THE PERSONALIZED MEDICINE REPORT

2017 · Opportunity, Challenges, and the Future

PMC

The Personalized Medicine Coalition gratefully acknowledges graduate students at Manchester University in North Manchester, Indiana, and at the University of Florida, who updated the appendix of this report under the guidance of David Kisor, Pharm.D., Director, Pharmacogenomics Education, Manchester University, and Stephan Schmidt, Ph.D., Associate Director, Pharmaceutics, University of Florida. The Coalition also acknowledges the contributions of its many members who offered insights and suggestions for the content in the 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 that help some patients are ineffective for others (Figure 1),[1] and the same medicine may cause side effects in only certain patients.

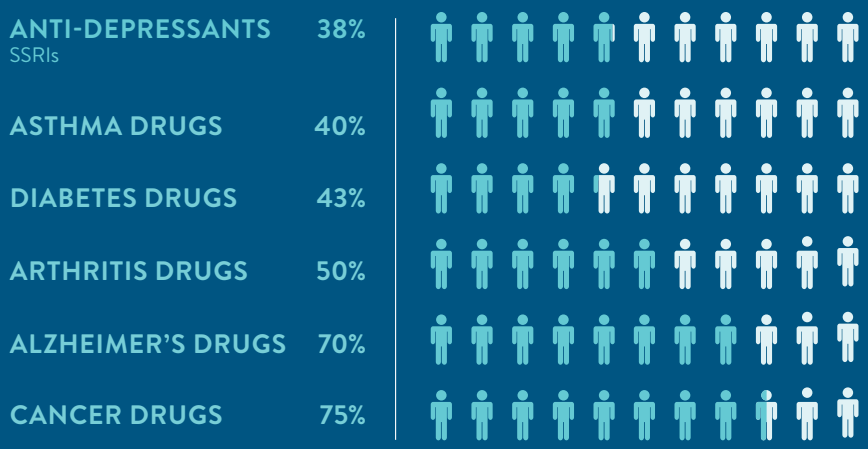
Yet, bound by the constructs of traditional care delivery models, many of today's doctors still prescribe therapies based on population averages. As a result, health care systems around the world continue to deliver inefficient care that fails to help significant portions of the patient population.

Enter personalized medicine. Personalized medicine, also called precision or individualized medicine, is an evolving field in which physicians use diagnostic tests to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted treatment and prevention 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 improving quality, accessibility, and affordability.

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 that utilizes patients' molecular information to inform health care decisions. Completing that transformation, however, will require a collaborative effort in the U.S. and abroad to keep up with the pace of progress in science and technology. A myriad of nuanced regulatory and reimbursement challenges as well as complexities regarding the clinical adoption of new medical norms and standards, in particular, continue to make it difficult for health care systems around the world to capitalize on innovative science and a growing body of knowledge pointing to a new era in the history of medicine.

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

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 adverse drug reactions
- Revealing additional targeted uses for medicines and drug candidates
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures
- 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 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, 4] 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 prophylactic surgery, chemoprevention, and more frequent mammography.

Personalized medicine also opens the door to early intervention for patients with familial hypercholesterolemia, which is characterized by a mutation in the LDL receptor gene. These patients can take drugs that block 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, diagnostic tests enable physicians to identify the most effective treatment for a patient immediately by testing for specific molecular characteristics, thus avoiding the frustrating and costly practice of trial-and-error medicine. Medicines that target those molecular characteristics often improve outcomes and reduce side effects. One of the most common applications of this practice 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 breast cancer patients who express this molecule, adding an antibody drug like trastuzumab (Herceptin®) to their chemotherapy regimen can reduce their recurrence risk by 52 percent.[5, 6] Molecular diagnostic tests for HER2 are used to identify the patients who will benefit from receiving Herceptin® and other drugs that target HER2, such as lapatinib (Tykerb®). Treatments targeting genetic variants involved in the molecular pathway of disease, such as BRAF in melanoma and ALK and EGFR in non-small cell lung cancer, represent a remarkable improvement over trial-and-error medicine, and we are moving toward an era in which we treat all cancer cases with a targeted course of treatment (Figure 2).[7]

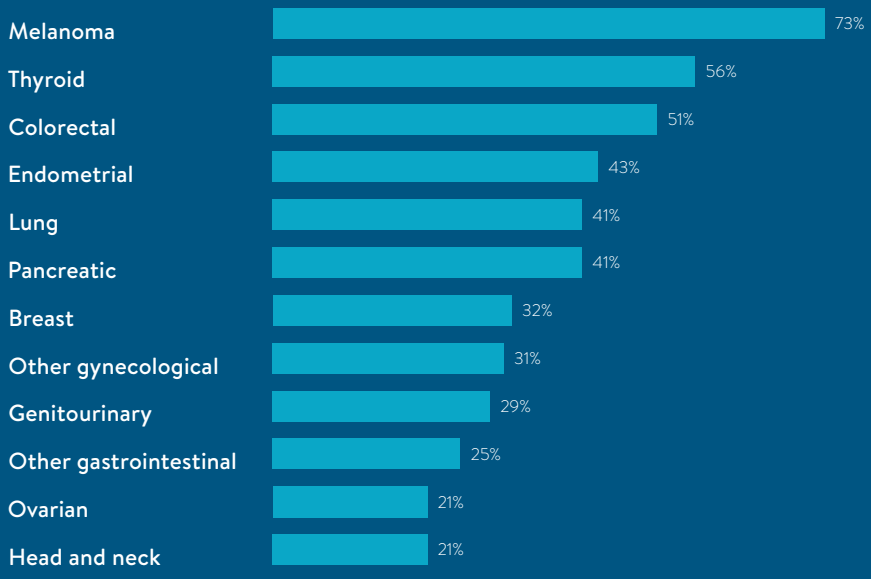
Other personalized medicine tests measure prognostic markers that help indicate how a disease may develop in an individual when a disorder is already diagnosed. Two complex tests, Oncotype DX® and MammaPrint®, for example, use prognostic markers to help physicians target the best course of treatment for breast cancer patients. Oncotype DX® can determine whether women with certain types of breast cancer are likely to benefit from chemotherapy.[8, 9, 10] MammaPrint® can detect which early-stage breast cancer patients are at risk of distant recurrence following surgery.[11] Both tests place patients into risk categories that inform physicians and patients of whether the cancer may be treated successfully with hormone therapy alone, as opposed to some combination of hormone therapy and chemotherapy, which is associated with an additional financial burden and toxic effects. Similar prognostic tests for prostate and colon cancer patients have also been developed.[12, 13, 14]

Reducing Adverse Drug Reactions

Another category of personalized medicine tests, called pharmacogenomic tests, help predict what medications at what doses will be 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).[15] Many ADRs are attributed to variations in genes that code for

FIGURE 2: FORGING A PATH TO PERSONALIZED CANCER CARE

TACKLING TUMORS: Percentage of patients whose tumors are driven by certain genetic mutations that could be targets for specific drugs, by types of cancer.



Reproduced with permission from: Winslow, R. Major shift in war on cancer. *Wall Street Journal.* June 5, 2011. Accessed September 13, 2016 at http://www.wsj.com/articles/SB10001424052702304432304576367802580935000.

drug-metabolizing enzymes, such as cytochrome P450 (CYP450).[16, 17] These variants 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 determining dose.

Pharmacogenomic testing can help guide the safe application of medicines in many health areas, including heart disease, hematologic disorders, HIV and other infectious diseases, cancer adjunct therapy, anesthesiology, dermatology, gastroenterology, neurology, psychiatry, and rheumatology. One of the first applications of pharmacogenomics was for patients that had been prescribed the drug warfarin, used to prevent blood clots. Genetic variations in a drug-metabolizing enzyme (CYP2C9) and an enzyme that activates vitamin K (VKORC1) complicate the safe use of warfarin.[18, 19] 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. FDA now recommends genotyping for all patients before warfarin treatment, which allows for more precise dosing. Although the data are still evolving, early evidence suggests that genetic testing in advance of prescribing warfarin helps patients avoid serious and possibly fatal adverse effects.[20, 21]

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 dosing 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.[22] Lowering the drug dose in individuals with this allele can help reduce adverse effects and increase treatment compliance. Similarly, the HLA-B*5701 mutation is associated with severe and life-threatening hypersensitivity to the HIV drug abacavir (Ziagen®/Epzicom®).[23] The HLA-B*5701 mutation is present in approximately five percent of HIV patients in the U.S.

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 demonstrate a survival advantage 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. However, continued clinical research

revealed benefits in patients who test positive for epidermal growth factor mutations. FDA approved Iressa® as a first-line treatment for this subset of patients in 2015.

Gene and protein analyses have also led to an evolution in the way tumors are evaluated and classified. With an increasing body of knowledge about the underlying genomic alterations and the expression of relevant biomarkers, tumor classification is shifting away from tissue of origin and toward molecular taxonomy, which is having a profound effect on the way that oncology treatment decisions are made. 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 some novel immune checkpoint inhibitors.[24] This has led to expanded approvals for immune checkpoint inhibitors like pembrolizumab (Keytruda®), which was initially approved in 2014 for melanoma.[25] FDA revised Keytruda's label in 2015 for use in non-small cell lung cancer and has fast-tracked review for its use in other indications.[26, 27] Similarly, FDA has also approved the use of nivolumab (Opdivo®) for multiple indications.[28, 29, 30, 31, 32]

Likewise, early studies indicate that crizotinib (Xalkori®), already approved to treat specific forms of non–small cell lung cancers, including those that are EML4-ALK-positive, is also effective against other types of tumors containing ALK alterations, such as aggressive forms of pediatric neuroblastoma and anaplastic large cell lymphoma.[33, 34] FDA has fast-tracked regulatory review for these expanded indications, which some observers believe is a precursor to an era in which the agency approves all personalized medicines faster based on the increased likelihood that a molecularly targeted drug will be safe and effective.

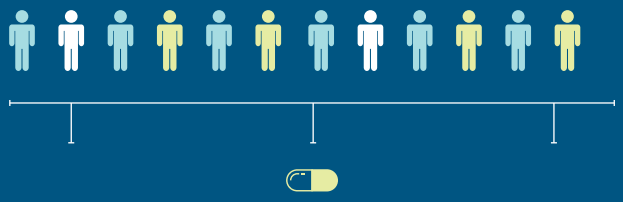
Increasing Patient Adherence to Treatment

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.[35]

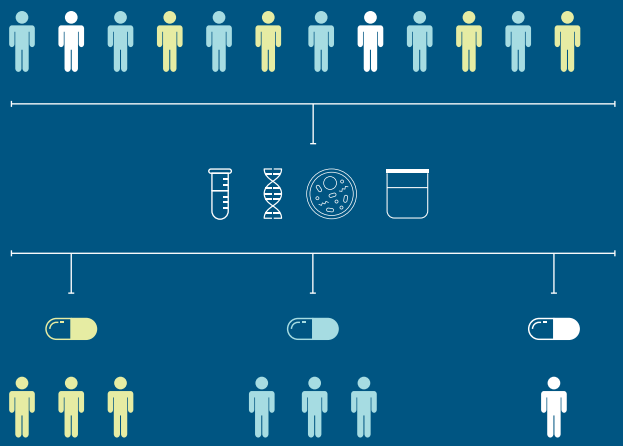
FIGURE 3: A NEW TREATMENT PARADIGM

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. *A New Treatment Paradigm*. Accessed September 13, 2016 at http://chartpack.phrma.org/personal-medicines-in-development-chartpack/a-new-treatment-paradigm/personalized-medicine-can-improve-efficiencies-within-the-health-care-system.

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.[36] 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.[37, 38]

Helping to Control the Overall Cost of Health Care

By introducing innovative science that can create efficiencies and sustainability, personalized medicine also has the potential to reduce health care costs worldwide. 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 health condition 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.

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. The Mayo Clinic and the pharmacy benefits manager Medco 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.[39] 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.[40] Another study found a $604 million annual savings among all patients when treatment with panitumumab (Vectibix®) or cetuximab (Erbitux®) was limited to patients with metastatic colorectal cancer whose KRAS gene was not mutated.[41]

"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.**
Interim Chief Medical Officer, Neon Therapeutics

SCIENTIFIC ADVANCEMENT

The scientific tools necessary to realize the benefits of personalized medicine are already at our disposal.

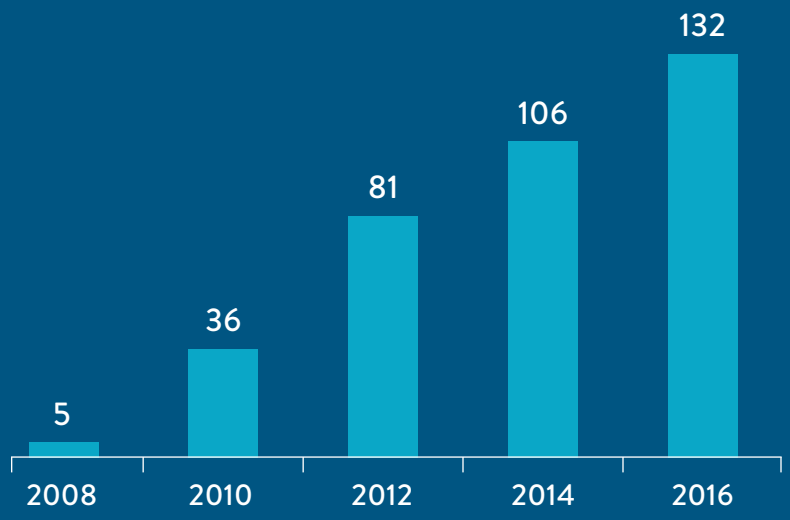
PMC counts 132 personalized medicines, that is, drugs that point to specific biomarker(s) in their labels to direct use, currently on the market (Figure 4; Appendix), and recent estimates by the genetic testing data company Concert Genetics indicate that there are now no fewer than 65,000 genetic tests available (Figure 5). Analysts peg the market value for drugs reliant on companion diagnostics (CDx) at over $25 billion in 2015 (Figure 6).

These numbers are likely to continue growing. A recent survey conducted by the Tufts Center for the Study of Drug Development showed that 42 percent of the drugs in the development pipeline now include biomarkers in their research and development design. The survey also suggested that biopharmaceutical manufacturers have nearly doubled their investment in personalized medicine over the past five years, and that these companies expect investment to increase by another 33 percent over the next five years (Figure 7).

Scientific developments in genomic sequencing, how an individual's biology impacts disease susceptibility, immunotherapy, gene therapy, and CRISPR-Cas9 gene editing are laying the groundwork for a new era in medical discovery.

FIGURE 4: COMING OF AGE

Number of Personalized Medicines Has Increased Steadily Since 2008*



Personalized Medicine Coalition. *The Case for Personalized Medicine* (eds. 1–4). 2008–2014; Personalized Medicine Coalition. *Applications: Therapies.* Accessed October 31, 2016 at http://www.personalizedmedicinecoalition.org/Education/Therapies.

*Methodological notes: The number of personalized medicines was calculated by combining information from former editions of PMC's *Case for Personalized Medicine* (2008–2014) with 2016 data from FDA's *Table of Pharmacogenomic Biomarkers in Drug Labeling*, accessed October 31, 2016 at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm and CPIC's *Genes-Drugs* tables, accessed October 31, 2016 at https://cpicpgx.org/genes-drugs/. A complete list of the 132 drugs counted as of October 2016 is available at http://www.personalizedmedicinecoalition.org/Education/Therapies and in the Appendix of this report.

Genomic Sequencing

It took $1 billion and 13 years to sequence the first draft of the human genome. Since then, sequencing technology has evolved from the manual Sanger method using radioactive labels to automated sequencing that employs color-coded fluorescent dyes. As a result, the cost of sequencing an entire genome has declined at a rate that exceeds Moore's law (Figure 8). The results reflect a general trend in the industry and an important transition around mid-2007 brought on by next-generation sequencing technology.

The cost to sequence a 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 in ten years the cost will be $100.[43] Additional costs and time are necessary, however, for analysis and annotation in a clinical setting.

Human Biology and Disease Susceptibility: The Role of DNA, RNA, Epigenetics, and Proteins

Understanding the role of genetic variation in disease has also become a central part of medical research. Most scientists believe that many common human ailments, such as heart disease, diabetes, and cancer, are significantly influenced by numerous rare genetic variations present within a single genome. Thus, one person might not carry the same set of variants as another, even if both have the same disease. These rare variants are, as National Institutes of Health (NIH) Director Francis Collins termed them, the "dark matter" in genetic patterns that remain undiscovered.

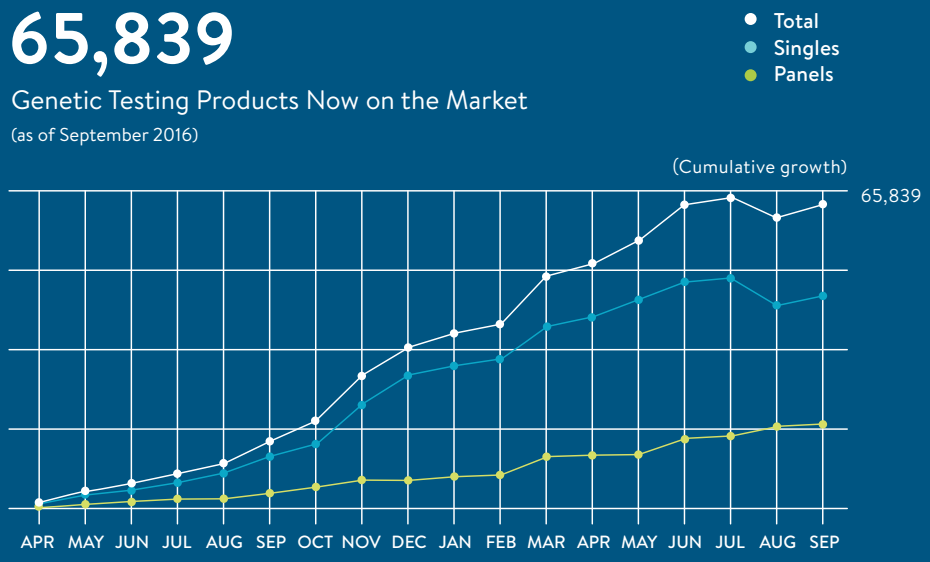
Thanks to the Human Genome Project and subsequent advancements in sequencing technology, the scientific community is now more equipped than ever to make sense of this "dark matter." It is now possible to simultaneously interrogate hundreds of thousands of sites in

FIGURE 5: PROGRESS BY THE THOUSANDS

65,839

Genetic Testing Products Now on the Market

(as of September 2016)



More Than 5,500 New Genetic Testing Products Came to Market Between April 2015 and September 2016*

Data provided by: Concert Genetics. Available at concertgenetics.com.

*Methodological notes: Concert Genetics began publishing the first reliable data on the number of genetic testing products available in January of 2016. PMC has published a list of 127 genetic tests commonly associated with the 132 personalized medicines listed in the Appendix of this document at http://www.personalizedmedicinecoalition.org/Education/Tests.

an individual's DNA to find associations between a given disease and genetic variation. In 2015, U.S. President Barack Obama launched the Precision Medicine Initiative (PMI), 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. 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.

But advances in personalized medicine are not confined to analysis of DNA. In fact, analyzing messenger RNA transcripts, the immediate downstream mediator of the genome, can sometimes detect gene expression in ways that DNA analysis cannot. RNA sequencing analysis represents an expanding share of the next-generation sequencing marketplace.[44, 45]

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 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. The NIH has developed the Roadmap Epigenomics Project to study the role of epigenetics in human diseases.[46]

In addition, scientists are working to standardize existing proteomic technologies such as mass spectrometry, leading to more robust identification of protein biomarkers, which indicate the presence or absence of disease apart from the risk prediction of genetic analysis. Entirely new approaches to protein biomarker detection[47] 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.

Immunotherapy

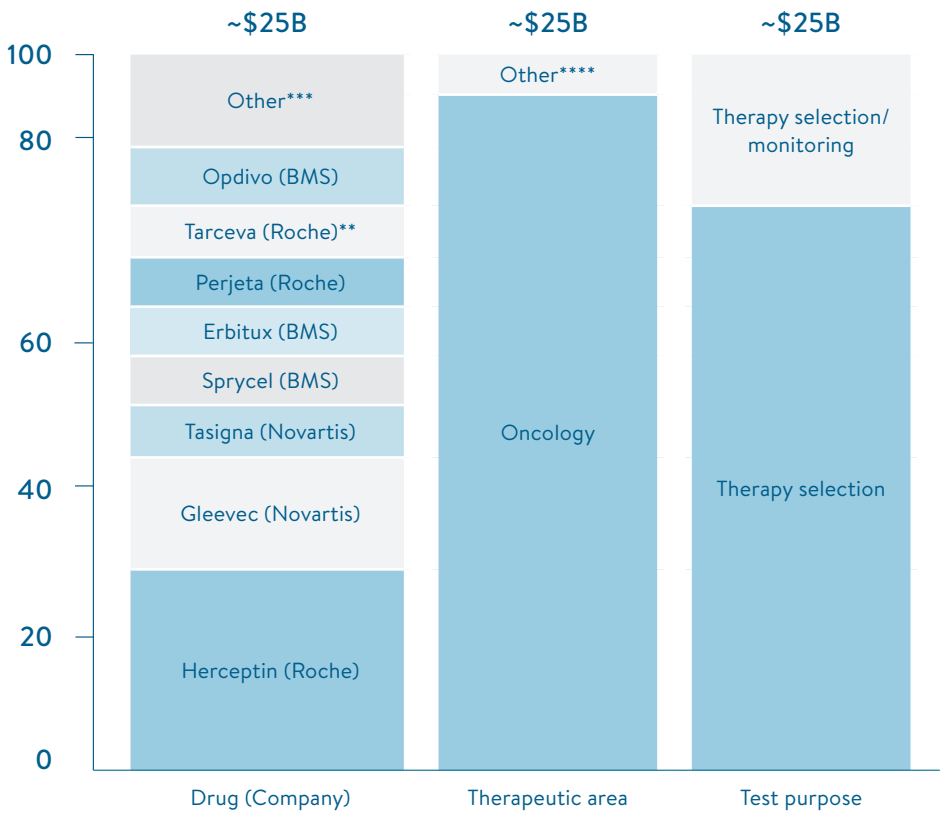
Researchers and pharmaceutical companies are also developing highly personalized treatment approaches that use the patient's own immune system to help fight cancer. These "immuno-therapies" work in different ways. Some provide a general boost to the body's immune system. Others help train the immune system to attack specific cancer cells by inhibiting a tumor's ability to use a substance called PD-L1 to put the "brakes" on immune cells. Novel immune checkpoint inhibitors like Keytruda® and Opdivo®, for example, block the ability of PD-L1 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. These therapies have been approved for the treatment of melanoma, non-small cell lung cancer, kidney cancer, and Hodgkin lymphoma.[48, 49] They are also being studied for use against many other types of cancer.

Gene Therapy

Medical researchers are also developing ways to introduce genetic material directly into cells to treat or prevent disease. Gene therapy, for example, may allow scientists to "knock out" or replace a mutated gene that causes illness, or to introduce a healthy copy of a gene to restore the function of a needed protein. The European Union has approved the first gene therapy, alipogene tiparvovec (Glybera®),[50] and several gene therapies have advanced to phase III trials in the U.S.[51] Although the clinical efficacy of these treatments has not yet been established,[52] proponents believe the therapies will begin to carve out a niche as the number of potential targets for these treatments continues to increase.

FIGURE 6: MARKETED THERAPEUTICS RELIANT ON A CDx GENERATED ~$25 BILLION IN THERAPEUTIC REVENUES IN 2015

Biopharma worldwide marketed CDx drug revenue segmentation (2015)*
Percent of revenues



* 2015 revenues are actual or analyst estimates; PHC products include those with labels that require/recommend CDx tests for candidacy

** Includes all Tarceva revenues, not just those from first-line treatment for EGFR+ non-small cell lung cancer patients

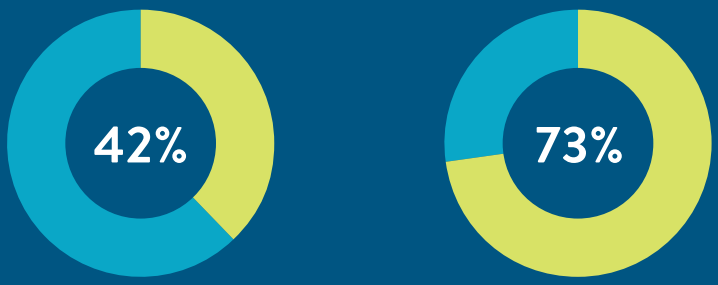
*** Other includes Alecensa, Aristada, Blincyto, Bosulif, Cholbam, Cotellic, Gilotrif, Ibrance, Iressa, Kadcyla, Lonsurf, Lynparza, Mekinist, Nucala, Orkambi, Praluent, Repatha, Rexulti, Selzentry, Tafinlar, Tagrisso, Tykerb/Tyverb, Vectibix, Victrelis, Xalkori, Zelboraf, and Zykadia drug revenues

**** Other includes infectious disease, neurology, cardiology, pediatrics, respiratory, and gastroenterology therapeutic areas

Republished with permission from: L.E.K. Consulting. "Marketed Therapeutics Reliant on a CDx Generated ~$25B in Therapeutic Revenues in 2015," PowerPoint presentation, updated January 27, 2016.

FIGURE 7: THE BIOPHARMACEUTICAL INDUSTRY IS COMMITTED TO PERSONALIZED MEDICINE

Drug development pipelines are full of targeted treatments that offer new hope for patients.



of all drugs in development are personalized medicines

of oncology drugs in development are personalized medicines

Personalized Medicines

- **42%** of all compounds and **73%** of oncology compounds in the pipeline have the potential to be personalized medicines
- Biopharmaceutical companies **nearly doubled** their R&D investment in personalized medicines over the past five years, and expect to increase their investment by an additional 33 percent in the next five years
- Biopharmaceutical researchers also predict a **69%** increase in the number of personalized medicines in development over the next five years

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Tufts Center for the Study of Drug Development. Personalized medicine gains traction but still faces multiple challenges. *Impact Report.* 2015;17(3).

CRISPR/Cas9 Gene Editing

A new tool called CRISPR/Cas9 gene editing is also generating excitement 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. Gene editing using the CRISPR/Cas9 technology may allow for the correction of disease-causing mutations in humans.[53] The potential application of this technology for personalized treatment strategies spans a wide spectrum of health conditions, from congenital blindness to cancer.

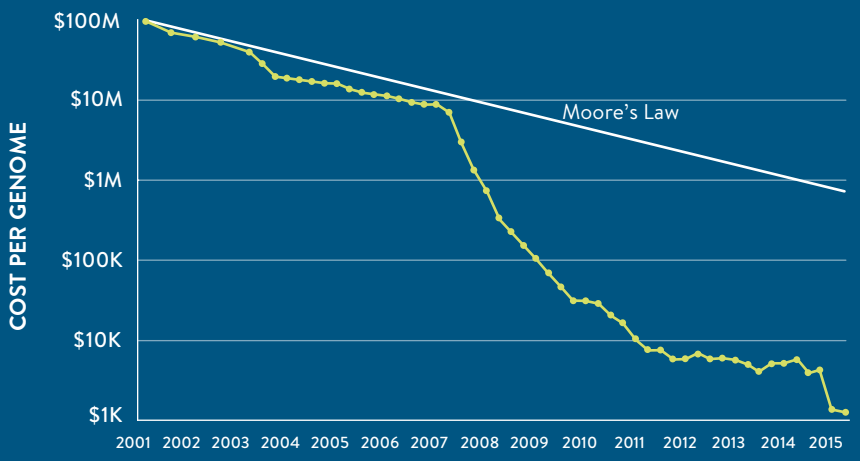
The potential of germ-line genetic modification, however, has raised ethical concerns about the appropriate use of the technology. These concerns are sure to lead to ethical debates going forward. Nonetheless, CRISPR/Cas9's application to treatment of diseases targeting somatic cells in adult patients will likely have a significant impact on medical technology, as will many of the other trends described here.

"[B]etween 2012 and 2016 we have invented technologies that allow us to change human genomes intentionally and permanently … We can now 'read' human genomes, and we can 'write' human genomes in a manner inconceivable just three or four years ago."

— **Siddhartha Mukherjee, M.D., D.Phil.**
author, *The Gene: An Intimate History*

FIGURE 8: 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 over time. The data capture the dramatic decline in sequencing costs through 2015, and the cost has continued to drop.



National Human Genome Research Institute. *The Cost of Sequencing a Human Genome.* Accessed September 13, 2016 at http://www.genome.gov/sequencingcosts.

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, FDA

REGULATORY POLICY

Scientific progress is driving an increase in the number of personalized medicine products and services subject to regulatory review. In fact, nearly one of every four drugs FDA approved from 2014 – 2016 was a personalized medicine, and personalized medicines accounted for 27 percent of new drug approvals in 2016. Those numbers are a sharp increase from 2005, when personalized medicines accounted for just 5 percent of new drug approvals (Figure 9). The agency has responded to the growing demand for regulatory clarity by issuing draft guidance documents (Figure 10). The 21st Century Cures Act, which Congress passed in 2016, encourages the agency to modernize its paradigm for considering "real-world evidence," the patient experience, and molecular pathways as they relate to clinical trial designs. The year 2017 will also mark the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA), which includes several provisions that will offer clarity in areas such as biomarker qualification, patient-focused drug development, and the use of innovative clinical trial designs.

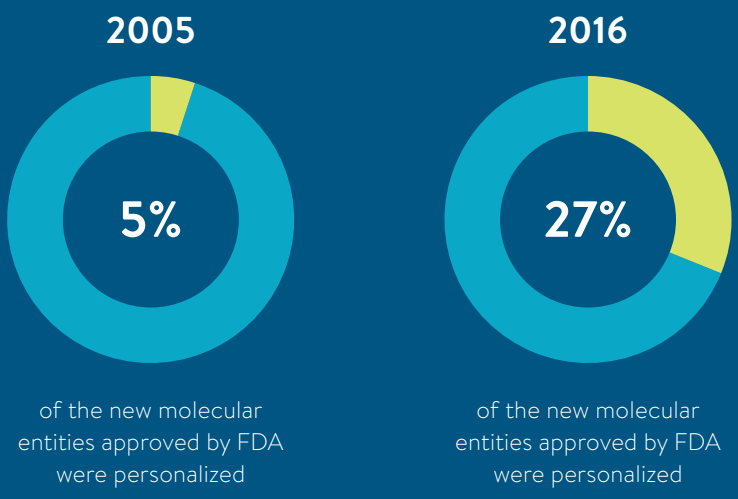
The landscape for regulation of personalized medicine, however, is still emerging, and the lack of a clear regulatory pathway for personalized medicine diagnostics continues to discourage investment in the field. Among the topics under continued discussion are FDA's proposed oversight policies related to laboratory-developed tests (LDTs) and next-generation sequencing technologies. In contrast, the agency's well-developed position on the codevelopment of personalized medicine products has removed an obstacle to the field's progress.

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: diagnostic kits and LDTs. The former are products containing all the reagents and materials needed to run the test, and are

FIGURE 9: PERSONALIZED MEDICINE AT FDA: THEN AND NOW

Personalized medicines accounted for just 5 percent of the new molecular entities FDA approved in 2005. In 2016, they accounted for more than 25 percent.



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).[54] Clinical laboratories can obtain CLIA certification directly from CMS, typically through state agencies that survey labs for compliance with CLIA requirements. A lab can also seek accreditation by one of the independent accreditation organizations approved by CMS, which include the College of American Pathologists (CAP), among others. Although FDA has historically claimed jurisdiction to regulate LDTs, the agency has also historically refrained from actively regulating these tests, under a policy it describes as "enforcement discretion."

In July of 2014, however, FDA outlined a draft framework for 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 2017. The uncertainty surrounding the future of the regulatory landscape for LDTs continues to discourage investment in innovative molecular diagnostics.

Regulatory Oversight of NGS-Based Diagnostic Tests

FDA is also working to understand how to regulate diagnostics that incorporate next-generation sequencing (NGS) technology, which yield 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 is developing a new approach to regulating NGS tests that the agency says will allow timely access to tools that have adequate analytical and clinical performance. Through 2016, only one NGS instrument (Illumina MiSeqDx™) and two accompanying assays for the diagnosis of cystic fibrosis (Illumina MiSeqDx,™ Cystic Fibrosis 139 Variant and Clinical Sequencing Assays) have been FDA-approved. Because it was impractical to detect every possible variant that might exist in a genomic sequence, analytical test performance

FIGURE 10: POLICY AND GUIDANCE DOCUMENTS FROM THE U.S. FDA

2005	*Pharmacogenomic Data Submissions* (final guidance)
2007	*Pharmacogenomic Tests and Genetic Tests for Heritable Markers* (final guidance)
2007	*In Vitro Diagnostic Multivariate Index Assays* (draft guidance)
2008	*E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data, and Sample Coding Categories* (final guidance)
2011	*E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualifications Submissions* (final guidance)
2012	*Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (draft guidance)
2013	*Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (final guidance)
2013	*Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (final guidance)
2014	*Qualification Process for Drug Development Tools* (final guidance)
2014	*In Vitro Companion Diagnostic Devices* (final guidance)
2014	*Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (draft guidance)
2014	*FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* (draft guidance)
2016	*Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases* (draft guidance)
2016	*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics* (draft guidance)
2016	*Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (draft guidance)
2017	*Discussion Paper on Laboratory Developed Tests (LDTs)* (discussion paper)

U.S. Food and Drug Administration. *Search for FDA Guidance Documents*. Accessed January 31, 2017 at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

for the MiSeqDx™ system was demonstrated for a representative number of subsets of types of variants in multiple sequencing contexts. The agency is considering extending this subset-based approach for other NGS platforms alongside other approaches for the establishment of analytic validity and clinical significance.

In 2014, FDA issued a discussion document seeking public input on these novel regulatory approaches, and in 2016 the agency released two draft guidance documents describing potential processes for analytic standards development and FDA-recognized public genome database development. Although the landscape remains ambiguous, many members of the personalized medicine community now believe the processes outlined in the documents reflect FDA's willingness to adapt to the changing landscape of medicine.

Codevelopment

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."[55] 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. 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.[56] The guidance describes conditions under which a targeted drug might be approved ahead of a corresponding diagnostic test. While these guidelines were in development, FDA, Health Canada, and the European Medicines Agency had, in several cases, either mandated or recommended that biomarker testing be performed prior to prescribing certain drugs. 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.[57]

In mid-2016, FDA published an additional draft guidance document on codevelopment called *Principles for Codevelopment 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 codeveloping products, removing one regulatory hurdle to the parallel regulation of targeted therapeutics and their companion diagnostic tests.

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

— **Alexis Borisy**
Partner, Third Rock Ventures

COVERAGE AND PAYMENT POLICY

Regulatory approval of personalized medicine products and services is critically important for advancing the field. However, it is only part of the story. Coverage and payment policies — both in the public and private sectors — play an equally 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."[58] However, under pressure to address rising health care costs, policymakers and payers are increasingly considering policies that may 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 the value of this new paradigm as they consider health technology and value assessment frameworks, procedural changes to the reimbursement landscape, and value-based payment models.

Evidence Requirements

As discussed, personalized medicine offers many benefits to patients, including an improved capacity to prevent disease, more effective treatments, improved side-effect profiles, and 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.[59] There is significant ambiguity regarding how that evidence should be developed and disseminated. Widespread insurance coverage of diagnostic tests, for example, will likely require practice-based evidence demonstrating value. Obtaining the real-world data necessary for generating this evidence, however, is difficult unless the products and services in question are covered by insurance policies. These realities have led to a challenging conundrum in demonstrating the value proposition for personalized medicine. A solution is not yet apparent.

Value Assessment Frameworks

Over the past several years, "value assessment frameworks" have emerged as tools for supporting health care decision-making by quantifying the value of treatments, and these frameworks have begun to influence coverage and payment decisions. The frameworks, like other evidence-based decision support tools, have the potential to encourage the use of personalized medicine if they incorporate explicit mechanisms for capturing the value of the field. Many of the frameworks, however, have been criticized for failing to account for the heterogeneity of treatment effects. For example, in 2016, the Institute for Clinical and Economic Review (ICER), a nonprofit organization that uses available evidence to examine the value of therapeutics based on a conceptual framework that combines its estimation of the clinical and economic value of a particular drug with several other factors, issued a value assessment determination on drugs for multiple myeloma that was largely based on population averages.[60] Patient groups responded negatively to the report, noting a lack of consideration of the clinical benefit of a drug to certain patients. As the Multiple Myeloma Research Foundation pointed out in its letter to ICER, "the promise of precision medicine is that each patient is unique and will consequently respond to treatment differently based on their particular genetic profile and further understanding of the biology of their disease."[61]

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 recently, 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 a consistent downward 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[62] that further exacerbated the downward pressure on utilization of these technologies. The rule lacks mechanisms that capture the value of targeted treatment, and may therefore threaten progress.

Value-Based Payment Models

CMS and private payers are also proposing new, "value-based" payment models, 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 and improvements to patient care. APMs should encourage physicians to tailor care based on an individual's genetics 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

CLINICAL ADOPTION

Despite rapid scientific and technological advancement, the health care system has been relatively slow to integrate personalized medicine into clinical practice.[63] Survey data shows, for example, that only four out of 10 consumers are aware of personalized medicine, and only 11 percent of patients say their doctor has discussed or recommended personalized medicine treatment options to them.[64] Recent surveys have also shown that most health care organizations do not have formalized plans to leverage advances in genomics and data analytics to personalize patient care, and are unprepared to implement personalized medicine programs.[65, 66] 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.

Recently, a number of efforts to understand how to best encourage the efficient clinical adoption of personalized medicine have been launched. The National Academy of Medicine, for example, has issued several reports on translating genomic-based research to health care.[67, 68, 69] The Personalized Medicine Coalition (PMC) also assembled a Health Care Working Group to develop a road map for integration of personalized medicine into health care,[70] and the International Consortium on Personalized Medicine (IC PerMed) has identified an index of barriers for clinical adoption.[71]

Integrating personalized medicine into health care requires: 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 to ensure access to personalized medicine technologies and services. To successfully integrate personalized medicine into health care, providers will need to implement a range of programs and processes (Figure 11) in each of these areas.

Education and Awareness

Perhaps the greatest challenge to integrating personalized medicine into health care is a lack of education and awareness among patients and throughout the health care delivery community. Freely available educational resources are being developed by a number of organizations[72, 73, 74, 75, 76] that are presented in multiple formats based on the needs of different stakeholders. However, they must be accurate, trusted, and updated regularly. PMC, which represents all sectors of the health care community, continues to work with personalized medicine's stakeholders to develop a content-rich website that can serve as the most reliable source for personalized medicine knowledge.[77]

Although many community education strategies are clear, building awareness and knowledge will not be easy, especially among physicians and other health care providers. In recognition of this reality, the Genomic Medicine Institute at Cleveland Clinic and others host accredited genetics education symposia for practicing health care providers. The 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.[78] These programs, however, reach only a fraction of the available population.

Pharmacists have also taken a proactive approach to education and awareness. Pharmacogenomics is now a required element of every doctor of pharmacy curriculum in the U.S.,[79] graduate programs in pharmacogenomics and precision medicine are now common,[80, 81] and certification programs are available regionally and nationally.[82, 83, 84, 85]

Patient Empowerment

The involvement of patients in their own treatment decisions and protection of their molecular information from being used in ways that would cause them concern, and, perhaps, long-term repercussions, such as discrimination, job loss, or loss of health insurance coverage, are also critical for the clinical adoption of personalized medicine.

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.[86, 87] 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. For example, biopharmaceutical development and commercial outsourcing services company Quintiles has initiated a Global Data Protection Program, which has issued global

FIGURE 11: 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 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 individual patient and clinical support information is comprehensive, useful, and user-friendly, and so that it can be used to 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.

corporate policies for the "protection of personal information" and "data confidentiality" related to patient and proprietary information exchange between industry and providers.[88]

Perhaps most importantly, practitioners are recognizing that they need to regularly involve patients in health care decision-making.[89] 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.[90, 91, 92] These developments are encouraging.

Value Recognition

While many stakeholders believe that personalized medicine provides benefits to patients and the health care system, payers and providers are still often reluctant to change policies and practices without having convincing evidence of its clinical and economic value.[93] 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.[94]

Payers also need to understand financial and risk reduction endpoints within the body of evidence, along with patient survival and disease progression information. Strategies for addressing these challenges have begun to emerge. Forums between payers and product developers, for example, may facilitate a better understanding of the evidence requirements necessary for positive coverage determinations. In 2015, the Molecular Evidence Development Consortium (MED-C) was launched to help bridge the gap between payers, providers, and industry in demonstrating the value of personalized treatment strategies by providing a forum to discuss and develop plans to gather molecular data on individual patients along with thorough information about their treatments and clinical outcomes.[95]

Infrastructure and Information Management

Effectively managing the massive amount of information associated with personalized medicine and coordinating programmatic processes and services related to its use are also major areas of need. Health care providers emphasize the need for data management processes that are straight-forward, user-friendly, and save time for the health care workforce. Institutional personalized medicine program policies and processes also need to be coordinated across research and clinical programs.

Many organizations are committed to overcoming challenges in these areas, but strategies need to be developed and implemented widely in order to have a meaningful impact on the larger health care system. 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.[96]

Some health care delivery organizations that have begun to implement personalized medicine programs are working with information management organizations to develop data management systems that function directly within electronic health records to alert treating physicians about relevant biomarker information that could help inform treatment decisions. For example, community health care provider Intermountain Healthcare has teamed up with Syapse, a health information technology company, and N-of-One, a clinical interpretation management company, to enable community oncologists to access tumor genome profiling, analysis, and drug procurement information through an integrated service platform.[97]

Ensuring Access to Care

Perhaps the most complex area of need is adapting health delivery approaches, processes, and service structures to ensure access to personalized medicine. The traditional fee-for-service medical paradigm does not lend itself to the efficient adoption of new technologies. To overcome that challenge, the Duke Center for Research on Personalized Health Care, for example, has proposed that health care systems incorporate new technologies as they are validated and continually generate outcomes data for use in predictive models.[98] Those practices, however, have not been widely adopted.

Clinical guidelines do not often reflect personalized medicine concepts either. The PharmGKB and the Pharmacogenomics Research Network, however, recently established the Clinical Pharmacogenetics Implementation Consortium (CPIC) to help develop updated pharmacogenomics clinical practice guidelines.[99] Nonetheless, in many cases, overcoming challenges to adapting health care delivery approaches requires cultural change as well as the implementation of new programs. Progress will likely require shifting the perspectives of many stakeholders toward a personalized medicine paradigm, which can be accelerated by improving the knowledge base, empowering patients, demonstrating value across stakeholder groups, and building effective program infrastructure and information management processes. Most initiatives to accomplish these goals, however, are still in their infancy.

"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

HEALTH INFORMATION TECHNOLOGY

Developing and providing access to novel personalized medicine products and services are only part of what is needed to achieve better human health by tailoring treatment based on the presence or absence of specific biomarkers. The health care system must also develop and implement health information systems that can capture, interpret, and share complex yet accurate patient data, including genomic information along with phenotypic and medical data.[100, 101, 102] All of this requires providers to adopt powerful health information technology (IT) platforms that enable instant 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.

Integrating these kinds of health IT platforms at the point of care represents an ongoing challenge, but government support as well as the widespread use of electronic health records (EHRs) and mobile technologies may someday contribute to a "learning health care system" that could accelerate progress dramatically.

Government Support

Government support for health IT is strong. The Health Information Technology for Economic and Clinical Health (HITECH) Act, included as part of the American Recovery and Reinvestment Act of 2009 (ARRA), formalized the Office of the National Coordinator for Health Information Technology and established a funding stream for infrastructure and incentive payments to providers 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 the EHRs in which molecular data are often stored.

Electronic Health Records

Now, with more than 80 percent of U.S. physicians using EHRs,[103, 104] the framework is in place (Figure 12) to leverage health IT investments to address ongoing concerns related to the clinical validity of endpoints, data interoperability, data sharing, and consent. Nonetheless, EHRs have remained essentially the same, and are ill-equipped to process complex genetic information. Although EHR technology itself is advancing, there are ongoing challenges related to its ability to deliver data-driven health care. To help EHR developers expand functionality, Health Level Seven (HL7), an organization committed to developing international standards, created the Fast Health Interoperability Resources (FHIR) program in 2014. FHIR is a set of clinical concepts and resources designed to help EHR developers manage clinical data with ease.

Widespread use of EHRs allows researchers, test developers, and regulators to analyze the data they hold for a better understanding of the scientific underpinnings and real-world applications of personalized medicine. EHRs can be used effectively in longitudinal cohort studies, where the availability of a sufficient amount of high-quality data can enable retrospective analysis and better use of tests and tools for identifying health trends and predicting disease.

Mobile Technologies

The ubiquity of mobile information devices such as smart phones as well as advances in sensing technologies and self-management platforms may also 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.[105] 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.[106]

FIGURE 12: TECHNOLOGICAL ADVANCES SINCE COMPLETION OF THE HUMAN GENOME PROJECT

	2003	2015
Genome Sequencing		
Cost to generate a human genome sequence (excluding cost of analysis)	$54 million[1]	$1,000[2]
Time to generate a human genome sequence	3–4 months[1]	1–2 days[1]
Number of human genomes sequenced annually	1[1]	228,000[3]
Human Genetics		
Number of genes with known phenotype/ disease-causing mutation	1,474[1]	2,937[4]
Genomic Medicine		
Drugs labeled with biomarker information	46[1]	132[5]
Genetic testing products on market	2–3 thousand (est.)[6]	65,839[7] (as of Sept. 2016)
Basic EHR use by office-based physicians	17%[8]	83%[9]

[1] National Human Genome Research Institute. *Quantitative Advances Since the Human Genome Project (HGP).* Accessed October 3, 2016 at https://www.genome.gov/images/illustrations/hgp_measures.pdf.

[2] Veritas Genetics. *myGenome.* Accessed October 4, 2016 at https://www.veritasgenetics.com/mygenome.

[3] According to Illumina President & CEO Francis de Souza. Source: Regalado, A. EmTech: Illumina says 228,000 human genomes will be sequenced this year. *MIT Technology Review.* September 24, 2014. Accessed October 4, 2016 at https://www.technologyreview.com/s/531091/emtech-illumina-says-228000-human-genomes-will-be-sequenced-this-year.

[4] Chong, JX, Buckingham, KJ, Jhangiani, SN, et al. The genetic basis of Mendelian phenotypes: Discoveries, challenges, and opportunities. *The American Journal of Human Genetics.* 2015;97(2):199-215.

[5] see Appendix.

[6] Gene Tests. *Disorders for Which Genetic Tests are Available and Laboratories Offering Tests 1993–2016.* Accessed October 11, 2016 at https://www.genetests.org.

[7] Data provided by: Concert Genetics. Available at concertgenetics.com.

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A 'Learning Health Care System'

EHRs and mobile technologies may someday enable a "learning health care system" that systematically captures, analyzes, and shares findings from every clinical interaction and research milestone into a continuous feedback loop. Linking clinical outcomes to new research on genetic and other molecular variation has two benefits: (1) physicians receive clinical decision support tools and (2) data on personalized diagnostics and treatments can support a rational basis for insurance coverage.

In addition to the adoption of health IT, a successful learning health care system requires active patient engagement, collaboration among providers and researchers within and across institutions, and policies that incentivize knowledge sharing. Leveraging health IT and fostering better collaboration among researchers, physicians, and patients will support the transition to a continuous learning health care system that aligns emerging science and data with clinical decisions.

"If we combine all these emerging technologies, if we focus them and make sure that the connections are made, then the possibility of discovering new cures, the possibility of applying medicines more efficiently and effectively so that the success rates are higher, so that there's less waste in the system … the possibilities are boundless."

— **former U.S. President Barack Obama**

THE FUTURE

"Personalized medicine stands right at the center of [the health care] revolution, with the science enabling greater precision that not only can improve the lives of patients, but can also create efficiencies within the health care system by delivering the right treatment to the right patient at the right time."

— **Stephen J. Ubl**
President and CEO, PhRMA

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 in the U.S. and elsewhere.

Technology continues to lead, with genomic sequencing and other molecular measurements likely to join other "democratized" technologies — a computer on every desk, a smart phone in every pocket, and someday a genomic sequence 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 guidelines for evaluating and approving personalized drugs and, significantly, the diagnostics that identify patients who can benefit from them. Translational research must identify the benefits of personalized medicine technologies. Payers must establish a path toward evaluating the clinical and economic utility of personalized medicine practices in order to facilitate their reimbursement. 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 data from everyday clinical encoun-

ters and helping physicians make decisions based on the vast amount of information linking genetic patterns to diseases and their 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.[107]

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 treatment or prevention to each and every patient.

"Personalized medicine is our chance to revolutionize health care, but it will require a team effort by innovators, entrepreneurs, regulators, payers, and policymakers."

— **Brook Byers**
Partner, Kleiner Perkins Caufield & Byers

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[12] Myriad. *Prolaris® Test Predicts Mortality Risk in Prostate Cancer Biopsy Study.* Accessed September 13, 2016 at http://investor.myriad.com/releasedetail.cfm?releaseid=848939.

[13] Agendia NV. *Coloprint® 18-Gene Colon Cancer Recurrence Assay.* Accessed September 13, 2016 at http://www.agendia.com/healthcare-professionals/colon-cancer/.

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APPENDIX

Selected Personalized Medicine Drugs and Relevant Biomarkers

as of September 2016

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Adjuvant Therapy			
1	Cevimeline (Evoxac®)	CYP2D6	Dry mouth
2	Rasburicase (Elitek®)	G6PD; CYB5R1-4	Hyperuricemia, hemolysis, and methemoglobinemia
3	Sodium phenylacetate and sodium benzoate (Ammonul®)	NAGS; CPS1; ASS1; OTC; ASL; ARG	Urea cycle disorders
4	Sodium phenylbutyrate (Buphenyl®)	CPS1; OTC; ASS1	Urea cycle disorders
Analgesia & Anesthesiology			
5	Celecoxib (Celebrex®)	CYP2C9	Pain
6	Codeine	CYP2D6; CYP3A4; UGT2B7	Pain
7	Mivacurium (Mivacron®)	Cholinesterase gene	Anesthesia adjunct
8	Tramadol (Ultram®)	CYP2D6	Pain
Cardiovascular			
9	Carvedilol (Coreg®)	CYP2D6	Cardiovascular disease
10	Clopidogrel (Plavix®)	CYP2C19	Antiplatelet response
11	Isosorbide and hydralazine (Bidil®)	NAT1; NAT2	Heart failure
12	Lomitapide	LDLR	Familial hypercholesterolemia
13	Metoprolol (Toprol-XL®)	CYP2D6	Cardiovascular disease
14	Mipomersen sodium (Kynamro®)	LDLR	Familial hypercholesterolemia
15	Pravastatin	LDR	High cholesterol
16	Propafenone (Rythmol SR®)	CYP2D6	Cardiac arrhythmia
17	Quinidine	CYP2D6	Cardiac arrhythmia, malaria
18	Simvastatin (Zocor®)	SLCO1B1	High cholesterol
19	Warfarin (Coumadin®)	CYP2C9; VKORC1; protein C or S deficiencies	Anti-blood clotting, stroke prevention
Endocrinology			
20	Glyburide	G6PD	Diabetes
21	Chlorpropamide	G6PD	Diabetes
22	Glimepiride	G6PD; CYP2C9	Diabetes
23	Glipizide	G6PD	Diabetes

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Gastroenterology			
24	Dexlansoprazole (Dexilant®)	CYP2C19	Heartburn, gastroesophageal reflux disease, and esophageal damage
25	Esomeprazole (Nexium®)	CYP2C19	Acid indigestion, peptic ulcer disease, and gastroesophageal reflux disease
26	Lansoprazole (Prevacid®)	CYP2C19	Peptic ulcer disease, gastroesophageal reflux disease
27	PEG-3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid (Moviprep®)	G6PD	Laxative
28	Rabeprazole (Aciphex®)	CYP2C19	Gastroesophageal reflux disease
Hematology			
29	Eltrombopag (Promacta®)	F5; SERPINC1	Thrombocytopenia, aplastic anemia
30	Methylene blue (Provayblue)	G6PD	Methemoglobinemia
Immunology			
31	Indacaterol (Arcapta®)	UGT1A1	COPD
Infectious Disease			
32	Abacavir (Ziagen®)	HLA-B*57:01	HIV
33	Atazanavir (Reyataz®)	UGT1A1	HIV
34	Boceprevir (Victrelis®)	IFNL3	Hepatitis C
35	Chloroquine (Aralen®)	G6PD	Malaria
36	Dapsone	G6PD	Leprosy
37	Isoniazid (Nydrazid®)	NAT1; NAT2	Tuberculosis
38	Mafenide (Sulfamylon®)	G6PD	Burns
39	Maraviroc (Selzentry®)	CCR5 receptor	HIV
40	Nitrofurantoin (Furadantin®)	G6PD	Urinary tract infections
41	Peginterferon alfa-2b (Pegasys®)	IL28B	Hepatitis B, hepatitis C
42	Primaquine	G6PD	Malaria
43	Pyrazinamide (Rifater®)	NAT1; NAT2	Tuberculosis
44	Quinine sulfate	G6PD; CYP2D6; CYP3A4	Malaria
45	Rifampin (Rifadin®)	NAT1; NAT2	Tuberculosis
46	Sulfamethox-azole and trimethoprim (Bactrim®)	G6PD	Bacterial infections
47	Telaprevir (Incivek®)	IFNL3	Hepatitis C
48	Voriconazole (Vfend®)	CYP2C19	Fungal infections

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Metabolic			
49	Allopurinol	HLA-B*58:01	High blood uric acid levels, gout
Neurology			
50	Carbamazepine (Tegretol®)	HLA-B*15:02; HLA-A*31:01	Epilepsy, bipolar disorder
51	Carisoprodol (Soma®)	CYP2C19	Musculoskeletal pain
52	Clobazam (Onfi®)	CYP2C19	Lennox-Gastaut syndrome
53	Dextrometorphan and quinidine (Nuedexta®)	CYP2D6	Pseudobulbar affect
54	Divalproex (Depakote®)	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Bipolar disorder (antiepileptic drug)
55	Phenytoin (Dilantin®)	HLA-B; CYP2C9	Prevention of seizures
56	Tetrabenazine (Xenazine®)	CYP2D6	Huntington's disease
57	Valproic acid (Depakene®)	OTC; POLG; NAGS; CPS1; ASS1; ASL; ABL2	Epilepsy
58	Vortioxetine (Trintellix™)	CYP2D6	Depression
Oncology			
59	Ado-trastuzumab emtansine (Kadcyla®)	ERBB2	Breast cancer
60	Afatinib (Gilotrif®)	EGFR	Metastatic non-small cell lung cancer
61	Anastrozole (Arimidex®)	ESR1; PGR	Breast cancer
62	Arsenic trioxide (Trisenox®)	PML-RARA	Acute promyelocytic leukemia
63	Busulfan (Busulfex® & Myleran®)	BCR-ABL1	Leukemia
64	Bosutinib (Bosulif®)	BCR-ABL1	Leukemia
65	Brentuximab vedotin (Adcetris™)	CD30	Hodgkin's lymphoma, anaplastic large cell lymphoma
66	Capecitabine (Xeloda®)	DPYD	Multiple cancers
67	Cetuximab (Erbitux®)	EGFR; KRAS	Colon cancer
68	Crizotinib (Xalkori®)	ALK	Lung cancer
69	Dabrafenib (Tafinlar®)	BRAF; G6PD	Melanoma
70	Dasatinib (Sprycel®)	BCR-ABL	Leukemia
71	Denileukin diftitox (Ontak®)	IL2RA	Lymphoma
72	Erlotinib (Tarceva®)	EGFR	Non-small cell lung cancer
73	Everolimus (Afinitor®)	ERBB2; ESR1	Breast cancer

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
74	Exemestane (Aromasin®)	ESR1; PGR	Breast cancer
75	5-Fluorouracil (5-FU) (Efudex®)	DPYD	Multiple cancers
76	Fulvestrant (Faslodex®)	ESR1; PGR	Breast cancer
77	Gefitinib (Iressa®)	EGFR	Non-small cell lung cancer
78	Imatinib (Gleevec®)	BCR-ABL; PDGFRB; KIT; FIP1L1-PDGFRA	Multiple cancers, myelodysplastic syndrome
79	Irinotecan (Camptosar®)	UGT1A1	Colon cancer, small cell lung cancer
80	Lapatinib (Tykerb®)	ERBB2; HLA-DQA1; HLA-DRB1	Breast cancer
81	Lenalidomide (Revlimid®)	Del (5q)	Multiple myeloma, mantle cell lymphoma, myelodysplastic syndrome
82	Letrozole (Femara®)	ESR1; PGR	Breast cancer
83	Mercaptopurine (Purinethol®)	TPMT	Acute lymphocytic leukemia, chronic myeloid leukemia, Crohn's disease, and ulcerative colitis
84	Nilotinib (Tasigna®)	UGT1A1; BCR-ABL1	Chronic myelogenous leukemia
85	Obinutuzumab (Gazyva®)	MS4A1	Chronic lymphocytic leukemia, follicular lymphoma
86	Omacetaxine mepesuccinate (Synribo®)	BCR-ABL1	Chronic myeloid leukemia
87	Panitumumab (Vectibix®)	EGFR; KRAS	Colon cancer
88	Pemetrexed (Alimta®)	TS	Lung cancer
89	Pertuzumab (Perjeta®)	ERBB2	Breast cancer
Platinum Therapies			
90	Carboplatin	ERCC1	Ovarian cancer
91	Cisplatin	TPMT	Multiple cancers
92	Oxaliplatin	ERCC1	Colorectal cancer
93	Nedaplatin	ERCC1	Multiple cancers
94	Triplatin tetranitrate	ERCC1	Multiple cancers
95	Satraplatin	ERCC1	Multiple cancers

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Oncology (cont.)			
96	Ponatinib (Iclusig®)	BCR-ABL1	Chronic lymphocytic leukemia, acute lymphocytic leukemia
97	Rituximab (Rituxan®)	MS4A1	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and autoimmune diseases
98	Tamoxifen (Nolvadex®)	ESR1; ESR2; PGR; F5; F2; CYP2D6	Breast cancer
99	Thioguanine (Tabloid®)	TPMT	Acute myeloid leukemia, acute lymphocytic leukemia, and chronic myeloid leukemia
100	Tositumomab (Bexxar®)	MS4A1	Non-Hodgkin's lymphoma
101	Trametinib (Mekinist®)	BRAF	Melanoma
102	Trastuzumab (Herceptin®)	ERBB2	Breast cancer
103	Tretinoin (Vesanoid®)	PML / RARα	Acute promyelocytic leukemia
104	Vemurafenib (Zelboraf™)	BRAF; NRAS	Melanoma
Psychiatry			
105	Aripiprazole (Abilify®)	CYP2D6	Schizophrenia, bipolar disorder
106	Amitriptyline (Elavil®)	CYP2D6; CYP2C19	Depression
107	Atomoxetine (Strattera®)	CYP2D6	ADHD
108	Citalopram (Celexa®)	CYP2C19	Depression
109	Clomipramine (Anafranil®)	CYP2D6	Depression
110	Clozapine (Clozaril®)	CYP2D6	Schizophrenia
111	Desipramine (Norpramin®)	CYP2D6	Depression
112	Doxepin (Silenor®)	CYP2D6; CYP2C19	Insomnia, depression
113	Fluoxetine (Prozac®)	CYP2D6	Depression
114	Fluvoxamine (Luvox CR®)	CYP2D6	Obsessive compulsive disorders
115	Iloperidone (Fanapt®)	CYP2D6	Schizophrenia
116	Imipramine (Tofranil-PM®)	CYP2D6; CYP2C19	Depression
117	Nortriptyline (Pamelor®)	CYP2D6	Depression
118	Paroxetine (Pexeva®)	CYP2D6	Major depressive disorder, obsessive compulsive disorder, panic disorder, and generalized anxiety disorder
119	Perphenazine (Trilafon®)	CYP2D6	Schizophrenia
120	Pimozide (Orap®)	CYP2D6	Tourette's syndrome

	Drug Name (Brand Name)	Biomarker(s)	Indication(s)
Psychiatry (cont.)			
121	Protriptyline (Vivactil®)	CYP2D6	Depression
122	Risperidone	CYP2D6	Schizophrenia, bipolar mania, irritability with autistic disorder
123	Thioridazine (Mellaril®)	CYP2D6	Schizophrenia
124	Trimipramine (Surmontil®)	CYP2D6; CYP2C19	Depression
Pulmonary			
125	Ivacaftor (Kalydeco®)	CFTR	Cystic fibrosis
Rheumatology			
126	Azathioprine (Imuran®)	TPMT	Rheumatoid arthritis, organ transplant
127	Flurbiprofen (Ansaid®)	CYP2C9	Arthritis
128	Pegloticase (Krystexxa®)	G6PD	Uric acid management, gout
Toxicology			
129	Sodium nitrite	G6PD	Cyanide poisoning
Transplantation			
130	Mycophenolic acid (Myfortic®)	HPRT1	Kidney transplant
131	Tacrolimus	CYP3A5	Organ transplant
Urology			
132	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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