed 5% (type I error risk α=0.05). 21 biomarker-negative samples were processed for a total of 220 replicates. Of the 220 aliquots, one failed prior to sequencing, and 219 replicates were available for the LoB analysis. 16 of the 21 biomarker-negative samples had TMB scores of 0 mut/Mb, and the mean TMB score for all 21 samples evaluated was 0.14 mut/Mb. All 219 replicates were below the TMB cut-off of 10 mut/Mb (non-TMB-H), resulting in a false positive rate of 0% and thus confirming the LoB of zero.

3. Analytical Specificity

a. Interfering Substances

To evaluate the potential impact of endogenous and exogenous interfering substances on the performance of the F1CDx assay for TMB calling, an *in silico* assessment of interfering substances data for the F1CDx platform (P170019) was conducted. A total of 19 FFPE specimens were included in the evaluation representing a range of tumor types including colon, breast, lung, ovary, skin, liver, gastroesophageal, kidney, and prostate tissues. Two TMB-H samples, including one sample close to the 10 mut/Mb threshold for TMB-H, were analyzed. The addition of interfering substances, including melanin (endogenous), ethanol (exogenous), proteinase K (exogenous), and molecular index barcodes (MIB) (exogenous), was evaluated to determine if they impacted TMB calling with respect to the qualitative cut-off of 10 mut/Mb (Table 11).

Table 11. Interfering substances evaluated

Substance	Level	# Samples	# Replicates/Sample
No interferent	-	19	2 (4 controls for MIB)
Melanin	0.025 µg/mL	5	2
Melanin	0.05 µg/mL	5	2
Melanin	0.1 µg/mL	5	2
Melanin	0.2 µg/mL	5	2
Proteinase K	0.04 mg/mL	18	2
Proteinase K	0.08 mg/mL	18	2
Ethanol	2.5%	18	2
Ethanol	5%	18	2
MIB	0	18	2 or 4
MIB	5%	5	4
MIB	15%	18	2 or 4
MIB	30%	18	2 or 4

Each interfering substance was evaluated by the concordance of TMB status with the corresponding control sample with respect to the 10 mut/Mb cut-off. A summary of the overall concordance results for each interferent with corresponding 95% CI using score method is provided in Table 12, below.

Table 12. TMB concordance across each interfering substance

Substance	# Concordant	# Total	Concordance (95% score CI)
No interferent	55	56	98.2% (90.6%, 99.7%)
Melanin	38	40	95% (83.5%, 98.6%)
Proteinase K	72	72	100% (94.9%, 100%)
Ethanol	72	72	100% (94.9%, 100%)
MIB	110	111	99.1% (95.1%, 99.8%)

The concordance for TMB calling was 100% for the proteinase K and ethanol evaluations, 99.1% for the MIB evaluation, and 95% for the melanin evaluation.

A post-market interfering substances study will be performed to evaluate the effects of endogenous interfering substances, including necrotic tissue and hemoglobin, on TMB calling (≥ 10 mut/Mb) in solid tumors across the intended use population.

4. **Carryover/Cross-Contamination**
   Please see Section IX.A.4 of Summary of Safety and Effectiveness Data for P170019.

5. **Precision and Reproducibility**
   a. **Intermediate Precision for TMB-H (≥ 10 mut/Mb)**
   A precision study was conducted to evaluate the intermediate precision for TMB-H calling with respect to the 10 mut/Mb cut-off in FFPE specimens across solid tumors. Samples were enriched for TMB-H status, and an additional analysis was performed to support F1CDx precision for TMB calling in non-TMB-H samples (please see Section IX.A.5(b), below). 46 samples were analyzed that represented prevalent solid tumors as well as the rare tumors included in the clinical validation study (please see Section X) covering 7 major organ systems: gastrointestinal, hepato-pancreatobiliary, urinary, endocrine, skin, thoracic, and reproductive. The study focused on the evaluation of F1CDx precision for TMB-H calling across challenging samples at low DNA input (i.e., close to the minimum requirement of 50 ng) with a range of TMB scores, including samples with TMB scores close to the 10

mut/Mb cut-off, and a range of tumor purities. Of the 46 samples, 22 were tested at challenging tumor purity levels near or below the established TMB LoD of 28.16% computational purity (please refer to Section IX.A.2(a), above).

Repeatability including intra-run performance (run on the same plate under the same conditions) and reproducibility including inter-run performance (run on different plates under different conditions) were assessed and compared across three different sequencers and two different reagent lots, over multiple days (typical assay workflow spans 10 days). A full factorial study design was executed with four replicates per reagent lot/sequencer combination for a total of 24 replicates per sample. The previous precision studies for F1CDx (P170019) and FoundationFocus CDx$_{BRCA}$ (P160018) were conducted with 36 replicates using a full factorial study design and yielded high agreement rates; thus, 24 replicates per sample to demonstrate F1CDx precision for TMB calling were deemed acceptable to support this PMA supplement due to adequate F1CDx platform precision in the previous studies.

Based on the cut-off of 10 mut/Mb for TMB-H, there were 44 TMB-H and 2 non-TMB-H samples in this precision analysis. The TMB scores for the selected samples ranged from 6.25 mut/Mb to 156.4 mut/Mb (based on the mean TMB score for valid replicates per sample), and 6 samples had TMB scores near the TMB-H threshold of 10 mut/Mb. Repeatability and reproducibility results with the corresponding two-sided exact 95% CI are summarized in Table 13, below.

Table 13. Precision results for TMB-H (≥ 10 mut/Mb)

TMB Cut-off	Repeatability Positive Call Rate (95% exact CI)	Repeatability Negative Call Rate (95% exact CI)	Reproducibility Positive Call Rate (95% exact CI)	Reproducibility Negative Call Rate (95% exact CI)
10 mut/Mb	99.61% (98.61%, 99.95%)	95.83% (78.88%, 99.89%)	99.81% (99.3%, 99.98%)	97.83% (88.47%, 99.94%)

For repeatability, the PPA for 44 TMB-H samples was 99.61% with 95% CI (98.61%, 99.95%), and the NPA for 2 non-TMB-H samples was 95.83% with 95% CI (78.88%, 99.89%). For reproducibility, the PPA was 99.81% with 95% CI (99.3%, 99.98%), and the NPA was 97.83% with 95% CI (88.47%, 99.94%). The overall repeatability agreement for samples tested was 99.54% with 95% CI (98.39%, 99.98%), and overall reproducibility was 99.72% with 95% CI (99.18%, 99.94%).

For repeatability and reproducibility of the TMB score as a continuous variable, the coefficient of variance (%CV) from variance component analysis was estimated for each sample. All samples had %CV < 30% for repeatability and reproducibility.

b. Intermediate Precision for non-TMB-H (< 10 mut/Mb)

To provide additional precision data for F1CDx TMB calling in non-TMB-H samples (< 10 mut/Mb), an analysis was conducted in 20 FFPE specimens across multiple tumor types including lung, colon, skin, thyroid, salivary gland, liver, and uterus cancers. The study included challenging samples with low DNA input (i.e., close to the minimum requirement of 50 ng) and a range of tumor purities. Repeatability including intra-run performance and reproducibility including inter-run performance were assessed and compared across three different sequencers, two different reagent lots, and multiple days (typical assay workflow spans 10 days). A full factorial study design was executed with three replicates per two runs for a total of 36 replicates across the paired reagent lot/sequencer combinations.

Of the 20 samples tested in the additional precision analysis to support F1CDx TMB calling in non-TMB-H samples, there were 1 TMB-H and 19 non-TMB-H samples based on the cut-off of ≥ 10 mut/Mb for TMB-H. Overall repeatability and reproducibility results with the corresponding two-sided exact 95% CI are summarized in Table 14, below.

Table 14. Precision results for non-TMB-H (< 10 mut/Mb)

TMB Cut-off	Overall Repeatability (95% exact CI)	Overall Reproducibility (95% exact CI)
10 mut/Mb	100% (98.4%, 100%)	100% (99.5%, 100%)

Repeatability and reproducibility of TMB status with respect to the 10 mut/Mb cut-off was 100% for all samples. The overall repeatability agreement for samples tested was 100% with 95% CI (98.4%, 100%), and overall reproducibility was 100% with 95% CI (99.5%, 100%).

c. Site-to-site Precision for TMB

A site-to-site precision study was performed to support F1CDx TMB calling at the second site in Morrisville, NC. 46 FFPE samples representing ovarian, breast, lung, colorectal, and skin cancers across a range of tumor purities were included. A total of 9 TMB-H samples and 37 non-TMB-H samples were evaluated for the site-to-site precision analysis. Repeatability including intra-run performance and reproducibility including inter-run performance were assessed. Each of the 46 samples was tested at two sites (Cambridge, MA and Morrisville, NC) with two replicates, two reagent lots, and on three non-consecutive days by multiple operators. A full factorial study design was conducted with a total of 24 replicates across the paired reagent lot/sequencer combination. For the evaluation of TMB with respect to the 10 mut/Mb cut-off, repeatability and reproducibility was 100% for all replicates for 45 of 46 samples. Only one sample demonstrated 79.17% reproducibility and 58.33%

repeatability with 5 discordant replicates near the 10 mut/Mb threshold; this sample had an average computational tumor purity of 11.02%, which was below the TMB LoD level of 28.16% tumor purity (see Section IX.A.2(a), above). The overall repeatability agreement for samples tested was 99.05% with 95% CI (97.79%, 99.69%), and overall reproducibility was 99.53% with 95% CI (98.91%, 99.85%).

Additional post-market data will be provided for the intermediate precision of the TMB component alterations, including repeatability and reproducibility.

6. Reagent Lot Interchangeability

There were no changes to the reagents and specifications between the FoundationFocus™ CDx$_{BRCA}$ assay and F1CDx. Therefore, for reagent lot interchangeability results, please see Section IX.A(g) of Summary of Safety and Effectiveness Data for P160018.

7. Stability

Please refer to the Summary of Safety and Effectiveness Data P170019 (Section IX.A.7(a,b)) for F1CDx platform validation of reagent, DNA, and FFPE slide stability. Additional post-market data for DNA and FFPE slide stability with respect to TMB biomarker (≥ 10 mut/Mb) calling will be provided based on the re-analysis of the existing F1CDx platform-level data with the updated bioinformatics pipeline (v3.3.x).

8. General Lab Equipment and Reagent Evaluation

a. DNA Amplification

There were no changes to the reagents and specifications between the FoundationFocus™ CDx$_{BRCA}$ assay and F1CDx. For equipment and reagent interchangeability results, please see Section IX.A.h(a) of Summary of Safety and Effectiveness Data for P160018.

b. DNA Extraction

The performance of DNA extraction from FFPE tumor specimens was measured by the concordance of TMB status based on the qualitative TMB-H cut-off of 10 mut/Mb. 35 FFPE specimens represented a range of tissue types including lung, breast, ovarian, colorectal, bladder, brain, liver, pancreas, thyroid, prostate, and skin cancers. The study included 7 TMB-H samples, including one sample near the threshold of 10 mut/Mb, as well as challenging samples at low tumor purities. Samples were run in duplicate employing two different KingFisher Flex Magnetic Particle Processors and comparing across two or three extraction reagent lots. Concordance of TMB calling was analyzed across replicates for each sample, and the overall results with respect to TMB status are summarized in Table 15, below.

Table 15. Summary of TMB concordance across replicates in DNA extraction study

TMB Status	# of Concordant Replicates	# of Total Replicates	Concordance Rate (95% 2-sided score CI)
TMB-H	63	63	100% (94.25%, 100%)
non-TMB-H	285	290	98.28% (96.03%, 99.26%)

For additional details on the F1CDx platform DNA extraction study, please refer to Section IX.A.8(b) of Summary of Safety and Effectiveness Data P170019.

9. Guard banding/Robustness

Please see Section IX.A.9 of Summary of Safety and Effectiveness Data for P170019. Additional post-market data for guard banding with respect to TMB biomarker (> 10 mut/Mb) calling will be provided based on the re-analysis of the existing F1CDx platform-level data with the updated bioinformatics pipeline (v3.3.x).

B. Animal Studies

No animal studies were conducted using the F1CDx assay.

C. Additional Studies

No additional studies were conducted using the F1CDx assay.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of FoundationOne®CDx (F1CDx) for detecting TMB-H (defined as TMB ≥ 10 mut/Mb) in patients with solid tumors was demonstrated in a prospectively-planned retrospective analysis of specimens from patients enrolled in the KEYNOTE-158 clinical study of pembrolizumab. Data generated from the KEYNOTE-158 trial supported the clinical validation of the F1CDx assay for the identification of TMB-H subjects (≥ 10 mut/Mb) with solid cancers who may benefit from pembrolizumab treatment.

A. FoundationOne®CDx Retrospective Analysis of TMB in KEYNOTE-158

The safety and effectiveness of F1CDx for detecting TMB-H patients with respect to the cut-point of 10 mut/Mb was demonstrated in a prospectively-planned retrospective analysis of patients enrolled in the KEYNOTE-158 study. TMB biomarker analysis was pre-specified in the clinical trial protocol and retrospectively analyzed by the F1CDx assay.

1. Study Design

KEYNOTE-158 is an ongoing, Phase 2, multicenter, non-randomized, open-label, multi-cohort study designed to evaluate the safety and efficacy of pembrolizumab monotherapy (200 mg intravenously [IV] every 3 weeks [Q3W]) in multiple types of advanced (unresectable or metastatic) solid cancers that have progressed

following prior treatment and who have no satisfactory alternative treatment options. The study included participants with solid tumors grouped into 10 different cohorts, A to J. The aim of KEYNOTE-158 is to evaluate predictive biomarkers for response to pembrolizumab monotherapy treatment across multiple tumor types, regardless of specific tumor histology.

Participants with any of the tumor types in cohorts A to J listed below for whom previous first-line treatment failed were eligible to enroll in KEYNOTE-158.

Cohorts:

A. Anal squamous cell carcinoma
B. Biliary adenocarcinoma (gallbladder or biliary tree [intrahepatic or extrahepatic] cholangiocarcinoma) except Ampulla of Vater cancers
C. Neuroendocrine tumors (well- and moderately-differentiated) of the lung, appendix, small intestine, colon, rectum, or pancreas
D. Endometrial carcinoma (sarcomas and mesenchymal tumors are excluded)
E. Cervical squamous cell carcinoma
F. Vulvar squamous cell carcinoma
G. Small cell lung carcinoma
H. Mesothelioma
I. Thyroid carcinoma
J. Salivary gland carcinoma (sarcomas and mesenchymal tumors are excluded)

In addition to having any of the advanced solid tumors noted above, participants were eligible for study enrollment if they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; life expectancy of > 3 months and previous treatment with standard therapies; no known active central nervous system (CNS) metastasis, autoimmune disease, immunosuppressive therapy, or prior treatment with anticancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1; and had adequate tumor tissue to test programmed death ligand-1 (PD-L1), gene expression profile (GEP), and microsatellite instability-high (MSI-H). The TMB biomarker was pre-specified and retrospectively analyzed by the F1CDx assay.

The primary endpoint was objective response rate (ORR), defined as the proportion of participants in the analysis population who had a response (complete response [CR] or partial response [PR]) as measured by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary endpoints were as follows:

- Duration of response (DOR), defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first;
- Progression free survival (PFS), defined as the time from randomization/the first dose of study treatment to documented progressive disease or death due to any cause, whichever occurred first; and

- Overall survival (OS), defined as the time from randomization/the first dose of study treatment to death due to any cause.

2. TMB Evaluation by F1CDx

Evaluation of the TMB biomarker was an objective for KEYNOTE-158. The interim analysis (IA)10 investigated the relationship between response to pembrolizumab treatment and TMB as determined by the F1CDx assay using a cut-point of 10 mut/Mb. Selection of 10 mut/Mb as the TMB score cut-point for TMB-H considered three key elements: 1) the ability to reliably enrich for objective response to pembrolizumab while preserving the percentage of responders (i.e., sensitivity) based on training data; 2) the relationship between TMB and inflammation in the tumor microenvironment as measured by gene expression; and 3) an effort to harmonize on a common TMB cut-off to define TMB-H across different sponsors working with TMB as an immunotherapy biomarker.

Pre-defined sample quality control (QC) testing parameters were used throughout the retrospective testing of KEYNOTE-158 clinical trial samples including, but not limited to, minimum DNA input, tumor purity, tissue volume, and average read depth to ensure adequate F1CDx performance of TMB calling.

The therapeutic efficacy (TE) population was the primary efficacy population to support the drug indication. For investigational testing and analysis of the TE population, a TMB result was valid if the following pre-specified sample inclusion criteria were met:

- Tissue volume ≥ 0.2 mm^3;
- Tumor nuclei content $\geq 10\%$; and
- Extracted DNA content > 55 ng.

For testing and analysis of the device validation (DV) population, a TMB result was considered valid if the following pre-specified sample inclusion criteria consistent with the F1CDx device specifications were met:

- Tissue volume > 0.6 mm^3;
- Tumor nuclei content $\geq 20\%$; and
- Extracted DNA content > 55 ng.

In addition, all TE and DV population samples had sufficient DNA quantity and quality following extraction, in-process QC metrics, and acceptable post-sequencing metrics to be considered valid.

B. <u>Study Population Demographics and Baseline Parameters</u>

Baseline demographics and disease characteristics were generally similar in the TMB-H and non-TMB-H populations for both the TE and DV analysis populations (Table 16). At the time of IA10, the trial was being conducted globally in 21 countries, including the U.S., of which 81 sites had enrolled participants to the study treatment. Compared to the non-TMB-H population, the TMB-H population had a

higher percentage of participants whose tumors were PD-L1 positive (CPS ≥ 1). This is consistent with the understanding of the biological mechanisms by which tumors with increased neoantigens up-regulate PD-L1 to evade immune recognition. As expected, all participants with MSI-H tumors were in the TMB-H group, as MSI-H is a subset of the overall TMB-H population.

Table 16. Comparison of demographic and disease characteristics between TMB-H and non-TMB-H subjects evaluated by F1CDx for TE and DV populations

	TE Population				DV Population			
	TMB >=10 mut/Mb		TMB <10 mut/Mb		TMB >=10 mut/Mb		TMB <10 mut/Mb	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	102		688		91		628	
Gender								
Male	35	(34.3)	253	(36.8)	31	(34.1)	226	(36.0)
Female	67	(65.7)	435	(63.2)	60	(65.9)	402	(64.0)
Age (Years)								
< 65	67	(65.7)	414	(60.2)	59	(64.8)	383	(61.0)
>= 65	35	(34.3)	274	(39.8)	32	(35.2)	245	(39.0)
Mean	60.0		60.2		59.7		60.1	
SD	10.7		12.0		11.2		12.0	
Median	61.0		61.0		60.0		61.0	
Range	27 to 80		22 to 87		27 to 80		22 to 85	
Race								
American Indian Or Alaska Native	0	(0.0)	4	(0.6)	0	(0.0)	3	(0.5)
Asian	17	(16.7)	133	(19.3)	15	(16.5)	118	(18.8)
Black Or African American	1	(1.0)	18	(2.6)	1	(1.1)	15	(2.4)
Multiple	0	(0.0)	6	(0.9)	0	(0.0)	5	(0.8)
American Indian Or Alaska Native, Black Or African American	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.2)
Black Or African American, White	0	(0.0)	5	(0.7)	0	(0.0)	4	(0.6)
Native Hawaiian Or Other Pacific Islander	1	(1.0)	1	(0.1)	1	(1.1)	1	(0.2)
White	83	(81.4)	526	(76.5)	74	(81.3)	486	(77.4)
Ethnicity								
Hispanic Or Latino	2	(2.0)	45	(6.5)	1	(1.1)	40	(6.4)
Not Hispanic Or Latino	92	(90.2)	587	(85.3)	83	(91.2)	538	(85.7)
Not Reported	8	(7.8)	56	(8.1)	7	(7.7)	50	(8.0)

Geographic Region								
US	20	(19.6)	163	(23.7)	19	(20.9)	144	(22.9)
Non-US	82	(80.4)	525	(76.3)	72	(79.1)	484	(77.1)
ECOG								
[0] Normal Activity	42	(41.2)	277	(40.3)	37	(40.7)	254	(40.4)
[1] Symptoms, but ambulatory	59	(57.8)	409	(59.4)	53	(58.2)	372	(59.2)
[2] Ambulatory but unable to work	1	(1.0)	2	(0.3)	1	(1.1)	2	(0.3)
Metastatic Staging								
M0	9	(8.8)	72	(10.5)	7	(7.7)	65	(10.4)
M1	93	(91.2)	616	(89.5)	84	(92.3)	563	(89.6)
Brain Metastases Present								
Yes	6	(5.9)	17	(2.5)	3	(3.3)	16	(2.5)
No	96	(94.1)	671	(97.5)	88	(96.7)	612	(97.5)
Number of Prior Lines of Therapy								
0*	1	(1.0)	23	(3.3)	1	(1.1)	21	(3.3)
Adjuvant/Neoadjuvant/ Definitive†	0	(0.0)	8	(1.2)	0	(0.0)	8	(1.3)
1	44	(43.1)	257	(37.4)	41	(45.1)	235	(37.4)
2	38	(37.3)	187	(27.2)	30	(33.0)	167	(26.6)
3	6	(5.9)	107	(15.6)	6	(6.6)	96	(15.3)
4	7	(6.9)	59	(8.6)	7	(7.7)	55	(8.8)
5 or more	6	(5.9)	47	(6.8)	6	(6.6)	46	(7.3)
Sum of Target Lesions Measurable at Baseline (mm)								
Subjects with data	102		684		91		624	
Mean	106.3		107.9		103.5		108.0	
SD	79.7		80.9		78.9		81.0	
Median	88.3		83.4		84.2		86.0	
Range	10.2 to 322.8		10.1 to 442.9		10.2 to 322.8		10.1 to 442.9	
Tumor Type								
ANAL	14	(13.7)	75	(10.9)	14	(15.4)	73	(11.6)
CERVICAL	16	(15.7)	59	(8.6)	15	(16.5)	52	(8.3)
CHOLANGIOCARCINOMA	0	(0.0)	63	(9.2)	0	(0.0)	55	(8.8)
ENDOMETRIAL	15	(14.7)	67	(9.7)	15	(16.5)	64	(10.2)
MESOTHELIOMA	1	(1.0)	84	(12.2)	1	(1.1)	80	(12.7)
NEUROENDOCRINE	5	(4.9)	82	(11.9)	5	(5.5)	73	(11.6)
SALIVARY	3	(2.9)	79	(11.5)	3	(3.3)	74	(11.8)
SMALL CELL LUNG	34	(33.3)	42	(6.1)	26	(28.6)	30	(4.8)
THYROID	2	(2.0)	78	(11.3)	2	(2.2)	75	(11.9)
VULVAR	12	(11.8)	59	(8.6)	10	(11.0)	52	(8.3)
Prior Radiation Therapy								

Yes	81	(79.4)	412	(59.9)	70	(76.9)	376	(59.9)
No	21	(20.6)	276	(40.1)	21	(23.1)	252	(40.1)
PD-L1 Status								
Positive	68	(66.7)	383	(55.7)	61	(67.0)	352	(56.1)
Negative	29	(28.4)	274	(39.8)	25	(27.5)	250	(39.8)
Not Evaluable	5	(4.9)	30	(4.4)	5	(5.5)	25	(4.0)
Missing	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.2)
MSI-H Status								
MSI-High	14	(13.7)	0	(0.0)	14	(15.4)	0	(0.0)
non-MSI-High	81	(79.4)	672	(97.7)	73	(80.2)	614	(97.8)
Missing	7	(6.9)	16	(2.3)	4	(4.4)	14	(2.2)

[†] Participants did not receive systemic chemotherapy.

[‡] Participants received adjuvant/neoadjuvant alone without recurrence < 12 months from completion of the therapy or received definitive therapy alone which cannot be considered as a line of therapy.

Subjects with unknown TMB status are not included.

(Database Cutoff Date: 27JUN2019).

The various tumor types in cohorts A through J were observed at different frequencies in the TMB-H and non-TMB-H populations. Small cell lung carcinoma (SCLC) was more common in the TMB-H population. Thyroid, neuroendocrine, mesothelioma, and salivary tumors each were more common in the non-TMB-H population. The differences in certain tumor types are based on small numbers, as 5 of the 10 tumor types were present in 5 or fewer participants in the TMB-H population. A high percentage of participants had received prior radiation therapy, which is consistent with the higher percentage of SCLC and other tumor types likely to be treated with radiation therapy.

C. Accountability of sPMA Cohort

At IA10 of KEYNOTE-158, a total of 1,072 participants were enrolled in the combined cohorts, A through J, of which 1,066 were treated with at least one dose of pembrolizumab (referred to as All Subjects as Treated [ASaT]) population). The safety analysis was conducted in the ASaT population of 1,066 participants, while the efficacy analysis population included 1,050 participants from the ASaT population who were enrolled 26 weeks prior to data cut-off.

From the enrolled population, 1,007 patients had samples that were accessioned at Foundation Medicine. One sample was lost in transit, resulting in a total of 1,006 sample test records.

Based on the F1CDx investigational sample specification requirements used to define the TE population, 808 subjects had a valid TMB result, and 199 subjects had samples that failed to meet the minimum test specifications: 5 participants did not pass pre-analytical QC due to insufficient samples for testing (n=1) or gender discordance (n=4); 36 did not pass pathology review based on TE specifications (i.e.,

≥ 10% tumor nuclei and ≥ 0.2 mm^3 viable nucleated tissue); 73 did not meet the minimum extracted DNA criterion (> 55 ng); and 86 yielded invalid results after sequencing and reporting. Among the 808 participants with a valid TMB result, 15 were enrolled < 26 weeks before the data cut-off for IA10, two were not treated, and one did not have a TMB score; as a result, the TE population consists of 790 patients with TMB data available. Of the 790 participants in the TE population with available TMB results, 102 were TMB-H (≥ 10 mut/Mb) and 688 were non-TMB-H (< 10 mut/Mb).

Based on the F1CDx final sample specification requirements used to define the DV population, 735 subjects had a valid TMB result, and 272 subjects had samples that failed to meet the minimum test specifications: 5 participants did not pass pre-analytical QC due to insufficient samples for testing (n=1) or gender discordance (n=4); 156 did not pass pathology review based on DV specifications (i.e., ≥ 20% tumor nuclei and ≥ 0.6 mm^3 of viable nucleated tissue); 40 did not meet the minimum extracted DNA criterion (> 55 ng); and 71 yielded invalid results after sequencing and reporting. Among the 735 patients with valid TMB results, 13 were enrolled < 26 weeks before the data cut-off for IA10, two were not treated, and one did not have a TMB score; as a result, the DV population consists of 719 patients with valid TMB scores. Of the 719 participants in the DV population with available TMB results, 91 were TMB-H (≥ 10 mut/Mb) and 628 were non-TMB-H (< 10 mut/Mb).

Information on the numbers of participants per cohort based on TMB-H versus non-TMB-H status are provided for the TE and DV populations, respectively, in Table 17 below.

Table 17. F1CDx TMB status availability by KEYNOTE-158 cohort

	TE Population		DV Population	
Cohort	**TMB Status Available**	**TMB Status Not Available**	**TMB Status Available**	**TMB Status Not Available**
A: Anal	89	23	87	25
B: Biliary	63	41	55	49
C: Neuroendocrine	87	20	78	29
D: Endometrial	82	25	79	28
E: Cervical	75	23	67	31
F: Vulvar	71	14	62	23
G: SCLC	76	31	56	51
H: Mesothelioma	85	33	81	37
I: Thyroid	80	23	77	26
J: Salivary Gland	82	27	77	32
Total	**790**	**260**	**719**	**331**

D. Safety and Effectiveness

1. Safety Results

The safety with respect to treatment with pembrolizumab was addressed during review of the sBLA and is not addressed in detail in this Summary of Safety and

Effectiveness Data. The safety profile of pembrolizumab in the TMB-H Safety Dataset is generally consistent with the established safety profile of pembrolizumab monotherapy. No new safety signals were identified in KEYNOTE-158. Please refer to Drugs@FDA for complete safety information on KEYTRUDA® (pembrolizumab).

2. **Effectiveness Results**

The effectiveness of F1CDx to identify TMB-H (≥ 10 mut/Mb) patients who may benefit from pembrolizumab treatment is supported by the efficacy results from IA10 of KEYNOTE-158. The efficacy results from KEYNOTE-158 show that pembrolizumab monotherapy provides a clinically meaningful benefit to participants with TMB-H advanced solid tumors that had progressed following prior treatment or who were intolerant to prior therapies. This was demonstrated by clinically meaningful ORR and DOR in the TE and DV populations.

The primary endpoint in KEYNOTE-158 was ORR, defined as the proportion of patients in the analysis population who had a response (CR or PR) as measured by central review (BIRC) per RECIST 1.1. For the pooled analysis across tumor types in cohorts A through J, response to pembrolizumab was enriched in TMB-H subjects, resulting in a clinically meaningful ORR of 29.4% in the TE population (Table 18) and 33% in the DV population (Table 19). By contrast, a lower ORR was observed in non-TMB-H subjects of 6.3% in the TE population and 6.5% in the DV population.

Table 18. Summary of best objective response based on RECIST 1.1 per central radiology assessment in TE population

Response Evaluation	TMB >=10 mut/Mb (N=102)			TMB <10 mut/Mb (N=688)		
	n	%	95% CI*	n	%	95% CI*
Complete Response (CR)	4	3.9	(1.1, 9.7)	11	1.6	(0.8, 2.8)
Partial Response (PR)	26	25.5	(17.4, 35.1)	32	4.7	(3.2, 6.5)
Objective Response (CR+PR)	**30**	**29.4**	**(20.8, 39.3)**	**43**	**6.3**	**(4.6, 8.3)**
Stable Disease (SD)	14	13.7	(7.7, 22.0)	227	33.0	(29.5, 36.6)
Non-CR/Non-PD (NN)	0	0.0	(0.0, 3.6)	3	0.4	(0.1, 1.3)
Progressive Disease (PD)	48	47.1	(37.1, 57.2)	349	50.7	(46.9, 54.5)
Non-evaluable (NE)	1	1.0	(0.0, 5.3)	13	1.9	(1.0, 3.2)
No Assessment	9	8.8	(4.1, 16.1)	53	7.7	(5.8, 10.0)

Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.

* Based on binomial exact confidence interval method.

'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

Subjects with unknown TMB status are not included.

(Database Cutoff Date: 27JUN2019).

Table 19. Summary of best objective response based on RECIST 1.1 per central radiology assessment in DV population

Response Evaluation	TMB >=10 mut/Mb (N=91)			TMB <10 mut/Mb (N=628)		
	n	%	95% CI[†]	n	%	95% CI[†]
Complete Response (CR)	4	4.4	(1.2, 10.9)	11	1.8	(0.9, 3.1)
Partial Response (PR)	26	28.6	(19.6, 39.0)	30	4.8	(3.2, 6.7)
Objective Response (CR+PR)	**30**	**33.0**	**(23.5, 43.6)**	**41**	**6.5**	**(4.7, 8.8)**
Stable Disease (SD)	14	15.4	(8.7, 24.5)	210	33.4	(29.8, 37.3)
Non-CR/Non-PD (NN)	0	0.0	(0.0, 4.0)	3	0.5	(0.1, 1.4)
Progressive Disease (PD)	39	42.9	(32.5, 53.7)	313	49.8	(45.9, 53.8)
Non-evaluable (NE)	0	0.0	(0.0, 4.0)	12	1.9	(1.0, 3.3)
No Assessment	8	8.8	(3.9, 16.6)	49	7.8	(5.8, 10.2)

Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.

[†] Based on binomial exact confidence interval method.

'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

Subjects with unknown TMB status are not included.

(Database Cutoff Date: 27JUN2019).

ORR was assessed by tumor type, and the results were similar in the TE and DV populations (Tables 20 and 21, respectively). ORR was generally higher in the TMB-H population for most tumor types than in the non-TMB-H population. Data from the biliary (cholangiocarcinoma) and mesothelioma tumor types were not informative, as there were no biliary participants and only one mesothelioma patient with TMB-H status. The enrichment of response in TMB-H anal cancer was not observed; however, participants with anal cancer, as well as participants with other tumor types, exhibited a spectrum of TMB.

Table 20. Summary of best objective response per tumor type based on RECIST 1.1 per central radiology assessment in TE population

Tumor Type	TMB >=10 mut/Mb				TMB <10 mut/Mb				ORR Ratio
	N	n	%	95% CI[†]	N	n	%	95% CI[†]	TMB >=10 mut/Mb vs. TMB <10 mut/Mb
Overall	102	30	29.4	(20.8, 39.3)	688	43	6.3	(4.6, 8.3)	4.7
Anal	14	1	7.1	(0.2, 33.9)	75	8	10.7	(4.7, 19.9)	0.7
Cholangiocarcinoma	0	0	--	--	63	2	3.2	(0.4, 11.0)	--
Neuroendocrine	5	2	40.0	(5.3, 85.3)	82	1	1.2	(0.0, 6.6)	32.8
Endometrial	15	7	46.7	(21.3, 73.4)	67	4	6.0	(1.7, 14.6)	7.8
Cervical	16	5	31.3	(11.0, 58.7)	59	7	11.9	(4.9, 22.9)	2.6
Vulvar	12	2	16.7	(2.1, 48.4)	59	2	3.4	(0.4, 11.7)	4.9
Small Cell Lung	34	10	29.4	(15.1, 47.5)	42	4	9.5	(2.7, 22.6)	3.1
Mesothelioma	1	0	0.0	(0.0, 97.5)	84	9	10.7	(5.0, 19.4)	0.0
Thyroid	2	2	100.0	(15.8, 100.0)	78	3	3.8	(0.8, 10.8)	26.0
Salivary	3	1	33.3	(0.8, 90.6)	79	3	3.8	(0.8, 10.7)	8.8

[†] Based on binomial exact confidence interval method.
Subjects with unknown TMB status are not included.
(Database Cutoff Date: 27JUN2019).

Table 21. Summary of best objective response per tumor type based on RECIST 1.1 per central radiology assessment in DV population

Tumor Type	TMB >=10 mut/Mb				TMB <10 mut/Mb				ORR Ratio
	N	n	%	95% CI[†]	N	n	%	95% CI[†]	TMB >=10 mut/Mb vs. TMB <10 mut/Mb
Overall	91	30	33.0	(23.5, 43.6)	628	41	6.5	(4.7, 8.8)	5.0
Anal	14	1	7.1	(0.2, 33.9)	73	8	11.0	(4.9, 20.5)	0.7
Cholangiocarcinoma	0	0	--	--	55	2	3.6	(0.4, 12.5)	--
Neuroendocrine	5	2	40.0	(5.3, 85.3)	73	1	1.4	(0.0, 7.4)	29.2
Endometrial	15	7	46.7	(21.3, 73.4)	64	3	4.7	(1.0, 13.1)	10.0
Cervical	15	5	33.3	(11.8, 61.6)	52	6	11.5	(4.4, 23.4)	2.9
Vulvar	10	2	20.0	(2.5, 55.6)	52	2	3.8	(0.5, 13.2)	5.2
Small Cell Lung	26	10	38.5	(20.2, 59.4)	30	4	13.3	(3.8, 30.7)	2.9
Mesothelioma	1	0	0.0	(0.0, 97.5)	80	9	11.3	(5.3, 20.3)	0.0
Thyroid	2	2	100.0	(15.8, 100.0)	75	3	4.0	(0.8, 11.2)	25.0
Salivary	3	1	33.3	(0.8, 90.6)	74	3	4.1	(0.8, 11.4)	8.2

[†] Based on binomial exact confidence interval method.
Subjects with unknown TMB status are not included.
(Database Cutoff Date: 27JUN2019).

In the TE population, responses were durable, with the median DOR not reached in the TMB-H population at the time of the IA10 data cut-off based on Kaplan-Meier (KM) estimation. 66.6% of responders in the TMB-H population had a

DOR ≥ 24 months. In the non-TMB-H population, median DOR was 33.1 months, and 58.5% had a DOR ≥ 24 months. In the DV population, responses were consistent with those observed in the TE population: 66.6% of responders in the TMB-H population had a DOR ≥ 24 months; and in the non-TMB-H population, median DOR was 33.1 months, and 56.6% had a DOR ≥ 24 months.

Clinical response based on ORR was assessed for each biomarker category (i.e., TMB, PD-L1, and MSI-H) in the TE and DV populations (Tables 22 and 23, respectively). ORR was not driven by MSI-H status, as the pooled response rate in TMB-H subjects was similar when MSI-H patients (n=14) were excluded from the TMB-H group. In the TE population, the ORR was 26.1% with MSI-H patients excluded (n=88) compared to an overall ORR of 29.4% (n=102). In the DV population, the ORR was 29.9% with MSI-H patients excluded (n=77) compared to an overall ORR of 33% (n=91). In addition, TMB-H was associated with efficacy of pembrolizumab in participants with either PD-L1 positive (CPS ≥ 1) or PD-L1 negative (CPS < 1) tumors. In TMB-H subjects in the TE population, ORR was 35.3% in patients who were also PD-L1 positive, and ORR was 20.7% in PD-L1 negative patients. Similarly, in TMB-H subjects in the DV population, ORR was 39.3% in patients who were also PD-L1 positive, and ORR was 24% in PD-L1 negative patients. These results indicate that TMB is associated with the efficacy of pembrolizumab monotherapy regardless of PD-L1 expression or MSI-H status.

Table 22. Summary of best objective response based on RECIST 1.1 per central radiology assessment by biomarkers in TE population

TMB Status	Biomarker Category	N	Responders (n)	ORR (95% CI)*
	Participants with CPS	754		
TMB-H [‡]	CPS >=1	68	24	35.3 (24.1, 47.8)
	CPS <1	29	6	20.7 (8.0, 39.7)
Non-TMB-H [‡]	CPS >=1	383	33	8.6 (6.0, 11.9)
	CPS <1	274	9	3.3 (1.5, 6.1)
	Participants with MSI status	767		
TMB-H [§]	MSI-H	14	7	50.0 (23.0, 77.0)
	non-MSI-H	81	23	28.4 (18.9, 39.5)
Non-TMB-H [§]	MSI-H	0	-	-
	non-MSI-H	672	43	6.4 (4.7, 8.5)
	Participants with CPS and MSI Status	732		
TMB-H [‖]	CPS >=1 and MSI-H	9	4	44.4 (13.7, 78.8)
	CPS >=1 and non-MSI-H	55	20	36.4 (23.8, 50.4)
	CPS <1 and MSI-H	5	3	60.0 (14.7, 94.7)
	CPS <1 and non-MSI-H	22	3	13.6 (2.9, 34.9)
Non-TMB-H [‖]	CPS >=1 and MSI-H	0	-	-

	CPS >=1 and non-MSI-H	377	33	8.8 (6.1, 12.1)
	CPS <1 and MSI-H	0	-	-
	CPS <1 and non-MSI-H	264	9	3.4 (1.6, 6.4)

Subjects with unknown TMB status are not included.
[†] Based on binomial exact confidence interval method.
[‡] Subjects with TMB status and PD-L1 status data available.
[§] Subjects with TMB status and MSI-H status data available.
[‖] Subjects with TMB status, PD-L1 status, and MSI-H status data available.
(Database Cutoff Date: 27JUN2019).

Table 23. Summary of best objective response based on RECIST 1.1 per central radiology assessment by biomarkers in DV population

TMB Status	Biomarker Category	N	Responders (n)	ORR (95% CI)[†]
	Participants with CPS	688		
TMB-H [‡]	CPS >=1	61	24	39.3 (27.1, 52.7)
	CPS <1	25	6	24.0 (9.4, 45.1)
Non-TMB-H [‡]	CPS >=1	352	32	9.1 (6.3, 12.6)
	CPS <1	250	8	3.2 (1.4, 6.2)
	Participants with MSI status	701		
TMB-H [§]	MSI-H	14	7	50.0 (23.0, 77.0)
	non-MSI-H	73	23	31.5 (21.1, 43.4)
Non-TMB-H [§]	MSI-H	0	-	-
	non-MSI-H	614	41	6.7 (4.8, 9.0)
	Participants with CPS and MSI Status	671		
TMB-H [‖]	CPS >=1 and MSI-H	9	4	44.4 (13.7, 78.8)
	CPS >=1 and non-MSI-H	50	20	40.0 (26.4, 54.8)
	CPS <1 and MSI-H	5	3	60.0 (14.7, 94.7)
	CPS <1 and non-MSI-H	19	3	15.8 (3.4, 39.6)
Non-TMB-H [‖]	CPS >=1 and MSI-H	0	-	-
	CPS >=1 and non-MSI-H	347	32	9.2 (6.4, 12.8)
	CPS <1 and MSI-H	0	-	-
	CPS <1 and non-MSI-H	241	8	3.3 (1.4, 6.4)

Subjects with unknown TMB status are not included.
[†] Based on binomial exact confidence interval method.
[‡] Subjects with TMB status and PD-L1 status data available.
[§] Subjects with TMB status and MSI-H status data available.
[‖] Subjects with TMB status, PD-L1 status, and MSI-H status data available.
(Database Cutoff Date: 27JUN2019).

A sensitivity analysis was conducted to evaluate the robustness of the ORR estimates in TMB-H patients in the KEYNOTE-158 study to the approximately

25% of participants with missing data in the TE population (260 subjects had TMB status not available of 1,050 total subjects) and 30% of participants with missing data in the DV population (331 subjects had TMB status not available of 1,050 total subjects). The imputation model was driven by a hierarchical Bayesian logistic regression. An analysis of the association between baseline variables, missingness, and clinical outcome to support a missing at random proposition led to the selection of a final model for imputing TMB status containing cancer cohort and objective response. For the TE population, the imputation-based ORR was 29.7% with 95% CI (21.3%, 38.1%). For the DV population, the imputation-based ORR was 30.3% with 95% CI (21.7%, 39%). These results were similar to the to the ORRs for the 790 subjects with valid F1CDx TMB results in the TE population (29.4% [20.8%, 39.3%]) and for the 719 subjects with valid TMB results in the DV population (33% [23.5%, 43.6%]). Therefore, the observed enrichment of ORR in patients with TMB-H tumors is robust to the absence of valid F1CDx TMB scores in some patients enrolled in KEYNOTE-158.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was leveraged to support approval in the pediatric population. The drug indication is for adult and pediatric patients with unresectable or metastatic solid tumors with TMB-H (≥ 10 mut/Mb) that have progressed following prior treatment and who have no satisfactory or alternative treatment options.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator who is a full-time employee of the sponsor and had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Proprietary interest in the product tested held by the investigator

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Molecular and Clinical Genetics Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the F1CDx assay to identify solid tumor patients with high TMB (TMB-H) to be treated with pembrolizumab was demonstrated through a retrospective analysis of KEYNOTE-158 clinical trial specimens. The data from the analytical and clinical validation support the reasonable assurance of safety and effectiveness of the F1CDx assay when used in accordance with the indications for use as an aid in selecting patients with TMB-H (≥ 10 mut/Mb) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Data from the KEYNOTE-158 trial demonstrate that patients who had TMB-H status with respect to the ≥ 10 mut/Mb cut-off received benefit from treatment with pembrolizumab and support the addition of the proposed CDx indication to F1CDx.

B. Safety Conclusions

The F1CDx assay is an *in vitro* diagnostic test, which involves testing of DNA extracted from FFPE tumor tissue. The assay can be performed using DNA extracted from existing (archival) tissue samples routinely collected as part of the diagnosis and patient care. The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Risks of the F1CDx assay are associated with failure of the device to perform as expected or failure to correctly interpret test results and, subsequently, inappropriate patient management decisions in cancer treatment.

Patients with false positive results may undergo treatment with Keytruda® (pembrolizumab) without clinical benefit and may experience adverse reactions associated with pembrolizumab therapy. Patients with false negative results may not be considered for treatment with Keytruda® (pembrolizumab). There is also a risk of delayed results, which may lead to delay of treatment with Keytruda® (pembrolizumab).

C. Benefit-Risk Determination

The probable benefits of the F1CDx assay for the TMB-H (≥ 10 mut/Mb) indication in patients with solid tumors were based on data collected in the KEYNOTE-158 clinical trial, which supports the clinical validation for PMA approval. The clinical benefit of F1CDx for the identification of patients with TMB-H solid tumors was demonstrated in a prospectively-planned retrospective analysis of efficacy and safety data obtained from the Phase 2 multicenter, non-randomized, open-label, multi-cohort study of pembrolizumab monotherapy in multiple types of advanced (unresectable or metastatic) solid cancers that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Potential risk associated with the use of this device are mainly due to: 1) false positives; 2) false negatives, and failure to provide a result; and 3) incorrect interpretation of test results by the user. The risks of the F1CDx assay are associated with the potential mismanagement of patients resulting from false results of the test. Patients who are determined to be false positive by the test may be exposed to a drug that is not beneficial, which may lead to adverse events. A false negative result may prevent a patient from accessing a potentially beneficial drug. However, the risk is mitigated by the clinical and analytical studies for F1CDx detection of TMB as a pan tumor qualitative biomarker with respect to the 10 mut/Mb cut-point. The supporting clinical validation analyses demonstrated that response to pembrolizumab was enriched in TMB-H subjects as determined by the F1CDx assay, resulting in a clinically meaningful ORR of 29.4% in the TE population and 33% in the DV population; by contrast, a lower ORR was observed in non-TMB-H subjects of 6.3% in the TE population and 6.5% in the DV population. Therefore, these results support the use of the F1CDx assay as an aid in selecting patients with TMB-H (≥ 10 mut/Mb) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. The risks of potential false positive and false negative results are partially mitigated by the analytical accuracy study, which showed an acceptable PPA and NPA, as described above, compared to WES.

The clinical and analytical performance of the device included in this submission demonstrate that the assay performance is expected to mitigate the potential risks associated with the use of this device. Although the overall clinical and analytical performance data were supportive of the indication, supplemental data for interfering substances and alteration level precision as well as additional *in silico* analyses for DNA and FFPE slide stability and guard banding studies are needed as conditions of approval to demonstrate robust performance of the F1CDx assay to identify solid tumor patients with TMB-H (≥ 10 mut/Mb) status to be treated with pembrolizumab.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, treatment with pembrolizumab provides meaningful clinical benefit to patients with TMB-H solid tumors, as measured by ORR demonstrated in the KEYNOTE-158 trial. Given the available information, the data supports the conclusion that F1CDx has probable benefit in selecting solid tumor patients with high TMB (≥ 10 mut/Mb) for treatment with pembrolizumab.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the clinical validation study support the performance of F1CDx as an aid for the identification of TMB-H patients with solid tumors for whom Keytruda® (pembrolizumab) may be indicated.

XIII. CDRH DECISION

CDRH issued an approval order on June 16, 2020. The final conditions of approval cited in the approval order are described below.

The applicant will provide the following in a post-approval report:

1. You must provide data evaluating the effects of endogenous interfering substances including necrotic tissue and hemoglobin. The samples selected for this assessment will represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples. The data from this study must be adequate to support that potential endogenous interfering substances in solid tumors do not adversely impact F1CDx TMB calling.

2. You must provide data from an evaluation to support robust TMB calling within the F1CDx stability claims for DNA and FFPE slide stability. You may leverage the existing F1CDx platform DNA and FFPE slide stability data (P170019); however, you must provide the study results with the data generated by the updated F1CDx bioinformatics pipeline v3.3.x. The samples included in the analyses to support DNA and FFPE slide stability with respect to TMB calling, respectively, must represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples. The data from this study must be adequate to support the F1CDx DNA and FFPE slide stability duration claims for TMB calling.

3. You must provide data from a guard banding study to support the performance of F1CDx TMB calling and the impact of process variation with regard to uncertainty in the measurement of DNA concentration at various stages of the process. You may leverage the existing F1CDx platform guard banding data (P170019); however, you must provide the study results with the data generated by the updated F1CDx bioinformatics pipeline v3.3.x. The samples included in the guard banding analysis must represent a range of solid tumors across the intended use population, including sufficient TMB-H (≥ 10 mut/Mb) samples.

4. You must provide the F1CDx intermediate precision results, including repeatability and reproducibility, for the TMB component alterations, i.e., percentage agreement of variant calls among the replicates under repeatability or reproducibility conditions. The data from this supplemental analysis must provide information regarding the F1CDx precision for the underlying component variants included in the TMB score.

5. You must provide a robust and high-quality data set and analysis to support reporting the quantitative TMB score. To support quantitative TMB reporting, you must include clinical validation data from a well-conducted clinical study for the quantitative TMB score measurement (i.e., clinically meaningful efficacy for every unit of change of each continuous output) by an appropriate statistical analysis where patients' response status is the response variable and TMB scores and cancer types

are the predictor variables. Sensitivity analysis should also be conducted on the missing quantitative TMB scores, and quantitative TMB scores should be compared among baseline demographic characteristics for statistical differences. The samples selected for these studies will represent a range of solid tumors and TMB scores across the intended use population. The data from the clinical study must be adequate to support that TMB score is a significant variable to predict patients' response status and clinically meaningful efficacy. The data from the analytical studies must be adequate to support robust quantitative TMB score reporting in the intended use population.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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APPENDIX F

KYMRIAH BOXED WARNING AND PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KYMRIAH safely and effectively. See full prescribing information for KYMRIAH.

KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion
Initial U.S. Approval: 2017

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids. (2.3, 2.4, 5.1)**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed. (5.2)**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. (5.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL) (1.2)	5/2018
Dosage and Administration, Dosage in Adult Relapsed or Refractory (r/r) Diffuse Large B-cell lymphoma (DLBCL) (2.2)	5/2018
Dosage and Administration, Administration (2.3)	5/2018
Warnings and Precautions (5.1, 5.2, 5.5, 5.6, 5.7)	5/2018

----------INDICATIONS AND USAGE----------

KYMRIAH is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. (1.1)
- Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

  Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma (1.2)

----------DOSAGE AND ADMINISTRATION----------

For autologous use only. For intravenous use only.

- Administer a lymphodepleting regimen if needed before infusion of KYMRIAH (2.3)
- Do NOT use a leukodepleting filter.
- Verify the patient's identity prior to infusion. (2)
- Premedicate with acetaminophen and an H1-antihistamine. (2.3)
- Confirm availability of tocilizumab prior to infusion. (2.3, 5.1)
- Dosing of KYMRIAH is based on the number of chimeric antigen receptor (CAR) positive viable T cells.
- **Pediatric and Young Adult B-cell ALL (up to 25 years of age)**
  - For patients 50 kg or less, administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight intravenously. (2.1)
  - For patients above 50 kg, administer 0.1 to 2.5 x 10^8 total CAR-positive viable T cells (non-weight based) intravenously. (2.1)
- **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma**
  - Administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells intravenously. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- **Pediatric and Young Adult B-cell ALL (up to 25 years of age)**

A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients more than 50 kg, suspended in a patient-specific infusion bag for i.v. infusion. (3)

- **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma**

A single dose of KYMRIAH contains 0.6 to 6.0 x 10^8 CAR-positive viable T cells suspended in one or more patient-specific infusion bag(s) for i.v. infusion. (3)

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion. (5.4)
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately. (5.5)
- Prolonged Cytopenias: Patients may exhibit ≥ Grade 3 cytopenias for several weeks following KYMRIAH infusion. Prolonged neutropenia has been associated with increased risk of infection. (5.6)
- Hypogammaglobulinemia: Monitor and provide replacement therapy until resolution. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH. (5.7)
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with KYMRIAH, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH. (5.8)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving KYMRIAH. (5.9)

----------ADVERSE REACTIONS----------

Pediatric and Young Adult B-cell ALL (up to 25 years of age): The most common adverse reactions (incidence greater than 20%) are cytokine release syndrome, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough and delirium. (6)

Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma: The most common adverse reactions (incidence greater than 20%) are CRS, infections-pathogen unspecified, pyrexia, diarrhea, nausea, fatigue, hypotension, edema and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.3, 2.4), Warnings and Precautions (5.1)]*.**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed *[see Warnings and Precautions (5.2)]*.**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

1.1 Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

1.2 Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL)

Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dosage in Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

KYMRIAH is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells.

Based on the patient weight reported at the time of leukapheresis:

- Patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
- Patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells

2.2 Dosage in Adult Relapsed or Refractory (r/r) Diffuse Large B-cell lymphoma (DLBCL)

KYMRIAH is provided as a single-dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells.

- For adult patients: administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells

2.3 Administration

Preparing Patient for KYMRIAH Administration with Lymphodepletion

- Confirm availability of KYMRIAH prior to starting the lymphodepleting regimen.

Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

- Lymphodepleting chemotherapy: Fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine). Infuse KYMRIAH 2 to 14 days after completion of the lymphodepleting chemotherapy.

Adult Relapsed or Refractory (r/r) Diffuse Large B-cell lymphoma (DLBCL)

- Lymphodepleting chemotherapy: Fludarabine (25 mg/m^2 i.v. daily for 3 days) and cyclophosphamide (250 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine).
- Alternate lymphodepleting chemotherapy: bendamustine 90 mg/m^2 i.v. daily for 2 days if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen.
- Infuse KYMRIAH 2 to 11 days after completion of the lymphodepleting chemotherapy.
- Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is less than or equal to 1 x 10^9/L within 1 week prior to KYMRIAH infusion.

Preparation of KYMRIAH for Infusion and Administration

Delay the infusion of KYMRIAH if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy *[see Warnings and Precautions (5.1)]*.

A KYMRIAH dose may be contained in up to three cryopreserved patient specific infusion bags. Verify the number of bags received for the dose of KYMRIAH with the Certificate of Conformance (CoC) and Certificate of Analysis (CoA). Coordinate the timing of thaw of KYMRIAH and infusion in the following manner. Confirm the infusion time in advance, and adjust the start time for thaw so that KYMRIAH is available for infusion when the recipient is ready. If more than one bag has been received for the treatment dose, thaw 1 bag at a time. Wait to thaw/infuse the next bag until it is determined that the previous bag is safely administered.

Preparation of KYMRIAH for Infusion

1. Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
2. Premedicate patient with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to KYMRIAH infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of KYMRIAH.

3. Confirm patient identity: Prior to KYMRIAH preparation, match the patient's identity with the patient identifiers on each KYMRIAH infusion bag(s). KYMRIAH is for autologous use only. Employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

   Note: The patient identifier number may be preceded by the letters DIN or Aph ID.

Figure 1. KYMRIAH Infusion Bag

4. Inspect the infusion bag(s) for any breaks or cracks prior to thawing. If a bag is compromised, do not infuse the contents. Call Novartis at 1-844-4KYMRIAH.
5. Place the infusion bag inside a second, sterile bag in case of a leak and to protect ports from contamination.
6. Thaw each infusion bag one at a time at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Remove bag from thawing device immediately; do not store product bag at 37°C. Once the infusion bag has been thawed and is at room temperature (20°C to 25°C), it should be infused within 30 minutes. Do not wash, spin down, and/or resuspend KYMRIAH in new media prior to infusion.
7. Inspect the contents of the thawed infusion bag for any visible cell clumps. If visible cell clumps remain, gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not infuse KYMRIAH if clumps are not dispersed, the infusion bag is damaged or leaking, or otherwise appears to be compromised. Call Novartis at 1-844-4KYMRIAH.

Administration

8. Confirm the patient's identity with the patient identifiers on the infusion bag.
9. Administer KYMRIAH as an intravenous infusion at 10 mL to 20 mL per minute, adjusted as appropriate for smaller children and smaller volumes. The volume in the infusion bag ranges from 10 mL to 50 mL. Do NOT use a leukocyte-depleting filter. If more than one bag is being infused for the treatment dose, wait to thaw/infuse the next bag until it is determined that the previous bag is safely administered.
   - Prime the tubing prior to infusion with normal saline.
   - Infuse all contents of the infusion bag.
   - Rinse the infusion bag with 10 mL to 30 mL normal saline while maintaining a closed tubing system to assure as many cells as possible are infused into the patient.
   - Cells from all the bag(s) must be infused to complete a single dose

KYMRIAH contains human cells genetically modified with a lentivirus. Follow local biosafety guidelines applicable for handling and disposal of such products.

Monitoring

- Administer KYMRIAH at a certified healthcare facility.

- Monitor patients 2-3 times during the first week following KYMRIAH infusion at the certified healthcare facility for signs and symptoms of CRS and neurologic toxicities *[see Warnings and Precautions (5.1, 5.2)]*.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.4 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1.

Table 1. Treatment of CRS

CRS Severity	Management
Prodromal Syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
CRS requiring mild intervention (one or more of the following): – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
CRS requiring moderate to aggressive intervention (one or more of the following): – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper.

3 DOSAGE FORMS AND STRENGTHS

Pediatric and Young Adult r/r B-cell ALL (up to 25 years of age): A single dose of KYMRIAH contains 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight for patients 50 kg and below or 0.1 to 2.5 x 10^8 CAR-positive viable T cells for patients above 50 kg, suspended in a single patient-specific infusion bag *[see How Supplied/Storage and Handling (16)]*.

Adult r/r DLBCL: A single dose of KYMRIAH contains 0.6 to 6.0 x 10^8 CAR-positive viable T cells, which may be suspended in one or more patient-specific infusion bag(s) *[see How Supplied/Storage and Handling (16)]*.

See the CoA for actual cell count. The volume in the infusion bag ranges from 10 mL to 50 mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. CRS occurred in 54 (79%) of the 68 pediatric and young adult patients with r/r ALL and 78 (74%) of the 106 adult patients with r/r DLBCL receiving KYMRIAH, including ≥ Grade 3 (Penn grading system[1]) in 49% of patients with r/r ALL and in 23% of patients with r/r DLBCL. The median time to onset was 3 days (range: 1-51), and in only two patients was onset after Day 10. The median time to resolution of CRS was 8 days (range: 1-36).

Of the 54 patients with r/r ALL who had CRS, 27 (50%) received tocilizumab. Seven (13%) patients received two doses of tocilizumab, 3 (6%) patients received three doses of tocilizumab, and 14 (26%) patients received addition of corticosteroids (e.g., methylprednisolone). Of the 78 patients with r/r DLBCL who had CRS, 16 (21%) received systemic tocilizumab or corticosteroids. Six (8%) patients received a single dose of tocilizumab, 10 (13%) patients received two doses of tocilizumab, and 10 (13%) patients received corticosteroids in addition to tocilizumab. Two patients with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab, and two patients received corticosteroids for persistent neurotoxicity after resolution of CRS.

Five deaths occurred within 30 days of KYMRIAH infusion. One patient with r/r ALL died with CRS and progressive leukemia, and one patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred. Of the 3 r/r DLBCL patients who died within 30 days of infusion, all had CRS in the setting of stable to progressive underlying disease, one of whom developed bowel necrosis. Among patients with CRS, key manifestations include fever (92% in r/r ALL and r/r DLBCL), hypotension (67% in r/r ALL; 47% in r/r DLBCL), hypoxia (20% in r/r ALL; 35% in r/r DLBCL) and tachycardia (30% in r/r ALL; 14% in r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Delay the infusion of KYMRIAH after lymphodepleting chemotherapy if the patient has unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden *[see Dosage and Administration (2.3)]*.

Ensure that two doses of tocilizumab are available on site prior to infusion of KYMRIAH. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated *[see Dosage and Administration (2.3, 2.4)]*.

Risk factors for severe CRS in the pediatric and young adult r/r B-cell ALL population are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Risk factors for developing severe CRS in adult r/r DLBCL are not known.

5.2 Neurological Toxicities

Neurological toxicities including severe or life-threatening reactions, occurred in 49 (72%) of the 68 patients with r/r ALL and 62 (58%) of the 106 patients with r/r DLBCL following treatment with KYMRIAH, including ≥ Grade 3 in 21% of patients with r/r ALL and 18% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 88% occurred within 8 weeks following KYMRIAH infusion.

Median time to the first event was 6 days from infusion (range: 1-359), and the median duration was 6 days for patients with r/r ALL and 14 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 79% of patients with r/r ALL and 61% of patients with r/r DLBCL. Encephalopathy lasting up to 50 days was noted.

The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

The most common neurological toxicities observed with KYMRIAH include headache (37% in r/r ALL; 21% in r/r DLBCL), encephalopathy (34% in r/r ALL; 16% in r/r DLBCL), delirium (21% in r/r ALL; 6% in r/r DLBCL), anxiety (13% in r/r ALL; 9% in r/r DLBCL), sleep disorders (10% in r/r ALL; 9% in r/r DLBCL), dizziness (6% in r/r ALL; 11% in r/r DLBCL), tremor (9% in r/r ALL; 7% r/r DLBCL) and peripheral neuropathy (4% in r/r ALL; 8% in r/r DLBCL). Other manifestations included seizures, mutism and aphasia.

Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIAH-associated neurological events.

5.3 KYMRIAH REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities

Because of the risk of CRS and neurological toxicities, KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*. The required components of the KYMRIAH REMS are:

- Healthcare facilities that dispense and administer KYMRIAH must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after KYMRIAH infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of CRS and neurological toxicities.

Further information is available at www.kymriah-rems.com or 1-844-4KYMRIAH.

5.4 Hypersensitivity Reactions

Allergic reactions may occur with infusion of KYMRIAH. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40 in KYMRIAH.

5.5 Serious Infections

Infections, including life-threatening or fatal infections, occurred in 95 (55%) of 174 patients with r/r ALL or r/r DLBCL after KYMRIAH infusion. Fifty eight patients (33%) experienced Grade ≥ 3 infections, including fatal infections in 2 patients (3%) with r/r ALL and 1 patient (1%) with r/r DLBCL. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start KYMRIAH treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately *[see Dosage and Administration (2.3)]*.

Febrile neutropenia (≥ Grade 3) was also observed in 37% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells.

Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion.

In the ELIANA study (Study 1), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included neutropenia (40%), and thrombocytopenia (27%) among 52 responding patients. At 56 days following KYMRIAH, 17% and 12% of responding patients had ≥ Grade 3 neutropenia or thrombocytopenia respectively.

In the JULIET study (Study 2), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (40%) and neutropenia (25%) among 106 treated patients.

Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

5.7 Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission (CR) after KYMRIAH infusion.

Hypogammaglobulinemia was reported in 43% of patients treated with KYMRIAH for r/r ALL and 14% of patients with r/r DLBCL *[see Clinical Pharmacology (12.3)]*.

Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.

Immunization with Live Vaccine

The safety of immunization with live viral vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

Pregnant women who have received KYMRIAH may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH.

5.8 Secondary Malignancies

Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurological events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following KYMRIAH infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS AND PRECAUTIONS and in this section reflect exposure to KYMRIAH in two non-randomized, single-arm studies in which 68 pediatric and young adult patients with relapsed/refractory (r/r) B-cell ALL (ELIANA Study) and 106 adults with r/r diffuse large B-cell lymphoma (JULIET Study) received a single dose of CAR-positive viable T cells.

Pediatric and Young Adult r/r B-cell Acute Lymphoblastic Leukemia (ALL) (up to 25 years of age)

Based on a recommended dose which was weight-based, all 68 patients in the ELIANA study (Study 1) received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.1)]*. The most common adverse reactions (> 20%) were cytokine release syndrome (79%), hypogammaglobulinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%),

tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (25%), acute kidney injury (24%), edema (21%), cough (21%), and delirium (21%).

The adverse reactions with greater or equal to 10% incidence for any Grade are summarized in Table 2.

Table 2. Selected Adverse Reactions Anytime After Infusion (≥ 10%) Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL (N = 68)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	37	37
Cardiac disorders		
[a]Tachycardia	26	4
Gastrointestinal disorders		
Nausea	26	3
Diarrhea	26	1
Vomiting	26	1
Constipation	18	0
[b]Abdominal pain	16	3
General disorders and administration site conditions		
Pyrexia	40	15
[c]Fatigue	25	0
[d]Edema	21	1
Chills	10	0
[e]Pain	18	3
Immune system disorders		
Cytokine release syndrome	79	49
[f]Hypogammaglobulinemia	43	7
Infections and infestations		
Infections-pathogen unspecified	41	16
Viral infectious disorders	26	18
Bacterial infectious disorders	19	13
Fungal infectious disorders	13	7
Investigations		
International normalized ratio increased	13	0
Metabolism and nutrition disorders		
Decreased appetite	37	15
Fluid overload	10	7
Musculoskeletal and connective tissue disorders		
Myalgia	15	0
Arthralgia	12	1
Back pain	10	3
Nervous system disorders		
[g]Headache	37	3
[h]Encephalopathy	34	10
Psychiatric disorders		

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
[j]Delirium	21	4
Anxiety	13	3
[i]Sleep disorders	10	0
Renal and urinary disorders		
[k]Acute kidney injury	24	15
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24	18
[l]Cough	21	0
[m]Dyspnea	16	12
Pulmonary edema	16	10
Tachypnea	12	6
Pleural effusion	10	4
Nasal congestion	10	0
Skin and subcutaneous tissue disorders		
[n]Rash	16	1
Vascular disorders		
Hypotension	31	22
Hypertension	19	6

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Abdominal pain includes abdominal pain, abdominal pain upper.*
[c]*Fatigue includes fatigue and malaise.*
[d]*Edema includes face edema, generalised edema, localised edema, edema peripheral.*
[e]*Pain includes pain and pain in the extremity.*
[f]*Hypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased.*
[g]*Headache includes headache and migraine.*
[h]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and unresponsive.*
[j]*Delirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.*
[i]*Sleep disorders includes sleep disorder, insomnia and nightmare.*
[k]*Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis, and blood creatinine increased.*
[l]*Cough includes cough and productive cough.*
[m]*Dyspnea includes dyspnea and respiratory distress, respiratory failure.*
[n]*Rash includes rash, rash maculo-papular, rash popular, and rash pruritic.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were:

Blood and lymphatic system disorders: disseminated intravascular coagulation (9%), histiocytosis lymphocytic hemophagocytosis (7%), coagulopathy (6%), Grade 3 and Grade 4 hypofibrinogenemia with Grade 3 and 4 CRS (16%)

Cardiac Disorders: cardiac arrest (4%), cardiac failure (7%)

Gastrointestinal disorders: abdominal compartment syndrome (1%)

General disorders and administration site conditions: multiple organ dysfunction syndrome (3%)

Immune system disorders: graft versus host disease (1%)

Investigations: activated partial thromboplastin time prolonged (6%)

Nervous System: tremor (9%), dizziness (6%), seizure (3%), speech disorder[a] (3%), motor dysfunction[b] (1%)

Respiratory, thoracic, and mediastinal disorders: respiratory distress (6%), respiratory failure (6%), acute respiratory distress syndrome (4%), oropharyngeal pain (6%)

Metabolism and nutrition disorders: tumor lysis syndrome (6%)

Vascular disorders: capillary leak syndrome (3%), thrombosis (3%)

Eye disorders: Visual impairment (3%)

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[a]*Speech disorder includes aphasia and dysarthria.*
[b]*Motor dysfunction includes muscle spasms.*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 3.

Table 3. Selected Other Laboratory Abnormalities Worsening (> 10%) from Baseline Grade 0-2 to Grade 3-4 Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL based on CTCAE[a] (N = 68)

Laboratory Abnormality	Grade 3 or 4 (%)
Increased Aspartate Aminotransferase	28
Hypokalemia	27
Increased Alanine Aminotransferase	21
Increased bilirubin	21
Hypophosphatemia	19

[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03

All patients experienced neutropenia, anemia and thrombocytopenia. See Table 4 for the incidences of ≥ Grade 3 prolonged thrombocytopenia and prolonged neutropenia in responding patients.

Table 4. Prolonged Cytopenias Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL

Prolonged Cytopenia	N = 52 (%)	N=52 (%)
	Day 28	Day 56
Prolonged neutropenia[a]	40	17
Prolonged thrombocytopenia[a]	27	12

[a]≥ Grade 3 observed within 14 days after Day 28 or Day 56 in responding patients

Adult r/r Diffuse Large B-cell Lymphoma (DLBCL)

In the JULIET study (Study 2) 106 adults with r/r DLBCL received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.2)]*. The most common adverse reactions (incidence > 20%) were cytokine release syndrome, infections-pathogen unspecified, diarrhea, nausea, pyrexia, fatigue, hypotension, edema and headache.

The study population characteristics were: median age of 56 years (range: 22 to 76 years), 79% DLBCL; a median of 3 prior lines of therapy (range: 1-6), 49% had a prior autologous hematopoietic stem cell transplantation, and 33% had received prior radiation therapy. Ninety-nine patients (93%) received lymphodepleting chemotherapy prior to KYMRIAH, that included fludarabine (n = 77) or bendamustine (n = 22).

The adverse reactions with greater than or equal to 10% incidence for any Grade are summarized in Table 5 below.

Table 5. Selected Adverse Reactions Anytime After Infusion Reported in ≥ 10% Following Treatment with KYMRIAH in Adult r/r DLBCL (N = 106)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	17	17
Cardiac disorders		
[a]Tachycardia	13	3
Gastrointestinal disorders		
Diarrhea	31	1
Nausea	27	1
Constipation	16	1
General disorders and administration site conditions		
Pyrexia	34	6
[b]Fatigue	26	7
[c]Edema	23	2

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
[d]Pain	15	3
Chills	13	0
Immune system disorders		
Cytokine release syndrome	74	23
[e]Hypogammaglobulinemia	14	4
Infections and infestations		
Infections-pathogen unspecified	42	25
Investigations		
Weight decreased	11	3
Metabolism and nutrition disorders		
Decreased appetite	12	4
Musculoskeletal and connective tissue disorders		
Arthralgia	10	0
Nervous system disorders		
[f]Headache	21	0
[g]Encephalopathy	16	11
[h]Dizziness	11	1
Renal and Urinary Disorders		
[i]Acute kidney injury	17	6
Respiratory, thoracic and mediastinal disorders		
[j]Cough	19	0
[k]Dyspnea	18	6
Vascular disorders		
[l]Hypotension	26	8

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Fatigue includes fatigue and malaise.*
[c]*Edema includes face edema, generalised edema, localized edema, edema peripheral, peripheral swelling.*
[d]*Pain includes pain and pain in the extremity.*
[e]*Hypogammaglobulinemia includes blood immunoglobulin G decreased, immunoglobulins decreased and hypogammaglobulinaemia.*
[f]*Headache includes headache and migraine.*
[g]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy and thinking abnormal.*
[h]*Dizziness includes dizziness, presyncope, and syncope.*
[i]*Acute kidney injury includes acute kidney injury and blood creatinine increased.*
[j]*Cough includes cough, productive cough, and upper-airway cough syndrome.*
[k]*Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.*
[l]*Hypotension includes hypotension and orthostatic hypotension.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 5 were:

Blood and lymphatic system disorders: disseminated intravascular coagulation (3%), pancytopenia (2%), histiocytosis hematophagic (1%)

Cardiac Disorders: arrhythmia[a] (6%)

Gastrointestinal disorders: vomiting (9%), abdominal pain[b] (9%), anal incontinence (1%)

General disorders and administration site conditions: asthenia (7%), multiple organ dysfunction syndrome (3%)

Infections and infestations: fungal infectious disorders (9%), viral infectious disorders (9%), bacterial infectious disorders (9%)

Musculoskeletal and connective tissue disorders: myalgia (7%), back pain (6%)

Nervous System: peripheral neuropathy[c] (8%), motor dysfunction[d] (6%), speech disorder[e] (3%), seizure[f] (3%), ischemic cerebral infarction (1%), tremor (7%), ataxia (2%)

Psychiatric disorders: anxiety (9%), delirium[g] (6%), sleep disorders[h] (9%)

Respiratory, thoracic, and mediastinal disorders: hypoxia (8%), oropharyngeal pain[i] (8%), pleural effusion (5%) pulmonary edema[j] (3%)

Metabolism and nutrition disorders: fluid overload (3%), tumor lysis syndrome (1%)

Vascular disorders: thrombosis[k] (7%), hypertension (2%), capillary leak syndrome (1%)

Skin and subcutaneous tissue disorders: rash[l] (8%), dermatitis[m] (4%)

Eye disorders: visual impairment[n] (7%)

[a] *Arrhythmia includes atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles.*
[b] *Abdominal pain includes abdominal pain and abdominal pain upper.*
[c] *Peripheral Neuropathy includes paraesthesia,hypoaesthesia, hyperaesthesia,peripheral sensory neuropathy, and neuropathy peripheral.*
[d] *Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.*
[e] *Speech disorder includes speech disorder, aphasia.*
[f] *Seizure includes PTs seizure and status epilepticus.*
[g] *Delirium includes delirium, agitation, and irritability.*
[h] *Sleep disorders includes sleep disorder, insomnia and nightmare.*
[i] *Oropharyngeal pain includes oral pain and oropharyngeal pain.*
[j] *Pulmonary edema includes acute pulmonary edema and pulmonary edema.*
[k] *Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis.*
[l] *Rash includes rash, rash maculo-papular, rash papular and rash pruritic.*
[m] *Dermatitis includes dermatitis, dermatitis acneiform and dermatitis contact.*
[n] *Visual impairment includes vision blurred and visual impairment*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 6.

Table 6. Grade 3 or 4 Laboratory Abnormalities occurring in > 10% of Patients Following KYMRIAH Infusion in Adult r/r DLBCL Patients Based on CTCAE[a] N = 106

Laboratory Parameter	Grade 3 or 4 (%)
Hematology	
Lymphopenia	94
Neutropenia	81
Leukopenia	77
Anemia	58
Thrombocytopenia	54
Biochemistry	
Hypophosphatemia	24
Hypokalemia	12
Hyponatremia	11

[a] CTCAE = Common Terminology Criteria for Adverse Events version 4.03

6.2 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIAH was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients, 86% in ELIANA (Study 1) and 91.4% in JULIET (Study 2) tested positive for pre-dose anti-mCAR19 antibodies prior to KYMRIAH infusion;

Treatment induced anti-mCAR19 antibodies were detected in 5% of the patients in JULIET. However, the preexisting and treatment-induced antibodies were not associated with an impact on clinical response and did not have an impact on the initial expansion and persistence of KYMRIAH. Persistence of KYMRIAH was similar between patients with positive post-infusion anti-mCAR19 antibodies compared with patients with negative post-infusion anti-mCAR19 antibodies. There is no evidence that the presence of preexisting and treatment-induced anti-mCAR19 antibodies impact the safety or effectiveness of KYMRIAH.

T cell immunogenicity responses were not observed in adult r/r DLBCL patients.

7 DRUG INTERACTIONS

HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NATs) tests may yield false-positive results in patients who have received KYMRIAH.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with KYMRIAH use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with KYMRIAH to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH administration should be discussed with the treating physician. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KYMRIAH in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIAH and any potential adverse effects on the breastfed infant from KYMRIAH or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with KYMRIAH.

Infertility

There are no data on the effect of KYMRIAH on fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIAH have been established in pediatric patients with r/r B-cell ALL. Use of KYMRIAH is supported by a single-arm trial *[see Clinical Studies (14.1)]* that included 52 pediatric patients with r/r B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less

than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial.

The safety and efficacy of KYMRIAH in pediatric patients with relapsed or refractory DLBCL has not been established.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients with r/r B-cell ALL. Clinical studies of KYMRIAH did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

KYMRIAH™ (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

KYMRIAH is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells, then transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag(s). The product is thawed prior to administration *[see Dosage and Administration (2.3), How Supplied/Storage and Handling (16)]*. The thawed product is a colorless to slightly yellow suspension of cells.

In addition to T cells, other cell populations, including monocytes, NK cells, and B cells, may be present. The formulation contains 31.25% (v/v) of Plasma-Lyte A, 31.25% (v/v) of 5% Dextrose/0.45% sodium chloride, 10 % Dextran 40 (LMD)/5% Dextrose, 20% (v/v) of 25% Human Serum Albumin (HSA), and 7.5% (v/v) Cryoserv® dimethylsulfoxide (DMSO).

Pediatric and Young Adult r/r B-cell ALL: A single dose of KYMRIAH may contain up to 2.5 x 10^8 CAR-positive viable T cells provided in a patient-specific infusion bag. Based on the patient's weight reported at the time of leukapheresis, one of two possible dose ranges will be prepared for the patient:

- For patients 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells

Adult r/r DLBCL: A single dose of KYMRIAH may contain 0.6 to 6.0 x 10^8 CAR-positive viable T cells provided in one or more patient-specific infusion bag(s).

The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis (CoA) that is shipped with KYMRIAH. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while 4-1BB enhances the expansion and persistence of KYMRIAH. Upon binding to CD19 expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the KYMRIAH cells.

12.3 Pharmacokinetics/Cellular Kinetics

Following infusion, KYMRIAH exhibited an initial rapid expansion followed by a bi-exponential decline in both pediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients, and adult relapsed/refractory diffuse large B-cell lymphoma patients.

A summary of pharmacokinetic parameters of KYMRIAH is provided in Table 7 below.

Table 7. Pharmacokinetic Parameters of KYMRIAH in Pediatric and Young Adult r/r B-cell ALL and Adult r/r DLBCL

Parameter	Summary Statistics	Pediatric ALL Responding Patients	Pediatric ALL Non-Responding Patients	r/r DLBCL Responding Patients (CR and PR)	r/r DLBCL Non-Responding Patients (SD/PD/Unknown)
		N = 62	N = 8	N = 34	N = 34
C_{max} (copies/mcg)	Geometric mean (CV%), n	34,700 (155.4), 61	20,000 (71.6%), 7	5210 (256.5), 33	6450 (408.2), 32
T_{max} (day)	Median [min; max], n	9.91 [0.008; 27], 61	20.0 [0.03; 62.7], 7	9.83 [5.73, 16.8], 33	8.39 [3.04, 27.7], 32
$AUC_{0\text{-}28d}$ (copies/mcg*day)	Geometric mean (CV%), n	318,000 (177.8), 61	156,000 (99.4), 6	58200 (165.1), 30	75800 (292.3), 25
$T_{½}$ (day)	Geometric mean (CV%), n	16.8 (155.9), 54	2.52 (171.9), 3	45.3 (157.7), 21	13.6 (167.0), 22

[1]A total of 7 patients had an early T_{max} (< 0.03 days), the next lowest T_{max} occurred at 5.7 days. Early T_{max} may not be representative of the true maximal expansion, but rather representative of the amount of transgene present in the catheter from which sample was collected.

Description of Pharmacokinetics in Pediatric and Young Adult r/r B-cell ALL (up to 25 years of age)

The C_{max} and $AUC_{0\text{-}28d}$ were approximately 2-fold higher in CR/CRi patients compared with non-responding (NR) patients.

KYMRIAH was present in the blood as well as bone marrow and was measurable beyond 2 years. Blood to bone marrow partitioning suggested that KYMRIAH distribution in bone marrow was 44% of that present in blood at Day 28 while at Months 3 and 6 KYMRIAH distributed at 67% and 69%, respectively, indicating high distribution to bone marrow. Children < 10 years and between 10-18 years of age had 1.5- to 2-fold higher C_{max} and $AUC_{0\text{-}28d}$ than adults. Due to small sample size and high variability, it is difficult to assess the impact of age on the pharmacokinetics of KYMRIAH.

Description of Pharmacokinetics in Adult r/r DLBCL

The C_{max} and $AUC_{0\text{-}28d}$ were similar between responding and non-responding (NR) patients.

KYMRIAH was present in adult r/r DLBCL patients up to 18 months in peripheral blood and up to 9 months in the bone marrow for patients having a complete response. The median time of maximal expansion of transgene levels (T_{max}) in peripheral blood occurred at 9-10 days in both responding and non-responding patients.

Tocilizumab and Corticosteroid use

Some patients required tocilizumab and corticosteroids for the management of CRS. KYMRIAH continues to expand and persist following tocilizumab administration. Patients who have higher expansion tended to have higher CRS Grades *[see Warnings and Precautions (5.1)]*.

Pediatric and young adult r/r B-cell ALL patients (n = 18) treated with tocilizumab had 265% and 183% higher KYMRIAH $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared to patients (n = 44) who did not receive tocilizumab. In addition, patients who received corticosteroids had 89% higher $AUC_{0\text{-}28d}$ compared with patients who did not receive corticosteroids.

Adult r/r DLBCL patients treated with tocilizumab (N = 15) had 199% (n = 11) and 257% (n = 13) higher KYMRIAH $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared to patients (N = 90) who did not receive tocilizumab. In addition, patients who received corticosteroids (N = 11) had 122% and 161% higher $AUC_{0\text{-}28d}$ and C_{max}, respectively, as compared with patients who did not receive corticosteroids (N = 94). Hepatic and renal impairment studies of KYMRIAH were not conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Genotoxicity assays and carcinogenicity assessment in rodent models were not performed for KYMRIAH. *In vitro* expansion studies with transduced T cells (KYMRIAH) from healthy donors and patients showed no evidence for transformation and/or immortalization of T cells. *In vivo* studies in immunocompromised mice did not show signs of abnormal cell growth or signs of clonal cell expansion for up to 7 months after cell injection. A genomic insertion site analysis was performed on KYMRIAH products from 14 individual donors (12 patients and 2 healthy volunteers). There was no evidence for preferential integration near genes of concern, or preferential outgrowth of cells harboring integration sites of concern

No studies on the effects of KYMRIAH on fertility have been conducted.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

The efficacy of KYMRIAH in pediatric and young adults with r/r B-cell precursor ALL was evaluated in an open-label, multicenter single-arm trial (ELIANA, NCT02228096). In total, 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Nine percent of the enrolled patients did not receive the product due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females of median age 12 years (range: 3-23 years). Seventy-three percent of patients were White, 10% were Asian, and 17% were of other races. Six (10%) had primary refractory disease, 30 (48%) had one prior stem cell transplantation, 5 patients (8%) had two stem cell transplantations. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of KYMRIAH. Of the 22 patients who had a WBC count < 1000/µL, 20 received lymphodepleting chemotherapy prior to KYMRIAH while 2 received KYMRIAH infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy.

The efficacy of KYMRIAH was established on the basis of complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative) (Table 8). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52). Table 8 shows the efficacy results from this study.

Table 8. Efficacy Results in Pediatric and Young Adult Patients with r/r B-cell ALL

Results	N = 63
CR/CRi[1,2]	52 (83%)
95% CI	(71%, 91%)
	p < 0.0001
CR[3]	40 (63%)
CRi[4]	12 (19%)
CR or CRi with MRD-negative bone marrow[5,6]	52 (83%)
95% CI	(71%, 91%)
	p < 0.0001
Duration of Remission[7]	**N = 52**
Median (months)	Not reached
95% CI	(7.5, NE[8])

[1]CR/CRi was calculated based on all patients who received KYMRIAH and completed at least 3 months follow-up, or discontinued earlier prior to the data cut-off. Requires remission status to be maintained for at least 28 days without clinical evidence of relapse.
[2] The null hypothesis of CR/CRi less than or equal to 20% was rejected.
[3]CR (complete remission) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and full recovery of peripheral blood counts (platelets greater than 100,000/microliter and absolute neutrophil counts [ANC] greater than 1,000/microliter) without blood transfusion.
[4]CRi (complete remission with incomplete blood count recovery) was defined as less than 5% of blasts in the bone marrow, no evidence of extramedullary disease, and without full recovery of peripheral blood counts with or without blood transfusion.
[5]MRD (minimal residual disease) negative was defined as MRD by flow cytometry less than 0.01%.
[6]The null hypothesis of MRD-negative remission rate less than or equal to 15% was rejected.
[7]DOR (duration of remission) was defined as time since onset of CR or CRi to relapse or death due to underlying cancer, whichever is earlier, censoring for new cancer therapy including stem cell transplantation (N = 52).
[8]Not Estimable.

14.2 Adult Relapsed or Refractory (r/r) Diffuse Large B-cell Lymphoma (DLBCL)

The efficacy and safety of KYMRIAH was evaluated in an open-label, multicenter, single-arm trial (JULIET; NCT02445248). Eligible patients were ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status > 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL.

Following 2 to 11 days after completion of lymphodepleting (LD) chemotherapy consisting of either fludarabine (25 mg/m^2 i.v. daily for 3 days) and cyclophosphamide (250 mg/m^2 i.v. daily for 3 days starting with the first dose of fludarabine) or bendamustine (90 mg/m^2 i.v. daily for 2 days), KYMRIAH was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and LD chemotherapy was permitted to control disease burden. LD chemotherapy could be omitted if the white blood cell count was < 1000 cells/µL. The major efficacy outcome measures were objective response rate per Lugano criteria [2014] as assessed by an independent review committee and duration of response.

Of the 160 patients enrolled, 106 patients received tisagenlecleucel, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of 160 patients enrolled did not receive tisagenlecleucel due to manufacturing failure. Thirty-eight other patients did not receive tisagenlecleucel, primarily due to death (n = 16), physician decision (n = 16), and adverse events (n = 3).

Of the 92 patients receiving KYMRIAH, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and KYMRIAH infusion, among whom the median number of bridging chemotherapy regimens was 1 (range: 1 to 5) with 83% of patients receiving ≤ 2 regimens. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy, prior to KYMRIAH infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to KYMRIAH infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range: 22 to 74 years); 71% male; 90% White, 4% Asian, and 3% Black or African American; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was 3 (range: 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Ninety percent of patients received lymphodepleting chemotherapy (66% of patients received fludarabine and 24% received bendamustine) and 10% did not receive any LD chemotherapy. The median time from leukapheresis and cryopreservation to KYMRIAH infusion was 113 days (range: 47 to 196 days). The median dose was 3.5×10^8 CAR-positive viable T cells (range: 1.0 to 5.2×10^8 cells). Seventy-three percent of patients received KYMRIAH in the inpatient setting.

Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 9 and Table 10). The median time to first response to KYMRIAH (CR or PR) was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR) (Table 12). Of

the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after KYMRIAH infusion.

Table 9. Response Rates in Relapsed or Refractory DLBCL in the JULIET Study

Response Rate	N = 68
Overall Response Rate (ORR) (CR+PR), n (%)	34 (50 %)
(95% CI)	(37.6%, 62.4%)
Complete Response Rate n (%)	22 (32%)
(95% CI)	(21.5%, 44.8%)
Partial Response Rate n (%)	12 (18%)
(95% CI)	(9.5%, 28.8%)

Table 10. Duration of Response[a] (Months) in Relapsed or Refractory DLBCL in the JULIET Study

Duration of Response	Results
Overall DOR for responders (months)	**N = 34**
Median DOR[a,b]	NE
(95% CI)	(5.1, NE)
Range[c]	(0.03+ – 11.3+)
Median Follow-up (95% CI)[b]	9.4 (7.9, 10.8)
DOR if BOR is CR	**N = 22**
Median DOR[a,b]	NE
(95% CI)	(10.0, NE)
Range[c]	(1.5+ – 11.3+)
DOR if BOR is PR	**N = 12**
Median DOR[a,b]	3.4
(95% CI)	(1.0, NE)
Range[c]	(0.03+ – 11.3+)

CR, Complete Response; DOR, Duration of Response; NE, not estimable, PR, partial response
[a]Among all responders. DOR measured from date of first objective response to date of progression or death from relapse.
[b]Kaplan-Meier estimate in months
[c]A + sign indicates a censored value

15 REFERENCES

1. Porter, D. et al (2015). Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia (Table S4A). Sci. Transl. Med., 303ra139. DOI: 10.1126/scitranslmed.aac5415

16 HOW SUPPLIED/STORAGE AND HANDLING

KYMRIAH is supplied as a frozen suspension of genetically modified autologous T cells in an infusion bag(s) labeled for the specific recipient. KYMRIAH is shipped directly to the cell lab associated with the infusion center in a liquid nitrogen Dewar. Product and patient-specific labels are located inside the Dewar.

Ped ALL: NDC 0078-0846-19

DLBCL: NDC 0078-0958-19

- Confirm patient identity upon receipt.
- Store infusion bag(s) in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system.
- Use closed, break-proof, leak-proof containers when transporting infusion bags within the facility.
- Thaw KYMRIAH prior to infusion *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk of manufacturing failure. This has been reported in up to 9% of manufacturing attempts. In case of a manufacturing failure, a second manufacturing of KYMRIAH may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.

Prior to infusion, advise patients of the following risks:

- Cytokine Release Syndrome (CRS) -- Report signs and symptoms of CRS (high fever, difficulty breathing, chills/shaking chills, severe nausea, severe vomiting, severe diarrhea, severe muscle pain, severe joint pain, very low blood pressure, or dizziness/lightheadedness) to their healthcare professional *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

- Neurological Toxicities -- Report altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding, or loss of balance to their healthcare professional *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*.

- Serious Infections -- KYMRIAH may cause serious infections. Advise patients that they will be screened for HBV, HCV, and HIV before collection of cells *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

- Hypogammaglobulinemia -- Patients may need to receive immunoglobulin replacement for an indefinite amount of time following treatment with KYMRIAH. Patients should tell their physician about their treatment with KYMRIAH before receiving a live virus vaccine *[see Warnings and Precautions (5.7), Adverse Reactions (6.1)]*.

- Driving and Engaging in Hazardous Occupations -- Patients should refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after treatment *[see Warnings and Precautions (5.9)]*.

- Prolonged Cytopenia -- Patient may exhibit signs or symptoms associated with bone marrow suppression (i.e., neutropenia, thrombocytopenia and anemia) for several weeks following lymphodepleting chemotherapy and KYMRIAH.

Patients should be instructed to contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH if they get secondary malignancies *[see Warnings and Precautions (5.8)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2018-

MEDICATION GUIDE
KYMRIAH™ (pronounced *KIM-RYE-AH*)
(tisagenlecleucel)

Read this Medication Guide before you start your KYMRIAH treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

What is the most important information I should know about KYMRIAH?

KYMRIAH may cause side effects that are severe or life-threatening. Call your healthcare provider or get emergency help right away if you get any of the following:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- severe muscle or joint pain
- very low blood pressure
- dizziness/lightheadedness

It is important that you tell your health care providers that you have received KYMRIAH. Your healthcare providers may give you other medicines to treat your side effects.

What is KYMRIAH?

KYMRIAH is made from your own white blood cells and is a prescription cancer treatment used in patients up to 25 years old who have acute lymphoblastic leukemia (ALL) that is either relapsing (went into remission, then came back) or refractory (did not go into remission after receiving other leukemia treatments). It is also used in patients with non-Hodgkin lymphoma that has relapsed or is refractory after having at least two other kinds of treatment.

How will I get KYMRIAH?

Since KYMRIAH is made from your own white blood cells, your healthcare provider has to take some of your blood. This is called "leukapheresis." It takes 3 to 6 hours and may need to be repeated. A tube (intravenous catheter) will be placed in your vein to collect your blood.

Your blood cells are frozen and sent to the manufacturing site to make KYMRIAH. It takes about 3-4 weeks from the time your cells are received at the manufacturing site and shipped back to your health care provider, but the time may vary.

Before you get KYMRIAH, your healthcare provider may give you chemotherapy for a few days to prepare your body.

When your body is ready, your healthcare provider will give you KYMRIAH through a tube (intravenous catheter) in your vein. This usually takes less than one hour.

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting KYMRIAH. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

What should I avoid after receiving KYMRIAH?

- Do not drive, operate heavy machinery, or do other dangerous things for 8 weeks after you get KYMRIAH because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, weakness, dizziness, and seizures.
- Do not donate blood, organs, tissues and cells for transplantation.

What are the possible or reasonably likely side effects of KYMRIAH?

The most common side effects of KYMRIAH are:

- difficulty breathing
- fever (100.4°F/38°C or higher)
- chills/shaking chills
- confusion
- severe nausea, vomiting, diarrhea
- severe muscle or joint pain
- very low blood pressure
- dizziness/lightheadedness
- headache

KYMRIAH can increase the risk of life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop fever, chills, or any signs or symptoms of an infection.

KYMRIAH can lower one or more types of your blood cells (red blood cells, white blood cells, or platelets). After treatment, your healthcare provider will test your blood to check for this. Tell your healthcare provider right away if you get a fever, are feeling tired, or have bruising or bleeding.

Having KYMRIAH in your blood may cause a false-positive HIV test result by some commercial tests.

These are not all the possible side effects of KYMRIAH. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KYMRIAH.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use KYMRIAH for a condition for which it was not prescribed.

Talk to your healthcare provider about any concerns. You can ask your healthcare provider for information about KYMRIAH that is written for healthcare professionals.

For more information, go to KYMRIAH.com or call 1-844-NVS-CART (1-844-687-2278).

Manufactured and Distributed by: **Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936.**

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2018

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APPENDIX G

KYMRIAH RISK EVALUATION AND MITIGATION STRATEGY (REMS) DOCUMENT

Risk Evaluation and Mitigation Strategy (REMS) Document

Kymriah (tisagenlecleucel) REMS Program

I. Administrative Information

Application Number: BLA 125646
Application Holder: Novartis Pharmaceuticals Corporation
Initial REMS Approval: 8/2017
Most Recent REMS Update: XX/2019

II. REMS Goals

The goals of the Kymriah® REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities.

III. REMS Requirements

Novartis must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense Kymriah must:

To become certified to dispense	1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours). 2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the hospital and their associated clinics. 3. Have the authorized representative take the Live Training Program provided by the REMS Program. 4. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program. 5. Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS program. 6. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program. 7. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment.

	8. Establish processes and procedures to ensure new staff involved in the prescribing, dispensing, or administration of Kymriah are trained and complete the Knowledge Assessment. 9. Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours). 10. Establish processes and procedures to provide patients with the Patient Wallet Card.
Before infusion	11. Provide the patient with the Patient Wallet Card. 12. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.
To maintain certification to dispense	13. Have the new authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form.
To maintain certification to dispense, if Kymriah has not been dispensed at least once annually from the date of certification in the REMS Program	14. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program. 15. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment.
At all times	16. Report any adverse events suggestive of cytokine release syndrome or neurological toxicities to the REMS Program. 17. Maintain records of staff training. 18. Maintain records that all processes and procedures are in place and are being followed. 19. Comply with audits carried out by Novartis or a third party acting on behalf of Novartis to ensure that all processes and procedures are in place and are being followed.
2. Patients who are prescribed Kymriah:	
Before infusion	1. Receive the Patient Wallet Card.

Novartis must provide training to hospital staff who prescribe, dispense, or administer Kymriah.

The training includes the following educational materials: Live Training Program and Knowledge Assessment. The training must be provided in-person or live webcast.

To support REMS Program operations, Novartis must:

1. Ensure Kymriah is only distributed to certified hospitals and their associated clinics.
2. Establish and maintain a REMS Program website, www.Kymriah-REMS.com. The REMS Program website must include the option to print the PI, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website.
3. Make the REMS Program website fully operational and all REMS materials available through website or call center.
4. Establish and maintain a REMS Program call center for REMS participants at 1-844-459-6742.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax, and phone.
7. Notify hospitals and their associated clinics after they become certified in the REMS Program.

To ensure REMS participants' compliance with the REMS Program, Novartis must:

8. Verify annually that the designated authorized representative for certified hospitals and associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Kymriah distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
10. Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of Kymriah to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Novartis' ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the Kymriah REMS Program based on monitoring and evaluation of the Kymriah REMS Program.

IV. REMS Assessment Timetable

Novartis must submit REMS Assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (8/30/2017). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Novartis must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Kymriah REMS:

Enrollment Forms:

Health Care Setting:

1. Hospital Enrollment Form

Training and Educational Materials

Patient:

2. Patient Wallet Card

Health Care Setting:

3. Live Training Program
4. Knowledge Assessment

Other Materials

5. REMS Program website

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Phone: 1-844-4KYMRIAH
Fax: 1-844-590-0840
E-mail: KymriahREMS@ubc.com
www.Kymriah-REMS.com

KYMRIAH® REMS PROGRAM HOSPITAL ENROLLMENT FORM

Instructions

Kymriah is only available through the Kymriah Risk Evaluation and Mitigation Strategy (REMS) Program. Hospitals and their associated clinics that dispense Kymriah must be certified in the Kymriah REMS Program. In order to become specially certified to dispense Kymriah, hospitals and associated clinics must designate an Authorized Representative to:

- **Complete the certification process by completing the *Kymriah REMS Program Hospital Enrollment Form* on behalf of the hospital and their associated clinics.**
- **Oversee implementation and compliance with the Kymriah REMS Program requirements as outlined below.**

Please complete all required fields below and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail.

If you have any questions, require additional information, or need further copies of any of the Kymriah REMS Program documents, please visit the REMS program website at www.Kymriah-REMS.com, or call the Kymriah REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

Authorized Representative Responsibilities

On behalf of my hospital/associated clinics, I understand and agree to comply with the following Kymriah REMS Program requirements:

- I must complete the *Kymriah REMS Live Training Program* and successfully complete the *Kymriah REMS Program Knowledge Assessment*.
  - Those participating in Kymriah clinical trials and/or the pre-approval safety training will be exempt from the live training but will be required to review the REMS materials on the REMS website.
- I must submit this completed *Kymriah REMS Program Hospital Enrollment Form* to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- I must submit the completed *Kymriah REMS Program Knowledge Assessment* form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- I will oversee implementation and compliance with the Kymriah REMS Program.
- I will ensure that my hospital and associated clinics will establish processes and procedures that are subject to monitoring by Novartis Pharmaceuticals Corporation (NPC), or a third party acting on behalf of NPC to help ensure compliance with the requirements of the Kymriah REMS Program, including the following, before administering Kymriah:
  a. Ensuring all relevant staff involved in the prescribing, dispensing or administering of Kymriah are trained on the REMS Program requirements and successfully complete the *Kymriah REMS Program Knowledge Assessment*, and maintain records of staff training.
  b. Performing routine re-education of all staff involved in the prescribing, dispensing or administering of Kymriah and maintaining records of re-training if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
  c. Prior to dispensing Kymriah, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on site for each patient and are ready for immediate administration (within 2 hours).
  d. Prior to dispensing Kymriah, provide patients and their guardians the *Patient Wallet Card*.

As a condition of certification, the certified hospital must:

- Ensure that if the hospital designates a new authorized representative, the new authorized representative must review the *Kymriah REMS Live Training Program*, complete the *Kymriah REMS Program Knowledge Assessment*, complete a new *Kymriah REMS Program Hospital Enrollment Form* and submit the forms via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com.
- Report any adverse events suggestive of cytokine release syndrome or neurological toxicities of Kymriah to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at https://psi.novartis.com or 1-888-669-6682.
- Dispense Kymriah to patients only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- Maintain documentation of all processes and procedures for the Kymriah REMS Program and provide documentation upon request to Novartis, or a third party acting on behalf of Novartis.
- Comply with audits by Novartis, or a third party acting on behalf of Novartis.

Hospital Information (All Fields Required)

Hospital Name:		
Address:		
City:	State:	Zip Code:
Phone:	Fax:	

Authorized Representative Information (All Fields Required)

First Name:	Last Name:	
Credentials: ☐ DO ☐ MD ☐ R.Ph ☐ NP/PA ☐ Other (please specify)		
Phone:	Fax:	E-mail:
Authorized Representative Signature:		**Date (MM/DD/YYYY):**

Next Steps

1. Please complete all required fields above and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail.
2. Completion of this form does not guarantee your hospital will be certified to administer Kymriah.
3. NPC will assess and provide confirmation of certification via E-mail after processing this enrollment form and a successfully completed Kymriah REMS Program Knowledge Assessment form.
4. Product orders cannot be placed until hospital certification is complete.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

KYMRIAH
(tisagenlecleucel)

3/19

KYM-120/302

PATIENT WALLET CARD

Have This Card With You At All Times

Show It To Any Doctor That Sees You And When You Go To The Hospital

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting Kymriah. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

Patient Information

Kymriah may cause side effects that are severe or life-threatening.

Call your oncologist or go to the emergency room if these signs appear.

SIGNS AND SYMPTOMS MAY INCLUDE:

- Difficulty breathing
- fever (100.4°F/38°C or higher)
- Chills/shaking chills
- Confusion
- Severe nausea, vomiting, diarrhea
- Severe muscle or joint pain
- Very low blood pressure
- Dizziness/lightheadedness
- Headache

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Novartis Pharmaceuticals Corporation

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INFORMATION FOR THE HEALTHCARE PROVIDER

This patient has received Kymriah (CAR-T cell) therapy

Following Kymriah treatment, Cytokine Release Syndrome (CRS) can happen. It may include neurological toxicities.

Please contact his/her treating oncologist in the following situations:

- before giving steroids or cytotoxic medications
- if the patient has a serious infection
- before the patient undergoes an invasive procedure

fold fold

Date received Kymriah:_____

Oncologist Name (for Kymriah therapy):_____

Phone Number:_____

Kymriah is a CD19-directed genetically modified autologous T Cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse and adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma

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REMS PROGRAM KNOWLEDGE ASSESSMENT

Hospital Information (All Fields Required)

Hospital Name:		
Address:		
City:	State:	Zip Code:
Phone:	Fax:	
First Name:	Last Name:	
Credentials: ☐ DO ☐ MD ☐ R.Ph ☐ NP/PA ☐ Other (please specify)		
Phone:	Fax:	E-mail:
Authorized Representative: ☐ Yes ☐ No		
Signature:		Date (MM/DD/YYYY):

If you are the Authorized Representative for your hospital, please complete and submit the knowledge assessment to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com, or complete online at www.Kymriah-REMS.com. All others please complete online or send the form to your hospital's Authorized Representative. Completion of this knowledge assessment does not guarantee your hospital will be certified to administer Kymriah®.

1- Kymriah® (tisagenlecleucel) is indicated for the treatment of:
- ❍ A- Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- ❍ B- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
- ❍ C- Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
- ❍ D- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- ❍ E- Both B and D

2- Delay Kymriah infusion if the patient has any of the following, **except**:
- ❍ A- Active uncontrolled infection
- ❍ B- Worsening of leukemia burden following lymphodepleting chemotherapy
- ❍ C- Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
- ❍ D- Active graft versus host disease
- ❍ E- Unresolved serious adverse reactions from preceding chemotherapies

3- Clinically, patients with CRS can manifest with the following signs and symptom **except**:
- ❍ A- High grade fever
- ❍ B- Hypotension
- ❍ C- Hair loss
- ❍ D- Respiratory distress
- ❍ E- Hypofibrinogenemia

4- Which one of the following is true regarding the time to onset of CRS? It typically occurs:
- ❍ A- 7-14 days following Kymriah infusion, with a median time to onset of 10 days
- ❍ B- 7-21 days following Kymriah infusion, with a median time to onset of 10 days
- ❍ C- Median time to onset is 3 days following Kymriah infusion
- ❍ D- Rarely starts during the first week following Kymriah infusion

5-As a part of planning for Kymriah infusion, it is required to have two doses of tocilizumab on site for each patient prior to dispensing and administering Kymriah to patients.

❍ A- True
❍ B- False

6- As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah.

❍ A- True
❍ B- False

7- A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high grade fever (40-41°C) with neutropenia and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O_2 saturation 97%). He was started on norepinephrine at a low dose and O_2 supplement via nasal cannula. All of the following are correct, **except**:

❍ A- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
❍ B- Sepsis should be considered and treated adequately with broad spectrum antibiotics
❍ C- Start myeloid growth factor to expedite neutrophil recovery
❍ D- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

8- Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, **except**:

❍ A- May occur in the context of CRS, following the resolution of CRS or without CRS
❍ B- Symptoms range from headache and confusion to encephalopathy and seizures
❍ C- The majority of events were transient and self-limiting
❍ D- Can be prevented with the administration of tocilizumab

9- Which one of the following about neurological toxicities as a result of Kymriah is correct:

❍ A- Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
❍ B- Management includes supportive care
❍ C- Majority occurred within 8 weeks following Kymriah infusion
❍ D- All of the above

10-A 30-year-old female with multiply relapsed DLBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:

❍ A- The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
❍ B- The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving Kymriah
❍ C- The patient should carry the Kymriah patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
❍ D- All of the above

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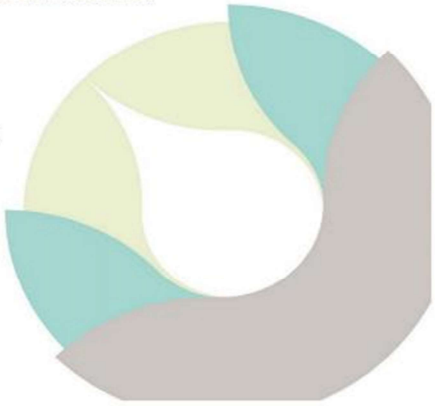
Risk Evaluation and Mitigation Strategy (REMS): Cytokine release syndrome and neurological toxicities

A REMS is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of KYMRIAH outweigh its risks.

The purpose of the KYMRIAH REMS is to inform healthcare providers of the risks of cytokine release syndrome and neurological toxicities observed with KYMRIAH.



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This educational module contains information on selected KYMRIAH-associated adverse events, including cytokine release syndrome and neurological toxicities, observed in clinical trials for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, and adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

2

KYMRIAH Indication

- KYMRIAH (tisagenlecleucel), previously known as CTL019, is a CD19-directed genetically modified autologous T cell immunotherapy

- Indicated for the treatment of:
  - Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

  - Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
    - Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

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3

KYMRIAH REMS Goal

- The goals of the KYMRIAH REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:
  - Ensuring that hospitals and their associated clinics that dispense KYMRIAH are specially certified and have on-site, immediate access to tocilizumab.
  - Ensuring those who prescribe, dispense, or administer KYMRIAH are aware of how to manage the risks of CRS and neurological toxicities.

KYMRIAH (tisagenlecleucel)

KYMRIAH REMS Materials

- KYMRIAH REMS Live Training Program Slides
  - Provides education on the risks of CRS and neurological toxicities
  - Addresses serious clinical manifestations, timing of events, monitoring and management, and importance of patient education
  - KYMRIAH REMS Program overview
- KYMRIAH REMS Program Patient Wallet Card
  - For patients and their guardians to keep with them at all times, reminds them of signs and symptoms that require immediate medical attention
  - Instructions to stay within 2 hours of treatment site for at least 4 weeks

KYMRIAH (tisagenlecleucel)

KYMRIAH REMS Materials, cont.

- KYMRIAH REMS Program Knowledge Assessment
  - Reinforces the messages about CRS and neurological toxicities, 10 questions, multiple choice
  - All staff involved in ordering, prescribing, or administering must successfully complete via email, in-person, fax, or online
- KYMRIAH REMS Program Hospital Enrollment Form
  - Must be completed by the authorized representative (via email, fax, or online) to certify the hospital
- KYMRIAH REMS Program Website
  - Holds all REMS educational tools for download/printing

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Site Certification

- To become certified* to dispense KYMRIAH, hospitals and their associated clinics must:
  - Designate an authorized representative to complete the certification process by submitting the completed KYMRIAH REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics
  - Ensure the authorized representative oversees implementation and compliance with KYMRIAH REMS Program requirements

***Completion of the enrollment form and knowledge assessment does not guarantee your hospital will be certified to administer KYMRIAH. Please contact 1-844-4KYMRIAH(1-844-459-6742) for more information**

7

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

Authorized Representative

- Completes KYMRIAH REMS Live training program and successfully completes KYMRIAH REMS Program Knowledge Assessment
- Ensures all relevant staff are trained and successfully complete knowledge assessment and maintain records of training
- Put processes and procedures in place to ensure that:
  - New staff is trained
  - Staff retrained if KYMRIAH has not been dispensed once annually from certification
  - Prior to dispensing KYMRIAH:
    - Verify 2 doses of tocilizumab are available onsite for each patient and ready for immediate administration
    - Provide patients and their guardians with KYMRIAH REMS Program Patient Wallet Card to inform them:
      - Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.
      - Importance of staying within 2 hours of the certified hospital and their associated clinic for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor.

KYMRIAH® (tisagenlecleucel) Suspension for Intravenous

8

Conditions of Certification

- Recertify in the KYMRIAH REMS Program if the hospital and their associated clinics designate a new authorized representative.
- Report any adverse events suggestive of CRS or neurological toxicities.
- Maintain documentation that all processes and procedures are in place and are being followed for the KYMRIAH REMS Program and provide that documentation upon request to Novartis or a third party acting on behalf of Novartis.
- Comply with audits by Novartis or a third party acting on behalf of Novartis to ensure that all training, processes and procedures are in place and are being followed for the KYMRIAH REMS Program.
- Dispense KYMRIAH only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.

KYMRIAH® (tisagenlecleucel)

KYMRIAH Boxed Warning

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH.

Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS.

Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

10

KYMRIAH-associated Cytokine Release Syndrome

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Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, was the most common adverse event in the KYMRIAH pivotal clinical trials in pediatric and young adult patients with r/r ALL and adult patients with r/r DLBCL
- In clinical trials, CRS was effectively managed in the majority of patients based on a CRS management algorithm
- Patients with CRS may require admission to the intensive care unit for supportive care

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

CRS in Pediatric and young adult patients up to 25 years of age with r/r B-cell ALL

- In the KYMRIAH pivotal clinical trial in pediatric and young adult patients with r/r B-cell ALL (ELIANA study)
  - 79% of patients developed CRS of any grade (Penn grading system); 49% developed CRS ≥ grade 3
- The median time to onset of CRS was 3 days (range: 1-51 days), and in only two patients was onset after day 10*
- The median time to resolution of CRS was 8 days (range: 1-36 days)*
- Of the patients who developed CRS, 50% received tocilizumab:
  - 13% received two doses, 6% received three doses of tocilizumab
  - 26% received addition of corticosteroids (e.g. methylprednisolone).

*Data for both ALL and DLBCL

13

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

Risk Factors for severe CRS in patients up to 25 years of age with r/r B-cell ALL

Pre-infusion tumor burden	• High pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy were associated with severe CRS • Efforts should be made to lower and control the patient's tumor burden prior to KYMRIAH administration
Infection	• Infections occur concurrently with CRS, may increase the risk of fatal events • Prior to administration of KYMRIAH, provide appropriate prophylactic and therapeutic treatment for infection, and ensure complete resolution of any existing infection
Onset of fever	• Early onset of fever can be associated with severe CRS
Inflammatory processes	• Active inflammatory processes may increase the risk of severe CRS

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

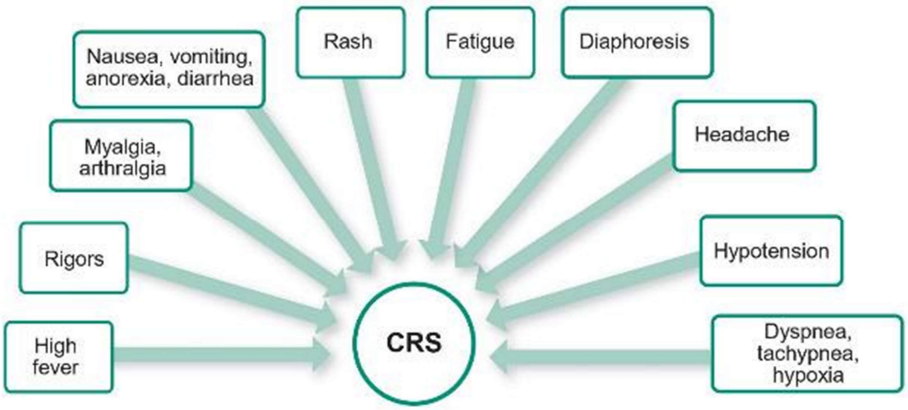
CRS in adult patients with r/r DLBCL

- In the KYMRIAH pivotal clinical trial in adult patients with r/r DLBCL (JULIET study)
  - 74% of patients developed CRS of any grade (Penn grading system); 23% developed CRS ≥ grade 3
- The median time to onset of CRS was 3 days (range: 1-51 days) following KYMRIAH infusion, and in only two patients was onset after day 10.* The median duration of CRS was 8 days (range: 1-36 days)*
- Of the patients who developed CRS, 21% received tocilizumab or corticosteroids:
  - 8% received one dose of tocilizumab and 13% received two doses of tocilizumab
  - 13% of patients received corticosteroids in addition to tocilizumab
  - Two patients received corticosteroids for CRS, without concomitant tocilizumab.
- Risk factors for developing severe CRS in adult with r/r DLBCL are not yet known

*Data for both ALL and DLBCL

KYMRIAH® (tisagenlecleucel)

CRS signs and symptoms



Diagnosis based on clinical symptoms and events

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

16

CRS: associating events and organ dysfunction

Liver	• Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia
Renal	• Renal insufficiency, may require dialysis
Respiratory	• Respiratory failure, pulmonary edema
Cardiac	• Transient cardiac insufficiency • Transient arrhythmia
Cytopenias lasting > 28 days	• Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAH infusion or until CRS has resolved (may exacerbate CRS)

17

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

CRS: associating events and organ dysfunction, cont.

Coagulopathy with hypofibrinogenemia

- May accompany severe CRS
- Prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), and low fibrinogen
- May result in bleeding
- Monitor coagulation panel (platelet count, PT/PTT and fibrinogen), replace as needed

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

Delay KYMRIAH infusion if the patient has:

- Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension)
- Active uncontrolled infection
- Active graft versus host disease (GVHD)
- Worsening of leukemia burden following lymphodepleting chemotherapy

KYMRIAH® (tisagenlecleucel) Suspension for Intravenous

CRS: Management

- Management of CRS is based solely upon clinical presentation
- Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
- At the first sign of CRS, immediately evaluate patient for hospitalization
- Evaluate for and treat other causes of fever, hypoxia, and hypotension (e.g. infection)
- CRS should be managed according to the KYMRIAH CRS management algorithm
- Interleukin-6 (IL-6) receptor antagonist, tocilizumab, is recommended for the management of moderate or severe CRS associated with KYMRIAH
- Before KYMRIAH infusion, verify two doses of tocilizumab are available on site for each patient and ready for immediate administration

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

CRS: Management, cont.

- Corticosteroids may be administered in cases of life-threatening emergencies
- Due to the known lympholytic effect of corticosteroids:
  - Do not use corticosteroids for premedication except in the case of a life-threatening emergency
  - Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies
  - Physiologic replacement doses are allowed for adrenal insufficiency

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

KYMRIAH CRS management algorithm (1/2)

CRS Severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
CRS requiring mild intervention (one or more of the following): – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

KYMRIAH CRS management algorithm, cont. (2/2)

CRS Severity	Management
CRS requiring moderate to aggressive intervention (one or more of the following): – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) • Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. • If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alterative measures for treatment of CRS • Limit to a maximum total of 4 doses of tocilizumab doses • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper.

Definition of high-dose vasopressors

Vasopressor	Dose for ≥ 3 Hours	
	Weight-based dosing	**Flat dosing (if this is institutional practice)**
Norepinephrine monotherapy	≥ 0.2 µg/kg/min	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min	≥ 1000 µg/min
Phenylephrine monotherapy	≥ 2 µg/kg/min	≥ 200 µg/min
Epinephrine monotherapy	≥ 0.1 µg/kg/min	≥ 10 µg/min
If on vasopressin	High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula)[a]	vasopressin + norepinephrine equivalent of ≥ 10 µg/min[b]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 µg/kg/min[a]	Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula)[b]

VASST* Vasopressor Equivalent Equation

[a] Norepinephrine-equivalent dose [body weight adjusted dosing (µg/kg/min dosing)] = [norepinephrine (µg/kg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/kg/min)] + [phenylephrine (µg/kg/min) ÷ 10][1]

[b] Norepinephrine-equivalent dose [flat dosing (µg/min)] = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10][2,3,4]

*See references slide

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

KYMRIAH-associated neurological toxicities

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Neurological toxicities

- Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH
- Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy and delirium
- The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion and were transient
- In KYMRIAH pivotal clinical trials, neurological toxicities, occurred after KYMRIAH infusion as follows:
  - In pediatric and young adult patients with r/r ALL (ELIANA study): seen in 72% of patients, with ≥ grade 3 in 21% of patients
  - In adult patients with r/r DLBCL (JULIET study): seen in 58% of patients, with ≥ grade 3 in 18% of patients
- All patients with r/r ALL and the majority of patients with r/r DLBCL were treated with supportive care alone.
  - 2 patients with r/r DLBCL received corticosteroids for persistent neurotoxicity after resolution of CRS
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of neurological toxicities.

KYMRIAH (tisagenlecleucel)

26

Neurological toxicities, cont.

Types of neurological toxicities	• Early: concurrent with CRS and high fevers during the development and at the time of maximal grade of CRS • Delayed onset: as CRS is resolving or following the resolution of CRS • In the absence of CRS
Onset and duration	• The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion • The majority of events were transient
Clinical presentation	• Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy, delirium or related events • Anxiety, dizziness, headache, peripheral neuropathy, and sleep disorders were the other most common neurological toxicities • Other related manifestations: seizures, mutism and aphasia • Patients should be monitored for neurological toxicities during and after resolution of CRS

KYMRIAH® (tisagenlecleucel) Suspension for Infusion

Neurological toxicities, cont.

Diagnostic work-up	• Neurological work-up should be considered, as appropriate, to exclude other causes for neurological symptoms
Management	• Supportive care should be given for KYMRIAH-associated neurological toxicities during or after resolution of CRS

Patients / guardians education	• Patients/guardians:
	  • Should be advised about the risk and symptoms of neurological toxicities that they may experience
	  • Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention
	  • Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities
	  • Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH.

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

Patients / Guardians Education

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Patients/Guardians education

Advise patients/guardians of the risks of CRS and neurological toxicities and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities

Patients/guardians should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor

Patients/guardians should carry KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention

Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH

KYMRIAH® (tisagenlecleucel) Suspension for IV Infusion

30

Reporting Adverse Events

Healthcare providers are encouraged to report suspected adverse events of Kymriah® to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at https://psi.novartis.com or by calling 1-888-669-6682.

KYMRIAH® (tisagenlecleucel) Suspension for Intravenous Infusion

For further information, please visit
www.KYMRIAH-REMS.com or call
1-844-4KYMRIAH(1-844-459-6742)

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References

1. Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric. The University of Texas MD Anderson Cancer Center website. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-pedi-web-algorithm.pdf. Published January 30, 2018. Accessed March 4, 2019. The pediatric guideline was approved by the Executive Committee of the Medical Staff on 1/30/2018.
2. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10;124(2):188-95. Erratum in: Blood. 2015 Aug 20;126(8):1048. Dosage error in article text.
3. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Supplementary material. Sci Transl Med. 2015 Sep 02;7(303):303ra139. doi:10.1126/scitranslmed.aac5415
4. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358(9):877-87. doi:10.1056/NEJMoa067373

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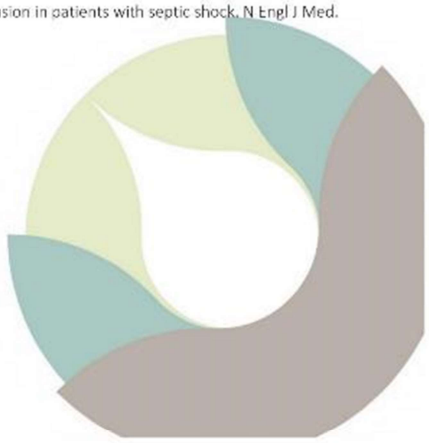


Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

3/19

KYD-1207304

KYMRIAH
(tisagenlecleucel)

Risk Evaluation and Mitigation Strategy
(REMS)

REMS Safety Information

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has required a REMS for Kymriah® (tisagenlecleucel).

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.

KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS.

Goals of the REMS

The goals of the Kymriah® (tisagenlecleucel) REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab
- Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities

Kymriah is only available at select treatment centers. For more information, please call the REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

To learn more about Kymriah and its serious risks and clinical manifestations, read the Prescribing Information and the Medication Guide.

The *Kymriah REMS Program Patient Wallet Card (English and Spanish)*, the *Kymriah REMS Live Training Program Slides*, and *Kymriah REMS Program Knowledge Assessment* can be ordered through the REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

You are encouraged to report suspected adverse events with Kymriah to Novartis at https://psi.novartis.com or 1-888-669-6682 or the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

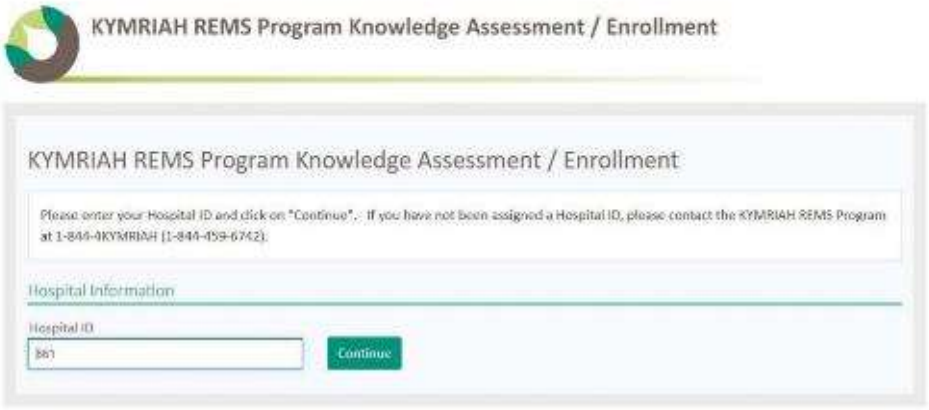
Continue to check back on this website; it will be updated to include additional or new information intended to assist in the proper communication of the serious risks associated with Kymriah.

- Kymriah Prescribing Information
- Kymriah Medication Guide
- Kymriah REMS Live Training Program Slides
- Kymriah REMS Program Knowledge Assessment
- Kymriah REMS Program Patient Wallet Card
- Kymriah REMS Program Patient Wallet Card (Español)

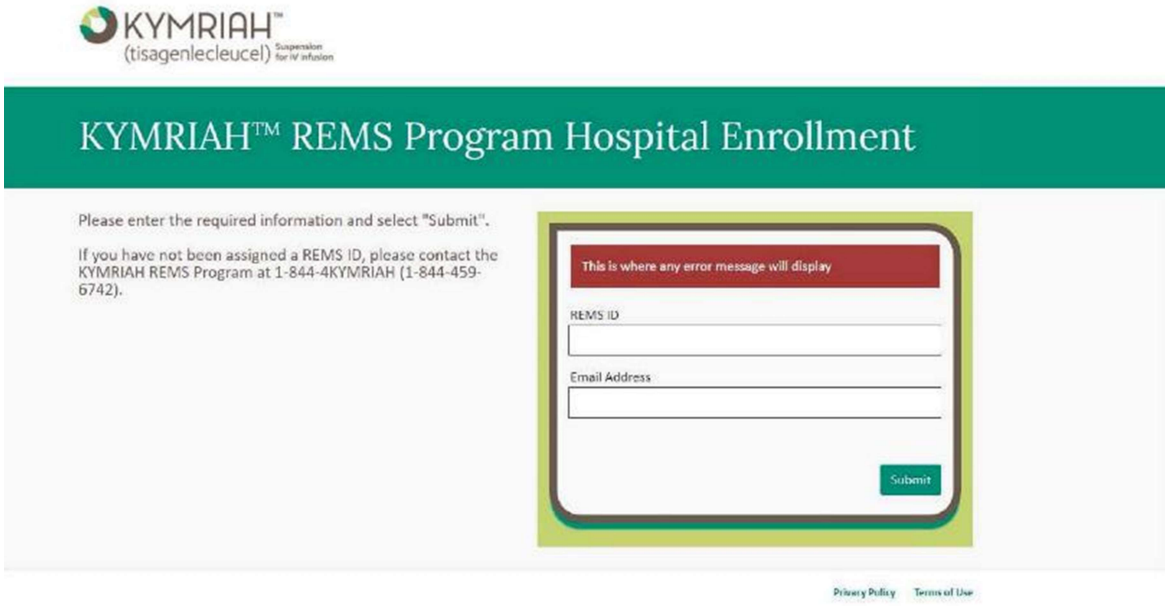
INDICATION:
Kymriah is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse and adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Click here to complete the Knowledge Assessment online


KYMRIAH REMS Program Knowledge Assessment / Enrollment
KYMRIAH REMS Program Knowledge Assessment / Enrollment
Please enter your Hospital ID and click on "Continue". If you have not been assigned a Hospital ID, please contact the KYMRIAH REMS Program at 1-844-4KYMRIAH (1-844-459-6742).
Hospital Information
Hospital ID
Continue


KYMRIAH REMS Program Knowledge Assessment / Enrollment
KYMRIAH REMS Program Knowledge Assessment / Enrollment
Please use the Training Assessment link below to navigate to the online training and assessment. If you are the Authorized Representative for your Hospital and you have not yet completed an Enrollment Form, please use the Hospital Enrollment link below to navigate to the online hospital enrollment form. If you are not sure if you have previously completed the Training Assessment or your Hospital Enrollment Form, please contact the Kymriah REMS Program at 1-844-4KYMRIAH for clarification.
XXXXXXXXXX - HOSPITAL NAME
Continue to
Training Assessment
Continue to
Hospital Enrollment


KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion
KYMRIAH™ REMS Program Hospital Enrollment
Please enter the required information and select "Submit".
If you have not been assigned a REMS ID, please contact the KYMRIAH REMS Program at 1-844-4KYMRIAH (1-844-459-6742).
This is where any error message will display
REMS ID
Email Address
Submit
Privacy Policy
Terms of Use

KYMRIAH™
(tisagenlecleucel)

KYMRIAH™ REMS Program Hospital Enrollment

KYMRIAH™ REMS Program Hospital Enrollment Form

Kymriah is only available through the Kymriah Risk Evaluation and Mitigation Strategy (REMS) Program. Hospitals and their associated clinics that dispense Kymriah must be certified in the Kymriah REMS Program. In order to become specially certified to dispense Kymriah, hospitals and associated clinics must designate an Authorized Representative to:

- Complete the certification process by completing the Kymriah REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics.
- Oversee implementation and compliance with the Kymriah REMS Program requirements as outlined below.

Please complete all required fields below and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840, E-mail at KymriahREMS@ubc.com or complete it online at www.Kymriah-REMS.com. You will receive a confirmation via E-mail.

If you have any questions, require additional information, or need further copies of any of the Kymriah REMS Program documents, please visit the REMS program website at www.Kymriah-REMS.com, or call the Kymriah REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

To submit this form, please complete the fields below. Required fields are denoted by "*".

Hospital Information

*Hospital Name | *Hospital National Provider Identifier (NPI)#

*Address | *City | *State – Please Select – | *Zip Code

*Phone | *Fax

Authorized Representative Information

*First Name | *Last Name

*Credentials:
○ DO ○ MD ○ R.Ph ○ NP/PA ○ Other

Other

*Phone | *Fax | *Email

Authorized Representative Responsibilities

On behalf of my hospital/associated clinics, I understand and agree to comply with the following Kymriah REMS Program requirements:

☐ *I must complete the *Kymriah REMS Live Training Program* and successfully complete the *Kymriah REMS Program Knowledge Assessment*.
- Those participating in Kymriah clinical trials and/or the per-approval safety training will be exempt from the live training but will be required to review the REMS materials on the REMS website.

☐ *I must submit this completed *Kymriah REMS Program Hospital Enrollment Form* to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.

☐ *I must submit the completed *Kymriah REMS Program Knowledge Assessment* form to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.

☐ *I will oversee implementation and compliance with the Kymriah REMS Program.

☐ *I will ensure that my hospital and associated clinics will establish processes and procedures that are subject to monitoring by Novartis Pharmaceuticals Corporation (NPC), FDA, or a third party acting on behalf of NPC or FDA to help ensure compliance with the requirements of the Kymriah REMS Program, including the following, before administering Kymriah:
a. Ensure that all relevant staff involved in the prescribing, dispensing or administering of Kymriah are trained on the REMS Program requirements and successfully complete the Kymriah REMS Program Knowledge Assessment, and maintain records of staff training.
b. Performing routine or occasional all staff involved in the prescribing, dispensing or administering of Kymriah and maintaining records of training if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
c. Prior to dispensing Kymriah, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on site for each patient and are ready for immediate administration (within 2 hours).
d. Prior to dispensing Kymriah, provide patients/caregivers the Patient Caregiver Wallet Card.

As a condition of certification, the certified hospital must:

☐ *Ensure that if the hospital designates a new authorized representative, the new authorized representative must review the Kymriah REMS Live Training Program, complete the Kymriah REMS Program Knowledge Assessment, complete a new Kymriah REMS Program Hospital Enrollment Form and submit the forms via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.

☐ *Report any adverse events suggestive of cytokine release syndrome or neurological toxicities of Kymriah to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at https://pvcu.novartis.com, or 1-888-669-6682.

☐ *Dispense Kymriah to patients only after verifying that a minimum of 2 doses of tocilizumab are available on site for such patient and are ready for immediate administration (within 2 hours).

☐ *Maintain documentation of all processes and procedures for the Kymriah REMS Program and provide documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis or FDA.

☐ *Comply with audits by Novartis, FDA, or a third party acting on behalf of Novartis or FDA.

*First Name | *Last Name | *Email

☐ *By entering my name and selecting this box, I am authorizing these elements as my signature representing that I have completed all required fields on this form.

Submit


KYMRIAH™
(tisagenlecleucel) Suspension for IV Infusion
KYMRIAH™ REMS Program Hospital Enrollment
KYMRIAH™ REMS Program Hospital Enrollment
An authorized representative for this hospital already exists. Please view the account representative information below. If this person is no longer the authorized representative for your hospital on the Kymriah REMS program, you may create a new authorized representative by clicking the button below.
First Name: Smith
Last Name: John
Credentials: MD
Phone: 555 555-1212
Fax: 555 555-3434
Email: a@a.com
Create New Authorized Representative
Privacy Policy
Terms of Use


KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion
KYMRIAH™ REMS Program Hospital Enrollment
KYMRIAH™ REMS Program Hospital Enrollment
There is no record of a completed training and knowledge assessment associated to the email address entered. You may begin the training or return to complete the knowledge assessment by clicking the button below.
REMS ID: 123456789
Email Address: a@a.com
Continue to Training
Privacy Policy
Terms of Use


KYMRIAH REMS Program Knowledge Assessment
KYMRIAH REMS Program Knowledge Assessment Registration
To submit this form, please complete all fields below
HOSPITAL 1 NAME
Representative Information
First name:
TEST1
Last name:
Test
Authorized Representative:
No
Yes
Credentials:
DO
MD
R.Ph
NP/PA
Other (please specify)
Phone:
Fax:
E-mail:
Test00@Test.com
SUBMIT

KYMRIAH REMS Program Knowledge Assessment

KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

Risk Evaluation and Mitigation Strategy (REMS): Cytokine release syndrome and neurological toxicities

A REMS is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of KYMRIAH outweigh its risks.

The purpose of the KYMRIAH REMS is to inform healthcare providers of the risks of cytokine release syndrome and neurological toxicities observed with KYMRIAH.

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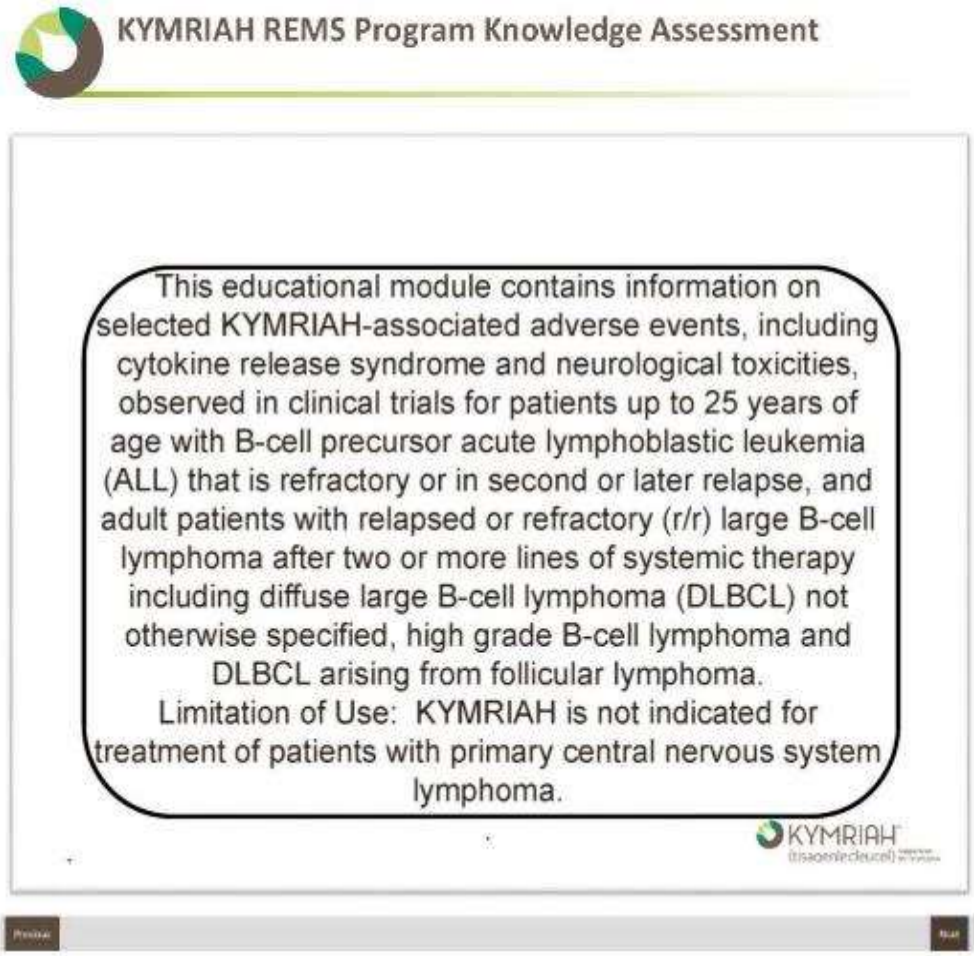
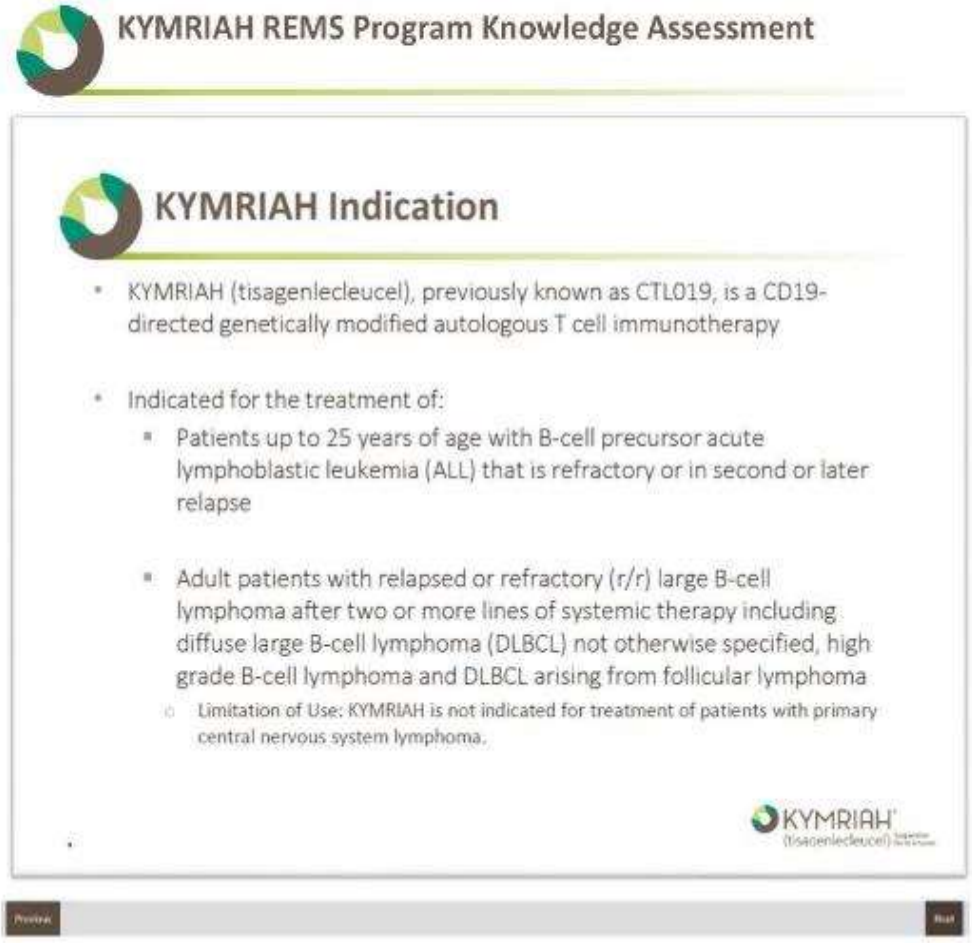

KYMRIAH REMS Program Knowledge Assessment
This educational module contains information on selected KYMRIAH-associated adverse events, including cytokine release syndrome and neurological toxicities, observed in clinical trials for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, and adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.
KYMRIAH

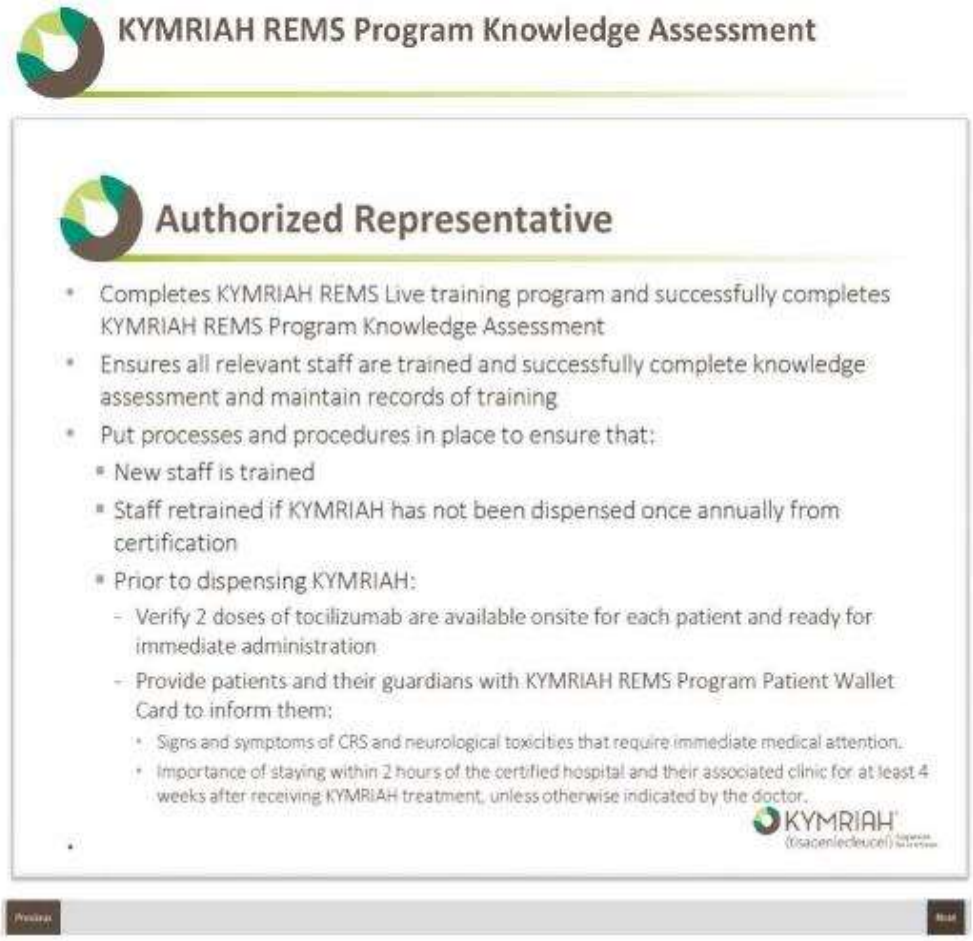

KYMRIAH REMS Program Knowledge Assessment
KYMRIAH Indication
KYMRIAH (tisagenlecleucel), previously known as CTL019, is a CD19-directed genetically modified autologous T cell immunotherapy
Indicated for the treatment of:
Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
KYMRIAH REMS Goal
The goals of the KYMRIAH REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:
Ensuring that hospitals and their associated clinics that dispense KYMRIAH are specially certified and have on-site, immediate access to tocilizumab.
Ensuring those who prescribe, dispense, or administer KYMRIAH are aware of how to manage the risks of CRS and neurological toxicities.
KYMRIAH

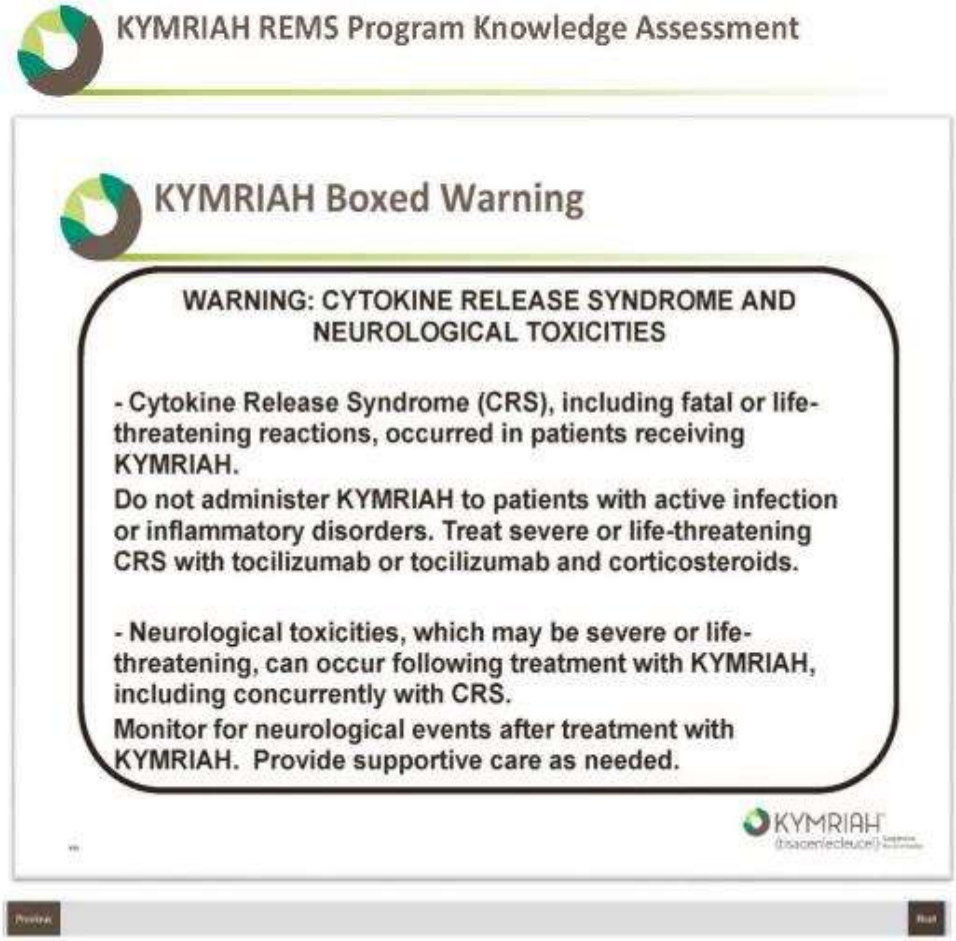

KYMRIAH REMS Program Knowledge Assessment
KYMRIAH REMS Materials
KYMRIAH REMS Live Training Program Slides
Provides education on the risks of CRS and neurological toxicities
Addresses serious clinical manifestations, timing of events, monitoring and management, and importance of patient education
KYMRIAH REMS Program overview
KYMRIAH REMS Program Patient Wallet Card
For patients and their guardians to keep with them at all times, reminds them of signs and symptoms that require immediate medical attention
Instructions to stay within 2 hours of treatment site for at least 4 weeks
KYMRIAH

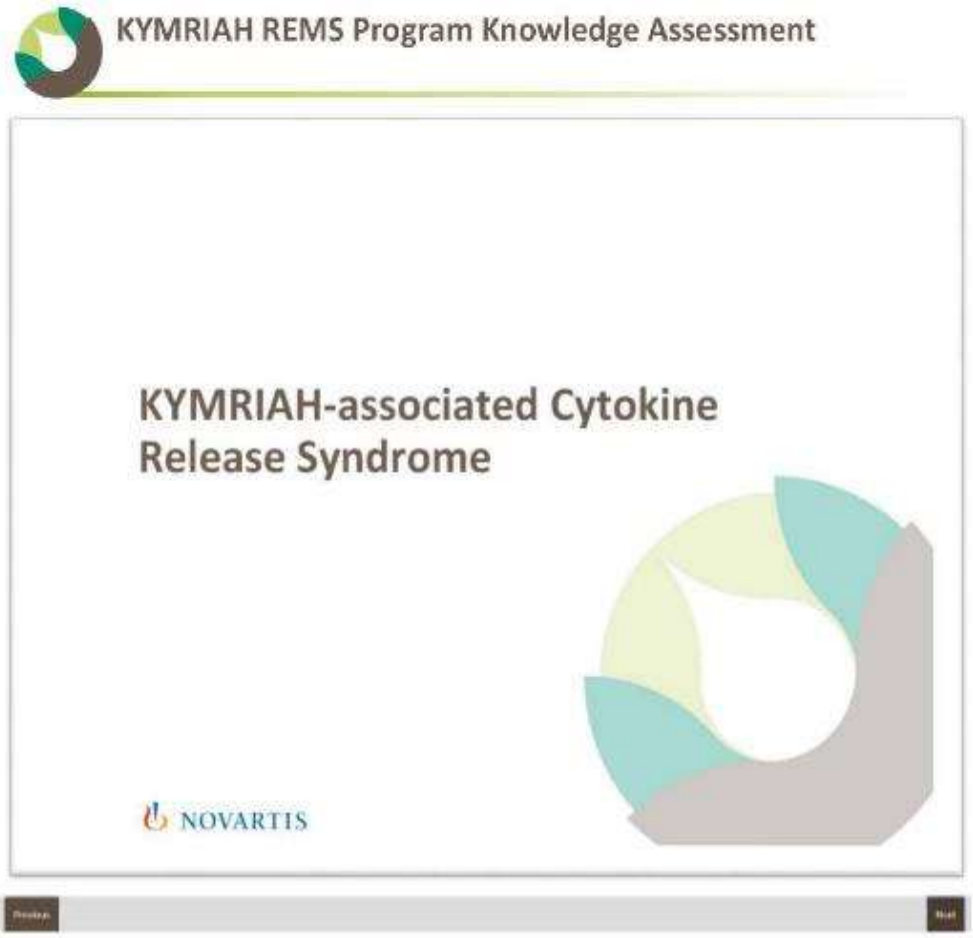

KYMRIAH REMS Program Knowledge Assessment
KYMRIAH REMS Materials, cont.
KYMRIAH REMS Program Knowledge Assessment
Reinforces the messages about CRS and neurological toxicities, 10 questions, multiple choice
All staff involved in ordering, prescribing, or administering must successfully complete via email, in-person, fax, or online
KYMRIAH REMS Program Hospital Enrollment Form
Must be completed by the authorized representative (via email, fax, or online) to certify the hospital
KYMRIAH REMS Program Website
Holds all REMS educational tools for download/printing
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Site Certification
To become certified* to dispense KYMRIAH, hospitals and their associated clinics must:
Designate an authorized representative to complete the certification process by submitting the completed KYMRIAH REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics
Ensure the authorized representative oversees implementation and compliance with KYMRIAH REMS Program requirements
*Completion of the enrollment form and knowledge assessment does not guarantee your hospital will be certified to administer KYMRIAH. Please contact 1-844-4KYMRIAH(1-844-459-6742) for more information
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Authorized Representative
Completes KYMRIAH REMS Live training program and successfully completes KYMRIAH REMS Program Knowledge Assessment
Ensures all relevant staff are trained and successfully complete knowledge assessment and maintain records of training
Put processes and procedures in place to ensure that:
New staff is trained
Staff retrained if KYMRIAH has not been dispensed once annually from certification
Prior to dispensing KYMRIAH:
Verify 2 doses of tocilizumab are available onsite for each patient and ready for immediate administration
Provide patients and their guardians with KYMRIAH REMS Program Patient Wallet Card to inform them:
Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.
Importance of staying within 2 hours of the certified hospital and their associated clinic for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor.
KYMRIAH
(tisagenlecleucel)


KYMRIAH REMS Program Knowledge Assessment
Conditions of Certification
• Recertify in the KYMRIAH REMS Program if the hospital and their associated clinics designate a new authorized representative.
• Report any adverse events suggestive of CRS or neurological toxicities.
• Maintain documentation that all processes and procedures are in place and are being followed for the KYMRIAH REMS Program and provide that documentation upon request to Novartis or a third party acting on behalf of Novartis.
• Comply with audits by Novartis or a third party acting on behalf of Novartis to ensure that all training, processes and procedures are in place and are being followed for the KYMRIAH REMS Program.
• Dispense KYMRIAH only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
KYMRIAH Boxed Warning
WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES
- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH.
Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS.
Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.
KYMRIAH

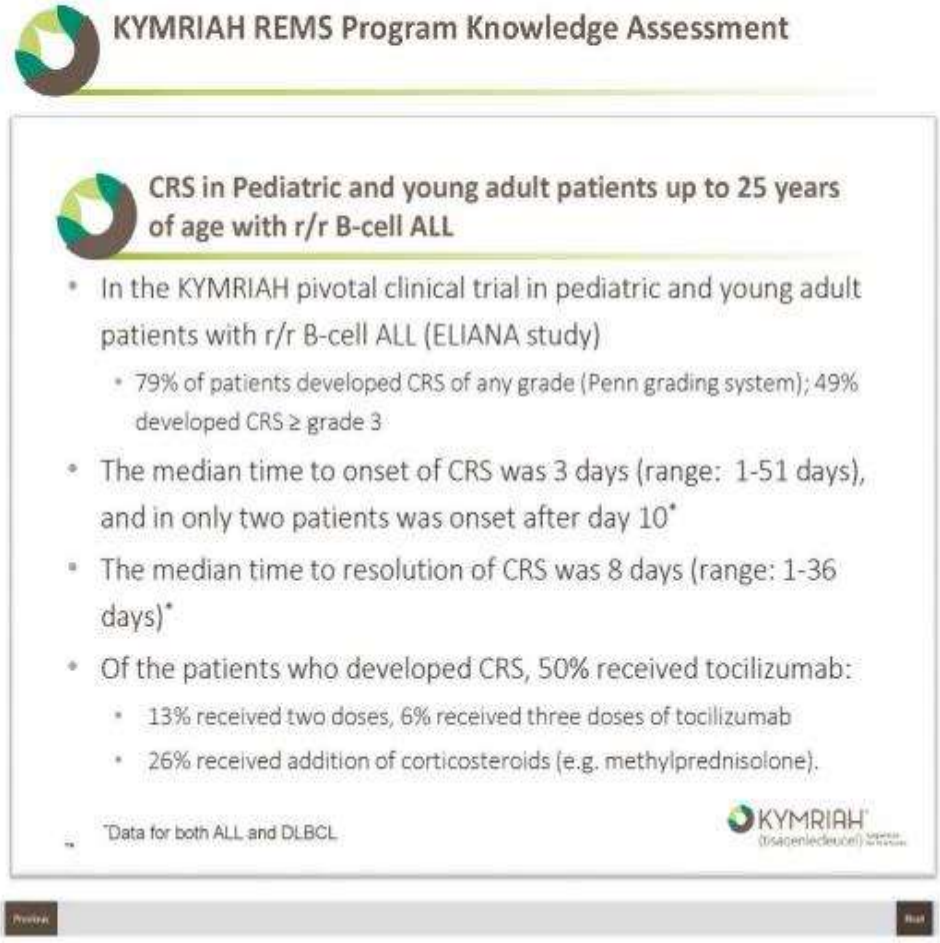

KYMRIAH REMS Program Knowledge Assessment
KYMRIAH-associated Cytokine Release Syndrome
NOVARTIS

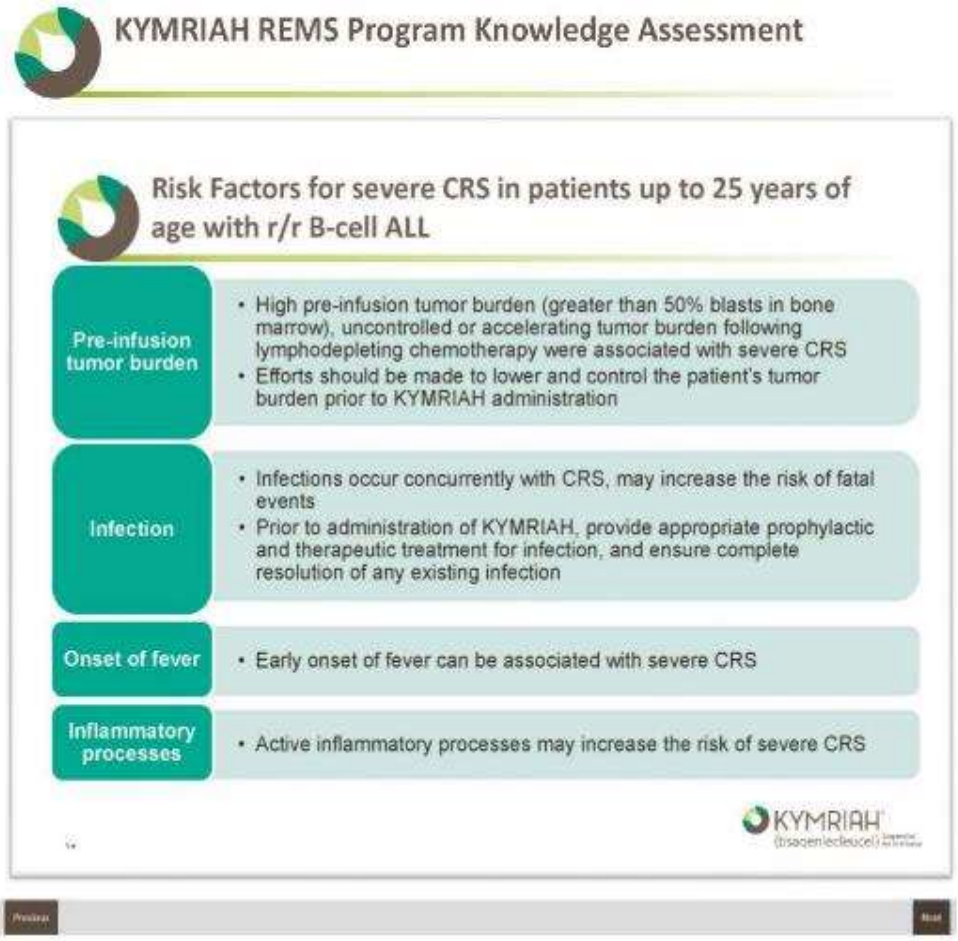
KYMRIAH REMS Program Knowledge Assessment

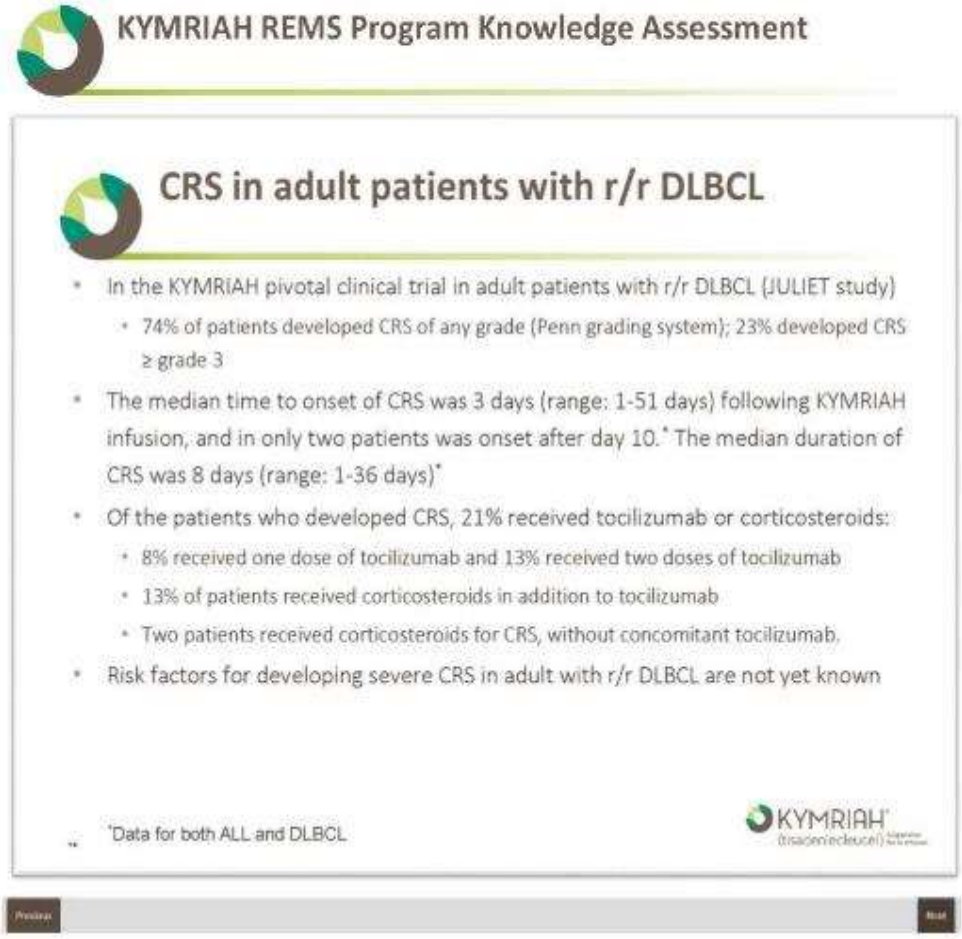
Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, was the most common adverse event in the KYMRIAH pivotal clinical trials in pediatric and young adult patients with r/r ALL and adult patients with r/r DLBCL
- In clinical trials, CRS was effectively managed in the majority of patients based on a CRS management algorithm
- Patients with CRS may require admission to the intensive care unit for supportive care

KYMRIAH

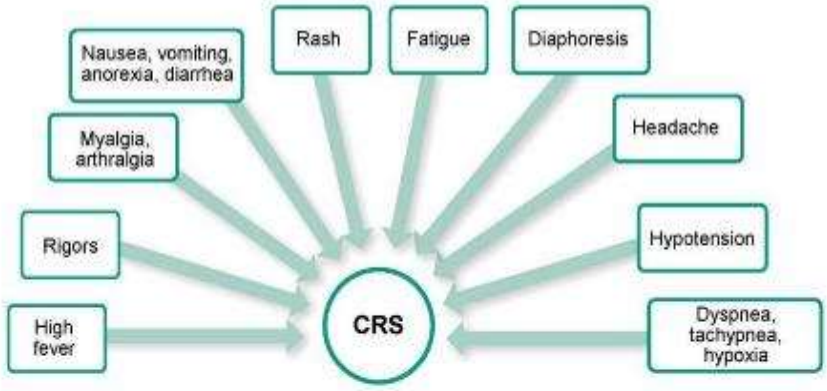

KYMRIAH REMS Program Knowledge Assessment
CRS in Pediatric and young adult patients up to 25 years of age with r/r B-cell ALL
In the KYMRIAH pivotal clinical trial in pediatric and young adult patients with r/r B-cell ALL (ELIANA study)
79% of patients developed CRS of any grade (Penn grading system); 49% developed CRS ≥ grade 3
The median time to onset of CRS was 3 days (range: 1-51 days), and in only two patients was onset after day 10*
The median time to resolution of CRS was 8 days (range: 1-36 days)*
Of the patients who developed CRS, 50% received tocilizumab:
13% received two doses, 6% received three doses of tocilizumab
26% received addition of corticosteroids (e.g. methylprednisolone).
*Data for both ALL and DLBCL
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Risk Factors for severe CRS in patients up to 25 years of age with r/r B-cell ALL
Pre-infusion tumor burden
• High pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy were associated with severe CRS
• Efforts should be made to lower and control the patient's tumor burden prior to KYMRIAH administration
Infection
• Infections occur concurrently with CRS, may increase the risk of fatal events
• Prior to administration of KYMRIAH, provide appropriate prophylactic and therapeutic treatment for infection, and ensure complete resolution of any existing infection
Onset of fever
• Early onset of fever can be associated with severe CRS
Inflammatory processes
• Active inflammatory processes may increase the risk of severe CRS
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
CRS in adult patients with r/r DLBCL
In the KYMRIAH pivotal clinical trial in adult patients with r/r DLBCL (JULIET study)
74% of patients developed CRS of any grade (Penn grading system); 23% developed CRS ≥ grade 3
The median time to onset of CRS was 3 days (range: 1-51 days) following KYMRIAH infusion, and in only two patients was onset after day 10.* The median duration of CRS was 8 days (range: 1-36 days)*
Of the patients who developed CRS, 21% received tocilizumab or corticosteroids:
8% received one dose of tocilizumab and 13% received two doses of tocilizumab
13% of patients received corticosteroids in addition to tocilizumab
Two patients received corticosteroids for CRS, without concomitant tocilizumab.
Risk factors for developing severe CRS in adult with r/r DLBCL are not yet known
*Data for both ALL and DLBCL
KYMRIAH

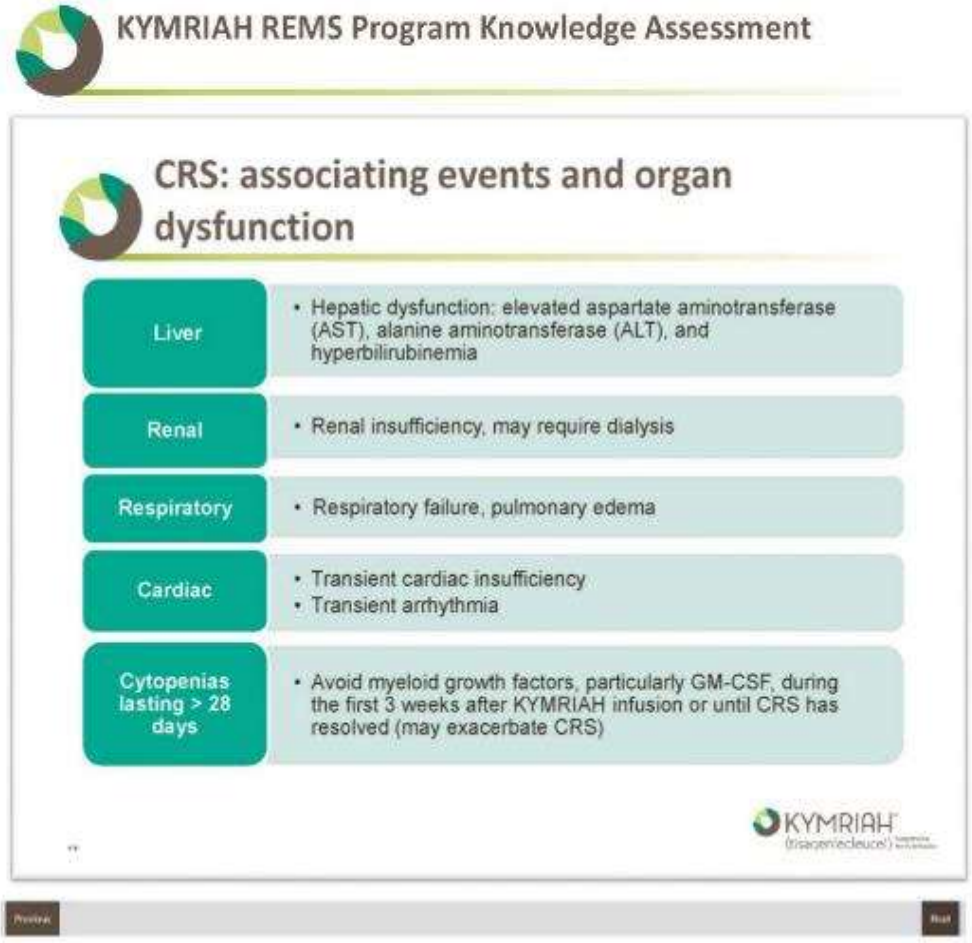
KYMRIAH REMS Program Knowledge Assessment

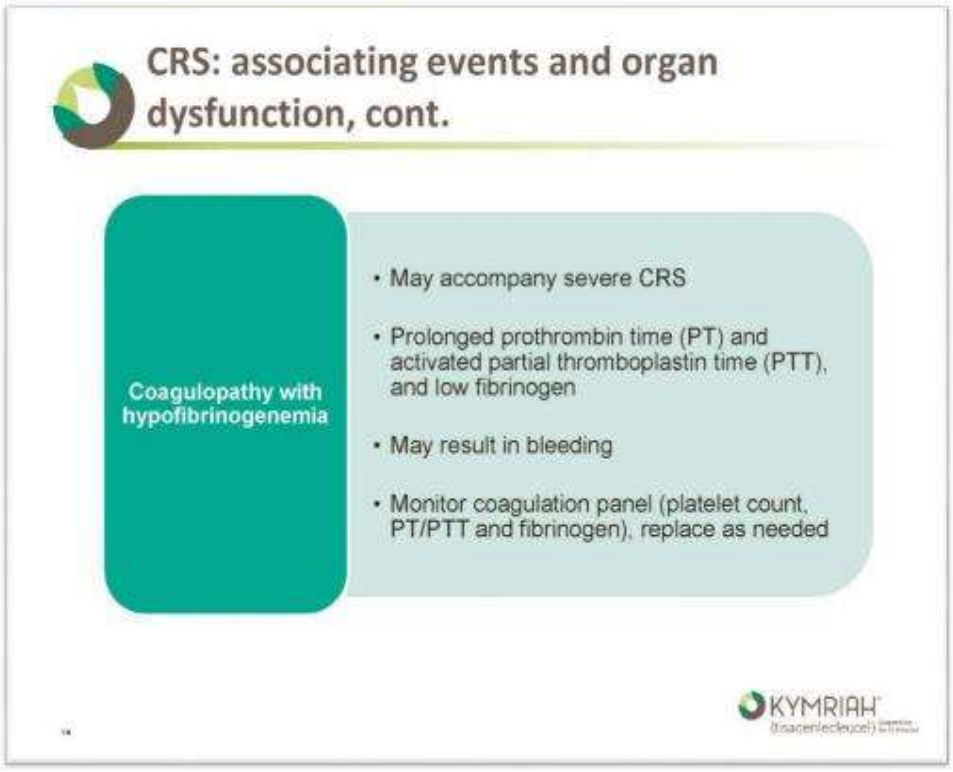
CRS signs and symptoms

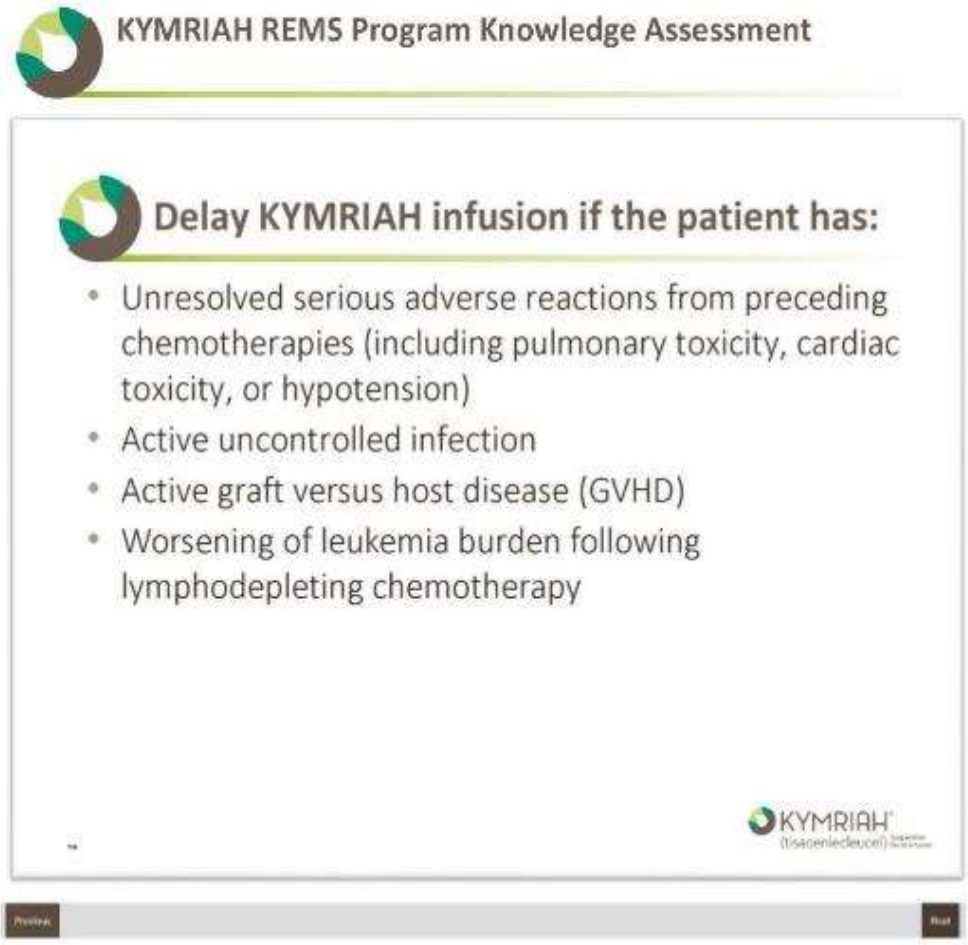


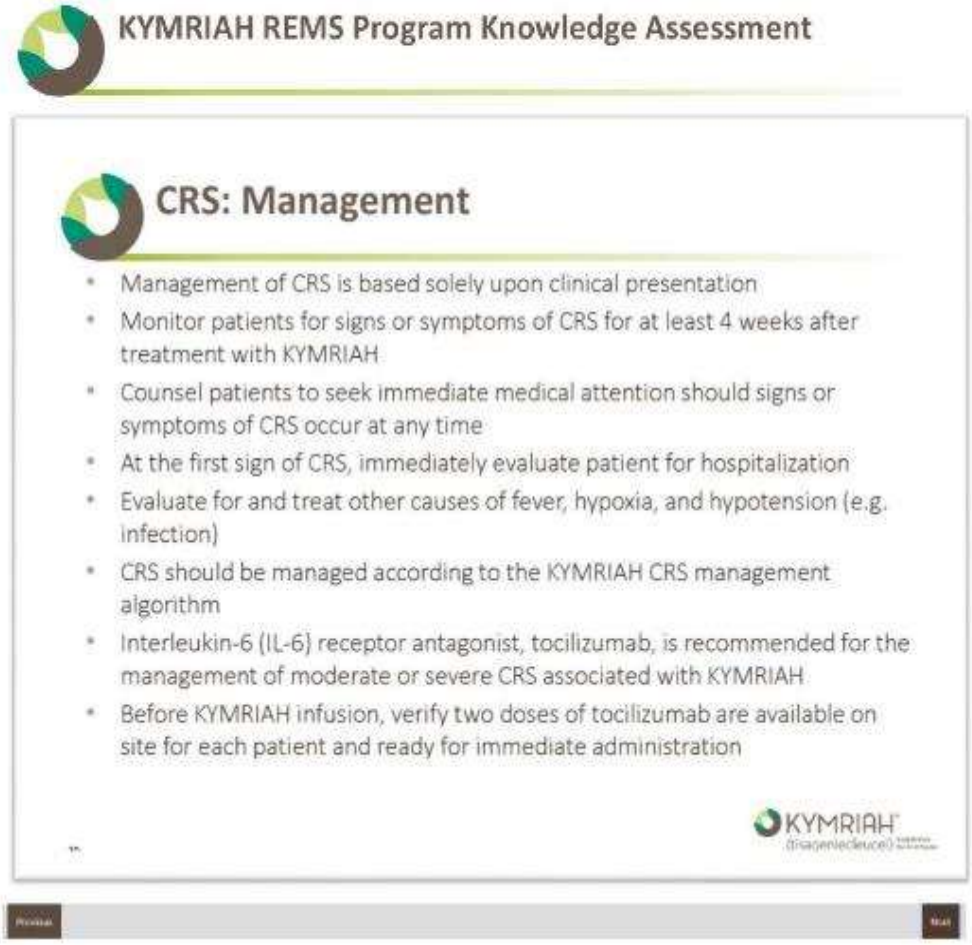
Diagnosis based on clinical symptoms and events

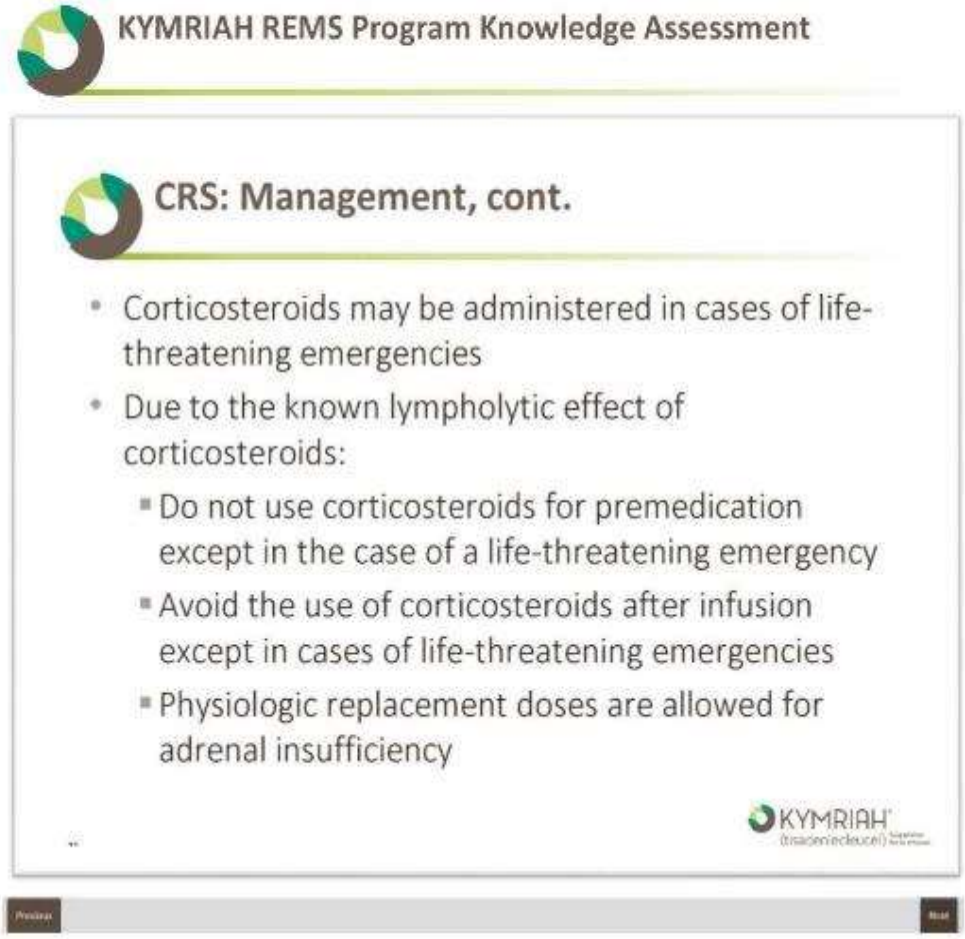
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
CRS: associating events and organ dysfunction
Liver
• Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia
Renal
• Renal insufficiency, may require dialysis
Respiratory
• Respiratory failure, pulmonary edema
Cardiac
• Transient cardiac insufficiency
• Transient arrhythmia
Cytopenias lasting > 28 days
• Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAH infusion or until CRS has resolved (may exacerbate CRS)
KYMRIAH

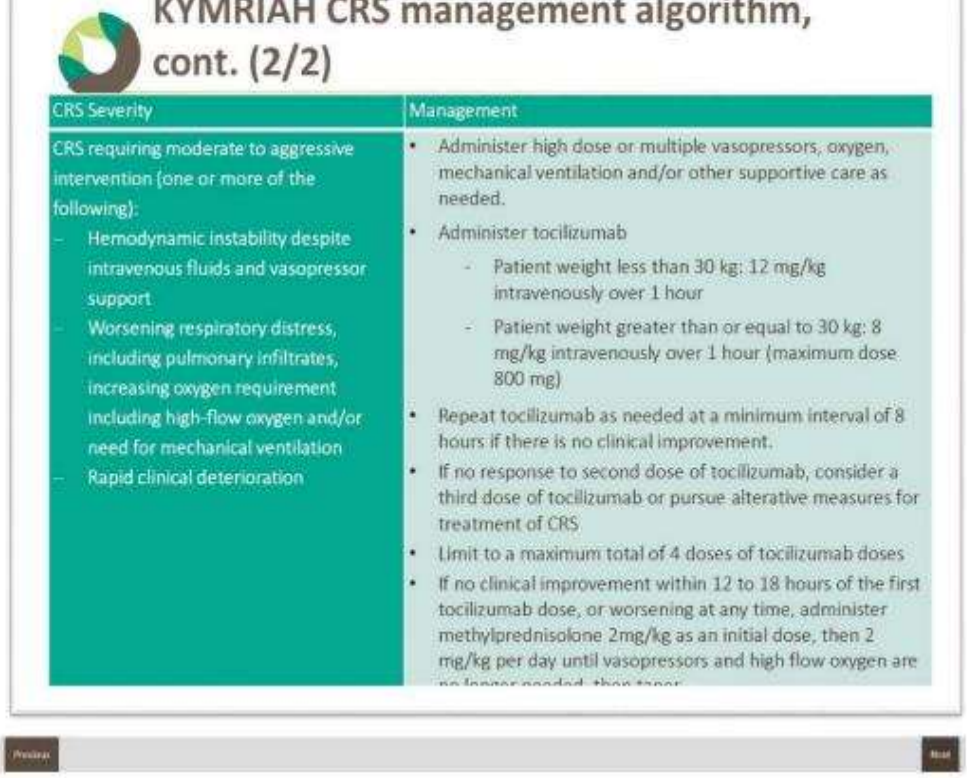

CRS: associating events and organ dysfunction, cont.
Coagulopathy with hypofibrinogenemia
• May accompany severe CRS
• Prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), and low fibrinogen
• May result in bleeding
• Monitor coagulation panel (platelet count, PT/PTT and fibrinogen), replace as needed
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Delay KYMRIAH infusion if the patient has:
• Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension)
• Active uncontrolled infection
• Active graft versus host disease (GVHD)
• Worsening of leukemia burden following lymphodepleting chemotherapy
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
CRS: Management
Management of CRS is based solely upon clinical presentation
Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH
Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
At the first sign of CRS, immediately evaluate patient for hospitalization
Evaluate for and treat other causes of fever, hypoxia, and hypotension (e.g. infection)
CRS should be managed according to the KYMRIAH CRS management algorithm
Interleukin-6 (IL-6) receptor antagonist, tocilizumab, is recommended for the management of moderate or severe CRS associated with KYMRIAH
Before KYMRIAH infusion, verify two doses of tocilizumab are available on site for each patient and ready for immediate administration
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
CRS: Management, cont.
• Corticosteroids may be administered in cases of life-threatening emergencies
• Due to the known lympholytic effect of corticosteroids:
▪ Do not use corticosteroids for premedication except in the case of a life-threatening emergency
▪ Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies
▪ Physiologic replacement doses are allowed for adrenal insufficiency
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
KYMRIAH CRS management algorithm (1/2)
CRS Severity
Management
Prodromal syndrome:
Low-grade fever, fatigue, anorexia
Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
CRS requiring mild intervention (one or more of the following):
- High fever
- Hypoxia
- Mild hypotension
Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
KYMRIAH



KYMRIAH CRS management algorithm, cont. (2/2)

CRS Severity	Management
CRS requiring moderate to aggressive intervention (one or more of the following): – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) • Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. • If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alterative measures for treatment of CRS • Limit to a maximum total of 4 doses of tocilizumab doses • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper

Definition of high-dose vasopressors

Vasopressor	Dose for ≥ 3 Hours	
	Weight-based dosing	Flat dosing (if this is institutional practice)
Norepinephrine monotherapy	≥ 0.2 µg/kg/min	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min	≥ 1000 µg/min
Phenylephrine monotherapy	≥ 2 µg/kg/min	≥ 200 µg/min
Epinephrine monotherapy	≥ 0.1 µg/kg/min	≥ 10 µg/min
If on vasopressin	High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula)[a]	vasopressin + norepinephrine equivalent of ≥ 10 µg/min[b]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 µg/kg/min[a]	Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula)[b]

VASST* Vasopressor Equivalent Equation

[a] Norepinephrine equivalent dose [body weight adjusted dosing (µg/kg/min dosing)] = [norepinephrine (µg/kg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/kg/min)] + [phenylephrine (µg/kg/min) ÷ 10][1]

[b] Norepinephrine equivalent dose [flat dosing (µg/min)] = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10][2,3,4]

*See references slide

KYMRIAH® (tisagenlecleucel)

KYMRIAH-associated neurological toxicities

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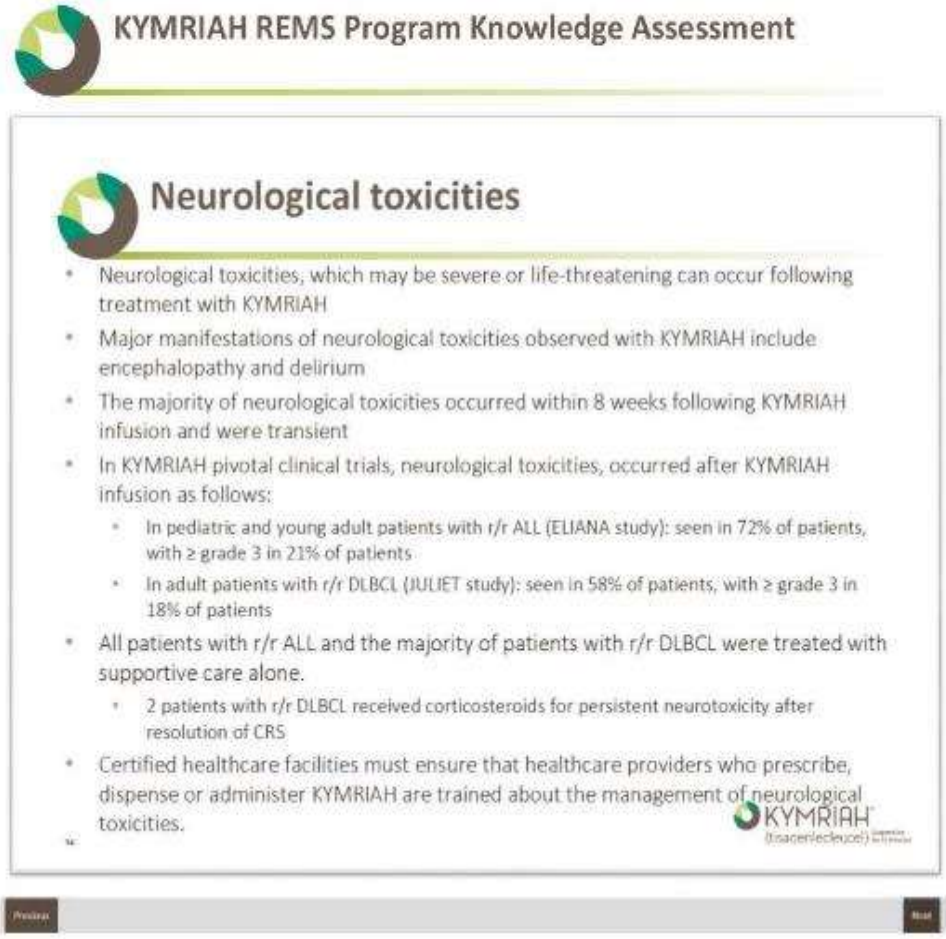
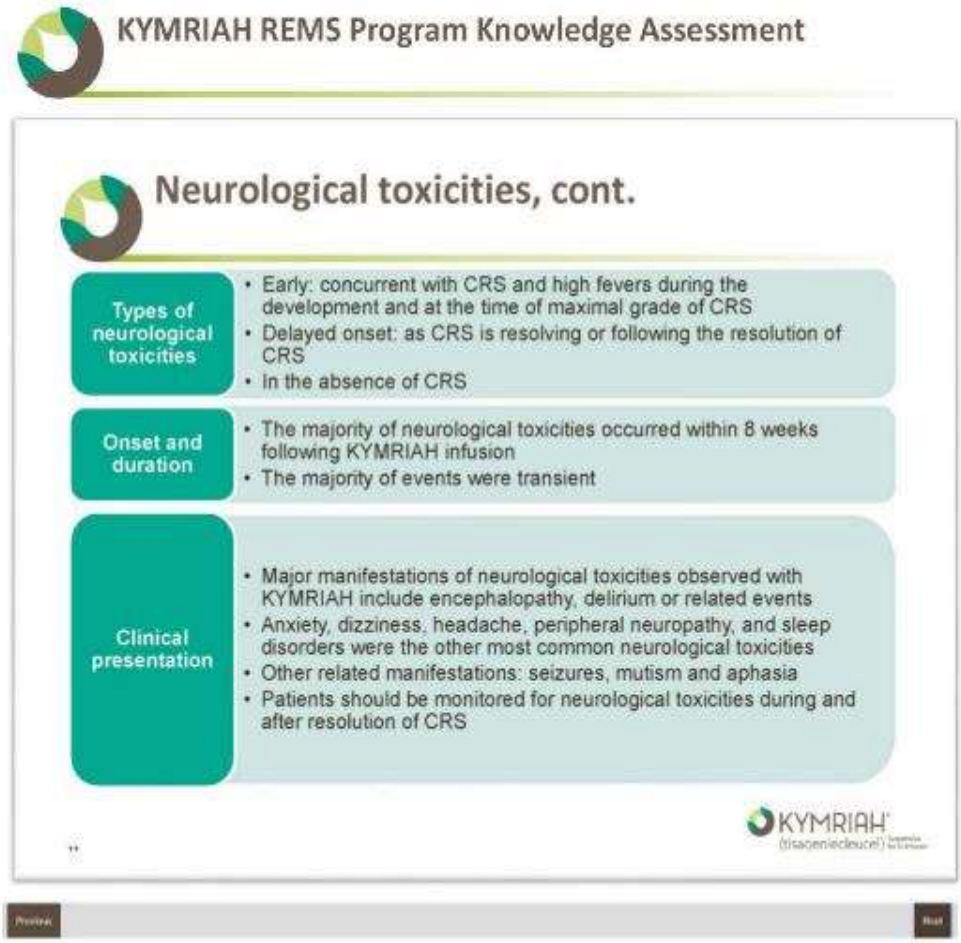
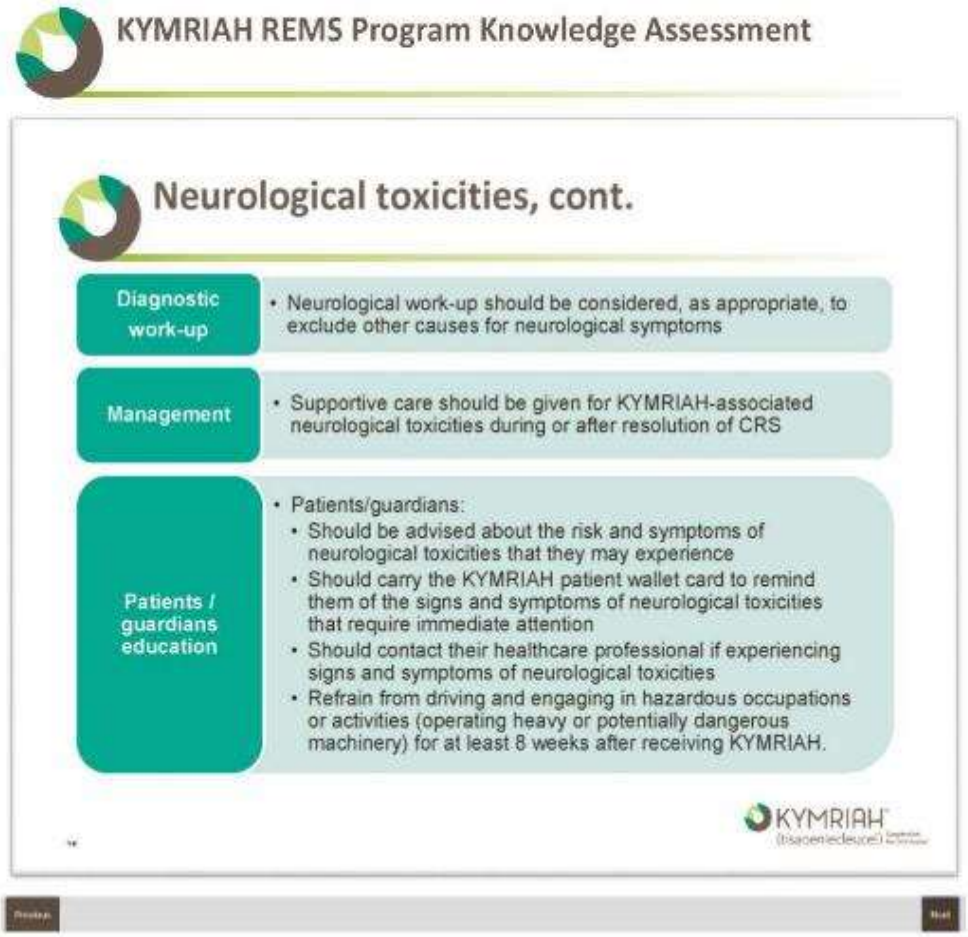
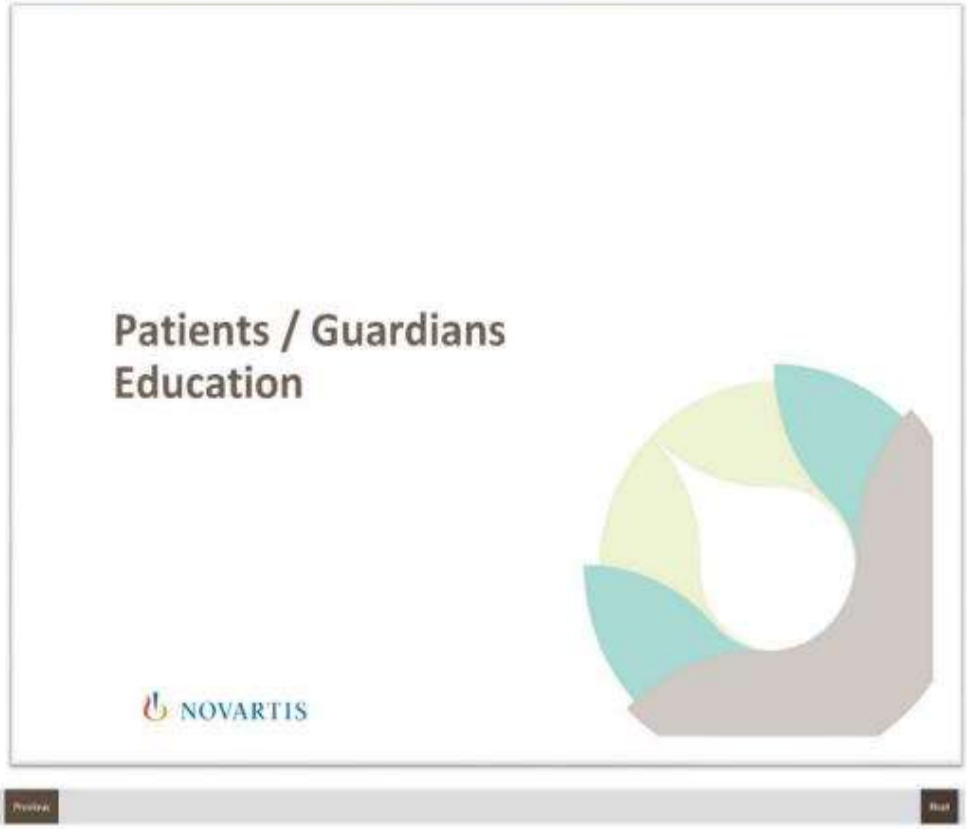
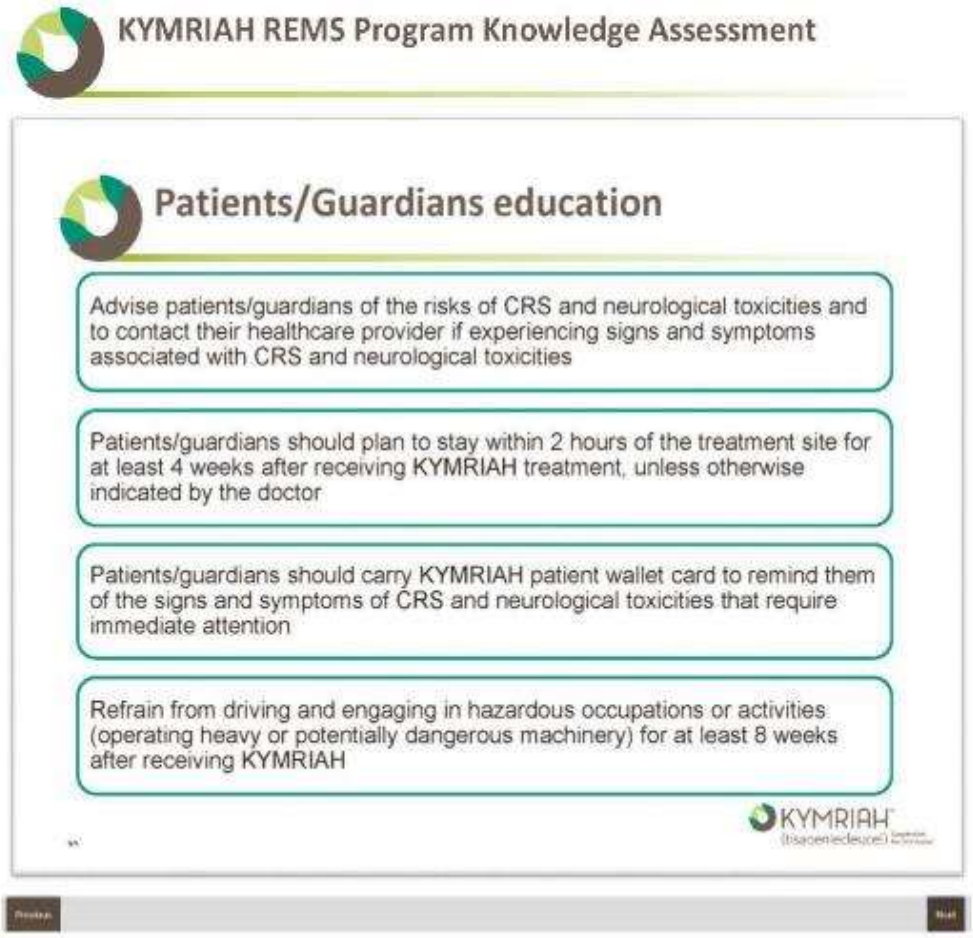

KYMRIAH REMS Program Knowledge Assessment
Neurological toxicities
Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH
Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy and delirium
The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion and were transient
In KYMRIAH pivotal clinical trials, neurological toxicities, occurred after KYMRIAH infusion as follows:
In pediatric and young adult patients with r/r ALL (ELIANA study): seen in 72% of patients, with ≥ grade 3 in 21% of patients
In adult patients with r/r DLBCL (JULIET study): seen in 58% of patients, with ≥ grade 3 in 18% of patients
All patients with r/r ALL and the majority of patients with r/r DLBCL were treated with supportive care alone.
2 patients with r/r DLBCL received corticosteroids for persistent neurotoxicity after resolution of CRS
Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of neurological toxicities.
KYMRIAH
Previous
Next


KYMRIAH REMS Program Knowledge Assessment
Neurological toxicities, cont.
Types of neurological toxicities
• Early: concurrent with CRS and high fevers during the development and at the time of maximal grade of CRS
• Delayed onset: as CRS is resolving or following the resolution of CRS
• In the absence of CRS
Onset and duration
• The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion
• The majority of events were transient
Clinical presentation
• Major manifestations of neurological toxicities observed with KYMRIAH include encephalopathy, delirium or related events
• Anxiety, dizziness, headache, peripheral neuropathy, and sleep disorders were the other most common neurological toxicities
• Other related manifestations: seizures, mutism and aphasia
• Patients should be monitored for neurological toxicities during and after resolution of CRS
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Neurological toxicities, cont.
Diagnostic work-up
• Neurological work-up should be considered, as appropriate, to exclude other causes for neurological symptoms
Management
• Supportive care should be given for KYMRIAH-associated neurological toxicities during or after resolution of CRS
Patients / guardians education
• Patients/guardians:
• Should be advised about the risk and symptoms of neurological toxicities that they may experience
• Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention
• Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities
• Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH.
KYMRIAH


Patients / Guardians
Education
NOVARTIS


KYMRIAH REMS Program Knowledge Assessment
Patients/Guardians education
Advise patients/guardians of the risks of CRS and neurological toxicities and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
Patients/guardians should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor
Patients/guardians should carry KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
Reporting Adverse Events
Healthcare providers are encouraged to report suspected adverse events of Kymriah® to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at https://psi.novartis.com or by calling 1-888-669-6682.
KYMRIAH


KYMRIAH REMS Program Knowledge Assessment
For further information, please visit
www.KYMRIAH-REMS.com or call
1-844-4KYMRIAH(1-844-459-6742)
NOVARTIS

KYMRIAH REMS Program Knowledge Assessment

References

1. Chimeric Antigen Receptor (CAR) Cell Therapy Toxicity Assessment and Management – Pediatric. The University of Texas MD Anderson Cancer Center website. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-pedi-web-algorithm.pdf. Published January 30, 2018. Accessed March 4, 2019. The pediatric guideline was approved by the Executive Committee of the Medical Staff on 1/30/2018.
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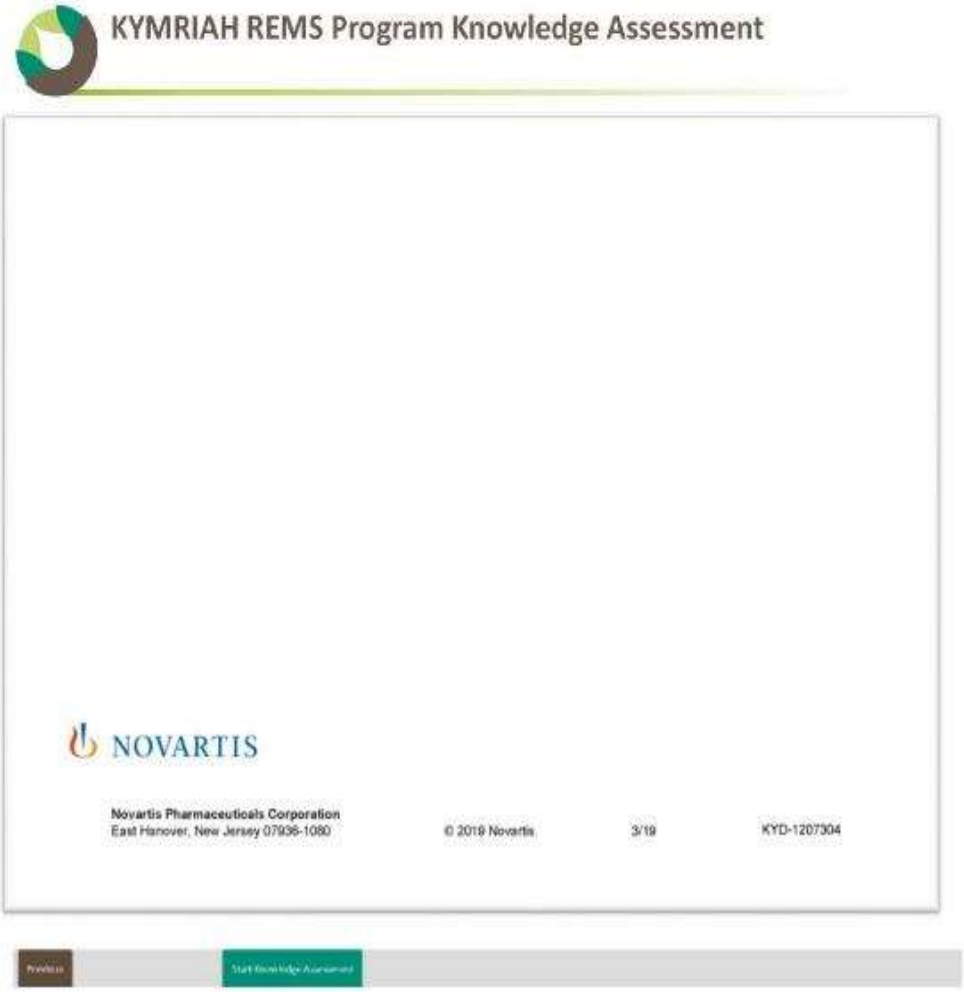
KYMRIAH REMS Program Knowledge Assessment
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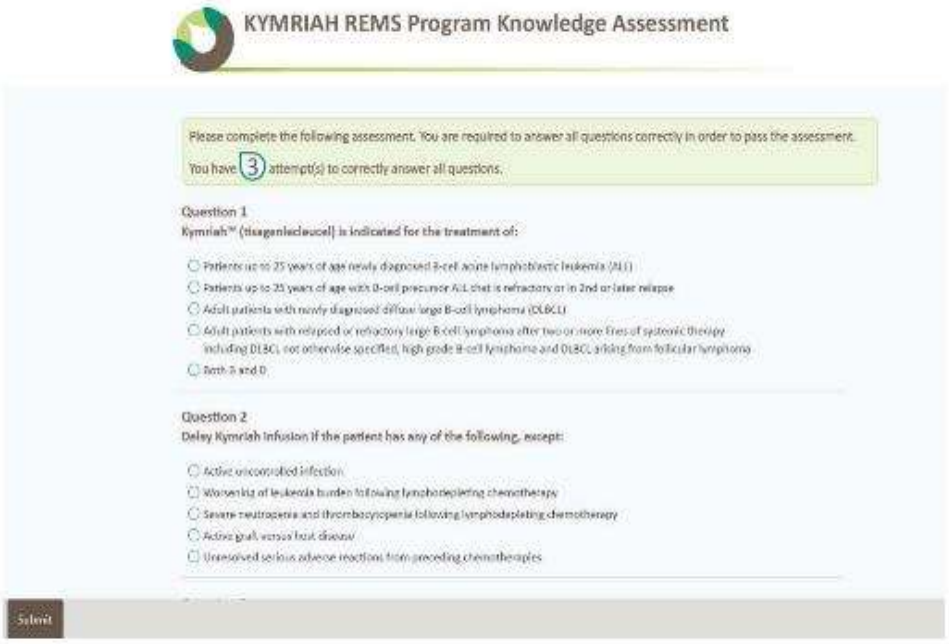
KYD-1207304


KYMRIAH REMS Program Knowledge Assessment
Please complete the following assessment. You are required to answer all questions correctly in order to pass the assessment.
You have 3 attempt(s) to correctly answer all questions.
Question 1
Kymriah™ (tisagenlecleucel) is indicated for the treatment of:
Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
Both B and D
Question 2
Delay Kymriah infusion if the patient has any of the following, except:
Active uncontrolled infection
Worsening of leukemia burden following lymphodepleting chemotherapy
Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
Active graft versus host disease
Unresolved serious adverse reactions from preceding chemotherapies
Submit

Question 3
Clinically, patients with CRS can manifest with the following signs and symptoms, except:

- High grade fever
- Hypotension
- Hair Loss
- Respiratory distress
- Hypofibrinogenemia

Question 4
Which one of the following is true regarding the time to onset of CRS? It typically occurs:

- 7-14 days following Kymriah infusion, with a median time to onset of 10 days
- 7-21 days following Kymriah infusion, with a median time to onset of 10 days
- Median time to onset is 3 days following Kymriah infusion
- Rarely starts during the first week following Kymriah infusion

Question 5
As a part of planning for Kymriah infusion, it is required to have two doses of tocilizumab on site for each patient prior to dispensing and administering Kymriah to patients:

- True
- False

Question 6
As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:

Submit

Question 6

As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:

- ◯ True
- ◯ False

Question 7

A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high grade fever (40-41°C) with neutropenia and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O_2 saturation 91%). He was started on norepinephrine at a low dose and O_2 supplement via nasal cannula. All of the following are correct, except:

- ◯ The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
- ◯ Sepsis should be considered and treated adequately with broad spectrum antibiotics
- ◯ Start myeloid growth factor to expedite neutrophil recovery
- ◯ Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

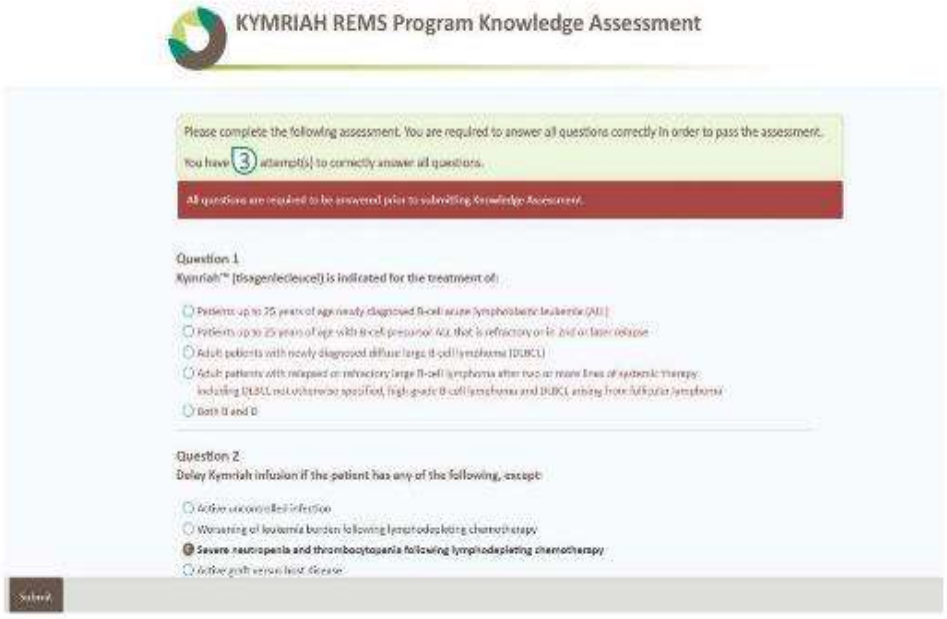
Question 8

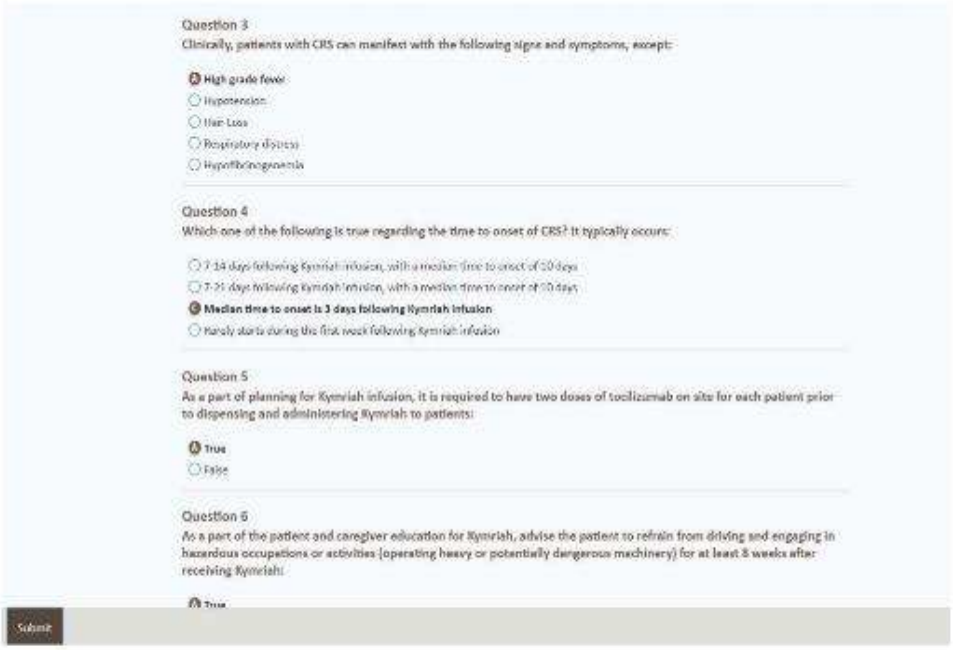
Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:

- ◯ May occur in the context of CRS, following the resolution of CRS or without CRS
- ◯ Symptoms range from headache and confusion to encephalopathy and seizures
- ◯ The majority of events were transient and self limiting
- ◯ Can be prevented with the administration of tocilizumab

Submit


Question 9
Which one of the following about neurological toxicities as a result of Kymriah is correct:
Perform neurological work up as appropriate to exclude other etiologies of neurological symptoms
Management includes supportive care
Majority occurred within 8 weeks following Kymriah infusion
All of the above
Question 10
A 30-year-old female with multiply relapsed DLBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:
The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH
The patient should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
All of the above
Submit


KYMRIAH REMS Program Knowledge Assessment
Please complete the following assessment. You are required to answer all questions correctly in order to pass the assessment.
You have 3 attempt(s) to correctly answer all questions.
All questions are required to be answered prior to submitting Knowledge Assessment.
Question 1
Kymriah™ (tisagenlecleucel) is indicated for the treatment of:
Question 2
Delay Kymriah infusion if the patient has any of the following, except:
Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy


Question 3
Clinically, patients with CRS can manifest with the following signs and symptoms, except:
High grade fever
Hypotension
Hair Loss
Respiratory distress
Hypofibrinogenemia
Question 4
Which one of the following is true regarding the time to onset of CRS? It typically occurs:
7-14 days following Kymriah infusion, with a median time to onset of 10 days
7-21 days following Kymriah infusion, with a median time to onset of 10 days
Median time to onset is 3 days following Kymriah infusion
Rarely starts during the first week following Kymriah infusion
Question 5
As a part of planning for Kymriah infusion, it is required to have two doses of tocilizumab on site for each patient prior to dispensing and administering Kymriah to patients:
True
False
Question 6
As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:
Submit

Question 6

As a part of the patient and caregiver education for Kymriah, advise the patient to refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving Kymriah:

- **True**
- False

Question 7

A 5-year-old male with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day following infusion, he developed high grade fever (40-41°C) with neutropenia and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O_2 saturation 91%). He was started on norepinephrine at a low dose and O_2 supplement via nasal cannula. All of the following are correct, except:

- The patient has symptoms consistent with cytokine release syndrome and should be managed according to the CRS management algorithm
- Sepsis should be considered and treated adequately with broad spectrum antibiotics
- **Start myeloid growth factor to expedite neutrophil recovery**
- Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

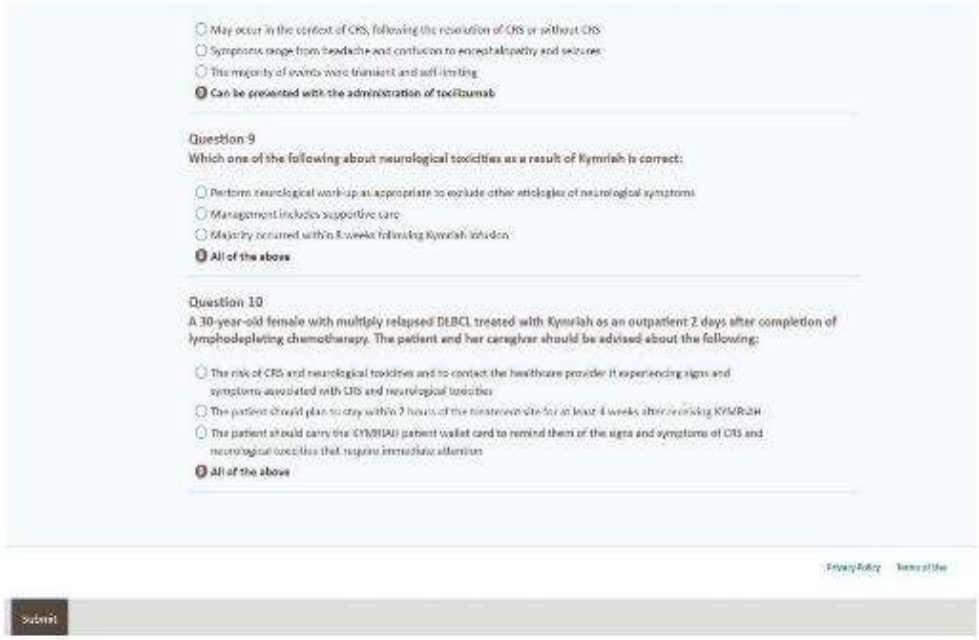
Question 8

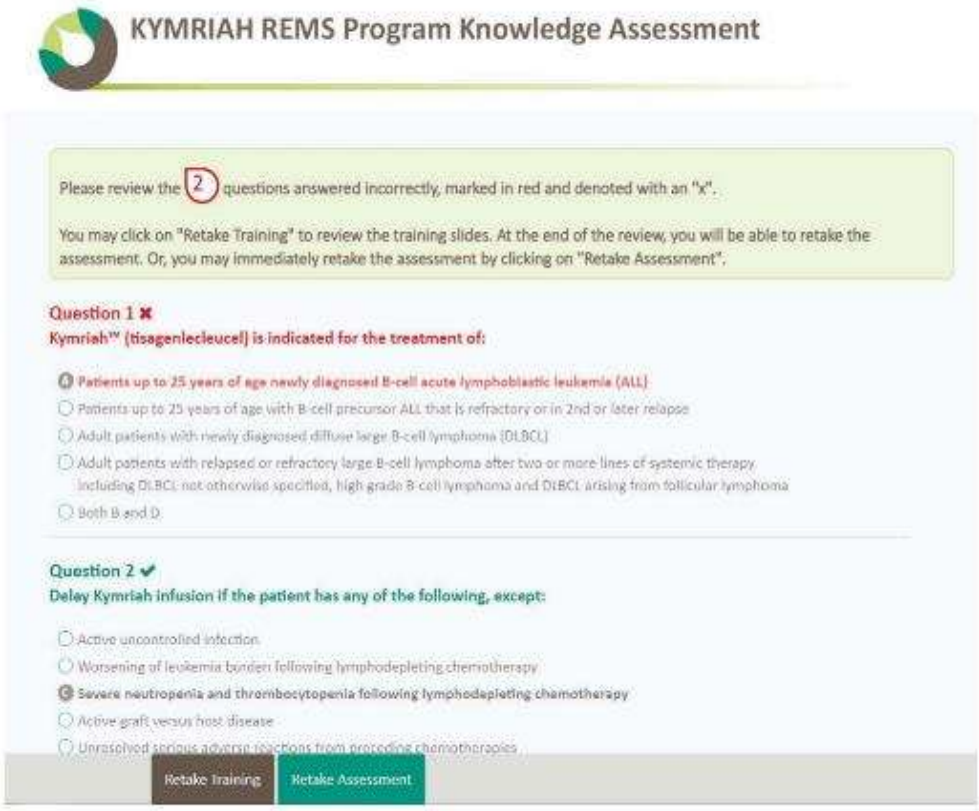
Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct, except:

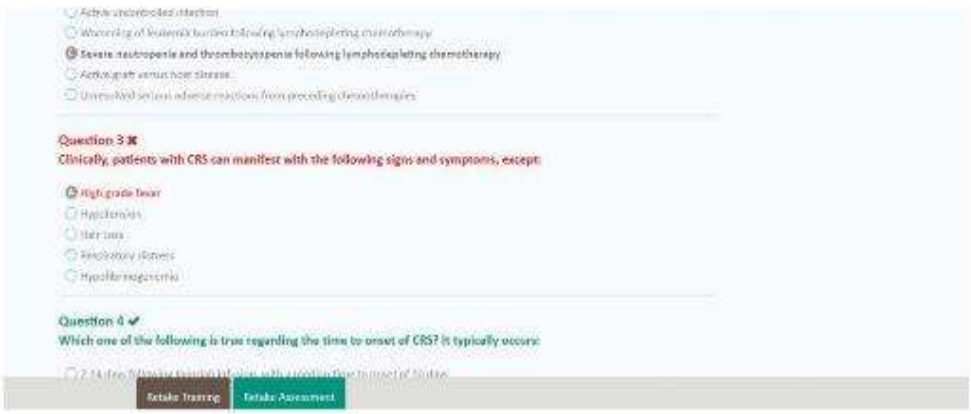
- May occur in the context of CRS, following the resolution of CRS or without CRS
- Symptoms range from headache and confusion to encephalopathy and seizures
- The majority of events were transient and self-limiting
- **Can be prevented with the administration of tocilizumab**

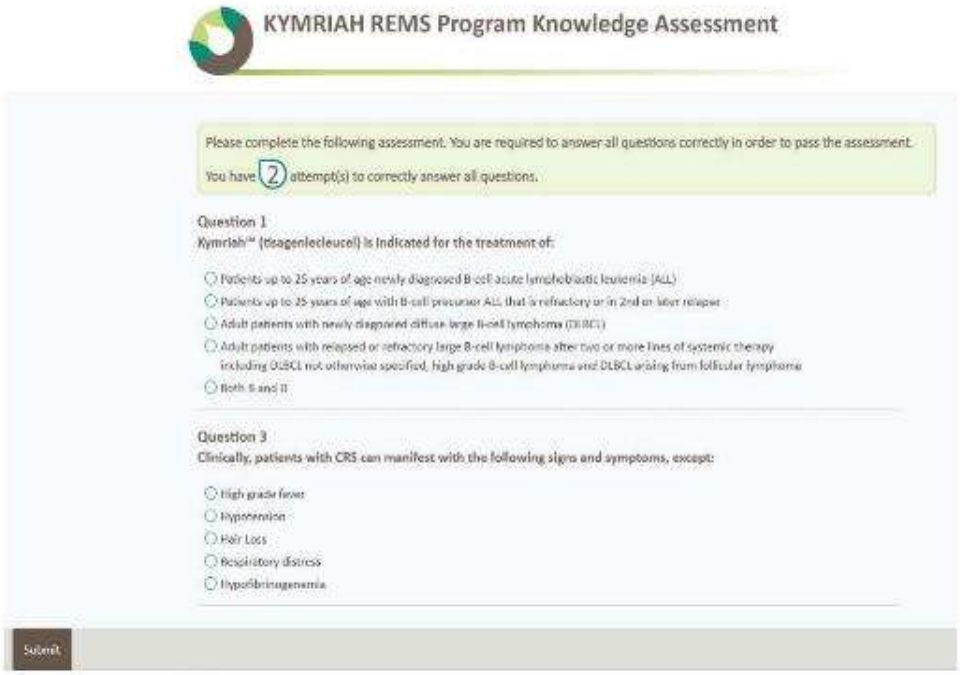
Question 9

Submit


May occur in the context of CRS, following the resolution of CRS or without CRS
Symptoms range from headache and confusion to encephalopathy and seizures
The majority of events were transient and self-limiting
Can be prevented with the administration of tocilizumab
Question 9
Which one of the following about neurological toxicities as a result of Kymriah is correct:
Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
Management includes supportive care
Majority occurred within 8 weeks following Kymriah infusion
All of the above
Question 10
A 30-year-old female with multiply relapsed DLBCL treated with Kymriah as an outpatient 2 days after completion of lymphodepleting chemotherapy. The patient and her caregiver should be advised about the following:
The risk of CRS and neurological toxicities and to contact the healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
The patient should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH
The patient should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
All of the above
Privacy Policy
Terms of Use
Submit


KYMRIAH REMS Program Knowledge Assessment
Please review the 2 questions answered incorrectly, marked in red and denoted with an "x".
You may click on "Retake Training" to review the training slides. At the end of the review, you will be able to retake the assessment. Or, you may immediately retake the assessment by clicking on "Retake Assessment".
Question 1 ✖
Kymriah™ (tisagenlecleucel) is indicated for the treatment of:
A Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
Both B and D
Question 2 ✔
Delay Kymriah infusion if the patient has any of the following, except:
Active uncontrolled infection
Worsening of leukemia burden following lymphodepleting chemotherapy
C Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
Active graft versus host disease
Unresolved serious adverse reactions from preceding chemotherapies
Retake Training
Retake Assessment


Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy
Question 3
Clinically, patients with CRS can manifest with the following signs and symptoms, except:
High grade fever
Question 4
Which one of the following is true regarding the time to onset of CRS? It typically occurs:
Retake Training
Retake Assessment


KYMRIAH REMS Program Knowledge Assessment
Please complete the following assessment. You are required to answer all questions correctly in order to pass the assessment.
You have 2 attempt(s) to correctly answer all questions.
Question 1
Kymriah™ (tisagenlecleucel) is indicated for the treatment of:
Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
Both I and II
Question 3
Clinically, patients with CRS can manifest with the following signs and symptoms, except:
High grade fever
Hypotension
Hair Loss
Respiratory distress
Hypofibrinogenemia
Submit

KYMRIAH REMS Program Knowledge Assessment

CONGRATULATIONS!

You have successfully completed the KYMRIAH Knowledge Assessment.

Click here for a copy of your Certificate of Completion

Certificate of Completion

KYMRIAH REMS Program

This is to certify that

Test test

IjNgEFA

661

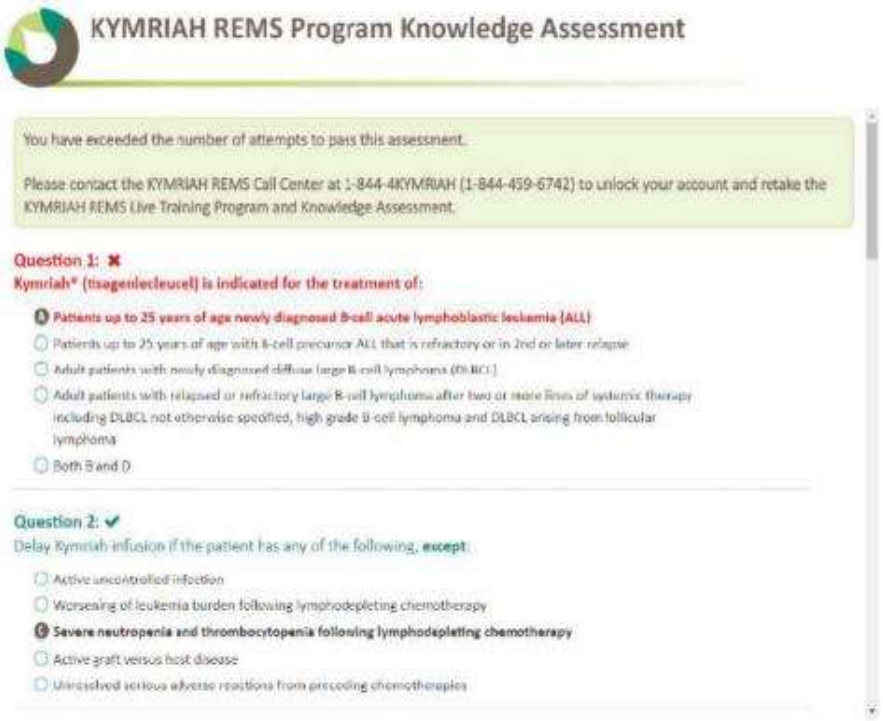
has successfully completed the
KYMRIAH REMS Program Knowledge Assessment on

October 13, 2017

Please print this certificate and provide it to your authorized representative.
If you are the authorized representative and you have not completed the KYMRIAH REMS Program Hospital Enrollment Form, please complete and fax the form to 1-844-590-0840 or email the form to KymriahREMS@sbc.com

KYMRIAH
Risk Evaluation and Mitigation Strategy (REMS)

KYMRIAH™
(tisagenlecleucel)



KYMRIAH REMS Program Knowledge Assessment

You have exceeded the number of attempts to pass this assessment.

Please contact the KYMRIAH REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742) to unlock your account and retake the KYMRIAH REMS Live Training Program and Knowledge Assessment.

Question 1: ✖

Kymriah® (tisagenlecleucel) is indicated for the treatment of:

- A **Patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)**
- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in 2nd or later relapse
- Adult patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL)
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma
- Both B and D

Question 2: ✔

Delay Kymriah infusion if the patient has any of the following, **except**:

- Active uncontrolled infection
- Worsening of leukemia burden following lymphodepleting chemotherapy
- C **Severe neutropenia and thrombocytopenia following lymphodepleting chemotherapy**
- Active graft versus host disease
- Unresolved serious adverse reactions from preceding chemotherapies

APPENDIX H

RISK EVALUATION AND MITIGATION STRATEGY (REMS) MEMORANDUM

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Office of Tissues and Advanced Therapies

NDA/BLA #s:	125646
Products:	Kymriah (tisagenlecleucel), suspension for intravenous infusion
APPLICANT:	Novartis
FROM:	Wilson Bryan, MD; OTAT Office Director
DATE:	August 2, 2017

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultation between the Office of Tissues and Advanced Therapies and the Office of Biostatistics and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Kymriah (tisagenlecleucel) to ensure that the benefits of the drug outweigh the risks of cytokine release syndrome (CRS) and neurotoxicity. During the review of this application, FDA determined that the Applicant's proposed REMS, which consisted of a communication plan for healthcare providers, was not adequate to mitigate these risks. Over 70% of patients developed CRS during the pre-market evaluation of this product, and many required intensive-care level facilities and the specific use of the monoclonal antibody tocilizumab to manage this adverse event.

Due to the severe adverse events of CRS and neurotoxicity, which will both be included in a boxed warning on the label, ETASU B and ETASU C will be required to ensure that the drug's benefits outweigh the risks. The REMS for Kymriah (tisagenlecleucel) will ensure that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate (i.e., within 2 hours) access to tocilizumab. The REMS will ensure that as part of certification, those who prescribe, dispense or administer Kymriah (tisagenlecleucel) are trained about neurotoxicity and the management of CRS based on a treatment algorithm that is part of the site training material. Site-certification will also entail providing patients with information on CRS and neurotoxicity and informing them of the importance of staying close to the certified

hospital or associated clinic after receiving Kymriah, so that they can return to the treatment site for the treatment of CRS if needed. Kymriah will only be dispensed to patients in certain health care settings, specifically, hospitals and their associated clinics.

In reaching this determination, we considered the following:

A. Kymriah (tisagenlecleucel), a genetically modified autologous immunotherapy, will be licensed to treat cases of relapsed and refractory B cell acute lymphoblastic leukemia (ALL) in ages 3-25 years. The incidence of new cases of pediatric ALL is approximately 3,100 in children and adolescents per year (PDQ, HCP April 2017[1]). Approximately 620 pediatric and young adult patients with ALL relapse each year in the United States after achieving an initial response (Maude et al. 2015[2]). Current treatment for de novo or relapsed B cell ALL includes combinations of chemotherapy, radiation therapy, and hematopoietic stem cell transplantation (HSCT).

B. Survival after relapse depends on the timing and type of the relapse. Relapses that occur within 18 months of initiation of therapy or while the patient is still on therapy have an extremely poor prognosis despite subsequent therapy. The only potential cure for relapse in recurrent pediatric ALL has been HSCT. For HSCT to succeed, the patient needs to be in complete remission with no minimal residual disease which is difficult to achieve after relapse. Overall, the prognosis for relapsed and refractory B cell ALL is very poor.

C. The pre-specified primary endpoint for the pivotal licensure trial was overall remission rate (ORR) during the 3 months after Kymriah (tisagenlecleucel) administration. The pivotal study enrolled 88 subjects, 63 of whom were infused with Kymriah (tisagenlecleucel) manufactured in the U.S. facility. A total of 52 subjects (82.5%) of 63 in the efficacy analysis set had an overall disease response of complete remission, and the result was statistically significant. The median time follow-up time for duration of response (DOR) was 4.8 months. The median DOR has not been reached. Below is a table of products that have been previously approved or licensed to treat relapsed and refractory B cell acute lymphoblastic leukemia (ALL) for this population. **Table: FDA Approved Therapies for R/R ALL in Pediatric and Young Adult Patients**

FDA-Approved Products	Approval/ Year	Results
Clofarabine (CLOLAR)	2004, accelerated	CR 11.5%
Vincristine lyophilized injection (MARQIBO)	2012, accelerated	CR 4.6%
Blinatumomab	2014	CR 17.1%; Median DOR 6.0

[1] https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032725/
[2] Maude SL, Teachey DT, Porter DL, et al (2015) CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood: 125:4017-23.

FDA-Approved Products	Approval/ Year	Results
(BLINCYTO)		months
Inotuzumab ozogamicin (BESPONSA)	2017	CR 35.8%; Median DOR 8.0 months

CR: complete remission; DOR: duration of response;
Source: USPI for CLOLAR, BLINCYTO, MARQIBO, BESPONSA

D. Patients between the ages of 3 and 25 years who have relapsed or refractory B cell ALL will be selected for this therapy within certain hospitals, which Novartis has chosen and have been accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). They will have a pheresis procedure to obtain peripheral blood mononuclear cells. These are frozen and sent to a Novartis manufacturing facility, where a lentiviral vector will be used to encode chimeric antigen receptor T cells from the drawn blood. This will then be shipped back to the ordering facility. The patient will be given lymphodepletion therapy, and will then get a single intravenous dose of Kymriah (tisagenlecleucel) derived from their T cells. The dose is decided by weight. If under 50 kilograms (kg) 2-5 x 10e6 Kmyriah cells/kg. Greater than or equal to 50 kg., 1-2.5 x 10e8 Kymriah cells as a flat dose. There are no repeat doses.

E. Patients with B cell precursor ALL do not have a baseline incidence of cytokine release syndrome. Neurological toxicity that was observed with the product as detailed below was not associated with ALL or prior therapies. In the pivotal study B2202, 54 of 68 (79%) subjects treated with Kymriah (tisagenlecleucel) experienced CRS, and 33/68 (49%) of the subjects had Grade 3/4 CRS. CRS results in a constellation of inflammatory symptoms ranging from a flu-like syndrome to severe multi-organ system failure and death. Specifically, Grade 3/4 CRS required treatment under ICU settings and based on a treatment algorithm that required use of antipyretics, broad spectrum antibiotics, oxygen supplementation and or mechanical ventilation, and multiple vasopressors along with the use of tocilizumab. The median time to onset of Grade 3/4 CRS was six days. The median duration of Grade 3/4 CRS was 9 days. Of the 54 subjects with CRS, 27 (50%) required 1-3 doses of tocilizumab. In addition, 44 /68 (65%) subjects had neurotoxicity (defined as events such as aphasia, tremor, seizures, confusion, headache, and encephalopathy) within the first 8 weeks, with 12 subjects (18 %) with grade 3 (and none being grade 4). Besides the boxed warning for CRS and neurotoxicity, the label will contain information regarding the following under Warnings: infections, febrile neutropenia, hypogammaglobinemia and impaired driving ability/operate machinery.

F. Kymriah (tisagenlecleucel) has been given a breakthrough designation in the IND phase and is a first in class gene therapy. Kymriah is a first in class CD19-directed genetically-modified autologous T cell immunotherapy. It is not a new molecular entity but it is a new technology and a new biologic class of products.

The REMS will consist of elements to assure safe use, including that hospitals and their associated clinics that dispense Kymriah (tisagenlecleucel) must be certified, and Kymriah

(tisagenlecleucel) must be dispensed to patients only in certain healthcare settings, an implementation system, and a timetable for submission of assessments of the REMS.

APPENDIX I

COMPARISON OF FDA AND HHS HUMAN SUBJECTS' PROTECTION REGULATIONS

Appendix 1: Comparison of FDA and HHS Human Subject Protection Regulations (FDA, 2009)

FDA Regulations	HHS Regulations
56.101 Scope IRBs that review clinical investigations regulated by the FDA under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.	46.101 Scope All research involving human subjects conducted or supported by HHS or conducted in an institution that agrees to assume responsibility for the research in accordance with 45 CFR 46 regardless of the source of funding.
56.102 and 50.3 Definitions Definitions for "Act"; "Application for research or marketing permit"; "Emergency use"; "Sponsor"; "Sponsor-investigator"; "Test article" do not have comparable terms defined in 45 CFR 46. FDA has defined "clinical investigation" to be synonymous with "research". "Clinical investigation" means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. "Human subject" means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.	46.102 Definitions Definitions for "Department or agency head"; "Certification" do not have comparable terms defined in 21 CFR 50 or 56 HHS has defined "research" as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. HHS has defined "Research subject to regulation" and similar terms as intending to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the FDA). "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. "IRB" means an institutional review board established in accord with and for the purposes expressed in this policy.

"Institutional Review Board" means any board, committee, or other group formally designated by an institution to review, to approve the initiation or, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act.	
Definitions for "IRB approval"; "Minimal Risk; "Institution"; Legally authorized representative" are identical.	
56.103 Circumstances in which IRB review is required. Except as provided in 56.104 and 56.105, any clinical investigationwhich must meet the requirements for prior submission to the FDAor considered in support of an application for a research or marketingpermit must have been reviewed and approved by, and remained subjectto continuing review by, an IRB meeting the requirements of thispart. [In diverging from the assurance requirement, FDA stated itsbelief that it is inappropriate for it to adopt the assurance mechanism.The benefits of assurance from IRBs that are subject to FDA jurisdiction,but not otherwise to HHS jurisdiction, do not justify the increasedadministrative burdens that would result from an assurance system.FDA relies on its Bioresearch Monitoring Program, along with itseducational efforts, to assure compliance with these regulations.]	46.103 Assuring compliance with this policy--research conducted or supported by any Federal Department or Agency Sections dealing with assurances and certifications (a), (b)(1)-(3), (c)-(f) are unique to the common rule and the HHS regulations.
56.104 Exemptions from IRB requirement a. Any investigation which commenced before 7/27/81, and was subjectto requirements for IRB review	46.101(b) Exemptions from this policy a. Research conducted in established or commonly accepted educationalsettings... b. Research involving the use of educational tests..., survey

under FDA regulations before thatdate, provided that the investigation remains subject to review ofan IRB which meets the FDA requirements in effect before 7/27/81. b. Any investigation that commenced before 7/27/81 and was not otherwisesubject to requirements for IRB review under FDA regulations beforethat date c. Emergency use of a test article, provided that such emergency useis reported to the IRB within 5 working days. Any subsequent useof the test article at the institution is subject to IRB review.	procedures,interview procedures or observation of public behavior... c. Research involving the use of educational tests (cognitive, diagnostic,aptitude achievement), survey procedures, interview procedures,...thatis not exempt if the human subjects are elected or appointed ... orif these sources are publicly available... d. Research and demonstration projects which are conducted by or subjectto the approval of department or agency heads, and which are designedto study ..public benefit or service programs...
Identical Exemption: Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe....	
56.105 Waiver of IRB requirement. On the application of a sponsor or sponsor-investigator, the FDA may waive any of the requirements contained in these regulations, including the requirement for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.	No comparable provision.
56.107 and 46.107 IRB Membership requirements are identical	
56.108 and 46.108 "IRB functions and operations" are virtually identical except 56.108 requires reporting to the FDA; 46.108 requires reporting to the department or agency head.	
56.109 and 46.109 "IRB review of research" are virtually identical with the following exceptions: □ 46.109(c) refers to the criteria in .117 for waiving the requirementfor a signed consent form -- .117(c)(1) is not included in FDA'sregulations because FDA	

	does not regulate research in which "theonly record linking the subject and the research would be the consentdocument and the principal risk would be potential harm resultingfrom a breach of confidentiality." ⊏ 56.109(c) and (e) contain additional language related to FDA'semergency research rule; HHS published identical criteria for emergencyresearch in a Secretarial announcement of waiver of the applicabilityof 45 CFR 46, 10/2/96.
56.110 and 46.110 "Expedited Review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research" are virtually identical, except: n 56.110 refers to the FDA and 46.110 refers to the Secretary, HHS,or the department or agency head n 56.110(d) states "The FDA may restrict, suspend, or terminatean institution's or IRB's use of the expedited review procedure whennecessary to protect the rights or welfare of subjects." 46.110(d)states that "The department or agency head may restrict, suspend,terminate, or choose not to authorize an institution's orIRB's use of the expedited review procedures."	
56.111 and 46.111 "Criteria for IRB approval of Research" are virtually identical except 56.111 contains references to sections in part 50 and 46.111 contains references to sections in part 46.	
56.112 and 46.112 "Review by institution" are identical.	
56.113 and 46.113 "Suspension or termination of IRB approval of research" are virtually identical except 56.113 refers to FDA and 46.113 refers to the department or agency head.	
56.114 Cooperative research In complying with these regulations, institutions involved in multi-institutionalstudies may use joint review, reliance upon the review of anotherqualified IRB, or similar arrangements aimed at avoidance of duplicationof effort.	46.114 Cooperative research Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.
56.115 and 46.115 "IRB Records" are virtually identical except ⊏ The list of IRB members required by 56.115(a)(5) is cross-referencedin 46.115(a)(5) to 46.103(b)(3)	

▫ 56.115(b) refers to FDA rather than the department or agency ▫ 56.115(c) states that "The FDA may refuse to consider a clinicalinvestigation...if the institution or the IRB that reviewed the investigationrefuses to allow an inspection under this section." Part 46does not contain a comparable requirement.	
56.120 Lesser administrative actions The agency may 1. Withhold approval of new studies; 2. Direct that no new subjects be added to ongoing studies; 3. Terminate ongoing studies when doing so would not endanger the subjects; or 4. When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB. The parent institution is presumed to be responsible for the operation of an IRB, and FDA will ordinarily direct any administrative action against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, FDA may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.	46.123 Early termination of research support; Evaluation of applications and proposals. 1. The department or agency head may require that...support for anyproject be terminated or suspended...when the department or agencyhead finds an institution has materially failed to comply with theterms of this policy. 2. In making decisions about supporting or approving applicationsor proposals...the department or agency head may take into account...factorssuch as whether the applicant has been subject to a termination orsuspension under...this section and whether the applicant or theperson or persons who would direct or has directed the scientificand technical aspects of an activity has, in the judgment of thedepartment...materially failed to discharge responsibility for theprotection of the rights and welfare of human subjects (whether ornot the research was subject to federal regulation).
56.121 Disqualification of an IRB or an institution	46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency

...The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that: 1. The IRB has refused or repeatedly failed to comply with any ofthe regulations set forth in this part, and 2. The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation....	The department or agency head will evaluate all applications and proposals involving human subjects.... This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one. 46.122 Use of Federal Funds Federal Funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.
56.122 Public disclosure of information regarding revocation A determination that the FDA has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20. 56.123 Reinstatement of an IRB or an institution An IRB or an institution may be reinstated if the Commissioner determines...that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part....	No comparable provisions.
56.124 Actions alternative or additional to disqualification Disqualification of an IRB...is independent of...other proceedings or actions authorized by the Act. The FDA may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu	46.124 Conditions With respect to any research project...the department...head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

of, and before, at the time of or after disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.	
50.20 and 46.116 General requirements for informed consent are virtually identical.	
50.25 and 46.116(a) Elements of informed consent are virtually identical except: - 50.25(a)(5) requires the confidentiality statement to note "thepossibility that the FDA may inspect the records." - 46.116(c) and (d) state the conditions under which the IRB mayapprove a consent procedure which does not include, or which alters,some or all of the elements of informed consent, or waive the requirementto obtain informed consent [the conditions could not apply in FDAregulated research]	
50.27 and 46.117 Documentation of informed consent are virtually identical except: - 46.117(c)(1) is not included in FDA's comparative section containedin 56.109(c). 46.117(c)(1) allows the IRB to waive the requirementfor the investigator to obtain a signed consent form if it findsthat the only record linking the subject and the research would bethe consent document and the principal risk would be potential harmresulting from a breach of confidentiality.	
50.23(a)-(c) Exception from general requirements Describes an exception from the general requirements for obtaining informed consent in circumstances that are life-threatening; informed consent cannot be obtained from the subject; time is not sufficient to obtain consent from the subject's legal representative; and there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.	No comparable provisions
50.23(d) Waiver of informed consent for military personnel Describes the criteria and standards that the President is to apply in making a	No comparable provision.

determination that informed consent is not feasible or is contrary to the best interests of the individual in military exigencies in accordance with the Strom Thurmond Defense Authorization Act for FY 1999	

1. In 1991 FDA's regulations were harmonized with the common rule to the extent permitted by statute.
2. Differences in the rules are due to differences in the statutory (1) scope or (2) requirements.
3. FDA has additional IRB requirements contained in parts 312, 812, and 814. For example, 812.2(b)(ii) states that research is considered to have an approved application for an IDE, unless FDA has notified the sponsor to the contrary, if IRB approval of the investigation is obtained after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk, and maintains such approval, (iii) and ensures informed consent is obtained in accordance with part 50.
4. HHS has special subparts relating to vulnerable populations, e.g., children, prisoners, pregnant women, etc. FDA does not have comparable provisions for these populations.
5. The HHS regulations require assurances and certifications from the grantee institution. FDA regulations generally require assurances of compliance from either or both the sponsor of the research and the clinical investigator.