THE PERSONALIZED MEDICINE REPORT

2020 · Opportunity, Challenges, and the Future

PMC

The Personalized Medicine Coalition gratefully acknowledges pharmacogenomics graduate students at Manchester University in Fort Wayne, Indiana, and at the University of Maryland, who updated the appendix of this report under the guidance of David Kisor, Pharm.D., Professor and Director of Pharmacogenomics, Manchester University, and Megan Ehret, Pharm.D., Associate Professor, University of Maryland School of Pharmacy. The Coalition also acknowledges the contributions of its many members who offered insights and suggestions for the content in this report.

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HISTORICAL PRECEDENT

For more than two millennia, medicine has maintained its aspiration of being personalized. In ancient times, Hippocrates combined an assessment of the four humors — blood, phlegm, yellow bile, and black bile — to determine the best course of treatment for each patient. Today, the sequence of the four chemical building blocks that comprise DNA, coupled with telltale proteins in the blood, enable more accurate medical predictions.

INTRODUCTION

When it comes to medicine, one size does not fit all. Treatments and prevention strategies that help some patients are ineffective for others,[1] and the same medicine may cause side effects or adverse reactions in only certain patients.

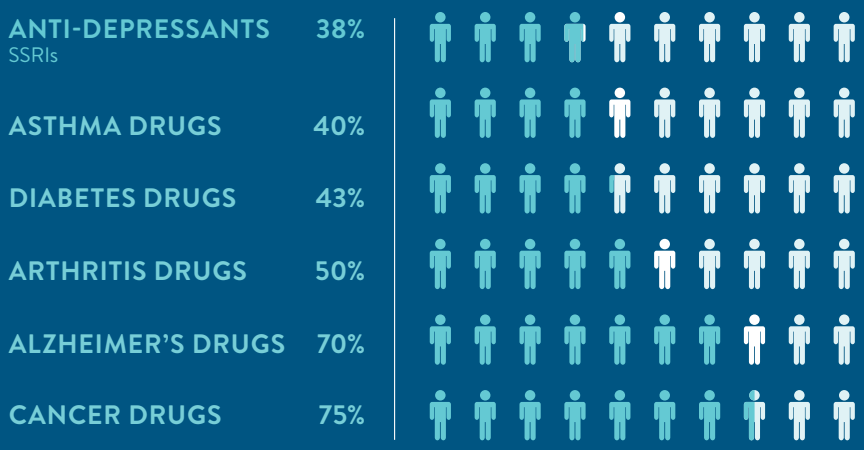
Yet physicians usually recommend medical interventions based on what works best for patients on average. As a result, many health care systems around the world deliver inefficient care that fails to help significant portions of the patient population. Especially as COVID-19 places new demands on already strained health care delivery systems, many countries are in dire need of new tools that can help physicians eliminate the wasteful portions of spending that are endemic to this one-size-fits-all approach.

Enter personalized medicine. Personalized medicine, also called precision or individualized medicine, is a rapidly evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms, often genetic, that cause disease or influence a patient's response to certain treatments. By combining molecular data with an individual's medical history, circumstances and values, health care providers can develop targeted prevention and treatment plans. Personalized health care has the capacity to detect the onset of disease at its earliest stages, pre-empt the progression of disease, and, at the same time, increase the efficiency of the health care system by targeting treatments to only those patients who will benefit.

Because our increasing understanding of human heterogeneity demands it, health care is in the midst of a transformation away from one-size-fits-all, trial-and-error medicine and toward this new, targeted approach in which, as is often said, the right patient will get the right treatment at the right time. Completing that transformation, however, will require a collaborative effort based on shared values across stakeholder groups to keep up with the pace of progress in science and technology. A myriad of complicated regulatory and reimbursement challenges as well as practical obstacles related to the clinical adoption of new medical practices and processes, however, make it difficult for health care systems around the world to capitalize on innovative groundbreaking science and technology that point to a new era in the history of medicine that for the first time promises to put the individual at the center of care.

FIGURE 1: ONE SIZE DOES NOT FIT ALL

Percentage of the patient population for which a particular drug in a class is ineffective, on average.



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THE OPPORTUNITY

"The power in tailored therapeutics is for us to say more clearly to payers, providers, and patients: 'this drug is not for everyone, but it is for you.' That is exceedingly powerful."

— **John C. Lechleiter, Ph.D.**
former Chairman, President, and CEO,
Eli Lilly and Company

THE BENEFITS

Personalized medicine benefits patients and the health system by:

- Shifting the emphasis in medicine from reaction to prevention
- Directing targeted therapy and reducing trial-and-error prescribing
- Reducing the frequency and magnitude of adverse drug reactions
- Using cell-based or gene therapy to replace or circumvent molecular pathways associated with disease
- Revealing additional targeted uses for medicines and drug candidates
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures
- Helping to shift physician-patient engagement toward patient-centered care
- Helping to control the overall cost of health care

Shifting the Emphasis in Medicine from Reaction to Prevention

Personalized medicine introduces the ability to uncover cellular and molecular markers that signal disease risk or presence before clinical signs and symptoms appear, offering an opportunity to focus on prevention and early intervention rather than on reaction at advanced stages of disease.

In some areas, early genetic testing can save lives. For example, women with certain BRCA1 or BRCA2 gene variations have up to an 85 percent lifetime chance of developing breast cancer, compared to a 13 percent chance among the general female population.[2,3] Women with harmful BRCA1 and BRCA2 mutations also have up to a 39 and 17 percent chance, respectively, of developing ovarian cancer, compared with a 1.3 percent chance among the general female population.[2] The BRCA1 and BRCA2 genetic tests can guide preventive measures, such as increased disease monitoring, chemoprevention, or risk-reducing surgery.

Personalized medicine's prevention and early intervention capacity is also evident outside of oncology. For example, patients with familial hypercholesterolemia carry a mutated LDL receptor gene, leading to significantly elevated cholesterol. These patients can take drugs that block the product of the PCSK9 gene (known as PCSK9 inhibitors) to reduce their cholesterol levels and potentially decrease their risk of developing coronary artery disease.

Directing Targeted Therapy and Reducing Trial-and-Error Prescribing

In many disease areas, predictive or prognostic diagnostic tests enable physicians to identify the most effective treatment strategy for a patient by testing for specific molecular characteristics, thus avoiding the frustrating and costly practice of trial-and-error medicine. Medicines that target molecular characteristics often improve outcomes, and they may also reduce side effects and adverse reactions.

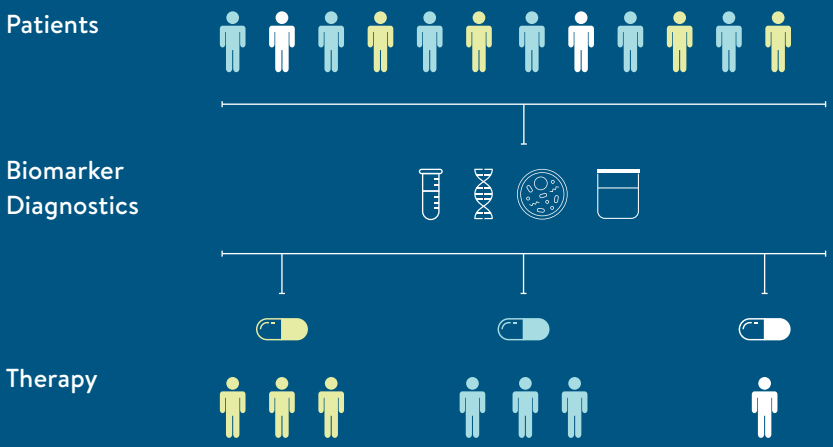
One of the most common applications of targeted treatment has been for women with breast cancer. About 30 percent of breast cancer cases are characterized by over-expression of a cell-surface protein called human epidermal growth factor receptor 2 (HER2). For patients with breast cancer whose tumors express this molecule, adding a targeted drug like trastuzumab (Herceptin®) or other drugs that target

FIGURE 2: A NEW TREATMENT PARADIGM

Without Personalized Medicine: Some Benefit, Some Do Not

Some patients benefit, some patients do not benefit, and some patients experience adverse effects

With Personalized Medicine: Each Patient Receives the Right Medicine



Each patient benefits from individualized treatment

Adapted with permission from: PhRMA. *Chart Pack: Value of Personalized Medicine* (p. 10). Accessed June 5, 2020, at https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/A-C/chart_pack-value_of_personalized_medicine4.pdf.

HER2, such as pertuzumab (Perjeta®), lapatinib (Tykerb®), neratinib (Nerlynx®) and trastuzumab emtansine (Kadcyla™) to their chemotherapy regimen can reduce their recurrence risk by 52 percent.[4,5]

Some of the tests underpinning personalized medicine can also be used to measure prognostic markers that help indicate how a disease may develop in an individual when a disorder is already diagnosed. Two complex tests, Oncotype DX® and MammaPrint®, for example, use prognostic markers to help physicians target the best course of treatment for certain breast cancer patients by helping determine which patients are likely to benefit from chemotherapy or are at risk of distant recurrence following surgery.[6,7,8]

Reducing the Frequency and Magnitude of Adverse Drug Reactions

Another category of personalized medicine tests, called pharmacogenomic tests, predicts what medications at what doses will be effective and safest for individuals based on their genetic makeup. Doing so is important. According to several studies, about 5.3 percent of all hospital admissions are associated with adverse drug reactions (ADRs).[9] Many ADRs are attributed to variations in genes that code for drug-metabolizing enzymes. One example is a family of genes called cytochrome P450 (CYP450).[10,11] Some variants of these genes cause drugs to be metabolized either faster or slower than normal. As a result, some individuals have trouble inactivating a drug and eliminating it from their bodies, leading to systemic overexposure to the drug, while others eliminate the drug too rapidly before it has had a chance to work. Thus, these genetic variations should be considered when selecting a given drug for use and/or determining a proper dose.

Pharmacogenomic testing can help guide the safe application of medicines for many health conditions. One of the first applications of pharmacogenomics was for patients who had been prescribed the drug warfarin, used to prevent blood clots. Genetic variations in some drug-metabolizing enzymes complicate the safe use of warfarin.[12] Dosing is typically adjusted for the individual patient through multiple rounds of trial-and-error, during which the patient may be at risk for excessive bleeding or further blood clots. Although the data are still evolving, available evidence suggests that genetic testing in advance of prescribing warfarin helps patients avoid serious and possibly fatal adverse effects.[13,14,15]

The use of genetic markers to facilitate safer and more effective drug dosing and selection takes on added significance at the population level. For example, adverse reactions to the HIV drug efavirenz (Stocrin®/Sustiva®) can occur at standard doses due to the presence of a genetic mutation (the CYP2B6*6 allele) in an enzyme that metabolizes the medicine. This results in slower metabolism of the drug and is found significantly more often in patients of African heritage than those of European heritage.[16] Lowering the drug dose in individuals with this allele can help reduce adverse effects and improve patient adherence to the treatment.

Using Cell-Based or Gene Therapy to Replace or Circumvent Molecular Pathways Associated with Disease

Gene and cell-based therapies are another category of personalized medicines. These therapies are designed to provide permanent or long-term benefits to patients by altering the molecular pathways associated with certain diseases. Gene

and cell-based therapies may involve replacing, repairing or inactivating a specific disease-causing gene or introducing a new or modified gene into a patient's own cells to help treat a disease.

In 2017, FDA approved the first cell-based therapies to treat some forms of lymphoma or leukemia, axicabtagene citoleucel (Yescarta®)[17] and tisagenlecleucel (Kymriah®). Several other gene and cell-based therapies have been made available since, with many more in the drug development pipeline.[18]

Revealing Additional Targeted Uses for Medicines and Drug Candidates

Molecular testing can also help identify the most appropriate uses for therapies that were initially targeted to the general population. The lung cancer drug gefitinib (Iressa®), for example, did not result in better survival in a general population of lung cancer patients in clinical trials, and was withdrawn from the market in 2005 after initially being granted accelerated approval in 2003. Continued clinical research, however, revealed benefits in patients whose tumors test positive for certain epidermal growth factor mutations. FDA approved Iressa as a first-line treatment for this subset of patients in 2015.

With an increasing body of knowledge about influential genetic alterations and the expression of relevant biomarkers, there has also been a significant increase in the number of oncology drugs that are approved for an expanded set of cancer types beyond those included in the original drug label. For example, trial results suggest that expression of the PD-L1 biomarker, which has been widely observed in cancers from multiple tissues of origin, can help doctors make more informed decisions about the use of novel drugs referred to as immune checkpoint inhibitors.[19] This has led to expanded approvals for immune checkpoint inhibitors such as pembrolizumab (Keytruda®).[20]

Increasing Patient Adherence to Treatment

Patient non-adherence with treatment leads to adverse health effects and increased overall health care costs. When personalized therapies prove more effective or present fewer side effects, patients may be more likely to comply with their treatment regimens. The greatest impact could be in the treatment of chronic diseases, for which non-adherence commonly exacerbates the condition.

For example, inherited forms of hypercholesterolemia (high cholesterol) can increase the risk of myocardial infarction before the age of 40 by more than 50-fold in men and 125-fold in women. Knowledge of a genetic predisposition for hypercholesterolemia provides patients with a powerful incentive to make lifestyle changes and manage their condition with drugs. Patients with a genetic diagnosis have shown more than 86 percent adherence to their treatment program after two years, compared to 38 percent prior to testing.[21]

Avoiding Invasive Testing Procedures

Molecular tests that simply require a blood sample can also sometimes replace invasive and uncomfortable tissue biopsies. For example, Allomap®, a multi-gene expression test, detects whether the immune system of heart transplant recipients is rejecting the new organ.[22] Approximately 25 percent of heart transplant patients experience a rejection, which can prove fatal. To monitor for rejection, heart tissue biopsies are performed as frequently as once a week after the transplant, and then every few

months thereafter for several years. This invasive procedure requires inserting a tube into a vein in the neck and threading it to the heart to obtain the biopsy, which is uncomfortable for patients and has risks associated with injury to the vein and heart. Patients who are monitored for rejection using Allomap® have equivalent outcomes as those who receive heart tissue biopsies, but without the associated risks and complications.[23,24]

Blood-based tests are also gaining traction as a viable alternative to traditional tissue-based diagnostic tests for cancer. These tests allow cancer care providers to screen patients for the presence of cancer indicators from a simple blood sample in some cases where a tumor tissue biopsy cannot be obtained or where there is not enough high-quality tissue sample to be used for genetic testing.[25] These liquid biopsies are also increasingly being used for monitoring relapse in cancer care.[26]

Helping to Shift Patient-Physician Engagement Toward Patient-Centered Care

Personalized medicine is also paving the way toward more patient-centered care. By integrating molecular diagnostic results into treatment decision-making, physicians can put aside one-size-fits-all medicine and integrate patient perspectives in pursuit of shared clinical decision-making.

For example, a patient who has undergone treatment for breast cancer can take advantage of prognostic genetic testing to help determine risk of recurrence before undergoing further treatment that might be associated with potential side effects. The physician and patient can then determine together how best to manage risks with consideration of the patient's preferences and values. While patients and physicians are both focused on improving outcomes and reducing hospitalizations wherever possible, patients may also want the peace of mind that comes with

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"The convenience of testing a blood sample may enable more rapid treatment decisions so that patients can feel reassured they are not losing time to fight their disease."

— **Levi Garraway, M.D., Ph.D.**
Executive Vice President, Chief Medical Officer and
Head of Global Product Development, Roche

knowing that they have received care based on the most up-to-date information about each of their bodies and diseases.

Helping to Control the Overall Cost of Health Care

Thus, by introducing innovative science that can create efficiencies and sustainability, personalized medicine has the potential to reduce health care costs while improving patient care. As noted, incorporating personalized medicine into the fabric of the health care system can help decrease costs associated with many embedded inefficiencies, such as trial-and-error dosing, hospitalizations due to adverse drug reactions, late-stage diagnoses, and reactive treatment. Personalized medicine can also play an important role in the implementation of value-based payment and delivery models, which can help coordinate patient care and reduce costs.

Morbidity and mortality related to non-optimized prescription medication use has been noted at an annual cost of $495.3 billion to $672.7 billion in 2016 dollars.[27] A personalized medicine approach may help to reduce these costs. As an example, data suggest that pharmacogenomic testing associated with the management of dosing of the blood thinning drug warfarin can eliminate costs associated with hospitalizations for bleeding or thromboembolism. Mayo Clinic and a pharmacy benefits manager put the model to the test in a 3,600-subject prospective study. Hospitalization rates for heart patients were reduced by about 30 percent when genetic information was available to doctors prescribing the drug.[28]

Additionally, breast cancer therapy guided by the Oncotype Dx® test has been estimated to provide a net cost savings of $2,256 per patient tested based on a reduction in chemotherapy use with an incremental cost-effectiveness ratio of $1,944 per life year saved.[29]

The potential cost-effectiveness of personalized medicine strategies, however, depends on their being implemented appropriately and effectively. Based on real-world data from a Flatiron Health nationwide oncology patient database, health economic researchers showed that next-generation sequencing (NGS)-based testing, which can streamline decision-making for cancer patients by using a single test to determine the likelihood that a patient will respond to one of several targeted therapies, has moderate cost-effectiveness compared to single marker genetic testing in advanced non-small cell lung cancer patients.[30] The data also revealed, however, that patients with actionable mutations do not always receive targeted therapies. Additional analysis estimated that cost-effectiveness would improve significantly if all patients who were eligible for targeted therapies received them.

"It's not really 'should we do this.' We have to do this. We don't get to decide what the biology of these diseases are, we just have to work with it."

— **Barbara Weber, M.D.**
President, CEO, Tango Therapeutics

THE SCIENCE

In pursuit of the benefits outlined above, scientists have been employing the cutting-edge diagnostic tests underpinning personalized medicine for more than a decade to uncover the biological characteristics that drive disease or may influence a patient's response to various treatment options. Using the results from these tests, physicians can determine whether the patient may benefit from a personalized prevention plan or a personalized therapy that addresses the molecular causes of a disease. More recently, scientists have begun feeding the data from multiple diagnostic tests as well as information about each patient's background and environment into advanced computational models to support recommendations that are tailored even more closely to each patient's biological characteristics, circumstances, and values. In this way, technological developments in advanced diagnostic testing, personalized treatments, information management, and digital health are working together to lay the groundwork for a new era in medical discovery and clinical care.

Advanced Diagnostic Testing

Diagnostic testing is at the core of personalized medicine. As demonstrated above, diagnostics can be used to determine important molecular characteristics that can affect an individual's health condition and guide prevention and treatment decisions. Diagnostic tests and the biological markers (biomarkers) they measure are often classified based on the circumstances under which they are used and the biomarker they assess [DNA or RNA (collectively known as genetics), proteins, metabolites, or epigenetic changes]. Biomarkers provide information about a patient at virtually every stage of care. They can help doctors evaluate the likelihood that a patient will develop a disease (predisposition biomarkers); diagnose a disorder (diagnostic biomarkers); evaluate the severity of a disorder and/or its likely progression (prognostic biomarkers); determine optimal treatment strategies (predictive biomarkers); and monitor response to treatment.[31]

Due to our relatively advanced understanding of how genes influence human health, genetic and genomic sequencing-based diagnostics are the most commonly used tools in personalized medicine. In recent years, however, scientists have also made notable progress in assessing epigenetic, proteomic and metabolic biomarkers.

Assessing Genetic and Genomic Biomarkers

Genetic variation plays a pivotal role in the molecular mechanisms of disease, and understanding this variation is important in the development of prevention and treatment strategies. Genetic tests that provide information essential for the safe and effective use of a corresponding treatment are considered companion diagnostic tests.[32] These tests are identified on the corresponding pharmaceutical's label, and only patients with certain test results are eligible for the use of the treatment. Other genetic tests are considered complementary diagnostics, which provide information that can aid in prevention and treatment decision-making but are not pre-requisites for receiving a drug.[33]

Since the completion of the Human Genome Project in 2003, notable technological advancements have been made in investigating the role of genetic variation in disease. Most scientists believe that many common human ailments, such as heart disease, diabetes, and cancer, are significantly influenced by numerous genetic variations present within a single genome, and this has become a central part of medical research.

In 2015, for example, U.S. President Barack Obama launched the Precision Medicine Initiative, and with it the *All of Us* Research Program, an effort to build a national research cohort of one million or more Americans who volunteer their genetic information for research aimed at finding more effective ways to improve health and treat disease.[34] The project is poised to fill a tremendous gap in our understanding of human genetic variation by making thousands and ultimately a million genome sequences securely available for scientific interrogation. Similar national sequencing and biobanking programs around the world, including the 100,000 Genomes Project in the United Kingdom,[35] a one million person sequencing effort in China,[36] the Personal Genome Project Canada,[37] Finland's FinnGen genomic sequencing and biobank project,[38] Israel's Genomic and Personalized Medicine Initiative,[39] the Qatar Biobank,[40] and Biobank Japan[41] bring the potential for understanding human variation on a global level with massive amounts of data.

Thanks to advancements in sequencing technology, it is now possible to simultaneously interrogate hundreds of thousands of sites in an individual's DNA to find associations between a given disease and genetic variation. It took $1 billion and 13 years to sequence the first draft of the human genome. Since then, the cost of sequencing an entire genome has declined at a rate that exceeds Moore's law. The results reflect a general trend in the industry and an important transition brought on by NGS technology.

The cost to sequence a whole human genome today, at approximately $1,000,[42] is comparable to the cost of other medical tests and procedures, and new innovations may continue to drive sequencing costs down. Current estimates suggest that by 2026 the cost will be $100.[43] Additional costs and time are necessary, however, to analyze and interpret this genomic information in a clinical setting.

To drive the costs of genomic sequencing down even further, scientists and industry leaders are also exploring the potential of sequencing only the regions of the genome that are known to be transcribed by human cells, a process called exome sequencing. The exome makes up approximately one to two percent of the genome. But it is thought to contain approximately 85 percent of disease-causing variants.[44]

Thanks to the improved sensitivity of mutation detection techniques, scientists can now use blood-based liquid biopsies in some circumstances to detect the genetic biomarkers expressed by a patient's tumor. These liquid biopsies work by detecting DNA from circulating tumor cells or fragments of DNA shed into the bloodstream by tumor cells. A recent study of metastatic colorectal cancer patients showed that liquid biopsies could detect 87.2 percent of the important gene mutations detected by traditional tissue biopsy.[45] FDA approved the first liquid biopsy indication for a companion diagnostic test for the detection of specific gene mutations in lung cancer patients in 2016.[46] Liquid biopsy tests are now regularly used for various cancer types, including for lung, breast, colorectal, and some rare types of cancer.

In addition to allowing for the molecular analysis of cancer patients for whom tumor tissue biopsies are not available, liquid biopsies may someday contribute to the detection of cancers at earlier stages, when they are easier and less expensive to treat. Although the underlying technologies are still undergoing validation and standardization, early studies show that these tests can significantly increase the number of cancers detected and localize the cancer type with high accuracy.[47, 48] Modeling results suggest that benefit of these future technologies is substantial and found that if all stage IV cancers were diagnosed at stages I–III, this could lead to a 24 percent reduction in cancer-related deaths.[49]

Assessing Epigenetic Factors

There is also a growing understanding of genomic changes that can alter the chemistry and structure of DNA without altering its sequence. These "epigenetic" changes — which can be assessed through testing — can occur in response to environmental factors, and influence whether certain genes are turned "on" or "off." Epigenetic factors have been linked to a number of health conditions, including heart disease, diabetes, and cancer. NIH has developed the Roadmap Epigenomics Project to study the role of epigenetics in human diseases.[50]

Assessing Proteomic Biomarkers

Scientists are also working to standardize existing proteomic technologies, which seek to examine the entire set of proteins that are produced or modified in our bodies. Proteomic analysis may indicate the presence or absence of disease in different ways than genetic analysis. Entirely new approaches to protein biomarker detection are promising to make proteomics as "simple" as genetic analysis, ushering in an era when diseases can be diagnosed — and treated — in their earliest stages.[51]

Assessing Metabolomic Biomarkers

Finally, great strides are being made in metabolomics, which focuses on the ways in which molecules build up in the human body and are subsequently broken down through cellular metabolic processes.[52]

Personalized Treatments

Guided by the insights from molecular diagnostics, the biopharmaceutical industry has invested deeply in the development of personalized treatments that can address the root causes of disease. The industry has also embraced diagnostics as a tool for identifying which patients will respond to certain drugs.

PMC counts 286 personalized medicines, that is, drugs that point to specific biomarker(s) in their labels to guide use, currently on the market (see Appendix B). Analysts peg the market value for drugs reliant on companion diagnostics (CDx) at over $25 billion.[53]

These numbers are likely to continue growing. A 2015 survey commissioned by the Personalized Medicine Coalition and conducted by the Tufts Center for the Study of Drug Development suggested that 42 percent of the drugs in the development pipeline at that time included biomarkers in their research and development design.[54] The survey also showed that biopharmaceutical manufacturers expected investment to increase by another 33 percent over the next five years. A more definitive database analysis by L.E.K. Consulting supports these estimates, showing that 61 percent of clinical trials for cancer treatments conducted in

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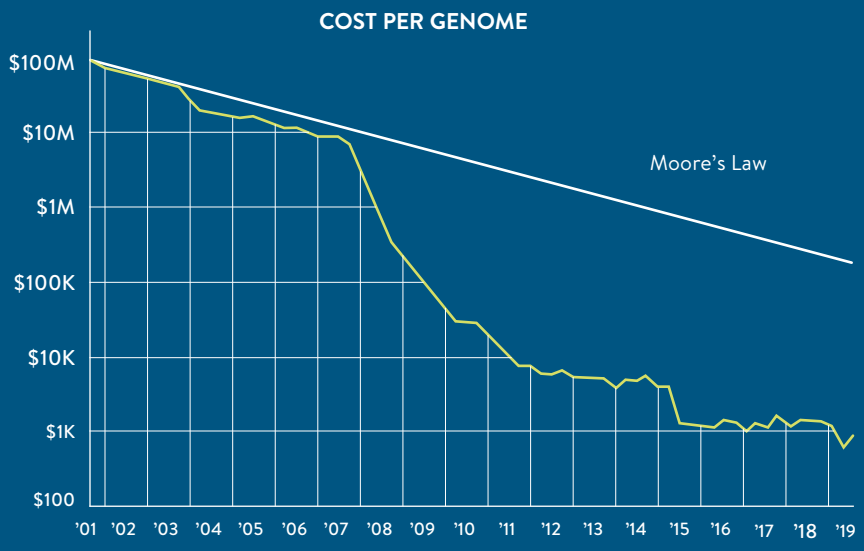
The fundamental challenge for systems biology and personalized medicine going forward is to combine genetic, epigenetic, proteomic, and metabolomic information in pursuit of an integrated approach to understanding human health and disease.

FIGURE 3: THE RAPIDLY DECREASING COST OF SEQUENCING HUMAN GENOMES

This graph shows the average cost of sequencing a genome for sequencing technology projects funded by the National Human Genome Research Institute. The data capture the dramatic decline in sequencing costs through 2019, and the cost has continued to drop.



U.S. National Human Genome Research Institute. *The Cost of Sequencing a Human Genome*. Accessed June 5, 2020, at http://www.genome.gov/sequencingcosts.

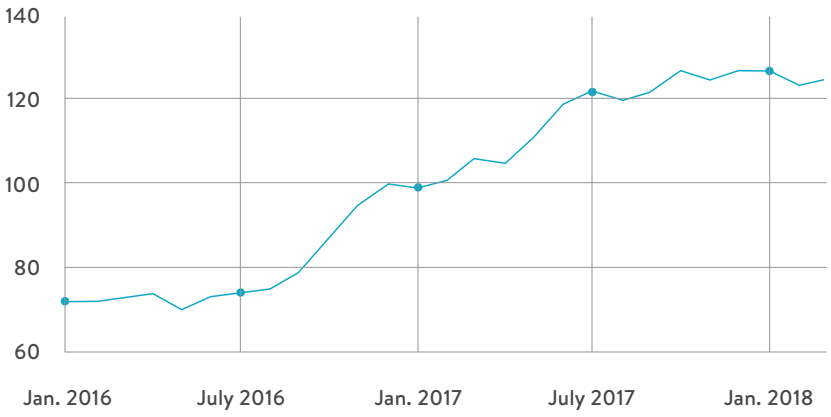
FIGURE 4: PROGRESS IN GENETIC TESTING

75,000+

Genetic Testing Products on the Market

PRONOUNCED GROWTH IN WHOLE-EXOME SEQUENCING

Clinical Exome Tests Offered by US-Based Labs



Concert Genetics. *The Current Landscape of Genetic Testing: Market Growth, Reimbursement Trends, Challenges and Opportunities*. Accessed June 5, 2020, at http://www.concertgenetics.com/wp-content/uploads/2018/04/12_ConcertGenetics_CurrentLandscapeOfGeneticTesting2018.pdf.

2019 involved the use of biomarkers, compared to just 18 percent in 2000.[55]

Targeted therapeutics, immunotherapies, gene and cell-based therapies, and gene editing techniques are all emerging treatment modalities that can deliver unprecedented benefits to patients and health systems based on the principles of personalized medicine.

Targeted Therapeutics

The personalized medicine treatments designed to interfere with, or target, a particular molecular pathway that can lead to disease are called targeted therapeutics. The efficacy and safety of a targeted therapy on any given patient depends on the molecular characteristics of the patient and the disease. The biomarkers that are targeted by these therapies are usually the genes that cause disease or the protein products of those genes.

New therapeutic strategies are also being developed to target RNA. A new class of personalized medicines called small interfering ribonucleic acid (siRNA) treatments work by selectively targeting and silencing a portion of RNA involved in causing disease. The first siRNA treatment, patisiran (Onpattro®), was approved by FDA in 2018.[56]

In cancer, drug development is shifting to focus less on the tissue type from which the tumor originated and more on the genetic basis of the disease. The National Cancer Institute's Molecular Analysis for Therapy Choice (NCI-MATCH), a phase II clinical trial, was launched in 2015 to determine whether targeted therapies for people whose tumors have certain gene mutations will be effective regardless of their cancer type.[57]

A first set of results published in 2018 suggests that tumors with specific mutations may sometimes be sensitive to a targeted drug regardless of tissue of origin.[58]

The number of research and development studies for tumor-agnostic cancer drugs — drugs for which clinical use is based on the presence of a specific biomarker regardless of the tumor's location in the body — has increased six-fold between 2015–2020.[59] From a regulatory standpoint, the expanded approval of pembrolizumab (Keytruda®) for all solid tumor types in advanced cancers with microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) is particularly significant, as it marks the first time a tissue-agnostic oncology drug has been approved.[60] Keytruda was granted further expanded approval for all cancer patients with solid tumors based on the total number of mutations found in the DNA of cancer cells. This indicator, termed tumor mutational burden-high (TMB-H), can help predict efficacy of the drug.[61] Other recently approved tissue-agnostic cancer therapeutics include larotrectinib (Vitrakvi®) and entrectinib (Rozlytrek®), both targeted therapies to treat patients with solid tumors anywhere in the body as long as they have a gene alteration known as a neurotrophic receptor tyrosine kinase (NTRK) gene fusion.[62,63]

Targeted therapies are also expanding their footprint among rare diseases. For example, FDA has now approved a suite of therapies that target mutated CFTR genes, the root cause of cystic fibrosis, a disease that often leads to respiratory failure. The first of these therapies was effective only for the 6 percent of patients with cystic

fibrosis who expressed specific types of CFTR mutations. Today, more than 90 percent of cystic fibrosis patients carry mutations targeted by an available therapy that can improve lung function.[64]

Immunotherapies

Researchers and pharmaceutical companies are also developing highly personalized treatment approaches that use the patient's own immune system to help fight cancer. These "immuno-therapies" work in different ways. Some provide a general boost to the body's immune system. Others help train the immune system to attack specific cancer cells by inhibiting a tumor's ability to put the "brakes" on immune cells. Novel immune checkpoint inhibitors like pembrolizumab (Keytruda®) and nivolumab (Opdivo®), for example, block the ability of the PD-L1 molecule to bind with its receptor, PD-1, which normally acts as a type of "off-switch" that helps keep a patient's immune system from attacking cancer cells.[65,66]

Other immunotherapeutic personalized strategies involve the development of antibodies that are customized to target specific markers on cancer cells. Some of these targeted antibodies, known as antibody-drug conjugates, are equipped with anti-cancer drugs that they can deliver directly to tumors.[67]

Yet another immunotherapeutic strategy involves adapted cell-based therapies. These novel cancer therapies involve taking a patient's own immune cells, expanding or otherwise modifying them, and reintroducing them to the patient so they can seek out and eliminate tumor cells.[68]

Gene and Cell-Based Therapies

For as long as medical researchers have been discovering genes that are responsible for contributing to particular diseases, they have been interested in developing ways to repair abnormal genes or introduce new genetic material directly into cells to treat or prevent disease. They have begun to realize this vision with the emergence of gene and cell-based therapies.

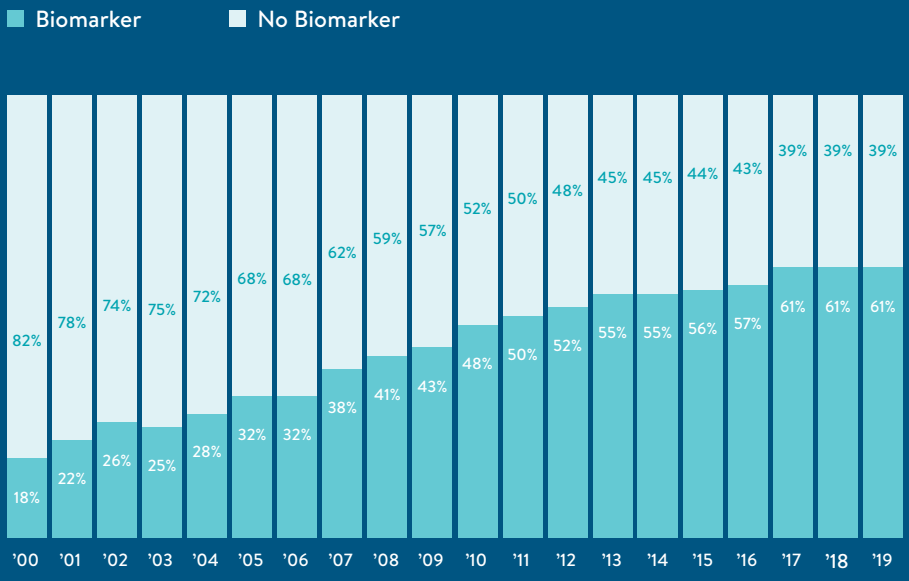
Gene and cell-based therapies are often designed to either "knock out" or replace a mutated gene that causes illness. They may also introduce a new or healthy copy of a gene to help treat a disease. The European Union approved the first cell-based gene therapy, alipogene tiparvovec (Glybera®) in 2012 for the treatment of lipoprotein lipase deficiency, an inherited condition that disrupts the normal breakdown of fats in the body.[69,70]

Since then, 10 cell-based or direct gene therapies have been approved by FDA to target a variety of diseases ranging from rare neuro-muscular disorders[71] to more common cancers.[72] These therapies have the potential to yield an unprecedented improvement in clinical outcomes in some disease areas.

FIGURE 5: TARGETING BIOMARKERS TO PERSONALIZE CANCER TREATMENT

For cancer treatments, the percentage of clinical trials incorporating biomarkers has risen from 18 percent in 2000 to 61 percent in 2019.

PERCENTAGE OF ONCOLOGY TRIALS INCORPORATING BIOMARKERS



Source: LEK Consulting

To administer axicabtagene citoleucel (Yescarta®) and tisagenlecleucel (Kymriah®), for example, doctors remove some of the patient's immune cells, called T-cells, and genetically modify them to express a specific receptor, called a chimeric antigen receptor (CAR), that binds to a certain protein on the patient's cancer cells. The modified "CAR-T cells" are then re-injected into the patient, where they replicate and destroy existing cancerous cells and those that may emerge in the future.[73]

FDA also approved in 2017 the first directly administered gene therapy that targets a disease caused by mutations in a specific gene. Voretigene neparvovec-rzyl (Luxturna®) can be used for the treatment of patients with biallelic RPE65 mutation-associated retinal dystrophy, which leads to vision loss and may cause complete blindness in certain patients. Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells.[74] FDA has since approved a similar gene therapy, onasemnogene abeparvovec-xioi (Zolgensma®), to treat spinal muscular atrophy (SMA), a severe neuromuscular disease. Like Luxturna, Zolgensma is designed to deliver long-lasting benefits by introducing new genetic material that will replace the function of the non-working or missing gene that causes SMA.[75]

Many other gene and cell-based therapies have shown promise in clinical trials and may be close to approval to treat patients. All phases of the process of developing these therapies, however, face unprecedented technological, ethical, and financial challenges.

CRISPR/Cas9 Gene Editing

A new tool called CRISPR/Cas9 gene editing is also generating excitement for gene and cell-based therapy in personalized medicine. The discovery of CRISPR (clustered regularly interspaced short palindromic repeats) and CRISPR-associated (Cas) genes has allowed for the development of efficient and reliable ways to make precise changes to the genomes of living cells.[76] Gene editing using the CRISPR/Cas9 technology may allow for the correction of disease-causing mutations in humans. CRISPR/Cas9 gene editing has many applications in clinical research and development including more efficient techniques to develop cell-based and gene therapies that target factors that influence immunity or infection severity. However, genetic modification has raised ethical concerns about the appropriate use of the technology, notably as it pertains to permanent alterations in the germline.[77]

Information Technology

Discrete data on diagnosis, treatment, medical claims and health outcomes traditionally have existed in different parts of the health care system, making it difficult to determine what works and how treatments differ across subgroups of patients. "Big data" in health care refers to the vast quantities of complex patient data, including health records, that are accumulating rapidly and may be analyzed computationally to reveal patterns, trends, and associations. To fully enable personalized medicine, our health systems must facilitate the seamless and rapid flow of these data.

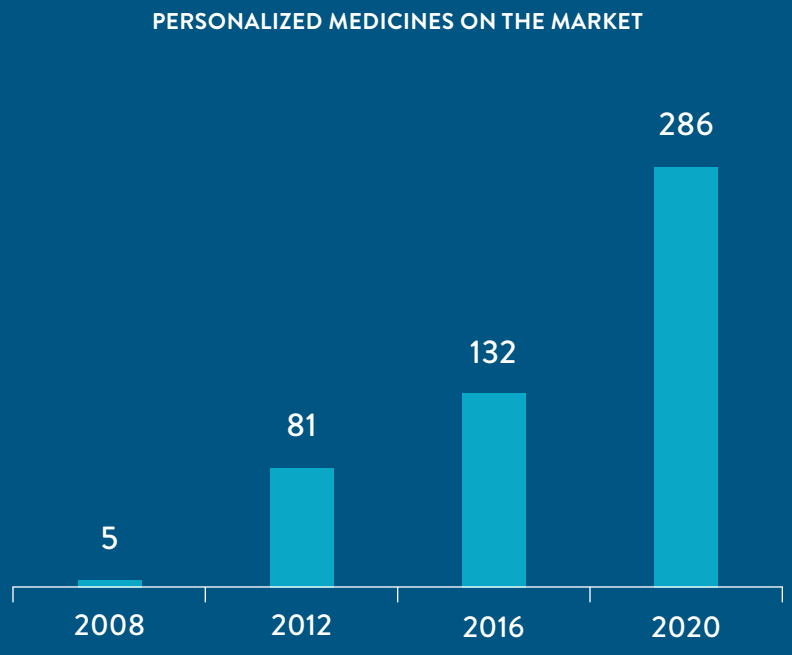
New mechanisms are being developed to connect data from multiple sources into databases, and machine learning technologies utilizing artificial intelligence could further accelerate the pace of discovery and validation of predictive biomarkers.[78] As we employ faster knowledge management to create "rapid learning" health care systems, we will enable evidence-based decision-making on the part of physicians and public health officials. Clinical decision support tools could also incorporate predictive modeling information and rapid learning evidence to enable optimal clinical decision-making in real time.

Digital Health

The ubiquity of mobile information devices such as smart phones as well as advances in sensing technologies and self-management platforms are also beginning to provide important tools for personalized medicine. Several ongoing clinical trials feature the use of wearable and environmental sensors to learn how to deliver real-time care to patients.[79] For example, some patients with type 2 diabetes are getting their blood glucose level data via mobile measurement while having it continually updated and graphed on their smart phone or tablet. As a result, these patients are far more engaged in their own personalized medical care.[80] FDA issued the *Digital Health Innovation Action Plan* in 2017, which addresses regulating these swiftly evolving products and includes testing a digital health software precertification pilot program.[81] In 2019, FDA qualified the first digital personalized medicine device development tool, the OsiriX CDE Software Module, a biomarker test for brain injury that can help innovators more efficiently enroll patients in clinical trials based on their individual characteristics in order to better treat mild traumatic brain injury.[82]

FIGURE 6: COMING OF AGE

The number of personalized medicines on the market has been increasing steadily since 2008. There were more than 280 such medicines on the market in 2020, and the number continues to grow.



* Methodological notes: The number of personalized medicines was calculated by combining information from the Personalized Medicine Coalition's *Case for Personalized Medicine* (2008 – 2014), *Personalized Medicine Report* (2017) and *Personalized Medicine at FDA: An Annual Research Report* (2014 – 2019) with data from the U.S. Food and Drug Administration's *Table of Pharmacogenomic Biomarkers in Drug Labeling*, accessed June 5, 2020, at https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling tables, and the Clinical Pharmacogenetic Implementation Consortium's *Genes-Drugs Table*, accessed June 5, 2020, at https://cpicpgx.org/genes-drugs. See Appendix B for a complete list of the 286 medicines counted in 2020.

THE CHALLENGES

"We are pleased to see substantial progress and look forward to continuing our efforts to advance biomarkers, which will help bring additional, important new therapies to patients in need."

— **Janet Woodcock, M.D.**
Director, Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

REGULATORY POLICY

Scientific progress is driving an increase in the number of personalized medicine products and services subject to regulatory review. In fact, more than one of every four drugs FDA approved from 2014 – 2019 was a personalized medicine, and personalized medicines accounted for 42 percent of new drug approvals in 2018. Those numbers are a sharp increase from 2005, when personalized medicines accounted for just 5 percent of new drug approvals.[83] Indeed, FDA has recognized the potential for biomarker-based strategies that target molecular subsets of disease that represent an unmet medical need to provide utility beyond original indications, and has implemented more fast-tracked regulatory reviews for many expanded indications. Some observers believe these steps are a precursor to an era in which the agency approves all personalized medicines faster based on the increased likelihood that a molecularly targeted drug can demonstrate safety and effectiveness.

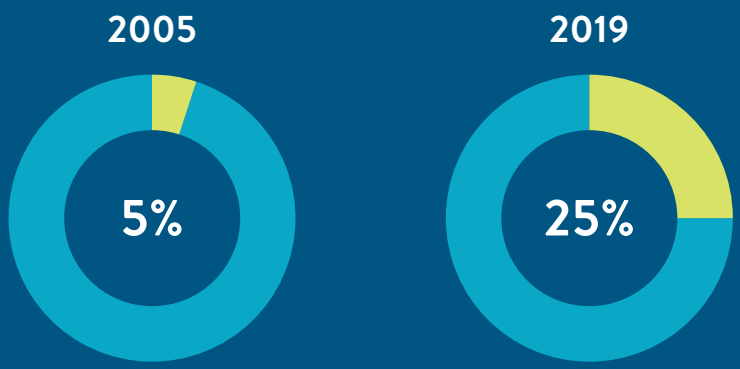
The agency continues to respond to the growing demand for regulatory clarity by issuing guidance documents (see Appendix A). For example, early in 2020, FDA finalized six guidance documents on the development of gene and cell-based therapies and released a new draft guidance on interpreting the sameness of gene therapies under existing orphan drug regulations.[84] These documents promise to encourage the development of personalized treatments by clarifying regulatory pathways for them.

The *21st Century Cures Act*, which Congress passed in 2016, encourages the agency to modernize its paradigm for considering real-world evidence (RWE), patient-centeredness, and molecular pathways as they relate to clinical trial design and regulatory policies moving forward. The sixth version of the *Prescription Drug User Fee Act* (2017), which is reauthorized every five years to update FDA policies for the collection of user fees from product developers and to make the drug review process more efficient, included several provisions that offer clarity in areas such as biomarker qualification, patient-focused drug development, and the use of innovative clinical trial designs.

But the landscape for regulation of personalized medicine is still emerging, and the lack of clear regulatory oversight pathways for certain personalized medicine diagnostics continues to discourage investment in the field. In addition to the topics mentioned above, FDA continues to discuss regulatory policies related to laboratory-developed tests (LDTs), NGS technologies, and genetic tests made available directly to consumers. In contrast, the agency's well-developed position on the co-development of personalized medicine products has removed an obstacle to the field's progress.

FIGURE 7: PERSONALIZED MEDICINE AT FDA — THEN AND NOW

Personalized medicines accounted for just 5 percent of the new drugs the U.S. Food and Drug Administration approved in 2005. In 2019, they accounted for 25 percent.



Regulatory Oversight of LDTs

The emergence of personalized medicine tests that inform clinical decision-making and guide drug selection and dosage has led FDA to re-examine its approach to regulating diagnostics. Traditionally, diagnostic tests have fallen into two main categories: LDTs and in vitro diagnostic kits (IVDs). An LDT is designed, performed, and used within a single laboratory. IVDs are products containing all the reagents and materials needed to run the test in any laboratory and are regulated by FDA as medical devices. Only a small portion of personalized medicine diagnostics falls under this category; most are LDTs, only a handful of which are FDA-approved.

The clinical laboratories that perform LDTs are subject to the Clinical Laboratory Improvement Amendment (CLIA) rules administered and implemented by the Centers for Medicare and Medicaid Services (CMS).[85] Clinical laboratories can obtain CLIA certification directly from CMS, typically through state agencies that survey laboratories for compliance with CLIA requirements. A laboratory can also seek accreditation by one of the independent accreditation organizations approved by CMS, which include the College of American Pathologists (CAP), among others.[86] Although FDA has always claimed authority to regulate LDTs, the agency has historically refrained from doing so under a policy of "enforcement discretion."

In 2014, however, FDA outlined a draft framework for new policies related to the agency's oversight of LDTs. Following publication, many organizations concluded that a legislative solution would be required to adequately address concerns raised by the different sectors of the laboratory community. FDA's efforts to finalize its own guidance document culminated only in a non-binding discussion paper published in January of 2017.

Shortly after the FDA discussion paper was published, Congressional Representatives Larry Bucshon (R-IN) and Diana DeGette (D-CO) released their own discussion draft, titled the *Diagnostic Accuracy and Innovation Act (DAIA)*, in an effort to provide a legislative solution that establishes a predictable and timely path to market for LDTs. Stakeholders throughout the personalized medicine community provided comments in response to the discussion draft and FDA provided technical assistance leading to broad revisions and the eventual release of the *Verifying Accurate Leading edge IVCT Development (VALID) Act* discussion draft in 2018, which replaced *DAIA*. The *VALID Act* was revised and introduced in 2020. The proposed legislation has again been amended based on public comments, but stakeholders are calling for further changes, making its fate uncertain and thereby confounding the future regulatory landscape for LDTs.

Regulatory Oversight of NGS-Based Diagnostic Tests

FDA is also working to understand how to regulate diagnostics that incorporate NGS technology, which yields insights from entire sets of genes. While current regulatory concepts are applicable for the regulation of conventional diagnostics that measure a limited number of endpoints associated with a disease or condition, diagnostic tests that use NGS technology can examine millions of DNA variants at a time, and therefore require a more flexible oversight approach.

FDA has developed new approaches to regulating NGS-based tests that the agency believes will allow timely access to tools that have adequate analytical and clinical performance. The first NGS-based assays that were cleared for use by FDA in 2016 involve the diagnosis of cystic fibrosis (Illumina MiSeqDx,™ Cystic Fibrosis 139 Variant and Clinical Sequencing Assays). Because it was impractical to detect every possible variant that might exist in a genomic sequence, analytical test performance for the MiSeqDx™ system was demonstrated for a representative number of subsets of types of variants in multiple sequencing contexts.[87] The agency extended this representative approach for establishing analytical validity and clinical significance to other NGS-based assays alongside other approaches for regulatory review.

FDA also released two guidance documents describing processes for developing analytic standards for germline NGS-based tests and for leveraging public genomic databases to support clinical validity for NGS-based IVDs. These policies begin to lay out a mechanism for oversight of multigene assays, including the addition of new genetic markers to tests as they are validated using data sources beyond traditional clinical trials.

Direct-to-Consumer Genetic Tests

While diagnostic testing has historically been conducted in the domain of clinical practice, several companies now offer direct-to-consumer (DTC) genetic tests, raising new regulatory questions.

Many DTC genetic health tests are considered LDTs provided to consumers through a prescription by a doctor in states where local laws permit. The companies offering DTC tests sometimes make a licensed medical professional, such as a physician or a genetic counselor, available to verify the laboratory's results and discuss the test reports.[88,89] Questions have arisen, however, about whether medical professionals are involved to an appropriate degree. There are concerns about the potential for false claims related to unvalidated

test results for some DTC products. And in some cases, FDA has issued a warning about test results that have not been reviewed by the agency. For example, FDA issued a safety communication in 2019 that warns patients and physicians against the use of some pharmacogenetic tests with unapproved claims to predict patient response to specific medications.[90]

DTC testing companies that have their tests authorized by FDA are permitted to sell tests directly to consumers without a prescription. In 2017, FDA authorized the first genetic tests for DTC marketing for 10 diseases and conditions (23andMe's Personal Genome Service Genetic Health Risk Tests®).[91] Sets of tests for other conditions and genetic assessments have since been authorized.[92,93] For all FDA-authorized DTC genetic tests, the agency reviews the accuracy of the test results and assesses whether consumers can safely use and understand the test reports.

Co-Development

According to FDA, "a companion diagnostic is an in vitro diagnostic or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product."[94] The need for a clear regulatory path for companion diagnostics has been a great concern for personalized medicine since the first therapeutic product with an accompanying diagnostic (Herceptin®) was approved six months apart from the diagnostic test (HercepTest™) in 1998.[95] In 2014, FDA released its final *In Vitro Companion Diagnostic Devices Guidance*, which helped clarify its method for conducting simultaneous reviews of a drug and its companion diagnostic.[96] The guidance describes conditions under which a targeted drug might be approved ahead of a corresponding diagnostic test. Recognizing that the class of companion therapeutics/diagnostics is likely to grow, FDA has also begun publishing a table of genomic biomarkers that it considers valid in guiding the clinical use of approved drugs.[97]

In 2016, FDA issued an additional draft guidance document on co-development called *Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product*. The document explains how therapeutic and diagnostic partners should engage with the agency when co-developing products, removing one regulatory hurdle to the parallel regulation of targeted therapeutics and their companion diagnostic tests. In 2020, the agency finalized guidance on labeling groups of drugs, entitled *Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products*.

"The top challenges facing personalized medicine are reimbursement, reimbursement, and reimbursement."

— **Alexis Borisy**
Founder, Chairman, CEO, EQRx

COVERAGE AND PAYMENT POLICY

Coverage and payment policies — both in the public and private sectors — also play an important role in ensuring patient access and encouraging continued innovation.

Health care policy leaders have contended that in order "to stimulate the development of a more robust diagnostics pipeline and to harness the benefits of personalized medicine in patient-centered care delivery, policymakers must create an environment that encourages increased investment in diagnostics, enables new advances in patient care that are safe, accurate and reliable, and establishes a viable pathway toward patient access."[98] However, under pressure to address rising health care costs, policymakers and payers sometimes consider policies that would result in across-the-board coverage and payment cuts. In addition to limiting patient access, these decisions may inadvertently discourage continued research and development in personalized medicine. Bringing personalized medicine to patients will depend on policymakers appreciating its value as they consider health technology and value assessment frameworks, procedural changes to the reimbursement landscape, how best to pay for gene and cell-based therapies that may only need to be administered one or a few times, and value-based payment models.

Evidence Requirements for Coverage and Reimbursement of Diagnostic Tests

As discussed, personalized medicine offers many benefits to patients, including an improved capacity to prevent disease, more effective treatments, improved side-effect profiles, and the reduced use of invasive testing procedures. By ensuring that only patients who will benefit from a particular intervention receive it, personalized medicine can also make the health care system more efficient. In assessing the value of personalized medicine products and services, however, payers look for convincing evidence of their clinical and economic impact.[99] There is significant ambiguity regarding how that evidence should be developed and disseminated. Widespread insurance coverage and appropriate value-based reimbursement of diagnostic tests, for example, will likely require practice-based evidence demonstrating clinical and economic utility. Obtaining the real-world data necessary for generating this evidence, however, is difficult and costly unless patients have access to the products and services in question through positive health insurance and clinical practice policies. These realities have led to a challenging conundrum in demonstrating the value proposition for personalized medicine. Public and private payers rely on health technology

assessments to determine coverage policies, but without RWE, including prospective trials, there is no clear consensus on what tests should be covered. This has led to an inconsistent and unpredictable coverage policy landscape that has hindered access to potentially valuable diagnostic tests for some patients.

Health technology assessment methods used to inform coverage determination are established for "traditional" diagnostic tests, where relatively simple statistics express the accuracy of diagnosis (e.g., true positive, false positive) against a single gold standard. Advanced personalized medicine diagnostics are evaluated for a much broader concept of their "clinical utility." More objective and reliable standards for these evaluation processes need to become broadly accepted.

Parallel review processes involving both regulatory review by FDA and a national coverage determination by CMS have provided a boost to some advanced molecular tests. For example, Foundation Medicine successfully navigated parallel review for its FoundationOne CDx®, a test that gauges somatic variants in 324 genes from tumor tissue samples and guides treatment decisions based on the results.[100] In granting national coverage, CMS extended a policy that covered not just Foundation Medicine's test but similar FDA-approved NGS-based companion diagnostics in an effort to encourage linking therapies to diagnostics.

The Changing Reimbursement Landscape for Diagnostics

Significant challenges also exist in establishing payment rates for diagnostic tests that appropriately reflect the value they bring to care. Until 2014, payments for diagnostic and molecular tests, the backbone of personalized medicine, were predictable and standardized, relying on payments based on "stacked codes." However, recently, a number of coding and payment policy changes have led to significant changes in reimbursement for molecular diagnostic tests. CMS' decision, for example, to use "gapfill" methodology, which allows regional contractors to set prices for laboratory and molecular diagnostic tests, coupled with other payment decisions, has resulted in decreased payment rates for many personalized medicine tests. This, in turn, has placed pressure on physicians and laboratories interested in using novel, high-value molecular diagnostics to inform treatment decisions.

The 2016 Clinical Laboratory Fee Schedule (CLFS) final rule entitled *Medicare Program: Medicare Clinical Diagnostic Laboratory Tests Payment System*, which was part of the *Protecting Access to Medicare Act (PAMA)*, implemented re-pricing and reporting requirements[101] that in some cases further exacerbated the downward pressure on utilization of these technologies. The rule lacks mechanisms that capture the value of targeted

treatment and places significant data submission burdens on laboratories. For these reasons, the rule may slow progress in personalized medicine. Congress passed the *Laboratory Access for Beneficiaries (LAB) Act* in 2019. The *LAB Act* delayed reporting required under *PAMA* until 2021.[102] The *Coronavirus Aid, Relief, and Economic Security Act (CARES Act)* of 2020 further delays *PAMA* reporting and rate cuts until 2022.[103]

Value Assessment Frameworks

Value assessment frameworks (VAFs) are designed to examine the cost-effectiveness of treatment options for a specific health condition. As such, they are often used to inform coverage and payment policies.

But many proponents for personalized medicine believe these frameworks — which are increasingly influential in shaping the reimbursement decisions that determine whether entire populations of patients have access to personalized treatment options — could do a better job of accounting for the role of diagnostic testing, RWE, heterogeneity of treatment effects, and the perspectives of patients themselves in determining the value of treatments. In July of 2020, for example, two researchers from the RAND Corporation suggested that VAF developers could align more closely with the perspectives of patients by formally involving them in value assessment processes, contending that consulting patients and their families "is the only way to estimate what matters most to the individuals who would be directly affected by the new treatment."[104]

In light of this and other suggestions, many stakeholders are working to improve the value assessment methodologies utilized by groups such as the Institute for Clinical and Economic Review, while others are building entirely new frameworks with the principles of personalized medicine in mind.

Paying for Cell-Based and Gene Therapies

Cell-based and gene therapies hold great promise to improve overall survival and replace a lifetime of expensive maintenance medications with one or a few up-front treatments. But because the research and development costs for these increasingly complex therapies typically exceed those associated with traditional pharmaceuticals and because the therapies must recoup those costs with the administration of fewer doses, the treatments have higher costs than traditional medicines. These costs, as well as the uncertainty surrounding the long-term efficacy of these relatively new forms of therapy and their sometimes life-threatening adverse events, initially led to payer concerns.

In 2019, CMS finalized its National Coverage Determination (NCD) for CAR T-cell therapies for patients with diffuse large B-cell lymphoma.[105] As a result of the NCD, coverage will be provided consistently on a national basis for the Medicare population. Due to a lack of comprehensive clinical and cost data at the time, CMS declined to create a new diagnosis-related group (MS-DRG) in 2019 and 2020, which would increase hospital reimbursement rates per case, though CMS has established a new MS-DRG for CAR T-cell therapy in fiscal year 2021 that will make CAR T-cell therapy more broadly accessible to patients.

To address cost concerns, some cell-based and gene therapy manufacturers are working with payers to devise novel payment schemes that will allow for value-based contracts and/or installment payments. For example, Spark Therapeutics entered into an outcomes-based contract with health insurer Harvard Pilgrim Healthcare to pay for the FDA-approved gene therapy Luxturna®, which aims to cure biallelic RPE65 mutation-associated retinal dystrophy, an inherited form of vision loss that can lead to blindness.[106] In an agreement that may serve as a model for future reimbursement solutions, Harvard Pilgrim agreed to pay for the treatment while Spark consented to provide refunds if the treatment does not work.

Value-Based Payment Models

CMS and private payers are also proposing other "value-based" payment schemes, also known as "alternative payment models" (APMs), that seek to drive improvements in care quality and efficiency. Understanding the changes and potential consequences these APMs will have on personalized medicine tests, pharmaceuticals, and companion diagnostics is essential to ensure continued progress in personalized medicine. APMs, it is hoped, will encourage physicians to tailor care based on an individual's molecular characteristics and other factors.

"I always tell my patients that genetic knowledge is power. It is not about good news or bad news. It is about understanding the underlying cause of disease and using it to tailor a road map of prevention."

— **Charis Eng, M.D., Ph.D.**
Founding Chair, Genomic Medicine Institute,
Cleveland Clinic

FIGURE 8: PRINCIPLES FOR INTEGRATING PERSONALIZED MEDICINE INTO HEALTH CARE

1. Health care providers, payers, employers, and policymakers, as well as patients and their families, need to have a better understanding of personalized medicine concepts and technologies.

2. Policies and practices related to patient engagement, privacy, data protections, and other ethical, legal, and societal issues regarding the use of individual molecular information must ensure appropriate consent and be acceptable to patients.

3. Best practices must be established for the collection and dissemination of evidence needed to demonstrate the clinical utility of personalized medicine and ensure the recognition of its value to care.

4. Effective health care delivery infrastructure and data management systems should be developed and applied so that patient and clinical support information is comprehensive, useful, and can guide clinical decisions.

5. Best practices for health care delivery approaches, processes, and program operations that ensure access to personalized medicine must be established and implemented.

CLINICAL ADOPTION

Despite rapid scientific and technological advancement, the health care system has been relatively slow to integrate personalized medicine into clinical practice. For example, based on a quantitative framework that assesses progress toward personalized medicine integration on a scale from one to five across multiple clinical areas, a recent survey of a representative sample of U.S. health care delivery institutions shows that most organizations are still achieving an overall score of two or three.[107] Public survey data separately reveal that only 11 percent of American patients say their doctor has discussed or recommended personalized medicine treatment options to them.[108]

Behind this lag in clinical adoption are novel challenges that health care delivery systems are encountering as they adapt to the new requirements, practices, and standards associated with the field. Accelerating the pace of progress will require:[109]

- increasing awareness and understanding of personalized medicine concepts amongst the public and health care workforce;
- placing a greater emphasis on patient perspectives;
- recognizing the value of molecular pathways in guiding care;
- building new infrastructure and information management processes; and
- reshaping health care delivery, including the development of updated clinical practice guidelines that help ensure access to personalized medicine technologies and services.

Education and Awareness

Perhaps the greatest challenge to integrating personalized medicine into health care is a lack of education and awareness among patients and health care professionals. Freely available educational resources are being developed by a number of organizations[110,111,112,113,114,115] that are presented in multiple formats based on the needs of different stakeholders. However, they must be accurate, trusted, and updated regularly.

Building awareness among physicians and other health care providers will not be easy. The Genomic Medicine Institute at Cleveland Clinic and others host accredited genetics education symposia for practicing health care providers. Mayo Clinic's Center for Individualized Medicine educates members of the health care team and patients about personalized medicine and its implications in practice through professional development courses, conferences, and ongoing education that is integrated into practice.[116] But even these well-developed programs reach only a fraction of the available population.

Pharmacists have taken a proactive approach to education and awareness. Pharmacogenomics has been a required element of every Doctor of Pharmacy curriculum in the U.S. since 2016.[117] Graduate programs in pharmacogenomics and precision medicine are now common,[118,119] and certification programs are available regionally and nationally.[120,121,122,123] The initiatives in pharmacology may inform efforts to integrate personalized medicine into educational programs in other areas of medicine.

Patient Empowerment

Advancing an era in which health care plans are tailored to each patient's biological characteristics, circumstances and values also requires health care providers to engage patients in entirely new ways. To encourage this engagement, policymakers and other decision-makers must alleviate patients' concerns about how the collection of molecular information may lead to an invasion of privacy, discrimination, job loss, or loss of health insurance coverage.

In 2008, Congress passed the *Genetics Information Nondiscrimination Act*, which provides protection against the misuse of genetic information in health insurance and employment. Other mechanisms that assure data privacy and security are also being developed.

Many health and research organizations in the public and private sectors are reconsidering current policies related to patient privacy and consent for the use of molecular information.[124,125] Programs are being developed that will establish the necessary partnerships among industry suppliers, providers, and patients and their families to ensure that patient data are presented in ways that are meaningful to each of these groups while ensuring privacy.[126]

Perhaps most importantly, practitioners are recognizing that they need to regularly involve patients in health care decision-making.[127] Some providers are developing genetic counseling service policies to ensure that patients, early in their care, are able to understand their individual molecular information and its implications so that they can make informed decisions regarding its disclosure and use before problems arise.[128,129,130] The demand for genetic counseling has led to a shortage of qualified genetic counselors available to engage with patients, highlighting an additional workforce challenge for optimal personalized medicine implementation.

Value Recognition

Although many health care decision-makers understand intuitively that personalized medicine provides benefits to patients and the health care system, payers and providers are often reluctant to change policies and practices without studies demonstrating the clinical and economic value of personalized medicine.[131] In some cases, however, the groundbreaking tests and treatments underpinning personalized medicine provide benefits that have not been considered in previous studies assessing the clinical utility of health care interventions, thereby limiting their impact.

To ensure that payers and providers appreciate all of the ways in which diagnostic tests underpinning personalized medicine can provide value to patients and the health care system, groups such as PMC and the Medical Device Innovation Consortium (MDIC) have developed modern definitions of the clinical utility of diagnostics.[132,133]

Payers also need to understand clinical utility and economic value endpoints within the body of evidence. Strategies for addressing these challenges have begun to emerge. To help build the evidence base for personalized medicine, regional Medicare contractor Palmetto GBA initiated the MolDx Program in 2011 to establish unique identifiers for molecular diagnostic tests to help facilitate claims processing and track utilization, as well as to establish clinical utility expectations and to complete technical assessments of published test data to determine clinical utility and coverage.[134]

Finally, long-term economic and cost-effectiveness analyses are being conducted to provide evidence of the economic value of personalized medicine strategies in clinical practice. Several of these studies have demonstrated the clinical and economic value of genomic testing in cancer care and for rare and undiagnosed diseases.[135,136,137]

Looking ahead, forums between payers and product developers may facilitate a better understanding of the evidence requirements necessary for positive coverage determinations and/or value-based reimbursement. Cost-effectiveness analyses may be designed with the help of payer advisory committees that can help ensure that results are meaningful for informing payer decision-making. Health technology assessment and value assessment framework methodologies should be designed with input from all stakeholders including payers, product developers, and patients.

Infrastructure and Health Information Management

To help clinicians make decisions based on a more complete understanding of a patient's health status and outlook, health care providers must manage the massive amounts of quantitative and qualitative information about each patient and make it accessible at the point of care. Capturing, interpreting, and sharing complex yet accurate patient data, including genomic information along with phenotypic and medical data, requires that providers adopt powerful health information technology platforms that enable connections between real-world clinical results and molecular data so that providers can make clinical decisions based on a body of scientific knowledge that exceeds the training, experience, or memory of any single practitioner.[138]

Fortunately, bioinformatics and clinical interpretation services for molecular diagnostic tests are increasingly available, allowing clinicians to more easily identify actionable alterations and related therapeutic options.[139] The accurate annotation of molecular alterations by clinical interpretation companies taking into consideration continuously updated scientific and clinical evidence provides useful information to clinicians about the detected variants and potential therapies. These approaches may someday enable a "learning health care system" that systematically captures, analyzes, and shares findings from every clinical interaction and research milestone in a continuous feedback loop. To bring us one step closer to this extraordinary vision for the future of medicine, decision-makers in the public and private sectors must make it easy for providers to use electronic health records; establish government support for health care that leverages sophisticated IT technologies; and encourage the sharing of data in ways that advance the frontiers of science while protecting patient privacy. They are making steady progress, though there remain no shortage of challenges in each of these areas.

Electronic Health Records

With more than 85 percent of physicians in the U.S. using electronic health records,[140,141,142] a more modern health care delivery system is coming into focus. But electronic health records are often ill-equipped to process complex molecular information. To help electronic health record developers expand functionality, Health Level Seven (HL7), an organization committed to devel-

oping international standards, created the Fast Health Interoperability Resources (FHIR) program in 2014.[143] FHIR is a set of clinical concepts and resources designed to help electronic health record developers manage clinical data with ease. FHIR programming is now being used or considered for use by most major developers of electronic health records and many information management support organizations.

Decisions about what information to include in electronic health records present another set of challenges. Efforts are underway to standardize a list of biomarkers that should be included in medical records. For example, utilizing the FHIR program, the Minimal Common Oncology Data Elements (mCODE™) initiative led by the American Society of Clinical Oncology (ASCO®) and MITRE Health has identified minimal cancer data elements that are essential for analyzing treatments across patients via their electronic health records to improve treatment and care coordination.[144]

Government Support

In the United States, government support for health IT is strong. The Human Genome Research Institute's Electronic Medical Records and Genomics Network (eMERGE), for example, has addressed the uptake of genetic information in electronic health record systems for genomic discovery and genomic medicine implementation research.[145] The *Health Information Technology for Economic and Clinical Health (HITECH) Act*, included as part of the *American Recovery and Reinvestment Act of 2009*, formalized the Office of the National Coordinator for Health Information Technology and established a funding stream for infrastructure and incentive payments to providers

"You have to create a system where you have the patients' permission to follow them throughout their lifetimes so that you can define the populations for whom a particular technology or treatment is beneficial."

— **William S. Dalton, Ph.D., M.D.**
CEO, M2Gen, Director, DeBartolo Family Personalized Medicine Institute at Moffitt Cancer Center

who adopt and use health IT in a meaningful way. Since 2015, hospitals and physicians face penalties for not using health IT. The passage of the *Affordable Care Act* in 2010 accelerated the need for change with unprecedented incentives and penalties that encourage hospitals to implement and utilize electronic health records. In 2016, Congress passed the *21st Century Cures Act*, which includes a number of additional provisions that push for greater information system interoperability, adoption of electronic health records that are accessible by patients, and the use of RWE for regulatory decision-making.

Data Sharing

Advances in biomedical informatics have also created new data-sharing tools that promise to link and analyze diverse types of data from multiple sources. Many research-funding agencies now mandate that grantees share data. NIH's *Genomic Data Sharing Policy*, for example, encourages NIH-funded research projects generating large-scale human genomic data to share those data within an NIH-recognized data repository such as the Database of Genotypes and Phenotypes (dbGaP).[146]

The flow of data to and from different projects, institutions, and sectors can foster a data-sharing environment consisting of networked resources. This concept aligns with NIH's *Strategic Plan for Data Science*, released in 2018, which uses the term "data ecosystem" to describe "a distributed, adaptive, open system with properties of self-organization, scalability and sustainability."[147] With the help of proper data-sharing safeguards and the supporting initiatives described above, many leaders in health care believe such a system will soon be within reach.

Reshaping Health Care Delivery Practices and Policies

Perhaps the most complex area of need when it comes to accelerating the clinical adoption of personalized medicine relates to the adaptation of health delivery approaches, processes, and service structures. Overcoming challenges to adapting health care delivery approaches requires cultural change as well as the implementation of new programs and up-to-date clinical guidelines that reflect value-driven personalized medicine strategies.

The traditional fee-for-service reimbursement paradigm, for example, does not lend itself to the efficient adoption of new technologies. To overcome this challenge, the Duke Center for Research on Personalized Health Care has proposed that health care systems incorporate new technologies as they are validated and continually generate outcomes data for use in predictive models.[148] These practices, however, have not been widely adopted.

Clinical guidelines do not often reflect personalized medicine concepts either, though the PharmGKB and the Pharmacogenomics Research Network have established the Clinical Pharmacogenetics Implementation Consortium (CPIC) to help develop and regularly update pharmacogenomics clinical practice guidelines.[149] Through 2019, CPIC has published 24 evidence-based pharmacogenomics guidelines, with others in development. However this is only part of the full sample of drug-gene interactions.[150]

Addressing the educational, cultural and technical challenges outlined above will help generate additional momentum for reshaping these and other health care delivery processes by orienting stakeholders toward personalized medicine.

FIGURE 9: TECHNOLOGICAL ADVANCES SINCE COMPLETION OF THE HUMAN GENOME PROJECT

	2003	2020
Genome Sequencing		
Cost to generate a human genome sequence (excluding analysis)	$10–50 million[1]	$942[2]
Time to generate a human genome sequence	3–4 months[1]	1 day[3]
Genomic Medicine		
Genetic testing products on market	2,000–3,000 (est.)[4]	75,000+[5]
Drugs labeled with biomarker information	46[1]	250+[6]
EHR use by office-based physicians in the U.S.	17%[7]	85.9%[8]

1 U.S. National Human Genome Research Institute. *Quantitative Advances Since the Human Genome Project (HGP).* Accessed September 29, 2020, at https://directorsblog.nih.gov/advances-since-hgp/.

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6 See "Figure 6: Coming of Age."

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THE FUTURE

"We have science and medicine and technologies that are far outpacing a structure that was really set up in a completely different era."

— **Peter Juhn, M.D., M.P.H.**
Global Head of Value-Based Partnerships, Amgen

CONCLUSION

Personalized medicine's advocates include representatives from every corner of the health care system, including clinicians, providers, insurers, industry, the patient advocacy community, and academia. These stakeholders all recognize that personalized medicine offers an extraordinary opportunity to improve the lives of patients around the world.

Technology continues to lead, with genomic sequencing and other molecular and multiplex measurements likely to join other "democratized" technologies — a computer on every desk, a smart phone in every pocket, and someday molecular information in every medical record. The result: We will likely continue to generate significantly more information than we are prepared to act upon.

To keep up with the technology, every corner of the health care spectrum must come together to advance science-driven, value-based solutions. Regulatory authorities must establish a clear set of oversight policies for evaluating diagnostic tests of all types so that patients can benefit from the treatments that will work best for them. Translational research must identify the benefits of personalized medicine technologies. Policymakers should consider real-world evidence from clinical practice in their evaluation of novel personalized therapies for patients. Pathways for evaluating the clinical and economic utility of personalized medicine practices must be established in order to facilitate their coverage and reimbursement as appropriate. Health care delivery organizations must successfully integrate personalized medicine into clinical practice. Patients must participate in their own health care choices, taking an active role in expressing their concerns about data sharing and access to personalized treatments. Finally, health information systems must incorporate features that support 21st century medicine, providing the ability to collect and analyze clinical practice data and helping physicians make decisions based on the vast amount of information linking molecular patterns to diseases and treatment.

Scientific discovery in personalized medicine will continue to accelerate, offering tremendous opportunities to both researchers and the patients who are looking to the next generation of medical advances. Personalizing care, however, requires the combined resources of multiple stakeholders — all of whom must be willing to invest in a paradigm change that can preserve innovation, improve outcomes, and reduce the overall costs of health care. In order to sustain continued advances in personalized care and treatment, emerging approaches for value assessment must evolve with the rapid pace of science and reflect important differences among patients. In short, to reap the benefits of personalized medicine, policymakers must create an environment that encourages increased investment in diagnostics and targeted drugs; enables new advances in patient care that are safe, accurate and reliable; and establishes a viable pathway toward patient access.[151]

Much work remains to be done in building the infrastructure for personalized medicine, but the resources we invest in completing the task now will enable us to realize the health and economic benefits of matching the right prevention or treatment strategy to each and every patient.

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APPENDIX A

FDA Policy and Guidance Documents Related to Personalized Medicine

2005

Pharmacogenomic Data Submissions

2007

Pharmacogenomic Tests and Genetic Tests for Heritable Markers

In Vitro Diagnostic Multivariate Index Assays

2008

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data, and Sample Coding Categories

2011

E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualifications Submissions

2012

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

2013

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling

2014

Qualification Process for Drug Development Tools

In Vitro Companion Diagnostic Devices

Framework for Regulatory Oversight of Laboratory Developed Tests

FDA Notification and Medical Device Reporting for Laboratory Developed Tests

2016

Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing-Based In Vitro Diagnostics Used for Diagnosing Germline Disorders

Principles for Co-development of an In Vitro Companion Diagnostic Device With a Therapeutic Product

2017

Discussion Paper on Laboratory Developed Tests

Deciding When to Submit a 510(k) for a Software Change to an Existing Device

Software as a Medical Device: Clinical Evaluation

2018

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing–Based In Vitro Diagnostics Intended to Aid in the Diagnosis of Suspected Germline Diseases

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

2019

Clinical Decision Support Software

Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act

Policy for Device Software Functions and Mobile Medical Applications

General Wellness: Policy for Low Risk Devices

Off-The-Shelf Software Use in Medical Devices

Qualification Process for Drug Development Tools

2020

Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products

Human Gene Therapy for Hemophilia

Human Gene Therapy for Rare Diseases

Human Gene Therapy for Retinal Disorders

Long Term Follow-up After Administration of Human Gene Therapy Products

Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications

APPENDIX B

Selected Personalized Medicine Drugs and Relevant Biomarkers

as of December 2019

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Adjuvant Therapy			
1	Cevimeline (Evoxac®)	CYP2D6	Dry mouth
2	Diazepam	CYP2C19	Status epilepticus
3	Dronabinol	CYP2C9	Anorexia, nausea, vomiting
4	Ondansetron (Zofran®)	CYP2D6	Nausea and vomiting
5	Rasburicase (Elitek®)	CYB5R; G6PD	Plasma uric acid levels
6	Sodium phenylacetate and sodium benzoate (Ammonul®)	NAGS; CPS1; ASS1; OTC; ASL; ARG	Urea cycle disorders
7	Sodium phenylbutyrate (Buphenyl®)	ASS1; CPS1; OTC	Urea cycle disorders
Analgesia & Anesthesiology			
8	Articaine and epinephrine	G6PD	Local dental anesthetic
9	Celecoxib	CYP2C9	Pain
10	Chloroprocaine (Aralen®)	G6PD	Local anesthesia
11	Codeine	CYP2D6	Pain
12	Desflurane	CACNA1S; RYR1	General anesthesia
13	Elagolix	SLCO1B1	Pain (endometriosis)
14	Enflurane	CACNA1S; RYR1	General anesthesia
15	Halothane	CACNA1S; RYR1	General anesthesia
16	Isoflurane	CACNA1S; RYR1	General anesthesia
17	Lidocaine and prilocaine	G6PD	Local anesthesia
18	Lidocaine and tetracaine	G6PD	Local anesthesia
19	Lofexidine (Lucemyra®)	CYP2D6	Opioid withdrawal
20	Mepivacaine	G6PD	Local anesthesia
21	Mivacurium (Mivacron®)	BCHE	General anasthesia
22	Oxymetazoline and tetracaine (Kovanaze®)	G6PD	Local anesthesia
23	Ropivacaine (Naropin®)	G6PD	Endocrine disorders
24	Sevoflurane (Ultane®)	CACNA1S; RYR1	General anasthesia
25	Succinylcholine (Anectine®)	BCHE; RYR1	Anesthesia
26	Tramadol (Ultram®)	CYP2D6	Pain

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Cardiovascular			
27	Carvedilol (Coreg®)	CYP2D6	Cardiovascular disease
28	Clopidogrel (Plavix®)	CYP2C19	Antiplatelet response
29	Hydralazine	NAT	Hypertension
30	Isosorbide dinitrate	CYB5R	Coronary artery disease
31	Isosorbide mononitrate	CYB5R	Coronary artery disease
32	Isosorbide and hydralazine	NAT1; NAT2	Heart failure
33	Lomitapide	LDLR	Familial hypercholesterolemia
34	Metoprolol (Toprol-XL®)	CYP2D6	Myocardial infarction
35	Mipomersen sodium	LDLR	Familial hypercholesterolemia
36	Nebivolol (Bystolic®)	CYP2D6	Hypertension
37	Prasugrel (Effient®)	CYP2C9; CYP2C19; CYP3A5; CYP2B6	Thrombotic cardiovascular events
38	Procainamide	NAT	Ventricular arrhythmias
39	Propafenone (Rythmol SR®)	CYP2D6	Paroxysmal atrial fibrillation/ flutter
40	Propranolol (Inderal®)	CYP2D6	Cardiac arrhythmias
41	Quinidine	CYP2D6	Conversion of atrial fibrillation/flutter
42	Rivaroxaban (Xarelto®)	F5	Stroke and systemic embolism
43	Simvastatin (Zocor®)	SCLO1B1	Hypercholesterolemia
44	Tafamidis (Vyndaqel®)	TTR	Cardiomyopathy
45	Ticagrelor (Brilnta®)	CYP2C19	Acute coronary syndrome
46	Warfarin (Coumadin®)	CYP2C9; PROC; PROS1; VKORC1	Venous thrombosis, pulmonary embolism
Endocrinology			
47	Chlorpropamide (Diabinese®)	G6PD	Diabetes
48	Glimepiride	G6PD	Diabetes
49	Glipizide (Glucotrol®)	G6PD	Diabetes
50	Glyburide	G6PD	Diabetes
51	Rosuvastatin (Crestor®)	SLCO1B1	Hypertriglyceridemia
52	Tolazamide	G6PD	Diabetes
53	Tolbutamide	G6PD	Diabetes

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Gastroenterology			
54	Ascorbic acid, PEG-3350, potassium chloride, sodium ascorbate, sodium chloride, and sodium sulfate (Moviprep®)	G6PD	Osmotic laxative for colonoscopy prep
55	Dexlansoprazole (Dexilant®)	CYP2C19	Gastroesophageal reflux disease, erosive esophagitis, heartburn
56	Esomeprazole (Nexium®)	CYP2C19	Acid indigestion, peptic ulcer disease, gastroesophageal reflux disease
57	Lansoprazole (Prevacid®)	CYP2C19	Heartburn
58	Metoclopramide (Reglan®)	CYB5R; G6PD; CYP2D6	Diabetic gastroparesis, gastroesophageal reflux
59	Omeprazole (Prilosec®)	CYP2C19	Ulcers, gastroesophageal reflux disease, erosive esophagitis
60	Palonosetron (Aloxi®)	CYP2D6	Nausea and vomiting
61	Pantoprazole (Protonix®)	CYP2C19	Erosive esophagitis, gastroesophageal reflux disease
62	Rabeprazole (Aciphex®)	CYP2C19	Gastroesophageal reflux disease
63	Sulfasalazine (Azulfidine®)	G6PD; NAT	Ulcerative colitis
Gynecology			
64	Drospirenone and ethinyl estradiol	CYP2C19	Oral contraceptive
65	Flibanserin (Addyi®)	CYP2C9; CYP2C19; CYP2D6	Hypoactive sexual desire disorder
66	Ospemifene (Osphena®)	CYP2C9; CYP2B6	Dyspareunia, vaginal dryness
Hematology			
67	Avatrombopag (Doptelet®)	F2; F5; PROC; PROS1; SERPINC1; CYP2C9	Thrombocytopenia
68	Eltrombopag (Promacta®)	F5 (Factor V Leiden); SERPINC1 (Antithrombin III); Chromosome 7del; Chromosome 13del	Thrombocytopenia, severe aplastic anemia
69	Emapalumab-lzsg (Gamifant®)	PRF1; rAB27A; SH2D1A; STXBP2; STX11; UNC13D; XIAP	Hemophagocytic lymphohistiocytosis
70	Lenalidomide (Revlimid®)	Chromosome 5q	Multiple myeloma, myelodysplastic syndromes, lymphoma
71	Lusutrombopag (Mulpleta®)	F2; F5; PROC; PROS1; SERPINC1	Thrombocytopenia
72	Methylene blue (Provayblue®)	G6PD	Drug-induced methemoglobinemia

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Immunology			
73	Ustekinumab (Stelara®)	IL12A; IL12B; IL23A	Psoriasis
Inborn Errors of Metabolism			
74	Carglumic acid (Carbaglu®)	NAGS	Hyperammonemia
75	Cerliponase alfa	TPP1	Tripeptidyl peptidase 1 deficiency
76	Eliglustat (Cerdelga®)	CYP2D6	Gaucher disease type 1
77	Elosulfase (Vimizim®)	GALNS	Mucopolysaccharidosis type IVA
78	Migalastat	GLA	Fabry disease
79	Parathyroid hormone	CASR	Hypoparathyroidism
Infectious Disease			
80	Abacavir (Ziagen®)	HLA-B	HIV
81	Atazanavir (Reyataz®)	UGT1A1	HIV
82	Boceprevir (Victrelis®)	IFNL3 (IL28B)	Hepatitis C
83	Ceftriaxone	G6PD	Bacterial infections
84	Chloroquine	G6PD	Malaria
85	Daclatasvir (Daklinza®)	IFNL3(IL28B)	Hepatitis C
86	Dapsone	G6PD	Leprosy
87	Dasabuvir, ombitasvir, paritaprevir, and ritonavir	IFNL3 (IL28B)	Hepatitis C
88	Dolutegravir (Tivicay®)	UGT1A1	HIV
89	Efavirenz (Sustiva® and Stocrin®)	CYP2B6	HIV
90	Elbasvir and grazoprevir (Zepatier™)	IFNL3 (IL28B)	Hepatitis C
91	Erythromycin and sulfisoxazole	G6PD	Ear infections
92	Hydroxychloroquine (Plaquenil®)	G6PD	Malaria, lupus erythematosus, rheumatoid arthritis
93	Isoniazid (Nydrazid®), pyrazinamide (Rifater®), and rifampin (Rifadin®)	NAT	Tuberculosis
94	Ledipasvir and sofosbuvir (Harvoni®)	IFNL3 (IL28B)	Hepatitis C
95	Mafenide (Sulfamylon®)	G6PD	Bacterial infections
96	Maraviroc (Selzentry®)	CCR5	HIV
97	Nalidixic acid	G6PD	Urinary tract infections
98	Nitrofurantoin (Furadantin®)	G6PD	Urinary tract infections
99	Ombitasvir, paritaprevir, and ritonavir	IFNL3 (IL28B)	Hepatitis C
100	Peginterferon alfa-2a (Pegasys®)	IFNL3 (IL28B)	Hepatitis C

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Infectious Disease (cont.)			
101	Peginterferon alfa-2b	IFNL3 (IL28B)	Hepatitis C
102	Primaquine	G6PD; CYB5R	Malaria
103	Quinine sulfate (Qualaquin®)	CYP2D6; G6PD	Malaria
104	Raltegravir (Isentress®)	UGT1A1	HIV
105	Ribavirin	IFNL3 (IL28B)	Hepatitis C
106	Simeprevir	IFNL3 (IL28B)	Hepatitis C
107	Sofosbuvir (Sovaldi®)	IFNL3 (IL28B)	Hepatitis C
108	Sofosbuvir and velpatasvir (Epclusa®)	IFNL3 (IL28B)	Hepatitis C
109	Sofosbuvir, velpatasvir, and voxilaprevir (Vosevi®)	IFNL3 (IL28B)	Hepatitis C
110	Sulfadiazine	G6PD	Sepsis
111	Sulfamethoxazole and trimethoprim (Bactrim®)	G6PD; NAT	Pneumonia, shigellosis, urinary tract infection
112	Tafenoquine	G6PD	Malaria
113	Telaprevir (Incivek®)	IFNL3 (IL28B)	Hepatitis C
114	Voriconazole (Vfend®)	CYP2C19	Fungal infections
Metabolic			
115	Allopurinol	HLA-B*58:01	High blood uric acid levels, gout
116	Lesinurad (Zurampic®)	CYP2C9	Gout
117	Pegloticase (Krystexxa®)	G6PD	Gout
Neurologic			
118	Amifampridine	NAT2	Lambert-Eaton myasthenic syndrome
119	Brivaracetam (Briviact®)	CYP2C19	Partial-onset seizures
120	Carbamazepine (Tegretol®)	HLA-A; HLA-B	Epilepsy
121	Clobazam (Onfi®)	CYP2C19	Lennox-Gastaut syndrome
122	Deutetrabenazine (Austedo®)	CYP2D6	Huntington's disease
123	Dextromethorphan and quinidine (Nuedexta®)	CYP2D6	Pseudobulbar affect
124	Divalproex (Depakote®)	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Bipolar disorder, epilepsy
125	Donepezil	CYP2D6	Alzhemier's disease
126	Eteplirsen (Exondys 51®)	DMD	Duchenne muscular dystrophy
127	Fosphenytoin (Cerebyx®)	HLA-B	Epilepsy

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Neurologic (cont.)			
128	Galantamine	CYP2D6	Dementia (Alzheimers)
129	Inotersen (Tegsedi®)	TTR	Polyneuropathy
130	Lacosamide (Vimpat®)	CYP2C19	Seizures
131	Meclizine	CYP2D6	Motion sickness
132	Nusinersen (Spinraza®)	SMN2	Spinal muscular atrophy
133	Oxcarbazepine (Trileptal®)	HLA-B	Seizures
134	Patisiran (Onpattro®)	TTR	Polyneuropathy
135	Phenytoin (Dilantin®)	CYP2C9; CYP2C19; HLA-B	Seizures
136	Siponimod (Mayzent®)	CYP2C9	Multiple sclerosis
137	Tetrabenazine (Xenazine®)	CYP2D6	Huntington's disease
138	Valbenazine (Ingrezza®)	CYP2D6	Tardive dyskinesia
139	Valproic Acid (Depakene®)	POLG	Epilepsy
Oncology			
140	Abemaciclib (Verzenio®)	ESR1; ERBB2 (HER2)	Breast cancer
141	Ado-trastuzumab emtansine (Kadcyla®)	ERBB2	Breast cancer
142	Afatinib (Gilotrif®)	EGFR	Non-small cell lung cancer
143	Alectinib (Alecensa®)	ALK	Non-small cell lung cancer
144	Alpelisib (Piqray®)	ERBB2 (HER2); ESR; PIK3CA	Breast cancer
145	Anastrozole (Arimidex®)	ESR; PGR	Breast cancer
146	Arsenic trioxide (Trisenox®)	PML-RARA	Relapsed or refractory APL
147	Atezolizumab (Tecentriq®)	CD274 (PD-L1); EGFR; ALK	Urothelial carcinoma, lung cancer, breast cancer
148	Avelumab (Bavencio®)	CD274 (PD-L1)	Metastatic merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
149	Belinostat (Beleodaq®)	UGT1A1	Lymphoma
150	Binimetinib (Mektovi®)	BRAF; UGT1A1	Melanoma
151	Blinatumomab (Blincyto®)	BCR-ABL1	Leukemia
152	Bosutinib (Bosulif®)	BCR-ABL1	Leukemia
153	Brentuximab vedotin (Adcetris™)	ALK; TNFRSF8 (CD30)	Lymphoma
154	Brigatinib (Alunbrig®)	ALK	Non-small cell lung cancer
155	Busulfan (Busulfex® and Myleran®)	BCR-ABL1	Leukemia
156	Cabozantinib (Cabometyx®)	RET	Renal cell carcinoma, hepatocellular carcinoma

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
157	Capecitabine (Xeloda®)	DPYD	Colon cancer, metastatic breast cancer
158	Carboplatin	ERCC1	Ovarian cancer
159	Ceritinib (Zykadia®)	ALK	Non-small cell lung cancer
160	Cetuximab (Erbitux®)	EGFR; RAS	Metastatic squamous cell carcinoma
161	Cisplatin	TMPT	Testicular cancer, ovarian cancer, bladder cancer
162	Cobimetinib (Cotellic®)	BRAF	Metastatic melanoma
163	Crizotinib (Xalkori®)	ALK; ROS1	Non-small cell lung cancer
164	Dabrafenib (Tafinlar®)	BRAF; G6PD; RAS	Metastatic melanoma
165	Dacomitinib (Vizimpro®)	EGFR	Non-small cell lung cancer
166	Dasatinib (Sprycel®)	BCR-ABL1	Myeloid leukemia
167	Denileukin Diftitox (Ontak®)	IL2A (CD25 antigen)	Lymphoma
168	Dinutuximab (Unituxin®)	MYCN	Neuroblastoma
169	Docetaxel	ESR; PGR	Breast cancer, non-small cell lung cancer, prostate cancer
170	Durvalumab (Imfinzi®)	CD274 (PD-L1)	Urothelial carcinoma
171	Duvelisib (Copiktra®)	Chromosome 17p	Chronic lymphocytic leukemia, small lymphocytic lymphoma, follicular lymphoma
172	Enasidenib (Idhifa®)	IDH2	HLH with refractory, recurrent or progressive disease with intolerance with conventional HLH therapy
173	Encorafenib (Braftovi™)	BRAF	Metastatic melanoma
174	Erdafitinib (Balversa™)	CYP2C9; FGFR	Metastatic urothelial carcinoma
175	Eribulin (Halaven®)	ERBB2 (HER2); ESR; PGR	Metastatic breast cancer
176	Erlotinib (Tarceva®)	EGFR	Non-small cell lung cancer, pancreatic cancer
177	Everolimus (Afinitor®)	ERBB2(HER2); ESR	Kidney transplantation
178	Exemestane (Aromasin®)	ESR; PGR	Breast cancer
179	Fluorouracil (Efudex®)	DYPD	Multiple cancers
180	Flutamide (Eulexin® and Drogenil®)	G6PD	Prostate cancer, metastatic carcinoma
181	Fulvestrant (Faslodex®)	ERBB2 (HER2); ESR; PGR	Breast cancer

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
182	Gefitinib (Iressa®)	EGFR; CYP2D6	Lung cancer
183	Gilteritinib (Xospata®)	FLT3	Leukemia
184	Goserelin (Zoladex®)	ESR; PGR	Prostate cancer
185	Ibrutinib (Imbruvica®)	Chromosome 17p; Chromosome 11q	Lymphoma, CLC, Waldenström's macroglobulinemia, graft versus host disease
186	Imatinib (Gleevec®)	KIT; BCR-AB1; PDGFRB; FIPIL1-PDGFRA	Multiple cancers, myelodysplastic syndrome
187	Inotuzumab ozogamicin (Besponsa®)	BCR-ABL1	Acute lymphoblastic leukemia
188	Ipilimumab (Yervoy®)	HLA-A	Multiple cancers
189	Irinotecan (Camptosar®)	UGT1A1	Colon cancer
190	Ivosidenib (Tibsovo®)	IDH1	Acute myeloid leukemia
191	Ixabepilone (Ixempra®)	ERBB2 (HER2); ESR; PGR	Breast cancer
192	Lapatinib (Tykerb®)	ERBB2 (HER2); ESR; PGR; HLA-DQA1; HLA-DRB1	Metastatic breast cancer
193	Larotrectinib (Vitrakvi®)	NTRK	Multiple cancers
194	Letrozole (Femara®)	ESR; PGR	Breast cancer
195	Lorlatinib (Lorbrena®)	ALK; ROS1	Lymphoma, metastatic non-small cell lung cancer
196	Mercaptopurine (Purinethol®)	TPMT; NUDT15	Acute lymphatic leukemia
197	Midostaurin (Rydapt®)	FLT3; NPM1; KIT	Acute myeloid leukemia, systemic mastocytosis
198	Neratinib (Nerlynx®)	ERBB2 (HER2); ESR; PGR	Breast cancer
199	Nilotinib (Tasigna®)	BCR-ABL1; UGT1A1	Chronic myeloid leukemia
200	Niraparib (Zejula®)	BRCA	Ovarian cancer
201	Nivolumab (Opdivo®)	BRAF; CD274 (PD-L1)	Melanoma, lung cancer, renal cell carcinoma, Hodgkin lymphoma
202	Obinutuzumab (Gazyva®)	MS4A1 (CD20 antigen)	Leukemia, lymphoma
203	Olaparib (Lynparza™)	BRCA; ERBB2 (HER2); ESR; PGR	Ovarian cancer
204	Olaratumab (Lartruvo®)	PDGFRA	Soft tissue sarcoma
205	Omacetaxine (Synribo®)	BCR-ABL1	Chronic myeloid leukemia
206	Osimertinib (Tagrisso®)	EGFR	Lung cancer
207	Palbociclib (Ibrance®)	ESR; ERBB2 (HER2)	Breast cancer
208	Panitumumab (Vectibix®)	EGFR; RAS	Colorectal cancer

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
209	Pazopanib (Votrient®)	HLA-B; UGT1A1	Renal cell carcinoma
210	Pembrolizumab (Keytruda®)	BRAF; CD274 (PD-L1); EGFR; ALK	Melanoma
211	Pemetrexed (Vectibix®)	EGFR; KRAS	Colon cancer
212	Pertuzumab (Perjeta®)	ERBB2 (HER2); ESR; PGR	Metastatic breast cancer
213	Ponatinib (Iclusig®)	BCR-ABL1	Chronic myeloid leukemia
214	Raloxifene (Evista®)	ESR	Osteoporosis
215	Ramucirumab (Cyramaza®)	EGFR; RAS	Gastric cancer
216	Regorafenib (Stivarga®)	RAS	Colorectal cancer
217	Ribociclib (Kisqali®)	ESR; PGR; ERBB2 (HER2)	Breast cancer
218	Rituximab (Rituxan®)	MS4A1 (CD20 Antigen)	Non-Hodgkin's lymphoma
219	Rucaparib (Rubraca®)	CYP2D6; CYP1A2; BRCA	Ovarian cancer
220	Talazoparib (Talzenna®)	BRCA; ERBB2 (HER2)	Breast cancer
221	Tamoxifen (Nolvadex®)	CYP2D6; F2; F5; ESR; PGR	Breast cancer
222	Thioguanine (Tabloid®)	NUDT15; TPMT	Acute nonlymphocytic leukemias
223	Tipiracil and trifluridine (Lonsurf®)	ERBB2 (HER2); RAS	Colorectal cancer
224	Toremifene (Fareston®)	ESR	Breast cancer
225	Tositumomab (Bexxar®)	MS4A1	Non-Hodgkin's lymphoma
226	Trametinib (Mekinist®)	BRAF; G6PD; RAS	Metastatic melanoma
227	Trastuzumab (Herceptin®)	ERBB2; ESR; PGR	Breast cancer
228	Tretinoin (Vesanoid®)	PML-RARA	Acne treatment
229	Vemurafenib (Zelboraf™)	BRAF; RAS	Metastatic melanoma
230	Venetoclax (Venclexta®)	Chromosome 17p; Chromosome 11q; TP53; IDH1; IDH2; IGH; NPM1; FLT3	Leukemia
231	Vincristine (Oncovin®)	BCR-ABL1	Leukemia

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Psychiatry			
232	Amitriptyline (Elavil®)	CYP2D6	Depression
233	Amoxapine	CYP2D6	Depression
234	Amphetamine	CYP2D6	ADHD
235	Aripiprazole (Abilify®)	CYP2D6	Schizophrenia
236	Aripiprazole lauroxil (Aristada®)	CYP2D6	Schizophrenia
237	Atomoxetine (Strattera®)	CYP2D6	ADHD
238	Brexpiprazole (Rexulti®)	CYP2D6	Major depressive disorder, schizophrenia
239	Cariprazine (Vraylar®)	CYP2D6	Schizophrenia, mania
240	Citalopram (Celexa®)	CYP2C19; CYP2D6	Depression
241	Clomipramine (Anafranil®)	CYP2D6	Obsessive-compulsive disorder
242	Clozapine (Clozaril®)	CYP2D6	Schizophrenia
243	Desipramine (Norpramin®)	CYP2D6	Depression
244	Desvenlafaxine (Pristiq®)	CYP2D6	Depression
245	Doxepin (Silenor®)	CYP2D6; CYP2C19	Insomnia
246	Duloxetine	CYP2D6	Major depressive disorder, anxiety, diabetic peripheral neuropathy, chronic musculoskeletal pain
247	Escitalopram	CYP2C19; CYP2D6	Major depressive disorder, anxiety
248	Fluoxetine (Prozac®)	CYP2D6	Major depressive disorder, obsessive compulsive disorder, bulimia nervosa, panic disorder
249	Fluvoxamine (Luvox CR®)	CYP2D6	Obsessive compulsive disorder
250	Iloperidone (Fanapt®)	CYP2D6	Schizophrenia
251	Imipramine (Tofranil-PM®)	CYP2D6	Depression, childhood enuresis
252	Modafinil (Provigil®)	CYP2D6	Narcolepsy, obstructive sleep apnea, shift work disorder
253	Nefazodone (Serzone®)	CYP2D6	Depression
254	Nortriptyline (Pamelor®)	CYP2D6	Depression
255	Paliperidone (Invega®)	CYP2D6	Schizophrenia
256	Paroxetine (Pexeva®)	CYP2D6	Major depressive disorder
257	Perphenazine (Trilafon®)	CYP2D6	Anxiety, depression
258	Pimozide (Orap®)	CYP2D6	Tourette's disorder
259	Protriptyline (Vivactil®)	CYP2D6	Depression

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
260	Risperidone (Risperdal®)	CYP2D6	Schizophrenia
261	Sertraline	CYP2C19	Depression
262	Thioridazine (Mellaril®)	CYP2D6	Schizophrenia
263	Trimipramine (Surmontil®)	CYP2D6	Depression
264	Venlafaxine (Effexor®)	CYP2D6	Major depressive disorder
265	Vortioxetine (Trintellix™)	CYP2D6	Major depressive disorder
Pulmonary			
266	Arformoterol (Brovana®)	UGT1A1; CYP2D6	COPD
267	Formoterol	CYP2D6; CYP2C191	COPD
268	Indacaterol (Arcapta®)	UGT1A1	COPD
269	Ivacaftor (Kalydeco®)	CFTR	Cystic fibrosis
270	Ivacaftor and lumacaftor (Orkambi®)	CFTR	Cystic fibrosis
271	Ivacaftor and tezacaftor (Symdeko®)	CFTR	Cystic fibrosis
272	Umeclidinium (Incruse® Ellipta®)	CYP2D6	COPD
Rheumatology			
273	Azathioprine (Imuran®)	TPMT; NUDT15	Rheumatoid arthritis, renal homotransplantation
274	Carisoprodol	CYP2C19	Musculoskeletal pain
275	Flurbiprofen (Ansaid®)	CYP2C9	Rheumatoid arthritis, osteoarthritis
276	Piroxicam (Feldene®)	CYP2C9	Pain, swelling, joint stiffness
277	Probenecid (Benemid® and Probalan®)	G6PD	Chronic gouty arthritis
Toxicology			
278	Sodium nitrite	G6PD	Acute cyanide poisoning
279	Succimer (Chemet®)	G6PD	Lead poisoning
Transplantation			
280	Mycophenolic acid (Myfortic®)	HPRT1	Kidney transplant
281	Tacrolimus (Prograf®)	HPRT1; CYP3A5	Kidney transplant
282	Darifenacin (Enablex®)	CYP2D6	Overactive bladder, urge urinary incontinence
283	Fesoterodine (Toviaz®)	CYP2D6	Overactive bladder
284	Mirabegron (Myrbetriq®)	CYP2D6	Overactive bladder
285	Tamsulosin	CYP2D6	Benign prostatic hyperplasia
286	Tolterodine (Detrol®)	CYP2D6	Overactive bladder

MISSION

The Personalized Medicine Coalition (PMC), representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

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