Introduction

In his January 20, 2015 State of the Union address, President Obama brought to the nation’s attention the promise of personalized medicine when he announced the Precision Medicine Initiative (the “PMI”). In announcing this initiative during his address, which was to be funded with $215 million in the President’s 2016 budget, the President gave many in the nation their first hint of the tremendous benefits to be gained by physicians being better able to tailor medical treatments to individual patients. This focus on the unique attributes of each patient – the patient’s environment, lifestyle, and, most notably, genetic characteristics – allow targeted therapies to be deployed that are more likely to be efficacious, less likely to lead to adverse side effects, and, in many circumstances, more cost-effective for both the patient and society at large than current approaches to many different illnesses.

The PMI is a far-reaching multi-disciplinary effort to foster the development of personalized medicine. Funds for the PMI were allocated to different government agencies as follows: (1) the National Institutes of Health (the “NIH”) to develop a national cohort that would facilitate understanding of and set the foundation for new ways of doing research; (2) the NIH Cancer Institute to identify genomic drivers in cancer and more effective approaches to therapy; (3) the FDA to advance development of high quality curated databases to support the regulatory structure needed to advance innovation in precision medicine; and (4) the Office of the National Coordinator for Health Information Technology for the development of interoperability standards to address privacy issues and enable the secure exchange of data across different systems. Perhaps the most ambitious aspect of the initiative is its call for the development of a one (1) million patient volunteer cohort, which would engage individuals as active partners in the undertaking and not just as patients or research subjects.

Personalized medicine, also often referred to as “precision medicine,” is the result of emerging technologies that allow scientists and physicians to build upon what has long been a focus on a patient’s individual characteristics in diagnosing illness (e.g., the patient’s family history, social history, prior medical history, and presenting symptoms). The development of genetic sequencing and the discovery and use of biomarkers has now given clinicians new tools to better diagnose patients and develop more targeted treatments. By way of example, before the advent of genetic sequencing, a clinical trial of a treatment for cancer might have demonstrated a twenty-five percent (25%) success rate, which, depending on the type of cancer and the other therapies available at the time, might have been viewed as a fairly good outcome. However, even with this degree of efficacy, of every four (4) patients treated only one (1) patient would benefit from the medication. The other three (3) patients would receive no benefit and would also be subject to any adverse side effects of the treatment.

Today, genetic sequencing might reveal the subset of patients with a specific genetic mutation who would be most likely to respond to a particular treatment thereby allowing for a much higher success rate with a particular drug. In many situations, genetic sequencing will provide physicians with the necessary knowledge so that they will only prescribe a drug for those patients who are likely to respond and will be able to avoid treating others with a particular medication when that therapy is unlikely to be successful. This benefit is emblematic of one of the most significant characteristics of personalized medicine – what is commonly referred to as “the right treatment, for the right patient, at the right time.”

Personalized medicine has been recognized as greatly improving patient outcomes. For instance, it has been reported that the 5-year survival rate for myelogenous leukemia doubled following the introduction of imatinib (a targeted therapeutic), the 5-year survival rate for colorectal cancer increased by fifteen percent (15%) following discovery of molecular receptors associated with tumor growth, and the hospitalization rate decreased by thirty percent (30%) when warfarin (otherwise known as Coumadin, a
frequently used anticoagulant) was dosed based on a patient’s genetic characteristics. The potential cost savings to the health care system by the adoption of personalized medicine are likewise projected to be dramatic. By way of example, it has been projected that the frequency of chemotherapy could be decreased by thirty-four percent (34%) in women with breast cancer if they all received genetic testing prior to treatment. Notwithstanding the clear benefits offered by personalized medicine, there are any number of legal and policy issues, including those related to approval of products by the FDA, intellectual property rights in genes and genetic information, and reimbursement of targeted therapies, that will need to be addressed for the full promise of personalized medicine to be realized.

**FDA and the Regulatory Requirements for Personalized Medicine Products**

When the Federal Food, Drug, and Cosmetic Act was passed in 1938, the term Personalized Medicine had not yet been coined. As result, the Food and Drug Administration’s (FDA) oversight activities related to precision or personalized medicine stem from FDA’s role in regulating drugs, biologics and medical devices rather than from specific requirements for “personalized medicine” products. These oversight activities are undertaken through three medical product review centers: the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER).

Each of these centers applies specific sets of regulations implementing different statutory authorities to different products. Thus, the personalized medicine effort at FDA has required significant coordination, which has not always been easy. In 2009, FDA created a Personalized Medicine Staff within the Office of In Vitro Diagnostic Device Evaluation and Safety to address the unique issues for diagnostics used in personalized medicine and to coordinate regulatory oversight between the devices and drugs/biologics centers to try and provide consistency and timeliness in regulatory decision-making for these products. There is also a multidisciplinary Genomics Evaluation Team for Safety (GETS) and the FDA Genomics Working Group, which is tasked with developing systems to deal with regulatory submissions including high-throughput sequencing data.

Personalized medicine often involves two medical products: a diagnostic test (a device), and a therapeutic. The diagnostic test is generally regulated as a medical device, and can include in vitro diagnostic assays or in vivo tests (e.g., diagnostic imaging). Although drugs and biologics are the most obvious therapeutics where personalized medicine is involved, all types of regulated products can be therapeutics.

Coordinating the testing, preparation and submission of the paired products can be challenging, especially when two companies have partnered to bring the two components to the market. A further challenge is that FDA’s review of each component is generally handled by a different center. In Guidance entitled “In Vitro Companion Diagnostic Devices”, FDA has recommended contemporaneous development of a drug and its corresponding diagnostic device. If the device and its test results are essential for the drug’s safety and efficacy, FDA will not approve the therapeutic or use of the product with the device if FDA has not also approved/cleared the device itself. However, FDA retains discretion to approve a drug for use with a companion device, even if FDA has not yet approved/cleared the device. In this situation, FDA would approve/clear the device subsequently, and then the therapeutic sponsors can revise relevant product labeling accordingly.

While the goal of individually tailoring medicines for individual patients carries the promise of great benefits, significant FDA challenges remain. The standards for FDA approval have not changed for personalized medicine products, and, in fact, the complexities associated with obtaining approvals for such products are often greater than those for traditional products. Early communication with the Agency can help applicants understand how any challenges can be addressed and overcome.

**Property Rights and Personalized Medicine**

It was expected that genomic medicine and technology would lead to new advances in the delivery of health care. Indeed, when the Human Genome Project was launched in 1990 to sequence the complete set of DNA in the human body, one of the project’s stated goals was to understand the genetic factors in human disease, paving the way for new strategies for their diagnosis, treatment and prevention. These discoveries are key to personalized medicine as they allow tailored therapies and medical strategies based on an individual’s genome. The impact of advances in genomic medicine and its application to diagnosis and treatment has not, however, been limited to new treatments and tests – it also has impacted over twenty years of U.S. patent practice by challenging what can, and cannot, be the subject of a United States patent.

A patent is a property right issued by a government to one or more inventors. In the United States, a patent allows the patent holder to prevent others from making, using, importing, offering for sale or selling the patented technology. However, not every discovery is patentable; only discoveries that meet the criteria of novelty, non-obviousness, and utility can be protected by a patent. The utility requirement ensures that the invention is useful and is of a class for which the patent office is authorized to grant patents. It has been the U.S. Supreme Court’s recent interpretation of this utility requirement (or more specifically what is patent-eligible) that has modified whether discoveries that relate to personalized medicine can be patented.

Medical diagnostics are key tools of many personalized therapies. Diagnostic methods can provide a physician with useful if not critical information to treat a patient. For decades, diagnostic methods that link a genetic characteristic to a treatment option were routinely held to be patentable in the United States, provided that the methods were novel and non-obvious. However, the Supreme Court changed this paradigm in their decision Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S.Ct. 1289, 1296 (2012). In Mayo, the Supreme Court determined that certain diagnostic analysis - such as a diagnostic test that correlates to a patient’s health...
or disease – is not patentable when only the correlation between the diagnostic reading and the health status of the patient is the subject of the patent. The Supreme Court unanimously held that broadly claimed diagnostic methods are not patent-eligible because they attempt to patent a law of nature. As a result, patent applications claiming diagnostic methods are now more critically examined for patent-eligibility as well as novelty and non-obviousness.

One year after limiting the scope of diagnostic method patents, the U.S. Supreme Court addressed the question whether isolated human genes are patent-eligible. In Ass’n. for Molecular Pathology v. Myriad Genetics, Inc., 133 S.Ct. 2107 (2013), a unanimous U.S. Supreme Court removed from patent-eligibility isolated, naturally occurring genes and gene fragments – a class of discoveries that has been an important driver of the biotechnology industry for the last few decades. Myriad sold a genetic test that confirms the presence of BRCA1 or BRCA2 gene mutations that are responsible for the majority of hereditary breast and ovarian cancers. Myriad had exclusive rights to provide the test in the United States by virtue of at least seven patents assigned or exclusively licensed from the University of Utah. The patent rights covered the genes as isolated from the human body, synthetic, or man-made genes, fragments of the genes, and use of the genes to perform screens and diagnostic tests. The Supreme Court held, however, that the patent rights to unmodified whole genes and gene fragments were invalid for claiming a product of nature. The holding of Myriad has since been extended to any isolated, naturally occurring and unmodified product of nature such as proteins, antibodies and plant extracts.

Personalized medicine has also raised new questions related to the ownership of genetic information. For instance, Myriad, by and through its genetic testing service, has collected a large amount of genetic and health information from the tests it has offered. The information can provide insight for new genetic tests and on genetic variants linked to diseases other than those focused on in Myriad’s test. Four patients, represented by the American Civil Liberties Union (ACLU) recently filed a complaint pursuant to the Health Insurance Portability and Accountability Act (HIPAA) with the U.S. Department of Health & Human Services to gain access to genetic information beyond what is contained in the report of their test results. The patients seek full access to the genetic information obtained from their individual tests to proactively monitor their own cancer risk and be able to share their data with other research groups. After initially refusing to provide the data to the patients, Myriad reversed course and provided the ACLU’s four clients with additional information. Nevertheless, the ACLU’s spokesman reported that the group wants an official decision supporting patients’ right to their genetic information.

Reimbursement Concerns

Although personalized medicine can lead to better patient care outcomes and lower costs of care, reimbursement has been an area of continuing challenge for this industry sector. As an initial condition for reimbursement, the developer/manufacturer must establish coverage through processes which are still, for the most part, unique to each payer. In other words, each payer will have its own data requirements that have to be satisfied, and each payer will have to be separately satisfied that it should cover the specific product. As part of the coverage process, the manufacturer must be able to establish product safety, clinical efficacy, and for some payers, economic efficiency. In some cases, payers may also expect clinical evidence showing that the product works better than products that are already covered, or is specifically helpful in a particular clinical population.

For therapeutic purposes, coverage generally requires that the product be approved by FDA for at least one use. For diagnostic testing, there currently is arguably more latitude for laboratory-developed tests (LDTs), although the FDA’s parameters require careful business planning and the regulatory landscape for LDTs is currently in flux. Other types of laboratory tests generally require FDA approval before coverage. One significant payer, the federal Medicare program, has a statutory requirement that coverage is limited to those items or services that are medically necessary and reasonable for the diagnosis or treatment of disease or injury (except for the limited preventive services which are specifically covered). This “medical necessity and reasonableness” approach may limit the diagnoses for which an item or service will be covered, or even preclude certain individuals (or categories of individuals, such as Medicare hospice patients who are limited to palliative care) from receiving coverage.

Once coverage is achieved, the level of reimbursement must still be set, again with each payer. In many cases, the payment is lower than hoped for by the manufacturer. In some states, there is developing pressure to limit the amount charged for certain costly drugs (although charges may have little to do with the amount that payers actually pay for a product). Some payers will set the level of reimbursement at the same level for what they determine to be comparable products that are already covered, without recognition of the “next generation” value of the new product. Few, if any, payers take into account the projected savings in hospital and other clinical care that can result from the use of the product. And while there is a general trend towards payment for successful clinical outcomes and payment for episodes of care rather than specific items or services, that approach requires significant changes in the current delivery system with significant details that remain to be determined.

Developers of personalized medicine products need to have a clear business plan from the earliest stages in order to be sure they have the necessary data to present to payers. In some cases, the need for payer data should even influence the design of clinical trials, and payment systems may even influence the choice of drug delivery options (e.g., oral vs. IV-administered). From the beginning of a product’s development, the developer must expect a long and tedious process towards achieving its ultimate goal of coverage and reimbursement. However, there are already success stories: many diagnostic tests and targeted therapies are already available and approved for patient use. In fact, many of these tests and therapies have even been approved for payment by the federal Medicare program, typically known as a conservative payer. For example, genetic testing for certain cancers is addressed in Noridian’s Local Coverage Determination L24308. The Molecular Diagnostic Services Program (MolDX™) was developed in 2012 to identify and establish coverage and reimbursement for molecular diagnostic tests, and continues in that role.
Conclusion

Personalized medicine promises to provide treatments tailored to the unique attributes of each individual patient that are more efficacious, less prone to side effects, and potentially less expensive than many of the therapies now available. However, before the benefits of personalized medicine can be fully realized, there are a number of challenges that must be addressed. The FDA must adopt and offer a path to regulatory approval that recognizes the issues unique to personalized medicine products, intellectual property issues must be resolved in a way that continues to incentivize development of new and innovative products while fostering collaboration and the sharing of information, and payers must adopt clearly articulated reimbursement policies that reflect the value provided by personalized tests and products.

Additional Resources

NOTE: Those interested in an in-depth exploration of the complex business issues, trends, and opportunities in personalized medicine may wish to check out the 4th Annual Business of Personalized Medicine Summit, to be held in San Francisco on September 29, 2016. This one-day, one-of-a-kind thought leadership forum will bring together key executives with varying stakeholder perspectives to deliver insights and strategies for capitalizing on this challenging yet profitable market. For details, visit www.personalizedmedicinesummit.com.


3A “biomarker” is “[a] biological molecule found in blood, other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.” See NCI Dictionary of Cancer Terms, http://www.cancer.gov/publications/dictionaries/cancer-terms?csid=45618 (last visited on June 13, 2016).
5Id.
6As a result of the White House initiative, FDA has now adopted the term precision medicine – see Precision Medicine, http://www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/default.htm (last visited June 13, 2016).
8Id.
10Patients Challenge Myriad Genetics for Access to Their Gene Data (May 19, 2016), https://www.statnews.com/2016/05/19/myriad-genetics-hipaa-access/