PMC
PERSONALIZED MEDICINE COALITION

THE CASE FOR

PERSONALIZED MEDICINE

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INTRODUCTION

For more than two millennia, medicine has not wavered from its aspiration of being personalized. In ancient times, Hippocrates combined an assessment of the four humours—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. These include whether an individual is developing an illness now or will develop it many years in the future, will respond positively to treatment, or will suffer a serious reaction to a drug. But what is different about medicine today—and the reason the word "personalized" has been added for emphasis—is that technology has brought us much closer to exquisite precision in disease diagnosis and treatment.

In a time of unprecedented scientific breakthroughs and technological advancements, 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. In the 10 years since the completion of the Human Genome Project (HGP), advances in genome technology have led to an exponential decrease in sequencing costs (more than 16,000-fold). Patients have benefited from major biological insights and medical advances, including the development of more than 100 drugs whose labels now include pharmacogenomic information (Figure 1).[1]

> **"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

Patients with melanoma, leukemia, or metastatic lung, breast, or brain cancers are now routinely offered a "molecular diagnosis" in some clinical centers; this allows their physicians to select tailored treatments that can greatly improve the chances of survival. Melanoma can now be sub-classified by its genetics (e.g., *BRAF* positive), and non-small cell lung cancer can be *EGFR* positive or *ALK* positive. Treatments targeting *BRAF, ALK,* and other gene mutations represent a remarkable improvement over trial-and-error medicine, and we are not far from a time at which most cancer cases will be given a targeted course of treatment (Figure 2).[2]

The genotyping of drug-metabolizing enzymes has produced improved dosing of drugs for conditions as wide-ranging as depression and anxiety, coronary and peripheral artery disease, inflammatory bowel disease, and cancer. This has helped patients avoid harmful side effects, adverse drug interactions, or ineffective treatment. Thousands of patients have seen dramatic results since the mapping of the genome more than a decade ago, yet much remains to be done to realize the promise of personalized medicine.

Such rapid developments, coupled with the public's demand for better medicine and society's need to increase the value of our health care system, make it imperative for us to encourage the development and adoption of personalized medicine. It is essential to have appropriate coverage and payment policies, as these will encourage

continued investment in new molecular diagnostics. We need regulatory guidelines that adapt to and encourage the coupling of diagnostics and medicines that target genetically defined populations. And professional education must be modernized to prepare the next generation of doctors and other health care professionals for personalized medicine. Momentum is building, but much remains to be done to keep up with ever-evolving developments in science and technology.

FIGURE 1: QUANTITATIVE ADVANCES SINCE THE HUMAN GENOME PROJECT (HGP)

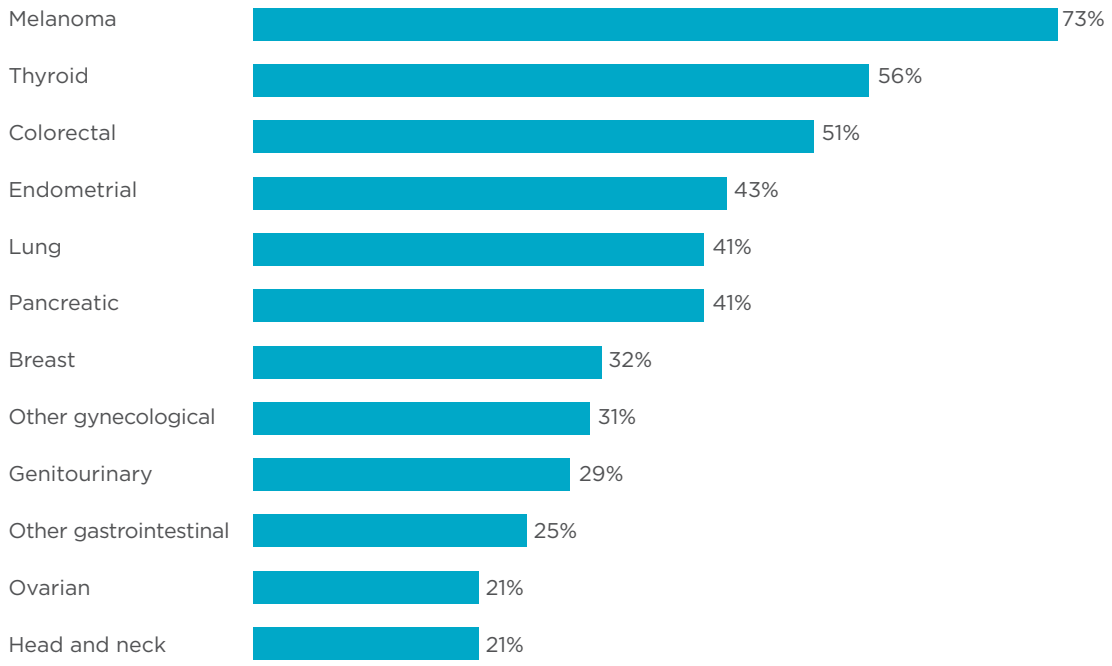
	HGP Begins	HGP Ends	10 years after HGP
Genome Sequencing			
Cost to Generate a Human Genome Sequence	$1 billion	$10-50 million	$3-5 thousand
Time to Generate a Human Genome Sequence	6-8 years	3-4 months	1-2 days
Human Genome Sequences	0	1	Thousands
Genome Sequence Data			
Total DNA Bases in GenBank	49 million	31 terabases	150 terabases
Whole-Genome Shotgun Bases in GenBank	0	9.6 terabases	391 terabases
Vertebrate Genome Sequences	0	3	112
Non-Vertabrate, Eukaryotic Genome Sequenes	0	14	455
Prokaryotic Genome Sequences	0	167	8760
Human Single-Nucleotide Polymorphisms	4.4 thousand	3.4 million	53.6 million
Human Genetics			
No. Genes with Known Phenotype/Disease-Causing Mutation	53	1474	2972
No. Phenotypes/Disorders with Known Molecular Bases	61	2264	4847
No. Published Genome-Wide Association Studies (GWAS)	0	0	1542
Replicated Disease-Associated Genetic Variants	0	6	2900
Genomic Medicine			
Drugs with Pharmacogenomics Information on Label	4	46	104

Since the beginning of the Human Genome Project, genomic data have steadily accumulated, laying the foundation for advances in human health.

Source: National Human Genome Institute.

FIGURE 2: FORGING A PATH TO PERSONALIZED CANCER CARE

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



Source: *Wall Street Journal* Copyright 2011 by DOW JONES & COMPANY, INC. Reproduced with permission of DOW JONES & COMPANY, INC.

GAINING MOMENTUM

In 1902, Sir Archibald Garrod made the first connection between genetic inheritance and susceptibility to a disease (called alkaptonuria).[3] About half a century later, in 1956, the first discovery of a genetic basis for selective toxicity was made (for the antimalarial drug primaquine).[4] In 1977, the discovery of cytochrome P450 metabolic enzymes and their role in chemically altering drugs so they can be eliminated from the bloodstream led to the realization that variation in these enzymes can have a significant influence on the effective dose of a drug. Yet, the real drive toward personalized medicine occurred in 2003 with the complete sequencing of the human genome. We are now moving beyond the genome into the entire spectrum of molecular medicine, including the proteome, metabolome, and epigenome.

The great opportunity for personalized medicine is its potential to introduce new scientific, business, and medical models. Segmenting populations into groups of patients who have a greater likelihood of responding to a particular treatment or avoiding side effects not only can change the dynamic of drug development but also the practice of medicine. Patients can benefit from better drugs, as well as new diagnostic and prognostic tools.

Shift the emphasis in medicine from reaction to prevention

Personalized medicine introduces the ability to use molecular markers that signal disease risk or presence before clinical signs and symptoms appear, and it offers the opportunity to focus on prevention and early intervention rather than on reaction at advanced stages of disease. In many areas, the clinical interventions can be life-saving.

For example, women with certain *BRCA1* or *BRCA2* gene variations have up to an 85 percent lifetime chance of developing breast cancer, compared with a 13 percent chance among the general female population.[5,6,7] These women also have up to a 60 percent chance of developing ovarian cancer, compared with a 1.7 percent chance among the general female population. The *BRCA1* and *BRCA2* genetic test can guide preventive measures, such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

PERSONALIZED MEDICINE CAN:

- Shift the emphasis in medicine from reaction to prevention
- Direct the selection of optimal therapy and reduce trial-and-error prescribing
- Help avoid adverse drug reactions
- Increase patient adherence to treatment
- Improve quality of life
- Reveal additional or alternative uses for medicines and drug candidates
- Help control the overall cost of health care

There are more than 15,000 tests for more than 2,800 genes.[8] These tests can identify inherited susceptibility to conditions ranging from hearing loss to sudden cardiac arrest.[9] A subset of these tests have a predictive capability, meaning the ability to spot the potential disease before symptoms appear. Although not every test is linked to a therapeutic option, a genetic diagnosis often permits targeted prevention or mitigation strategies; it also can help eliminate the need for further costly and/or

invasive diagnostic testing. A patient who learns he or she has inherited cardiomyopathy, for example, can benefit from suggested lifestyle changes and disease-monitoring options to avoid the risk of sudden death.[10]

Direct the selection of optimal therapy and reduce trial-and-error prescribing

Many patients do not benefit from the first drug they are offered in treatment. For example, 38 percent of depression patients, 50 percent of arthritis patients, 40 percent of asthma patients, and 43 percent of diabetic patients will not respond to initial treatment (Figure 3).[11] Studies have linked these differences in response to the differences in genes that code for drug-metabolizing enzymes, drug transporters, or drug targets.[12,13,14] The majority of patients, for example, have at least one DNA-based variation in the enzymes that metabolize half of the most commonly prescribed medicines. The use of genetic and other forms of molecular screening allows the physician to select an optimal therapy the first time, thus avoiding the frustrating and costly practice of trial-and-error prescribing.

> **"We used to think HIV costs would overwhelm us...but we figured it out and let drug development progress... similarly, cancer care will evolve."**
>
> **Ira Klein, M.D., M.B.A., FACP**
> Medical Director, Aetna

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 women with this form of the disease, an antibody drug called Herceptin® (trastuzumab) can reduce the recurrence of a tumor by 52 percent when used in combination with chemotherapy, in comparison to chemotherapy alone.[15,16] 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 Tykerb® (lapatinib).

Two complex diagnostic tests, Onco*type* DX® and MammaPrint,® for example, use genetic information to help physicians chart the best course of treatment for breast cancer patients. Onco*type* DX® can determine whether women with certain types of breast cancer are likely to benefit from chemotherapy.[17,18,19] MammaPrint® can detect which early-stage breast cancer patients are at risk of distant recurrence following surgery.[20] Both tests place patients into risk categories that inform physicians and patients of whether the cancer may be treated successfully with

hormone therapy alone, avoiding the expense and toxic effects of chemotherapy, or whether a more aggressive treatment is needed. OVA1,® another example of a new diagnostic that can inform the right treatment, is a five-protein test that can assess whether a woman's ovarian mass is malignant and requires surgery.[21,22]

A growing number of drugs are now available to treat colon cancer, and a genetic test can be used to evaluate which drugs may be the best (or worst) candidates. For example, approximately 40 percent of patients with metastatic colon cancer are unlikely to respond to Erbitux® (cetuximab) and Vectibix® (panitumumab) because their tumors have a mutated form of the *KRAS* gene.[23] Current practice guidelines recommend that only patients with the normal (wild-type) form of the *KRAS* gene should be treated with these drugs in conjunction with chemotherapy.[24]

> **"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.**
> President and Chief Executive Officer
> Eli Lilly and Company

Meanwhile, targeted therapies paired with genetic tests are giving fresh hope to late-stage cancer patients and their families. Approved in August 2011, Zelboraf® (vemurafenib) treats melanoma that cannot be surgically removed in patients who have the *BRAF V600E* gene mutation. Xalkori® (crizotinib), indicated for the treatment of non-small cell lung cancer, is only effective for patients who express the abnormal anaplastic lymphoma kinase (*ALK*) gene. Both *BRAF* and *ALK* mutations can be detected by commercially available tests, as well as by laboratory-developed tests. In April 2014, the FDA approved Zykadia® (ceritinib) for the treatment of patients with *ALK*+ metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib.

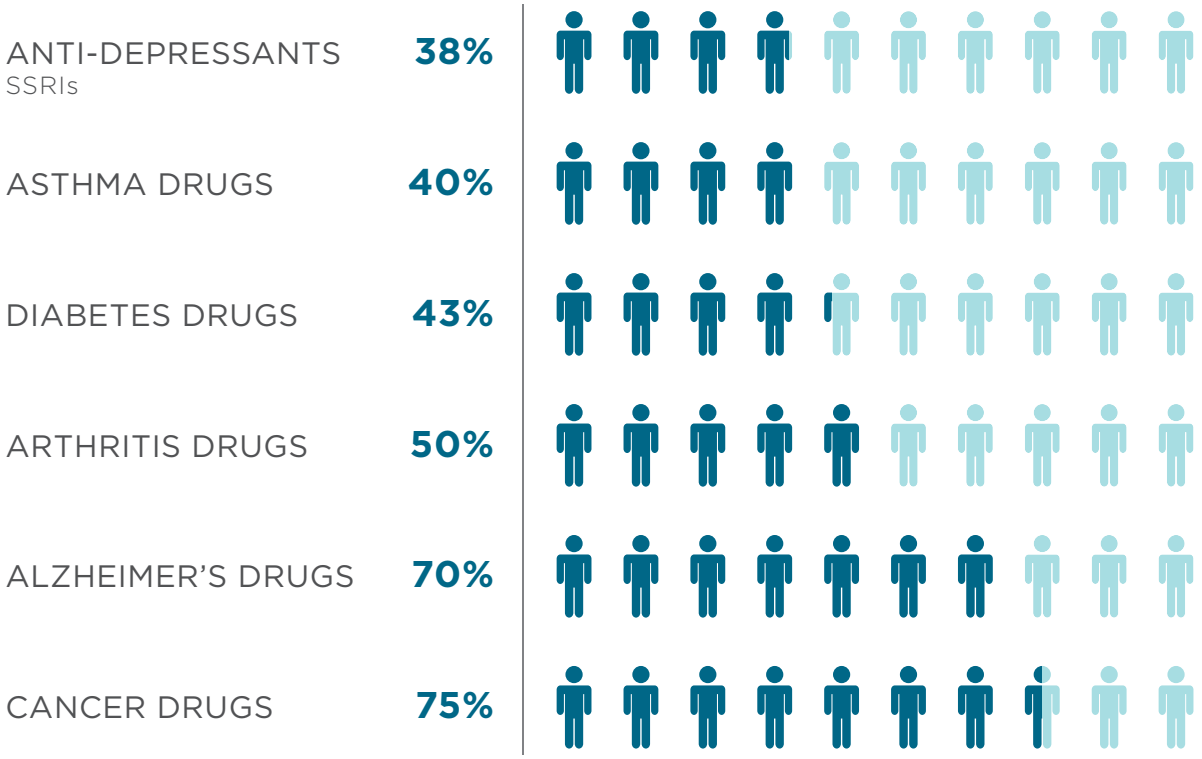
Interestingly, genome sequencing of tumors has identified the existence of identical mutations in different cancer types; the FDA has expanded the indication for these already-approved drugs. *BRAF V600* mutations are common in melanoma and also have been widely observed in other cancers,[25] especially hairy cell leukemia,[26] leading to the expanded use of and the production of more clinical studies supporting the use of vemurafenib as an effective treatment option for refractory hairy cell leukemia.[27] Similarly, early studies indicate that crizotinib, targeting *EML4-ALK*–positive, non–small cell lung cancers, is effective against other types of tumors containing *ALK* alterations, such as aggressive forms of pediatric neuroblastoma and anaplastic large cell lymphoma.[28,29] Genomic

analysis of tumors has led to an evolution in the way they are classified. With an increasing body of knowledge about the underlying genomic alterations, 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. Sequencing is illuminating the analysis of resistant tumors. For example, non-small cell lung cancer patients treated with crizotinib often relapse, leading researchers to develop the next generation of *ALK* inhibitors to overcome this resistance and use combinations of targeted therapies to fight it. [30]

FIGURE 3: ONE SIZE DOES NOT FIT ALL

Patients can respond differently to the same medicine.

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



Source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, pages 201-204.

Outside oncology, Plavix® (clopidogrel), a drug designed to prevent blood clots, presents another case for using genetic testing to select the best course of treatment. Plavix® can have a different impact on protecting stent patients from thrombosis depending on patients' genetic variance within *CYP2C19*, which encodes an enzyme that converts the drug from an inactive to an active state. About 25 to 30 percent of stent patients have a three-fold risk of stent thrombosis when using Plavix® in comparison to other patients.[31] An inexpensive genetic test can reveal the risk and allow physicians to craft an alternative course of treatment, such as the administration of the drug Effiant® (prasugrel), which helps prevent stroke or blood clots in patients who have undergone cardiac surgery, have had a heart attack, or have an implanted stent.

But Plavix® is just one example outside of oncology. Complex individualized diagnostic tests are being used in the field of transplantations and cardiovascular disease—AlloMap® is an 11-gene blood RNA signature for monitoring rejection after cardiac transplant,[32] and Corus CAD® is a 23-gene blood RNA signature used to screen for obstructive coronary artery disease.[33,34] And in 2014, a dental insurance company introduced risk-based dental preventive care that incorporates a reimbursed *IL-1* genetic test (PerioPredict®) plus two other risk factors to guide the frequency of care to prevent periodontitis, one of the most common chronic inflammatory diseases.

Many more treatments that use molecular markers to aid in clinical decision-making are in development. A 2010 survey conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) found that at least 50 percent of clinical trials are collecting DNA from study participants to aid in the discovery of drug-related safety and efficacy biomarkers, and 30 percent of the companies surveyed require all compounds in development to have a biomarker.[35]

Help avoid adverse drug reactions

The life sciences community strives to improve the safety and efficacy of its products, but much more work remains. Progress in developing and adopting diagnostics to identify which medicines work best for which patients, thus reducing adverse events, has been slow. In fact, between 2000 and 2011, the number of adverse events recorded by the FDA nearly tripled.[36]

According to several studies, about 5.3 percent of all hospital admissions are associated with adverse drug reactions (ADRs).[37] Many ADRs result from variations in genes that code for drug-metabolizing enzymes, such as cytochrome P450 (*CYP450*).[38,39] 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 "overdose toxicity;" others eliminate the drug too rapidly before it has had a chance to work. If these genetic variations are not considered when dosing, the consequences can range from unpleasant to fatal.

Panel-based tests that can detect dozens of variations in *CYP450* genes are available at several laboratories. These genes, linked to the metabolism of about 25 percent of all drugs prescribed, can improve care for large population segments.[40] Follow-on multiplex assays—tests that are especially useful for comprehensive polypharmacy management and prevalent in the elderly and seriously ill—also are available.

Administration of the drug warfarin, used to prevent blood clots, is complicated by genetic variations in a drug-metabolizing enzyme (*CYP2C9*) and an enzyme that activates vitamin K *(VKORC1*). Dosing is typically adjusted for the individual patient through multiple rounds of trial-and-error, during which the patient may be at risk of excessive bleeding or further blood clots. The 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 this helps patients avoid serious and possibly fatal adverse effects.[41,42]

> **"We are on the tipping point of a whole new game in how we develop drugs [for cancer]."**
>
> **Janet Woodcock, M.D.**
> Director, FDA Center for Drug Evaluation and Research

Infectious disease has seen advances in personalized treatments. About five to eight percent of HIV patients treated with Ziagen® (abacavir) can experience multi-organ system hypersensitivity to the drug, which in some cases can be fatal. This adverse reaction is strongly associated with the *HLA-B*5701* gene, easily identified through genetic testing. Nearly all patients receiving the drug are tested for the gene, significantly improving the safety of its administration. And in chronic hepatitis C infection, the *IL28B* genotype test for response to pegylated interferon/ribavirin therapy has seen widespread adoption.[43]

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 drugs Stocrin® and Sustiva® (efavirenz) can occur at standard dosing due to the presence of the *CYP2B6*6* allele. This results in slower metabolism of the drug and is found significantly more often in African- than in European-based populations.[44] Lowering the drug dose in individuals with this allele can help reduce adverse effects and increase treatment compliance.

Increase patient adherence to treatment

Patient non-compliance 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 treatments. The greatest impact could be for the treatment of chronic diseases, such as asthma and diabetes, in which non-compliance 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. 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.[45]

> **"As the field advances, we expect to see more efficient clinical trials based on a more thorough understanding of the genetic basis of disease. We also anticipate that some previously failed medications will be recognized as safe and effective and will be approved for subgroups of patients with specific genetic markers."[47]**
>
> **Margaret Hamburg, M.D.**
> Commissioner, U.S. Food and Drug Administration
>
> **Francis Collins, M.D., Ph.D.**
> Director, National Institutes of Health

Improve quality of life

A molecular diagnostic test that simply requires a blood sample can replace invasive and uncomfortable tissue biopsies. Allomap,® a multi-gene expression test, detects whether the immune system of heart transplant recipients is rejecting the new organ. Approximately 25 percent of heart transplant patients experience a rejection, which can prove fatal. To monitor for rejection, endomyocardial 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. A recent study suggests that outcomes may be equivalent for patients who are monitored for rejection using Allomap® and those who receive endomyocardial biopsies, which several major health insurance companies deem medically necessary.[46]

Reveal additional or alternative uses for medicines and drug candidates

A medicine that may show weaker efficacy in a more generalized patient population may show greater benefits when its use is limited to genetically defined patient populations. The lung cancer drug Iressa® (gefitinib) did not demonstrate a survival advantage in a general population of patients in clinical trials, and was withdrawn from the market after initially being granted accelerated approval. However, the sponsoring company has been using pharmacogenetics to demonstrate benefit in about 10 percent of patients who test positive for epidermal growth factor mutations, and it has won approval as a first-line treatment for that patient population in the United Kingdom.

> **"Health care today is in crisis as it is expensive, reactive, inefficient, and focused largely on one-size-fits-all treatments for events of late stage disease. An answer is personalized, predictive, preventive, and participatory medicine."**
>
> **Ralph Snyderman, M.D.**
> Chancellor Emeritus, Duke University

Help control the overall cost of health care

Personalized medical care has the potential to reduce health care costs worldwide, an effect particularly salient to the United States, where the cost of health care is on an unsustainable upward climb. Incorporating personalized medicine into the fabric of the health care system can help resolve many embedded inefficiencies, such as trial-and-error dosing, hospitalizations due to adverse drug reactions, late diagnoses, and reactive treatment. As such, it can also play an important role in the implementation of Accountable Care Organizations (ACOs) set up under the Affordable Care Act (ACA) to coordinate patient care and reduce costs. Research demonstrated that genetic testing to target dosing of the blood thinner drug warfarin resulted in 31 percent fewer hospitalizations overall for patients and up to 48 percent fewer hospitalizations for bleeding or thromboembolism.[48]

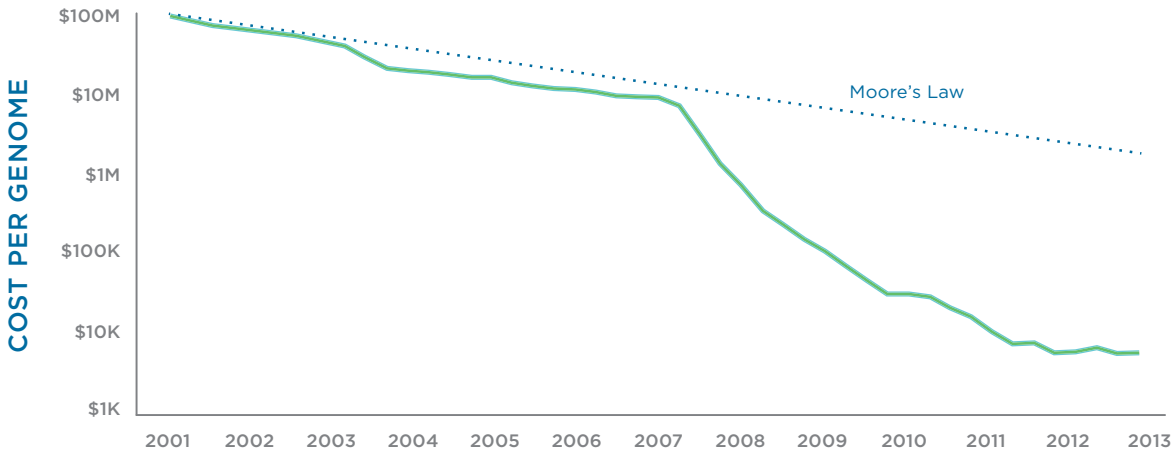
The Mayo Clinic and the pharmacy benefits manager Medco put the model to the test in a 3,600-subject prospective study. Hospitalization rates for heart patients were reduced by about 30 percent when genetic information was available to doctors prescribing the drug.[49]

An economic analysis of the Onco*type* Dx® test looked at the real costs of treating women with breast cancer in a health plan with two million members. If half of the 773 eligible patients received the test, then the savings in terms of adjuvant chemotherapy, supportive care, and management of adverse events would be about $1,930 per patient tested (based on a 34 percent reduction in chemotherapy use).[50] Another study found a $604 million annual savings among all patients when Vectibix® (panitumumab) or Erbitux® (cetuximab) were limited to patients with metastatic colorectal cancer and whose *KRAS* gene was not mutated.[51]

TECHNOLOGY

Technological developments have enabled advances in our understanding of human genetics and its influence on disease and treatment, but the technology that launched the biomedical revolution—genomic DNA sequencing—has accelerated so rapidly that it is once again poised to transform biomedical research and clinical care. The National Human Genome Research Institute (NHGRI), which has funded a number of projects aimed at developing technology to sequence an entire genome for less than $1,000, has tracked the performance for those projects over time. The results reflect a general trend in the industry and an important transition around mid-2007 brought on by next-generation sequencing technology (Figure 4).

FIGURE 4: THE RAPIDLY DECREASING COST OF SEQUENCING HUMAN GENOMES



Average cost of sequencing a genome for NHGRI-funded sequencing technology projects over time. This graph captures the dramatic decline in sequencing costs through April 2013, and the cost has continued to drop. http://www.genome.gov/sequencingcosts.

It took $1 billion and 13 years to sequence the first draft of the human genome. During that time, sequencing technology evolved from the manual Sanger method using radioactive labels to automated sequencing using color-coded fluorescent dyes. As a result, the cost of sequencing an entire genome declined at a rate that exceeds Moore's law—the rule that has reliably predicted the exponential increase in performance of computer technology for the past 40 years. Whole-genome sequencing costs fell from between $100-$300 million in 2001 to about $10 million in 2007. This price, however, confined such sequencing to the purview of well-funded labs or government initiatives.

In 2008, as second-generation DNA sequencing instruments were taken up broadly by the research market, the ability to sequence entire genomes accelerated at a rate far exceeding that ever experienced by the semiconductor and computer industries. By the following year, the cost and duration of sequencing an entire genome had decreased to $50,000 and two months;[52] in May 2011, Illumina announced that it had lowered the price for sequencing whole human genomes to $5,000 per genome;[53] and in January 2014, Illumina introduced a new machine that can sequence a human genome for $1,000.[54] It is important to recognize that additional costs and time are necessary for analysis and annotation in a clinical setting.

As the cost and duration of genomic sequencing continues on a sharp downward curve, many scientists believe, with the help of private and public investment, that the widely available $1,000 genome will arrive within a few years.[55] This price point is considered a critical benchmark because it is comparable to costs of existing medical tests and procedures, and could begin to attract a "consumer" market of patients (though the $1,000 price does not reflect the cost of interpreting genomic data).[56] Costs have already fallen to the point that full genomic sequencing has been employed in an increasing number of cases to resolve difficult diagnoses, with insurers determining that the approach was cost-effective enough to be reimbursed.[57,58]

Capturing individual genomes of entire populations will be a boon for research. When thousands and ultimately millions of genome sequences are made available securely to researchers, a tremendous gap in human genetic variation data will be filled. It is thought that many common human ailments, such as heart disease, diabetes, and cancer, are actually the result of 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. Personal genomes will provide a powerful tool to identify those rare genetic variants and a more accurate means to predict disease susceptibility and treatment response. These rare variants are, as National Institutes of Health (NIH) Director Francis Collins termed them, the "dark matter" of genetic patterns that remain undiscovered, even after extensive mapping by the SNP Consortium, the International HapMap Project, and numerous association studies involving the analysis of the entire genome.

As mass sequencing efforts continue, a third generation of sequencing technologies are preparing for their debut. These budding technologies include reading off base pairs of DNA strands as they thread through nanopores,[59] identifying nucleotides as they are synthesized onto templates attached to beads, using microfluidic glass wafers to drastically reduce reagent usage and cost, and using atomic force microscopy or electron microscopy to visually identify individual nucleotides along the length of DNA fragments.[60]

We are now celebrating the 61st anniversary of Watson and Crick's landmark discovery of the structure of DNA,[61] and it seems fitting that the FDA has granted marketing authorization for the first high-throughput (next-generation) genomic sequencer, Illumina's MiSeqDx. Illumina evaluated the performance of its instrument and reagent systems against a publically available quality-weighted human reference genome created through a collaboration between the FDA and the National Institute of Standards and Technology (NIST). Marketing authorization of a sequencing platform for clinical use, according to Francis Collins and Margaret Hamburg, anticipates the incorporation of genetic information into medical practice.[62]

But advances are not confined to the realm of sequencing technology. There is a growing understanding of genomic changes that can alter the chemistry and structure of DNA without altering its sequence, through modifications such as adding single-carbon methyl groups to the DNA chain. These "epigenetic" changes can occur in response to environments and lifestyles, and influence whether certain genes are turned "on" or "off." They represent an area of intense study and have already been linked to heart disease, diabetes, and cancer. The NIH Roadmap Epigenomics Program and the Epigenetics Consortium were set up to identify this supplemental "parts list" of the human genome.

In addition, efforts by the National Cancer Institute (NCI) to standardize existing proteomic technologies such as mass spectrometry are 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 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.

Proponents of personalized medicine envision a future in which all individuals will have their full genomic sequence linked to their medical record. The information from a personal genome, with an "overlay" of clinical interpretation, will allow physicians to develop a more holistic, proactive health care strategy based on the patient's susceptibility to different diseases and anticipated responses to different types of medicine.

At present, our ability to collect data outpaces the medical community's ability to understand and act on it. But, over time, as researchers identify additional genetic variations that correlate to disease and treatment response, and as they develop decision-support tools to aid health care professionals in identifying and managing those patients with specific genetic and other characteristics, health information technology (health IT) will transform the practice of medicine.

REGULATORY POLICY

Although the potential benefits of personalized health care are straightforward—knowing what works, understanding why it works, learning for whom it works, and applying that knowledge to address patient needs—the laws and regulations that govern personalized medicine products and services used in clinical practice are far more complex. These laws and regulations play a large role in determining the pace of personalized medicine's development and adoption. FDA policies pertaining to personalized medicine tests, pharmaceuticals, and companion diagnostics are of particular importance (Figure 5).

FIGURE 5: POLICY AND GUIDANCE DOCUMENTS FROM THE FDA

2005	Guidance on PG Data Submissions Concept Paper on Drug-Diagnostic Co-Development
2007	Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
2010	Guidance on Qualification Process for Drug Development Tools
2011	E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions
	Guidance on in vitro Companion Diagnostic Devices
2012	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Guidance on Clinical Trial Designs Employing Enrichment Designs
2013	Guidance on Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
In Process	Guidance on Drug-Diagnostic Co-development

Source: Policy and guidance documents from the FDA.[72]

Personalized Medicine Tests

The emergence of personalized medicine tests informing clinical decision-making, along with tests to guide drug selection and dose, has led the FDA to publish guidance documents on the regulation of these products. Traditionally, diagnostic tests have fallen into two main categories, which include diagnostic kits and laboratory-developed tests (LDTs). The former are products containing all the reagents and materials needed to run the test, and are regulated by the FDA as medical devices. Very few personalized medicine diagnostics fall under this category; most are considered LDTs. Although the FDA has long regulated in vitro diagnostic products (IVDs) as medical devices—and has taken the position that it has the authority to regulate LDTs—the agency has exercised what it describes as "enforcement discretion" and has not actively regulated LDTs. The agency stated its intention to apply risk-based oversight of LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act, although some question whether the FDA has jurisdiction and whether it is the appropriate regulatory authority to do so. The Centers for Medicare and Medicaid Services (CMS) also claim jurisdiction over LDTs. The laboratories that perform these tests are subject to the Clinical Laboratory Improvement Amendment (CLIA) rules, administered and implemented by CMS.

Clinical labs can obtain CLIA certification directly from CMS, typically through state agencies that survey labs for compliance with CLIA requirements. In addition,

certification can occur if a lab is accredited by one of the independent accreditation organizations approved by CMS. These include the College of American Pathologists (CAP) and COLA, among others. Before approving an independent accreditation organization, CMS must determine that the organization's standards are equal to or more stringent than those set forth in the CLIA regulations, though the standards may differ from CLIA by including additional requirements. For a more in-depth review of this topic, see PMC's white paper, *Personalized Medicine Regulation: Pathways for Oversight of Diagnostics*.[63]

Developments in personalized medicine, in particular the proliferation of complex new diagnostic tests and services linked to major health decisions and targeted directly to consumers, have prompted concerns in some sectors about their safety. The concept of test "safety" comes into play when one considers the consequences of misinterpretation. These consequences may include an ineffective therapy, an unnecessary preventive surgery, or any number of suboptimal, and sometimes irreversible, medical decisions. Some have argued that the FDA should assume a more active role in regulating certain molecular diagnostic tests used in the selection, dosing, or exclusion of treatments.

> **"It's an unprecedented time to make science count for patients."**
>
> **Kenneth C. Anderson, M.D.**
> Director, Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute; Kraft Family Professor of Medicine, Harvard Medical School

Although landmark FDA approvals have been conferred upon LDTs used in personalized medicine (e.g. Mammaprint® and AlloMap®), the vast majority of molecular tests have not been submitted for FDA approval. Due to the sheer volume of these tests and the long-term outcomes associated with many of them, the FDA has declared its intention to take a tiered approach to their regulation. Tests linked to riskier clinical decisions will be more rigorously studied and reviewed for clinical outcomes and safety, while CLIA certification might continue to suffice for laboratories performing other LDTs. In addition, the NIH has created the Genetic Testing Registry (GTR)[64] to provide some transparency for molecular tests offered by clinical laboratories. It provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. To date, the GTR contains more than 16,000 tests from nearly 400 labs.

Pharmaceuticals

The FDA's Voluntary Exploratory Data Submissions (VXDS) program, introduced in 2004 under a slightly different name (the Voluntary Genomic Data Submission program), continues to have a positive impact on drug and biologic development. While the clinical regulation of genetic testing is debated, this program enables companies and the FDA to work together to better understand pharmacogenomics before regulatory standards are issued. The informal communication that this program facilitates, as well as the agency's policy of supporting adaptive clinical trials that can genetically "enrich" a study population, helps companies integrate genomics into their product development.[65] As a result, most development projects are supported by data on the effects of genetic variation or other biomarkers regarding the safety and efficacy of the treatment. The molecular information has found its way onto about 10 percent of product labels that inform or recommend molecular or genetic testing for optimal treatment.[66] At least 13 of those labels *require* the use of a genetic or protein marker-based diagnostic test to guide appropriate selection and dosing of the drug (Table 1).[67,68]

> **"The concept of personalized medicine is not new. The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions. What is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects."**
>
> **Margaret A. Hamburg, M.D.**
> Commissioner of Food and Drugs
> *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*

Companion Diagnostics

According to the 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."[69] The need for a clear regulatory path for companion diagnostics has been a great concern since the first therapeutic product with an accompanying diagnostic (Herceptin®) was approved six months apart from the diagnostic test (HercepTest™) in 1998. Although no definitive guidelines have been published, regulatory agencies, including the FDA and the European Medicines Agency (EMA), have indicated that they intend to clarify the regulatory path by which companion diagnostics enter the market. In 2011, the FDA released its

Draft Guidance for In Vitro Companion Diagnostic Devices, which helped clarify its intention to conduct simultaneous reviews of a drug and its companion diagnostic.[70] The guidance suggests conditions under which a targeted drug might be approved ahead of a corresponding diagnostic test. While these guidelines were in development, the FDA, Health Canada, and the EMA 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, the FDA has begun publishing a table of genomic biomarkers that it considers valid in guiding the clinical use of approved drugs.[71]

There remain many logistical difficulties in the coordinated development of drugs and diagnostic tests, and a defined path for the regulatory approval of such product combinations would be a significant step forward. The FDA's renewed focus on personalized medicine has been signaled by the creation of a Director for Personalized Medicine in the Office of In Vitro Diagnostics and Radiological Health and the release of its new report, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, which describes many of the developments and impending advances in personalized medicine.[72]

COVERAGE AND PAYMENT POLICY

Regulatory approval of personalized medicine products and services is only part of the story. Coverage and payment policies—whether in government programs like Medicare or those of private payers—play an equally important role.

Payers recognize the benefits of personalized medicine products in patient care management, but they increasingly seek additional evidence of their clinical, if not economic, value. In addition, both private payers and the CMS are expanding new models for health care payment and delivery that could have a significant impact on the ability of patients to gain access to personalized medicine products and services. Understanding the changes and potential consequences these policies will have on personalized medicine tests, pharmaceuticals, and companion diagnostics is essential to ensure continued progress in the field and improvements to patient care.

Key Coverage and Payment Policy Challenges

Emerging personalized medicine products and services often cause disruptive changes in health care. As a result, they require extra efforts to overcome payment policies grounded in traditional approaches to coverage and reimbursement. Challenges include cuts to Medicare payment for diagnostic tests, proposed cuts to Medicare reimbursement for tailored therapies, proposals for coverage and payment policy based on one-size-fits-all assessments, and expensive cost-sharing for tailored therapies and diagnostics that guide treatment decisions.

CMS and private payers are proposing new payment models that seek to drive improvements in care quality and efficiency, partially reacting to increasing demands to drive down health care costs. If properly implemented, these alternative payment models (APMs) can support the emergence of personalized medicine concepts and products; improperly constructed, they will create significant new barriers to its development and adoption.

Adequate Reimbursement for Personalized Medicine Diagnostics and Tailored Therapy

Under pressure to address rising health care costs, policymakers and payers are increasingly pursuing policies that may result in across-the-board coverage and payment cuts, inadvertently discouraging continued developments in personalized medicine. Leaders in the cancer community, including PMC, 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 and regulators 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."[73]

Recent changes to payment and reimbursement policies for diagnostic tests demonstrate how poorly conceived policies can have a negative impact on personalized 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, payment and reimbursement policy changes have led to significant disruptions for laboratories and developers of personalized medicine products. CMS' decision, for example, to use "gapfill" methodology, which allowed regional contractors to set prices for laboratory and molecular diagnostic tests, coupled with other payment decisions, unfortunately caused a near complete cessation of federal payments for genomic tests in 2013.[74]

Medicare also lowered its effective payments for many traditional genetic tests between 2012 and 2013. Although lower prices can reflect more efficient and more widely dispersed technologies, reimbursement levels must also ensure access to high-quality diagnostics as well as encourage investment in the development of a pipeline of innovative tests. On the horizon, CMS will face even larger policy decisions with implications for the future of medicine.

Payment and Delivery System Reform

Traditionally, Medicare and private payers have paid for items and services on a fee-for-service basis, in which doctors, hospitals, and other health care providers are paid for each unit of service provided. APMs are intended to pay providers for the value of the care that they provide, rather than the volume of services delivered. If implemented appropriately, APMs, such as medical homes, ACOs, and pathway- or episode-based payments, improve health care by encouraging the adoption of personalized medicine, but only if they are designed in ways that support continued advancements in and adoption of personalized medicine products and services (as noted above). APMs should encourage physicians to tailor care based on an individual's genetics and other factors, and support the adoption of novel targeted therapies. Accordingly, these models would include sufficient incentives to augment clinical care quality and not focus exclusively on cost control, ensure that patients have access to and are aware of all their diagnostic and treatment options, and encourage innovation that improves patient outcomes and quality of life. As APMs continue to be adopted, they should be aligned with the principles of personalized medicine and biomedical innovation so that, again, both patients and the health system benefit.

Tailoring Policy to Patients

Proposals that create barriers to patient access to personalized medicine concepts and products often overlook significant differences in patient needs. Many patients do not fit models based on broad, average results but can benefit from selected treatments, which is the core tenet of personalized medicine. To justify coverage of advanced diagnostics and tailored therapies, it has been suggested that, unfortunately, those products and services should be subjected to a more rigorous assessment of risk-benefit and analysis of impact on health outcomes than is currently used.[75]

Diagnostic tests increasingly demonstrate that medicines that appear similar on average can have important clinical differences for individual patients. Policies that rely on broad judgments about clinical similarity often ignore these individual differences. Unfortunately, proposals that seek to contain costs by promoting the least expensive treatment on average, rather than the best care for the individual, will discourage the development and adoption of molecular diagnostic tests and targeted therapies, which can have a higher up-front cost but will offer substantial clinical and economic benefits over the long-term.

Conclusion

Personalized medicine offers significant short- and long-term benefits, especially for chronic and complex diseases. Payment and reimbursement policies should not discourage interventions that may raise short-term costs but improve clinical/cost value over time. Policies that recognize the principles of personalized medicine will allow physicians to individualize treatment plans for patients through the early diagnosis of disease, target treatments to optimize clinical outcomes, and prevent unnecessary hospitalizations and care, thus reducing long-term costs.

Innovators are responsible for developing the collective evidence to justify the contention that personalized medicine can improve outcomes while controlling costs. Except in the case of some individual products, to date they have not proven that contention. When they do, our argument will be more compelling.

HEALTH INFORMATION TECHNOLOGY

In 1990, the HGP took its first steps toward a future that included a sequenced genome for every person. The first working draft of a human genome was completed in 2001, at a cost of about $1 billion. With the astounding rate of technological advances in sequencing (Figure 4, p. 18), a genome can now be completed for less than $5,000 in about a day. But massive sequencing capacity is only the first stage in achieving better human health by tailoring treatment to an individual's genomic characteristics. The next critical stage is to develop and implement health information systems that can capture, help interpret, and share complex yet accurate patient data, including genomic information along with phenotypic and medical data.[76,77,78]

Health IT powers personalized medicine, but personalized medicine cannot reach its full potential or become widely adopted until nearly every hospital, clinic, and physician's office incorporates health IT into its organization and practice. The ongoing challenges include creating an instant connection between real-world clinical results and molecular data to establish and refine correlations in real-time so that health care providers can make clinical decisions based on a body of scientific knowledge that is beyond the training, experience, or memory of any single practitioner.

Government support for health IT remains strong. The Obama administration made implementation of health IT a top priority by including $44 billion of funding in The Health Information Technology for Economic and Clinical Health (HITECH) Act. Included as part of the American Recovery and Reinvestment Act of 2009 (ARRA), HITECH 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 at an as-yet minimally defined standard of implementation termed "meaningful use." Moreover, after 2015, hospitals and physicians face penalties for *not* using health IT, such as electronic health records (EHRs) that include molecular information, in a meaningful way. The passage of the ACA in 2010 accelerated the need for change with unprecedented incentives and penalties that encourage hospitals to implement, utilize, and demonstrate "meaningful use" of EHRs.

> **"You have to create a system where you have the patients' permission to follow them throughout their lifetimes so that you can define the population 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

With more than 90 percent of U.S. physicians using EHRs,[79,80] the framework is in place to leverage health IT investments and address ongoing concerns such as interoperability, data sharing, and complex consent. Widespread use of EHRs creates the potential for the millions of files of data they hold to be analyzed by researchers, test developers, and regulators to better develop, refine, and understand the underpinnings and real-world applications of personalized medicine. EHR data can effectively be used 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. Critical therefore, is a robust, transparent framework of informed consent that both allows patients to understand how their

data may be used and enables researchers to respect the limits of data use. In December 2013, the U.S. Department of Health & Human Services (HHS) launched a new "meaningful consent" website[81] aimed at aiding providers in their efforts to engage patients in determining the best way to share their electronic information. The site provides strategies and tools for providers, as well as background information on laws, policies, and regulations.

Although many hurdles to implementing an interoperable, nationwide system of EHRs remain, much progress has been made. The commitment from the federal government to complete the transition to EHRs as an essential part of health care reform, coupled with the explosive development of tools and technologies to collect, analyze, and use health data, continue to transform the way research is conducted and health care is delivered. While the driving force may be to use health IT to reduce medical errors and costs, the more substantive and long-term value will be its use as a central component of personalized medicine. EHRs, mobile technologies, and data interoperability are just some of the health IT elements that can enable a "learning health care system" that systematically captures and disseminates 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: physicians receive clinical decision support tools and 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 and leads to better health outcomes.

LEGISLATION

As the role of genetics in medicine has become more prominent, genetic privacy has come into sharper focus. The knowledge of a person's susceptibility to disease, even before he or she shows signs or symptoms, can be a powerful tool in improving health and quality of life—but it can also be a means to discriminate in the workplace. The information could be used to limit access to insurance and other resources. To the extent that laws can confine genetic and other predictive medical information to decisions benefiting patients and their medical care, those laws will enable rather than inhibit the adoption of personalized medicine. Four laws are of particular importance in this area.

The Health Insurance Portability and Accountability Act

Although there existed at the time only a patchwork of protections against genetic discrimination, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 attempted to limit misuse of medical and genetic information by controlling access to it. However, the rules only applied to federally funded institutions, and gaps remained in privacy protections with respect to employers and insurance providers.

The Genetic Information Nondiscrimination Act

In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law, and it explicitly prohibited employers and health insurers from discriminating against individuals on the basis of their genetic risk factors. This federal law has established a foundation for genetic privacy and non-discrimination that is building confidence among the public that genetic information will not be used against them. This confidence has opened the door to greater participation in research, as well as the acceptance of genetic information as part of medical records. In November 2010, the Equal Employment Opportunity Commission (EEOC) stepped in to provide greater clarification of its interpretation of GINA, generally strengthening its provisions (although some employers, such as the military, are exempt).

> **"Personalized medicine will allow this country to attack health care in a way that will provide for prevention and therefore ultimately address cost effectiveness."**
>
> **Sue Siegel**
> CEO, GE Ventures & healthymagination

GINA sets a minimum standard of protection that must be met in all states, and it does not weaken the protections provided by any state law. Recognizing that the law does not protect against genetic discrimination outside employment and health insurance, several states have sought to improve protections against genetic discrimination in other areas. In September 2011, for example, California Gov. Jerry Brown signed the California Genetic Information Nondiscrimination Act, which protects citizens against genetic-based discrimination in housing, employment, education, public accommodations, health insurance, life insurance, mortgage lending, and elections.[82] Similar legislation has been introduced in Massachusetts and Vermont. The growing prevalence of genetic and genomic data in the medical

record is likely to prompt more states to follow suit in closing these gaps. GINA provided important protections, but they need to be maintained and strengthened as large-scale genomic sequencing becomes more common.

The Affordable Care Act

The ACA of 2010[83] establishes guaranteed issue, meaning that issuers offering insurance in either the group or individual market must provide coverage for all individuals who request it. The law prohibits issuers of health insurance from discriminating against patients with genetic diseases by refusing coverage because of "pre-existing conditions." ACA offers additional protections for patients with genetic diseases by establishing that certain health insurance issuers may only vary premiums based on a few specified factors, such as age or geographic area, thereby prohibiting the adjustment of premiums because of medical conditions.[84]

The Americans with Disabilities Act

The Americans with Disabilities Act (ADA)[85] prohibits discrimination in employment, public services, accommodations, and communications based on a disability. In 1995, the EEOC issued an interpretation suggesting that discrimination based on genetic information relating to illness, disease, or other disorders is prohibited by the ADA.

Although laws on genetic privacy are evolving to meet the needs of patients, current laws can make it harder to collect and analyze aggregated clinical data for the development of new personalized treatments and diagnostics. The expectation to protect privacy and the need to encourage research must be properly balanced so that medical care can continue to improve.

MEDICAL AND ALLIED HEALTH EDUCATION

Personalized medicine is an exciting and powerful field, offering new tools to deliver better care to patients. But part of the challenge with any medical advance is the need to encourage doctors to adopt it in their practice in order to get it to patients.

Physicians and health care providers have a number of challenges: to administer and advise on the application of growing numbers of molecular and genetic tests and pharmacogenomic drugs; make treatment decisions based on more predictive evidence and estimations of risk; use information systems for managing patient care; and deal with new ethical and legal issues that have arisen from molecular and genetic testing. The adoption of personalized medicine technology and approaches depends heavily on the degree to which the provider community is educated in the field and is prepared to engage in medical practice focused on risk assessment and predictive/prognostic modeling.

Studies have documented the deficit in genetics education for the health care profession and the barriers it presents to the full integration of genetics into medical practice.[86] Reasons for the continuing genetics deficit in medical education programs include crowded curricula that leave little room for the introduction of new topics, prevalent misconceptions of genetics as being relevant mostly to rare Mendelian-inherited disorders rather than to common chronic diseases, medical school faculty who are not trained or prepared to teach the topic, and little or no representation of genomic issues on medical certification exams. Even when genetics instruction is integrated into basic science curricula, it is usually left out of clinical training.

Moving genomics training from the classroom to the clinic will be an essential feature of a new approach to medical education. Although the current state of medical education is far from adequate in preparing the next generation of physicians, nurses, pharmacists, and other health care workers for the coming wave of genomic medicine, several programs have emerged as role models for medical education in the future.

> **"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 roadmap of prevention."**
>
> **Charis Eng, M.D., Ph.D.**
> Founding Chair of Cleveland Clinic's Genomic Medicine Institute and Director of its clinical arm, the Center for Personalized Genetic Healthcare

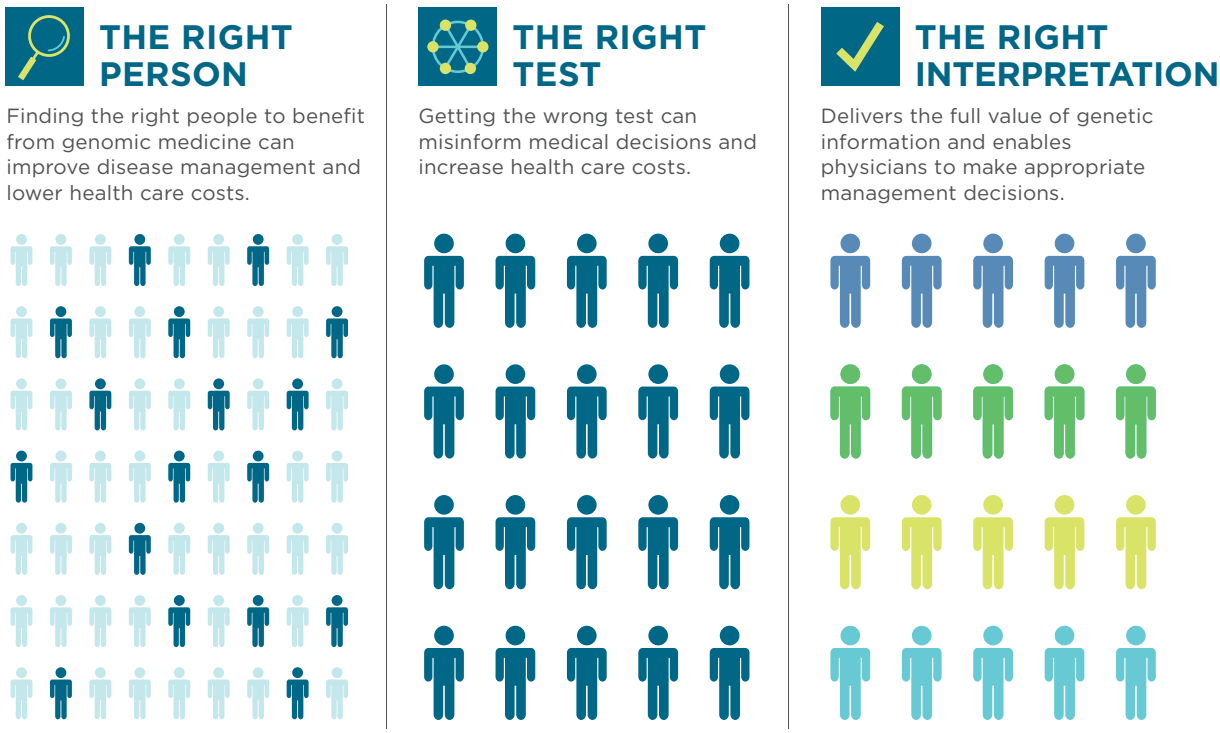
Harvard Medical School has one of the longest-standing student programs, in which a two- to three-year course of training with 12-month clinical rotations is offered at Brigham and Women's Hospital, Children's Hospital of Boston, and Massachusetts General Hospital. Brigham and Women's Hospital offers a five-year clinical genetics training program that explores the diagnosis and management of monogenic and genomic diseases, providing clinical laboratory rotations and specialty clinics in cardiovascular, cancer, renal, pulmonary, and endocrine genetics. A number of other leading medical education institutions, including Duke University School of Medicine, Ohio State University, Vanderbilt University, and Stanford University, have made significant commitments to combine classroom and clinical training in genomic approaches for internal and pediatric medicine.

But medical training doesn't stop after medical school. In recognition of this reality, The Genomic Medicine Institute at Cleveland Clinic hosts CME-accredited genetics education symposia for practicing health care providers. Physician education

is also one of four core initiatives of the El Camino Hospital Genomic Medicine Institute,[87] which provides El Camino's medical staff with information and resources about clinically useful genomic tests, including access to genetic counselors for consultation. The Mayo Clinic's Center for Individualized Medicine educates members of the health care team and patients about personalized or genomics medicine and its implications in practice through professional development courses, conferences, and ongoing education that is integrated into practice.[88]

Allied health care specialists, including nurses, genetic counselors, and pharmacists, continue to play a more prominent role in providing care and advice to patients and will also require better genomic education in their training curricula. Genomic education has been formalized in nursing through the Genetic Nursing Credentialing Commission (GNCC). In addition, NHGRI and NCI collaborated on a series of genetic/genomic articles for nursing educators.[89] The vast majority of colleges have formalized genomic and pharmacogenomic education,[90] and the Accreditation Council for Pharmacy Education has included genomic and pharmacogenomic education as a required component of all colleges of pharmacy curricula.

FIGURE 6: THE RIGHT TEST FOR THE RIGHT PERSON, WITH THE RIGHT INTERPRETATION



Source: DNA Direct®.

CONCLUSION

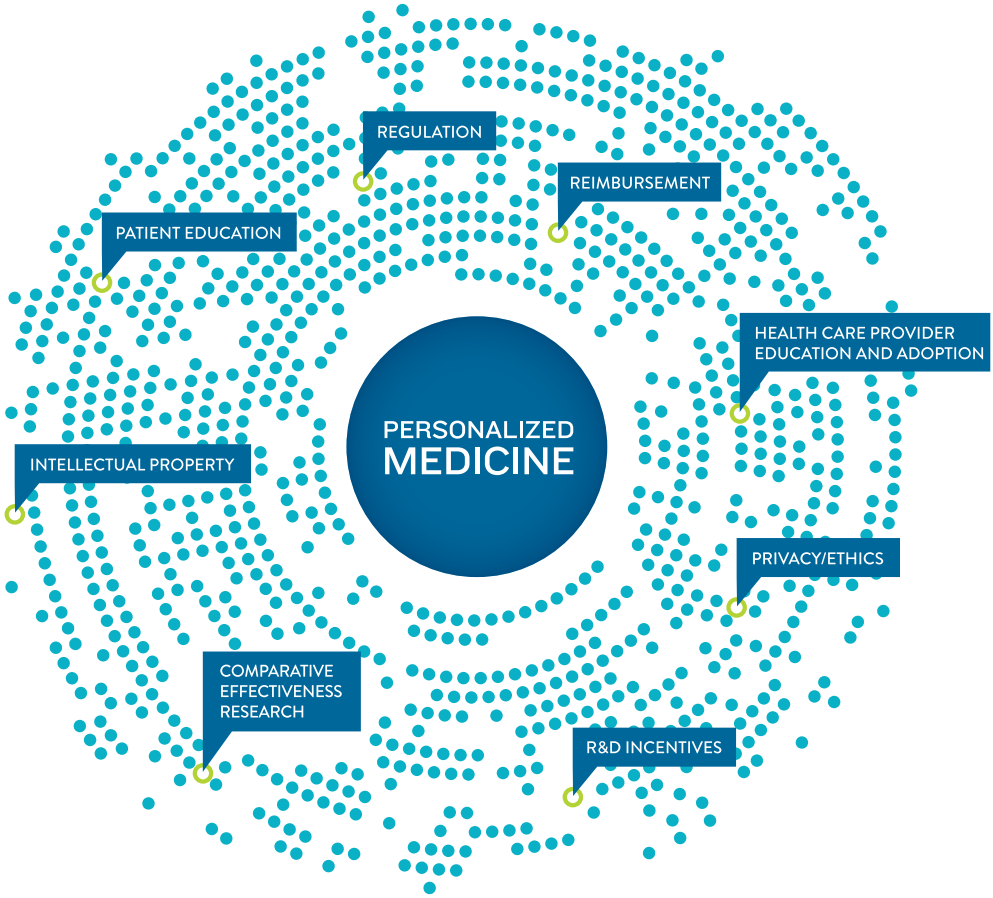
The long arc of medical history has been one in which diagnostic capability has evolved from the metaphysical to the anatomical to the cellular and ultimately to the molecular level. Now that diseases can be sub-classified into categories that presage the course of disease and its likely response to treatment—using evidence well beyond what is visibly obvious—there is an obligation to act on that information.

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

To keep up with the technology, serious effort will be required from every corner of the health care spectrum (Figure 7). Regulatory authorities must establish a clear set of guidelines for evaluating and approving personalized drugs and the diagnostics that identify patients who can benefit from them. Translational research

FIGURE 7: ISSUES WITH AN IMPACT ON PERSONALIZED MEDICINE

The implementation of personalized medicine requires a confluence of multiple factors. Full implementation of personalized medicine can only be achieved when all sectors converge toward the center.



must identify the benefits of personalized medicine technologies. Medicare and private insurers must establish a path toward evaluating the clinical and economic utility of personalized medicine practices in order to facilitate their reimbursement. Educational institutions must prepare the next generation of physicians for the inevitable arrival of personalized medicine, and hospitals and physician practices must adopt EHRs. 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 encounters and helping physicians make decisions based on the vast amount of information linking genetic patterns to diseases and their treatment.

We have much more to learn about the benefits of personalized medicine, but it represents a great opportunity for our generation. To make this a reality is going to require 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.[91]

> **"We face significant challenges in accelerating growth in this field—scientific, business, regulatory and policy challenges. Together we must break down the barriers and move personalized medicine forward."**
>
> **John Castellani**
> President and Chief Executive Officer,
> Pharmaceutical Research and Manufacturers of America (PhRMA)

Hippocrates warned us more than 2,400 years ago that while "the arc is long, life is short, opportunity is fleeting, experiment is fallible, and judgment is difficult." 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 seize the opportunity from the new developments in science and technology and realize the full health and economic benefits of matching the right treatment or prevention to each and every patient.

TABLE 1: SELECTED PERSONALIZED MEDICINE DRUGS AND RELEVANT GENES AS OF MAY 2014

Drug name (Brand name)	Biomarker	Indication
Adjuvant therapy		
Cevimeline (Evoxac®)	*CYP2D6*	**Dry mouth:** Cevimeline should be used with caution in individuals known or suspected to be deficient in *CYP2D6* activity, based on previous experience, as they may be at a higher risk of adverse events.
Rasburicase (Elitek®)	*G6PD*	**Hyperuricemia:** Rasburicase administered to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. Do not administer *the drug* to patients with *G6PD* deficiency. Screen patients at higher risk for *G6PD* deficiency (*e.g.*, patients of African or Mediterranean ancestry) prior to using the drug.
Sodium phenylacetate & sodium benzoate (Ammonul®)	NAGS; CPS; ASS; OTC; ASL; ARG	**Urea cycle disorders:** Urea cycle disorders can result from decreased activity of any of the following enzymes: N-acetylglutamate synthetase (NAGS), carbamyl phosphate synthetase (CPS), argininosuccinate synthetase (ASS), ornithine transcarbamylase (OTC), argininosuccinate lyase (ASL), or arginase (ARG).Sodium phenylacetate and sodium benzoate are metabolically active compounds that can serve as alternatives to urea for the excretion of waste nitrogen.
Sodium phenylbutyrate (Buphenyl®)	CPS; OTC; ASS	**Urea cycle disorders:** Indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS).
Analgesia & Anesthesiology		
Celecoxib (Celebrex®)	*CYP2C9*	**Pain:** Patients who are known or suspected to be *CYP2C9* poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.
Codeine	*CYP2D6*	**Pain:** Some individuals may be ultra-rapid metabolizers because of a specific *CYP2D6* genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Some individuals may be poor metabolizers because of a specific genotype. These individuals do not convert codeine to morphine sufficiently and may have no pain relief.
Mivacurium (Mivacron®)	Cholinesterase gene	**Anesthesia adjunct:** Is metabolized by plasma cholinesterase and should be used with great caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.
Tramadol (Ultram®)	*CYP2D6*	**Pain:** Based on a population pharmacokinetic analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.
Cardiovascular (CV)		
Carvedilol (Coreg®)	*CYP2D6*	Retrospective analysis of side effects in clinical trials showed that poor *CYP2D6* metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the Ð-blocking R(+)-enantiomer.

Drug name (Brand name)	Biomarker	Indication
Clopidogrel (Plavix®)	*CYP2C19*	*CYP2C19* poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with the drug at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function.
Isosorbide and hydralazine (Bidil®)	*NAT1, NAT2*	In patients with heart failure, mean absolute bioavailability of a single dose of hydralazine 75mg varies from 10 to 26%, with higher percentages in slow acetylators. About 50% of patients are fast acetylators and have lower exposure.
Metoprolol (Toprol-XL®)	*CYP2D6*	Metoprolol is metabolized predominantly by *CYP2D6*, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. *CYP2D6* can be inhibited by a number of drugs. Poor metabolizers as well as extensive metabolizers who concomitantly use *CYP2D6* inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.
Mipomersen sodium (Kynamro®)	ApoB (Apolipoprotein B)	Indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), ApoB, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).
Propafenone (Rythmol SR®)	*CYP2D6*	The combination of *CYP3A4* inhibition and either *CYP2D6* deficiency or *CYP2D6* inhibition with the simultaneous administration of propafenone may significantly increase the concentration of propafenone and thereby increase the risk of pro-arrhythmia and other adverse events.
Warfarin (Coumadin®) *cf. Table 2*	*CYP2C9*	Patients with one or more variant *CYP2C9* alleles have decreased S-warfarin clearance. The frequencies of these alleles in Caucasians are approximately 11% and 7% for *CYP2C9*2* and *CYP2C9*3*, respectively.
	VKORC1	Certain single nucleotide polymorphisms in the *VKORC1* gene (e.g., –1639G>A) have been associated with variable warfarin dose requirements.
	Protein C or S deficiencies	Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration.
Dermatology		
5-Fluorouracil (5-FU) (CaracTM cream)	*DPD*	**Contraindication:** 5-FU should not be used in patients with dihydro-pyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of the drug is catabolized by DPD. DPD enzyme deficiency can result in shunting of 5-FU to the anabolic pathway leading to cytotoxic activity and potential toxicities.
Gastroenterology		
Dexlansoprazole (Dexilant®)	*CYP2C19*	**GERD:** Systemic exposure of deslansoprazole is generally higher in intermediate and poor metabolizers.
Esomeprazole (Nexium®)	*CYP2C19*	**GERD:** *CYP2C19* isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack *CYP2C19* and are termed poor metabolizers. At steady state, the ratio of area under the curve (AUC) in poor metabolizers to AUC in the rest of the population (extensive metabolizers) is approximately 2.
Rabeprazole (Aciphex®)	*CYP2C19*	**GERD:** Gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers.

Drug name (Brand name)	Biomarker	Indication
Orphan disease		
Ivacaftor (Kalydeco®)	G551D mutation in the *CFTR* gene	**Cystic Fibrosis:** Indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use.
Hematology		
Eltrombopag (Promacta®)	Factor-V-Leiden *ATIII* deficiency	Potential for an increased risk of thromboembolism when administering eltrombopag to patients with known risk factors for thromboembolism (e.g. Factor-V-Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). Follow dose adjustment guidelines to achieve and maintain target platelet counts.
Lenalidomide (Revlimid®)	5q deletion	**Myelodysplastic syndrome:** For patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities.
Immunology		
Indacaterol (Arcapta®)	*UGT1A1*	**COPD:** The pharmacokinetics of indacaterol were prospectively investigated in subjects with the *UGT1A1* (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)6 genotype. Steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.
Mycophenolic acid (Myfortic®)	*HGPRT*	**Transplantation:** Patients with Hereditary Deficiency of Hypoxanthine-guanine Phosphoribosyl-transferase (HGPRT): May cause exacerbation of disease symptoms; avoid use.
Infectious disease		
Abacavir (Ziagen®)	*HLA-B*57:01*	**HIV:** Patients who carry the *HLA-B*57:01* allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the *HLA-B*57:01* allele is recommended.
Boceprevir (Victrelis®)	*IL28B*	**Hepatitis C:** A genetic variant near the gene encoding interferon-lambda-3 (*IL28B rs12979860*, a C to T change) is a strong predictor of response to PegInterferon alfa-2b/Ribavirin. Among subjects that received at least one dose of placebo or boceprevir, sustained virological response rates tended to be lower in subjects with the C/T and T/T genotypes compared to those with the C/C genotype, particularly among previously untreated subjects receiving 48 weeks of PegInterferon alfa-2b and Ribavirin.
Chloroquine (Aralen®)	*G6PD*	**Malaria:** The drug should be administered with caution to patients having G-6-PD deficiency.
Isoniazid (Nydrazid®)	*NAT*	**Tuberculosis:** Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.
Maraviroc (Selzentry®)	*CCR5 receptor*	**HIV:** In combination with other antiretroviral agents, it is indicated for treatment experienced adult patients infected with only *CCR5*-tropic HIV.
Peginterferon alfa-2b (Pegasys®)	*IL28B*	**Hepatitis C:** A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (*IL28B*) was associated with variable sustained virological response rates.

Drug name (Brand name)	Biomarker	Indication
Pyrazinamide (Rifater®)	*NAT*	**Tuberculosis:** Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.
Rifampin (Rifadin®)	*NAT*	**Tuberculosis:** Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.
Telaprevir (Incivek®)	*IL28B*	**Hepatitis C:** A genetic variant near the gene encoding interferon-lambda-3 (IL28B rs12979860, a C to T change) is a strong predictor of response to peginterferon alfa and ribavirin (PR). SVR rates tended to be lower in subjects with the CT and TT genotypes compared to those with the CC genotype, particularly among treatment-naïve subjects receiving PR48. Among both treatment-naïve and previous treatment failures, subjects of all *IL28B* genotypes appeared to have higher SVR rates with regimens containing telaprevir.
Voriconazole (Vfend®)	*CYP2C19*	**Antifungal:** Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCt) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.
Neurology		
Carbamazepine (Tegretol®)	*HLA-B*15:02*	**Epilepsy and bipolar disorder:** Serious dermatologic reactions are associated with the *HLA-B*15:02* allele in patients treated with carbamazepine. Patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with Carbamazepine. Patients testing positive for the allele should not be treated with the drug unless the benefit clearly outweighs the risk.
Carisoprodol (Soma®)	*CYP2C19*	**Musculoskeletal pain:** Patients with reduced *CYP2C19* activity have higher exposure to carisoprodol. Caution should be exercised in administration of carisoprodol to these patients as it has been shown that CYP2C19 poor metabolizers have a 4-fold increase in exposure to carisoprodol compared to normal *CYP2C19* metabolizers.
Clobazam (Onfi®)	*CYP2C19*	**Lennox-Gastaut syndrome:** Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in *CYP2C19* poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended.
Dextrometorphan & Quinidine (Nuedexta®)	*CYP2D6*	**Neurological disorders:** Approximately 7-10% of Caucasians and 3-8% of African Americans lack the capacity to metabolize *CYP2D6* substrates and are classified as poor metabolizers. The quinidine component is not expected to contribute to the effectiveness in poor metabolizers, but adverse events of the quinidine are still possible. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are poor metabolizers should be considered prior to making the decision to treat with dextromethorphan and quinidine.
Divalproex (Depakote®)	*UCD (NAGS; CPS; ASS; OTC; ASL; ARG)*	**Bipolar disorder (antiepileptic drug):** Hyper-ammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, particularly ornithine transcarbamylase deficiency.
Phenytoin (Dilantin®)	*HLA-B*15:02*	Studies have found an association between the risk of developing Stevens Johnson Syndrome/Toxic Epidermal Necrolysis and the presence of the *HLA-B*15:02* variant in patients using another anticonvulsive drug. Consideration should be given to avoid use of drugs associated with SJS/TEN, including phenytoin, in *HLA-B*15:02* positive patients when alternative therapies are otherwise equally available.

Drug name (Brand name)	Biomarker	Indication
Tetrabenazine (Xenazine®)	*CYP2D6*	**Huntington's disease:** Patients who require doses of tetrabenazine greater than 50 mg per day, should be first tested and genotyped to determine if they are poor or extensive metabolizers by their ability to express the drug metabolizing enzyme, *CYP2D6*. The dose of tetrabenazine should then be individualized accordingly to their status as either poor or extensive metabolizers.
Valproic acid (Depakene®)	*UCD; especially OTC*	**Epilepsy:** Hyper-ammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.
Oncology		
ado-trastuzumab emtansine (Kadcyla®)	*ERBB2 (HER2)*	**Breast cancer:** Indicated, as a single agent, for the treatment of patients with *HER2-positive,* metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.
Afatinib (Gilotrif®) *cf. Table 2*	*EGFR*	**NSCLC:** Indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (*EGFR*) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
Anastrozole (Arimidex®)	*HR*	**Breast cancer:** Indicated for i) adjuvant treatment of postmenopausal women with Hormone receptor *(HR)-positive* early breast cancer; ii) first-line treatment of postmenopausal women with HR-positive or HR unknown locally advanced or metastatic breast cancer.
Arsenic trioxide (Trisenox®)	*PML / RARĐ*	**Leukemia:** For induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t (15;17) translocation or *PML / RAR-alpha* gene expression.
Azathioprine (Imuran®)	*TPMT*	**Leukemia:** Guides adjustment of dose in treatment of acute lymphoblastic leukemia: Patients with inherited little or no thiopurine S-methyl-transferase (TPMT) activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for *TPMT*.
Busulfan (Busulfex® & Myleran®)	*Philadelphia Chromosome/ BCR-ABL*	**Leukemia:** Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph1) chromosome.
Bosutinib (Bosulif®)	*BCR-ABL1*	**Leukemia:** The molecular response measured by *BCR-ABL1 RT-qPCR* assists in identifying suboptimal responses and can help inform the decision to switch to alternative therapies that may be more efficacious (or to pursue more stringent monitoring). Furthermore, the tyrosine kinase inhibitor–mediated molecular response provides valuable risk stratification and prognostic information on long-term outcomes.
Brentuximab Vedotin (AdcetrisTM)	*CD30*	**Lymphoma:** Targets CD30 protein present on the surface of certain cells for the treatment of Hodgkins lymphoma and systemic anaplastic large cell lymphoma.
Capecitabine (Xeloda®)	*DPD*	**Multiple cancers:** Contraindicated in patients with known DPD deficiency.
Carboplatin (Daraplatin®) *cf. Table 2*	*RRMI*	**Lung cancer:** Low levels of *RRM1* gene expression are associated with improved response to platin therapy.

Drug name (Brand name)	Biomarker	Indication
Cetuximab (Erbitux®) *cf. Table 2*	*EGFR, KRAS*	**Colon cancer:** treatment of K-Ras mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests.
	BRAF	**Colon cancer:** A mutation in *BRAF* identifies 12-15 percent of metastatic colorectal cancer patients who fail to respond to TKI's. Non-mutated forms of *BRAF* and *KRAS* genes are required for response.
Crizotinib (Xalkori®) *cf. Table 2*	*ALK*	**Lung cancer:** Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase *(ALK)-positive* as detected by an FDA-approved test. The ALK abnormality occurs in 1-7% of NSCLC patients.
Dabrafenib (Tafinlar®) *cf. Table 2*	*BRAF*	**Melanoma:** Indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test.
Dasatinib (Sprycel®)	*Philadelphia Chromosome/ BCR-ABL*	**Leukemia:** Indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
Denileukin diftitox (Ontak®)	*CD25*	**Lymphoma:** Indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.
Erlotinib (Tarceva®) *cf. Table 2*	*KRAS*	**Colon cancer:** Retrospective analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the *EGFR* inhibitors in patients whose tumors had KRAS mutations in codon 12 or 13.
	EGFR expression and activating mutations	**Lung cancer:** *EGFR* activating mutations occur in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients. Data from multiple studies indicate a predictive role for EGFR activating mutations with respect to response rate and progression-free survival with tyrosin kinase inhibitor therapy, particularly in the first-line setting.
Everolimus (Afinitor®)	*HR*	**Breast cancer:** Indicated for the treatment of postmenopausal women with advanced HR positive, *HER2-negative* breast cancer (advanced HR+ breast cancer) in combination with exemestane after failure of treatment with letrozole or anasrozole.
Exemestane (Aromasin®)	*ER*	**Breast cancer:** Indicated for adjuvant treatment of postmenopausal women with Estrogen Receptor (ER)-positive early breast cancer who have received two to three years of tamoxifen and are switched to the drug for completion of a total of five consecutive years of adjuvant hormonal therapy.
5-Fluorouracil (5-FU) (Efudex®) *cf. Table 2*	*DPD*	**Warnings:** Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to deficiency of DPD activity.
	TS	**Multiple cancers:** **Gastrointestinal cancers:** High levels thymidylate synthetase (TS) gene expression correlate with tumor resistance (low response) to 5-FU in gastric and colon cancers. **Lung cancer:** Patients with high levels of TS in their tumors tend to respond less favorably to TS inhibitors such as 5-FU and pemetrexed. **Pancreatic cancer:** High TS expression also correlates with gemcitabine and 5-FU resistance in pancreatic cancers.
Fulvestrant (Faslodex®)	*ER*	**Breast cancer:** Indicated for the treatment of HR-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

Drug name (Brand name)	Biomarker	Indication
Gefitinib (Iressa®)*cf. Table 2*	*KRAS*	**Colon cancer:** Retrospective analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the *EGFR* inhibitors in patients whose tumors had *KRAS* mutations in codon 12 or 13.
Gemcitabine (Gemzar®) *cf. Table 2*	*TS*	**Pancreatic cancer:** High TS expression correlates with gemcitabine and 5-FU resistance in pancreatic cancers.
	RRMI	**Lung cancer:** Gemcitabine interferes with the DNA synthesis function of ribonucleotide reductase through its active subunit (RRM1). Low levels of *RRM1* gene expression are associated with improved response to gemcitabine therapy.
Imatinib (Gleevec®) *cf. Table 2*	*Philadelphia Chromosome/ BCR-ABL*	**Leukemia:** Indicated for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive [indicated by presence of *BCR-ABL*] chronic myeloid leukemia (CML) in chronic phase.
	PDGFR (platelet-derived growth factor receptor)	**Myelodysplastic syndrome:** Indicated for adult patients with myelo-dysplastic / myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (*PDGFR*) gene re-arrangements.
	c-KIT	**Stomach cancer:** Indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).
Irinotecan (Camptosar®) *cf. Table 2*	*UGT1A1*	**Colon cancer:** Individuals who are homozygous for the *UGT1A1*28* allele are at increased risk for neutropenia following initiation of irinotecan treatment. A reduction in the starting dose by at least one level of the drug should be considered for patients known to be homozygous for the *UGT1A1*28* allele.
	ERCC1	**Colon cancer:** High expression of *ERCC1* is associated with response to irinotecan therapy.
Lapatinib (Tykerb®)	*HER2 / neu receptor*	**Breast cancer:** For the treatment of patients with metastatic breast cancer whose tumors overexpress the Human Epidermal growth factor Receptor 2 (*HER2*) protein and who have received one or more chemotherapy regimens for their metastatic disease.
Letrozole (Femara®)	*HR*	**Breast cancer:** Indicated for i) adjuvant treatment of postmenopausal women with HR-positive early breast cancer; ii) first and second-line treatment of postmenopausal women with HR-positive or unknown advanced breast cancer.
Mercaptopurine (Purinethol®)	*TPMT*	**Leukemia:** Guidance for dose adjustment during treatment of acute lymphoblastic leukemia: Patients with inherited little or no *TPMT* activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for *TPMT*.
Nilotinib (Tasigna®)	*UGT1A1, Ph+*	**Leukemia:** Indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adults resistant to imitinab. *UGT1A1*28* patients have a high risk of hyperbilirubinemia.
Omacetaxine mepe-succinate (Synribo®)	*BCR-ABL & B-ALL*	**Leukemia:** Treatment with omacetaxine decreased the number of leukemia stem cells and prolonged the survival of mice with *BCR-ABL-induced CML* or *B-ALL*.

Drug name (Brand name)	Biomarker	Indication
Panitumumab (Vectibix®) *cf. Table 2*	*EGFR*	**Colon cancer:** Indicated as a single agent for the treatment of metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.
	KRAS	**Colon cancer:** Is NOT indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom *KRAS* mCRC status is unknown. Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the drug in patients whose tumors had *KRAS* mutations in codon 12 or 13.
	BRAF	**Colon cancer:** A mutation in *BRAF* identifies 12-15% of metastatic colorectal cancer patients who fail to respond to TKI's. Non-mutated forms of *BRAF* and *KRAS* genes are required for response.
Pemetrexed (Alimta®) *cf. Table 2*	*TS*	**Lung cancer:** Patients with high levels of TS in their tumors tend to respond less favorably to TS inhibitors such as 5-FU and pemetrexed.
Pertuzumab (Perjeta®) *cf. Table 2*	*HER2 / neu receptor*	**Breast cancer:** Indicated in combination with trastuzumab and docetaxel for the treatment of patients with *HER2-postive* metastatic breast cancer who have not received prior *anti-HER2* therapy or chemotherapy for metastatic disease.
Platinum therapies *cf. Table 2*	*ERCC1*	**Multiple cancers:** **Bladder cancer:** Low *ERCC1* expression is associated with greater survival in bladder cancer patients treated with platinum-based therapies. **Colon cancer:** In a study of advanced colorectal cancer treated with 5-fluorouracil/oxaliplatin, low *ERCC1* expression is associated with longer survival. High expression of *ERCC1* is associated with response to irinotecan therapy. **Gastric cancer:** Patients treated with (5-fluorouracil/leucovorin/oxaliplatin) regimen or first-line cisplatin-based regimens respond significantly better if they show lower levels of *ERCC1* expression. **Lung cancer:** Enzyme excision repair complementing factor 1 *(ERCC1)* helps repair DNA damage caused by platinum-based therapy. Low ERCC1 is a favorable indicator for response to platinum therapy.
Ponatinib (Iclusig®)	*BCR-ABL1*	**Leukemia:** The molecular response measured by BCR-ABL1 RT-qPCR assists in identifying suboptimal responses and can help inform the decision to switch to alternative therapies that may be more efficacious (or to pursue more stringent monitoring). Ponatinib is a kinase inhibitor, which inhibits the in vitro tyrosine kinase activity of ABL and T315I mutant ABL.
Tamoxifen (Nolvadex®) *cf. Table 2*	*ER*	**Breast cancer:** Available evidence indicates that patients whose tumors are ER positive are more likely to benefit from tamoxifen therapy.
Thioguanine (Tabloid®)	*TPMT*	**Leukemia:** Guidance for dose adjustment during treatment of acute lymphoblastic leukemia: Patients with inherited little or no *TPMT* activity are at increased risk for severe drug toxicity from conventional doses. It is recommended that consideration be given to either genotype or phenotype patients for *TPMT*.
Tositumomab (Bexxar®)	*CD20*	**Lymphoma:** Is indicated for the treatment of patients with CD20 antigen expressing non-Hodgkin's lymphoma.
Trametinib (Mekinist®) *cf. Table 2*	*BRAF*	**Melanoma:** Indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test.

Drug name (Brand name)	Biomarker	Indication
Trastuzumab (Herceptin®) *cf. Table 2*	*HER2 / neu receptor*	**Breast cancer:** Indicated for i) the treatment of *HER2* overexpressing breast cancer; ii) the treatment of *HER2* overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.
Tretinoin (Vesanoid®)	*PML / RARĐ*	**Leukemia:** For induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t (15;17) translocation or *PML/RAR-alpha* gene expression.
Vemurafenib (ZelborafTM) *cf. Table 2*	*BRAF V600E*	**Melanoma:** Indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test. The *BRAF* V600E mutation is found in about half of melanoma patients.
Psychiatry		
Aripiprazole (Abilify®)	*CYP2D6*	**Psychotic disorders:** Poor Metabolizers have approximately 80% increase in aripiprazole exposure and approximately 30% decrease in exposure to the active metabolite compared to extensive metabolizers, resulting in approximately 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to extensive metabolizers. Poor metabolizers have higher exposure to aripiprazole compared to extensive metabolizers; hence, poor metabolizers should have their initial dose reduced by one-half. Laboratory tests are available to identify *CYP2D6* poor metabolizers.
Amitriptyline (Elavil®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Atomoxetine (Strattera®)	*CYP2D6*	**ADHD:** Atomoxetine is metabolized primarily through the *CYP2D6* enzymatic pathway. People with reduced activity in this pathway (poor metabolizers) have higher plasma concentrations of atomoxetine compared to people with normal activity (extensive metabolizers). For poor metabolizers, AUC of atomoxetine is approximately 10-fold and Css max is about 5-fold greater than in extensive metabolizers. Dose adjustment may be necessary.
Citalopram (Celexa®)	*CYP2C19*	**Depression:** In *CYP2C19* poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. 20 mg/day is the maximum recommended dose in *CYP2C19* poor metabolizers due to the risk of QT prolongation.
Clomipramine (Anafranil®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Clozapine (Clozaril®)	*CYP2D6*	**Psychotic disorders:** Dose reduction may be necessary in patients who are *CYP2D6* poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted.
Desipramine (Norpramin®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Doxepin (Silenor®)	*CYP2D6* *CYP2C19*	**Insomnia:** Poor metabolizers of *CYP2C19* and *CYP2D6* may have higher doxepin plasma levels than normal subjects.

Drug name (Brand name)	Biomarker	Indication
Fluvoxamine (Luvox CR®)	*CYP2D6*	**Obsessive compulsive disorders:** Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme.
Iloperidone (Fanapt®)	*CYP2D6*	**Psychotic disorders:** Iloperidone dose should be reduced by one-half for poor metabolizers of *CYP2D6*.
Imipramine (Tofranil-PM®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Nortriptyline (Pamelor®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Perphenazine (Trilafon®)	*CYP2D6*	**Psychotic disorders:** *CYP2D6* poor metabolizers will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or "extensive" metabolizers.
Pimozide (Orap®)	*CYP2D6*	**Tourette's Syndrome:** Individuals with genetic variations resulting *in poor CYP2D6 metabolism* (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive *CYP2D6* metabolizers. Alternative dosing strategies are recommended in patients who are genetically poor *CYP2D6* metabolizers.
Protriptyline (Vivactil®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Thioridazine (Mellaril®)	*CYP2D6*	**Psychotic disorders:** Reduced *CYP2D6* isozyme activity, drugs which inhibit this isozyme, and certain other drugs appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias.
Trimipramine (Surmontil®)	*CYP2D6*	**Depression:** Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by *CYP2D6*, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Rheumatology		
Flurbiprofen (Ansaid®)	*CYP2C9*	**Arthritis:** Patients who are known or suspected to be *CYP2C9* poor metabolizers based on previous history/experience with other *CYP2C9* substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Drug name (Brand name)	Biomarker	Indication
Urology		
Tolterodine (Detrol®)	*CYP2D6*	**Overactive bladder:** A subset (about 7%) of the population is devoid of *CYP2D6*, the enzyme responsible for the formation of the 5-hydroxy-methyl metabolite of tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via *CYP3A4* to N-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers." Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite.

TABLE 2: SELECTED PERSONALIZED MEDICINE GENETIC TESTS WITH RESPECT TO DRUGS AND/OR DISEASE.

Drug/gene combinations from Table 1 have been cross-referenced in Table 2 if a respective genetic test is available
* Drugs cross-referenced with Table 1

Drug Name (Brand name)	Test/Kit	Indication
Cardiovascular (CV)		
	AlloMap Molecular Expression Testing	**Heart Transplant:** Aid in the identification of heart transplant recipients with stable allograft function who have a low probability of moderate/severe acute cellular rejection (ACR) at the time of testing in conjunction with standard clinical assessment.
	Corus® CAD	**Obstructive Coronary Artery Disease:** Gene expression test is a decision-making tool that can help identify patients unlikely to have obstructive CAD and help determine appropriate next steps.
	Familion® 5-gene profile	**CV:** Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Statins *	SINM PhyzioType™	**CV:** Predicts risk of statin-induced neuro-myopathy, based on a patient's combinatorial genotype for 50 genes.
Warfarin * (Coumadin®)	eQ-PCR LC Warfarin Genotyping kit	Genotyping single nucleotide polymorphisms (SNPs) in the cytochrome P450 enzyme gene *CYP2C9* known as *CYP2C9*2* (C430T), *CYP2C9*3* (A1075C), and a SNP in the vitamin K epoxide reductase complex 1 gene (*VKORC1*) known as *VKORC1* (-1639G>A).
	eSensor Warfarin Sensitivity Test	Detection and genotyping of *CYP450* 2C9 (*2 and *3) and *VKORC1* (-1639G>A)
	Gentris Rapid Genotyping Assay - *CYP2C9* & *VKORCI*	Intended to detect the presence of *CYP2C9* *2 and *3 and *VKORC1* 1173 C>T alleles. Information about the *CYP2C9* and *VKORC1* genotypes may be used as an aid in the identification of patients with greater risk for warfarin sensitivity.
	INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin	Identify *CYP450* 2C9 and *VKORC1* genetic variants.
	PGx Predict™	**CV:** Determines *CYP2C9* and *VKORC1* genotypes to predict likelihood of adverse events with warfarin therapy.
	Verigene Warfarin Metabolism Nucleic Acid Test and Verigene System	The two most common alleles of CYP2C9 that affect warfarin metabolism are *CYP2C9*2* (also known as R144C) and *CYP2C9*3* (also known as I359L). The *VKORC1* gene, located on the short arm of human chromosome 16 (16p11.2), encodes the *VKORC1* protein which plays an essential role in gamma-carboxylation of Vitamin K-dependent blood clotting factors.
Drug metabolism		
	AmpliChip CYP450 microarray	Detection of gene variations — including deletions and duplications — for the *CYP2D6* and *CYP2C19* genes, the expressed enzymes play a major role in the metabolism of an estimated 25% of all prescription drugs.
	INFINITI *CYP2C19* Assay	Determining therapeutic strategy for therapeutics that are metabolized by the *CYP450 2C19* gene product, specifically *2, *3, *17.
	Verigene *CYP2C 19* Nucleic Acid Test	Identifies a patient's CYP2C19 *2, *3 and *17 genotype.
	xTAG® *CYP2D6* Kit	*Determine therapeutic strategy for therapeutics that are metabolized by the CYP2D6 gene product.*

Drug Name (Brand name)	Test/Kit	Indication
Genetic disease		
	AneuVysion	Detect alpha satellite sequences in the centromere regions of chromosomes 18, X, and Y, and LSI 13/21 probe to detect the 13q14 region and the 21q22.13 to 21q22.2 region.
	CEP 8 Spectrumorange DNA Probe Kit	Detect AT rich alpha satellite sequences in the centromere region of chromosome 8 in conjunction with routine diagnostic cytogenetic testing.
	eSensor® CF Genotyping Test	**Cystic Fibrosis:** Provide patients with accurate genetic carrier screening results. Panel includes 23 ACOG/ACMG recommended mutations.
	xTAG Cystic Fibrosis 39 Kit v2 xTAG Cystic Fibrosis 60 Kit v2	**Cystic Fibrosis:** Test for the most prevalent CFTR gene mutations in a variety of populations. Tests a patient for only the 23 CFTR mutations recommended by the ACMG/ACOG or to also test for an additional 16 (with the xTAG Cystic Fibrosis (*CFTR*) 39 kit v2) or an additional 37 (with the xTAG Cystic Fibrosis *(CFTR)* 60 kit v2) of the world's most common and North American-prevalent mutations.
	Verigene® CFTR and Verigene® CFTR PolyT Nucleic Acid Tests	**Cystic Fibrosis:** Panel includes mutations and variants recommended by the 2004 American College of Medical Genetics (ACMG) and the 2005 American College of Obstetricians and Gynecologists (ACOG). It provides information intended to be used for carrier testing in adults of reproductive age and in confirmatory diagnostic testing of newborns and children.
	InPlex CF Molecular Test	**Cystic Fibrosis:** Tests for twenty-three separate mutations in the Cystic Fibrosis Transmembrane Receptor (*CFTR*) gene. In addition, the IVS8-5T/7T/9T markers are automatically reflexed as part of the test. All mutations contained in the assay are recommended for testing by the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG).
	Cystic Fibrosis Genotyping Assay	**Cystic Fibrosis:** Genotype a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in genomic DNA isolated from human whole blood specimens. The panel includes mutations and variants recommended by the American College of Medical Genetics (ACMG, 2004) and the American College of Obstetricians and Gynecologists (ACOG, 2005), plus additional multiethnic mutations and variants. It provides information intended to be used for carrier screening in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children.
Hematology		
	CEP X SpectrumOrange/ Y SpectrumGreen DNA Probe Kit	Indicated for use as an adjunct to standard cytogenetic analysis for identifying and enumerating chromosomes X and Y in interphase nuclei and metaphase spreads obtained from bone marrow specimens in subjects who received opposite-sex bone marrow transplantation for **chronic myelogenous leukemia (CML), acute myeloid leukemia (AML), myeloproliferative disorder (MPD), myelodysplastic syndrome (MDS), acute and lymphoid leukemia (ALL),** or **hematological disorder not otherwise specified (HDNOS).**
	eSensor Thrombophilia Risk Test	All four thrombophilia-related genetic markers: FV, FII, *MTHFR 677, MTHFR 1298.*
	Factor II (Prothrombin) G20210A Kit	Detection and genotyping of a single point mutation (G to A at position 20210) of the human Factor II gene from DNA isolated from human whole peripheral blood. Detection and genotyping of the Factor II (Prothrombin) G20210A mutation as an aid to diagnosis in the evaluation of patients with suspected thrombophilia.

Drug Name (Brand name)	Test/Kit	Indication
	Factor V leiden Kit	Detection and genotyping of a single point mutation (G to A at position 1691) of the human Factor V gene, referred to as Factor V Leiden mutation. Detection and genotyping of the Factor V Leiden mutation as an aid to diagnosis in the evaluation of patients with suspected **thrombophilia**.
	Illumina VeraCode Genotyping Test for Factor V and Factor II	Detection and genotyping of Factor V Leiden G1691A and Factor II (Prothrombin) G20210A point mutations in DNA obtained from EDTA-anticoagulated human blood samples. It is indicated for use as an aid to diagnosis in the evaluation of patients with suspected thrombophilia.
	INFINITI System	Identify genetic variants for Factor II, Factor V, and *MTHFR* genes.
	Invader Factor V	Detect a single nucleotide substitution mutation, causing a change in the translated protein's amino acid at 506th position from Arginine to Glutamine.
	Invader Factor II	Detect G20210A mutation that is characterized by a guanine to adenine transition at position 20210 in the 3' untranslated region of the Factor II gene.
	Invader *MTHFR* 677	Detect a polymorphism at the 677 position of the gene that causes a Cytosine to Thymine substitution.
	Invader *MTHFR* 1298	Detect a polymorphism at the 1298 position of the gene that causes an Adenine to Cytosine substitution.
	Verigene F5 Nucleic Acid Test Verigene F2 Nucleic Acid Test Verigene MTHFR Nucleic Acid Test	Detection and genotyping of a single point mutation (G to A at position 1691; also known as Factor V Leiden) of the human Factor V gene (*F5*; Coagulation Factor V gene) in patients with suspected **thrombophilia**. Verigene *F2* :(G to A at position 20210) of the human Factor II gene (F2; prothrombin gene), *Verigene MTHFR*: (C to T at position 677) of the human 5,10 methylene-tetra-hydro-folate reductase gene (*MTHFR*).
	Xpert HemosIL FII & FV	Detection of Factor II (FII) and Factor V (FV) alleles. Performed on the Cepheid GeneXpert System, the test is intended to provide rapid results for FII (G20210A) and FV Leiden (G1691A) mutations as an aid in the diagnosis of suspected **thrombophilia**.
Immunology		
	AlloMap® gene signature	**Heart transplantation:** Monitors patient's immune response to heart transplant to guide immunosuppressive therapy.
Budesonide (Entocort®)	Prometheus® IBD Serology 7	**Inflammatory bowel disease:** Identifies subset of patients who will benefit from budesonide.
	ImmuKnow®	**Post-Transplant Immune Status:** Is an immune cell function assay that detects cell-mediated immunity in an immunosuppressed population.
Oncology		
Afatinib * (Gilotrif®)	therascreen *EGFR* RGQ PCR Kit	**Lung cancer:** Detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the epidermal growth factor receptor *(EGFR)* gene in non-small cell lung cancer (NSCLC) tumor tissue. It is intended to be used to select patients with NSCLC for whom Afatinib is indicated.
	CancerTYPE ID®	Classifies 28 main tumor types and 50 subtypes.
Carboplatin *	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS,* and *EML4-ALK* provide information for the selection of various therapies.

Drug Name (Brand name)	Test/Kit	Indication
	CEP 12 SpectrumOrange Direct Labeled Chromosome Enumeration DNA Probe	**B-cell chronic lymphocytic leukemia:** Detect AT rich alpha satellite sequences in the centromere region of chromosome 12 in conjunction with routine diagnostic cytogenetic testing. It is indicated for use as an adjunct to standard cytogenetic analysis for identifying and enumerating chromosome 12 via fluorescence in situ hybridization (FISH) in interphase nuclei of cells obtained from peripheral blood lymphocytes in patients with B-cell chronic lymphocytic leukemia (CLL).
Cetuximab * (Erbutix®)	therascreen *KRAS* RGQ PCR Kit	Colorectal cancer: Detection of seven somatic mutations in the human *KRAS* oncogene in colorectal cancer (CRC) tissue. It is intended to aid in the identification of CRC patients for treatment with Cetuximab based on a *KRAS* no mutation detected test result.
	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	Target GI™	**Colon cancer:** Provides information of the expression of key molecular targets—*KRAS, TS,* and *TOPO1*—to guide therapy.
	DAKO *EGFR* PharmDx Kit	**Colorectal cancer:** Identify *EGFR* expression in normal and neoplastic tissue. It detects the *EGFR (HER1)* protein in *EGFR*-expressing cells. It is indicated as an aid in identifying colorectal cancer patients eligible for treatment with Cetuximab.
	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS,* and *EML4-ALK* provide information for the selection of various therapies.
	CompanDx® 31-gene signature	**Breast cancer:** The test predicts "time to event" for metastasis of breast cancer, following surgery or biopsy.
Crizotinib * (Xalkori®)	Vysis *ALK* Break Apart FISH Probe Kit	**Lung cancer:** To detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH), in non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with Crizotinib.
	CupPrint™	**Multiple cancers:** Determines cancer classification for tumors of unknown primary origin.
Dabrafenib * (Tafinlar®)	THxID™ BRAF Kit	**Melanoma:** Qualitative detection of the *BRAF* V600E and V600K mutations in human melanoma tissue. It is intended to be used as an aid in selecting melanoma patients whose tumors carry the *BRAF* V600E mutation for treatment with Dabrafenib.
	Dako *TOP2A* FISH PharmDx Kit	**Breast cancer:** Detect amplifications and deletions of the *TOP2A* gene in human breast cancer tissue. Deletions and amplifications of the *TOP2A* gene serve as a marker for poor prognosis in high risk breast cancer patients.
Erlotinib * (Tarceva®)	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS*, and *EML4-ALK* provide information for the selection of various therapies.
	Cobas *EGFR* Mutation Test	**Lung cancer:** Qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the epidermal growth factor receptor (*EGFR*) gene in human non-small cell lung cancer (NSCLC) tumor tissue. It is intended to be used as an aid in selecting patients with metastatic NSCLC for Erlotinib use.

Drug Name (Brand name)	Test/Kit	Indication
5-FU * (Adrucil®)	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS*, *EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS*, and *EML4-ALK* provide information for the selection of various therapies.
	ResponseDx: Gastric™	**Stomach cancer:** Expression profiles and mutations in *ERCC1, TS*, and *HER2* provide information for the selection of various therapies.
Gefitinib * (Iressa®)	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS,* and *EML4-ALK* provide information for the selection of various therapies.
Gemcitabine * (Gemzar®)	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	ResponseDx: Lung™	**Lung cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS,* and *EML4-ALK* provide information for the selection of various therapies.
	GeneSearch Breast Lymph Node (BLN) Test	**Breast Cancer:** First intra-operative and gene-based test approved for use in the US to detect the spread of breast cancer into the lymph nodes.
Imatinib mesylate * (Gleevec®)	DAKO *C-KIT* PharmDx	**GIST:** Specifically detect the c-kit protein in CD 117 antigen-expressing cells. It is indicated as an aid in the differential diagnosis of gastrointestinal stromal tumors (GIST) for those patients eligible for treatment with Imatinib mesylate.
Irinotecan * (Camptosar®)	Target GI™	**Colon cancer:** Provides information of the expression of key molecular targets—*KRAS, TS,* and *TOPO1*—to guide therapy.
	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	Invader® *UGT1A1* Molecular Assay	Determines the UGT1A1 *28 genotype as recommended in the label for the chemotherapeutic drug irinotecan, which is approved as a first-line therapy for metastatic colorectal cancer. Patients with a heterozygous-deficient *1 / *28 genotype or homozygous-deficient *28 / *28 genotype have greater risk for severe toxicity when treated with irinotecan therapy.
	MammaPrint	**Breast cancer:** First and only FDA-cleared IVDMIA breast cancer recurrence assay. The unique 70-gene signature of MammaPrint provides you with the unprecedented ability to identify which early-stage breast cancer patients are at risk of distant recurrence following surgery, independent of Estrogen Receptor status and any prior treatment.
	Mammostrat®	**Breast cancer:** Test used for postmenopausal, node negative, estrogen receptor expressing breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy.
	NADiA ProsVue	**Prostate Cancer:** The NADiA ProsVue assay is performed for patients having less than 0.1 ng/mL serum tPSA values (determined by standard-of-care assays that are FDA approved/cleared) in the first sample collected more than 6 weeks after radical prostatectomy. It is indicated for use as a prognostic marker in conjunction with clinical evaluation as an aid in identifying those patients at reduced risk for recurrence of prostate cancer for the eight year period following prostatectomy.

Drug Name (Brand name)	Test/Kit	Indication
	Oncotype DX® 16-gene signature	**Breast cancer:** A 16-gene signature (plus five reference genes) indicates whether a patient has a low, intermediate, or high risk of having a tumor return within 10 years. Low-risk patients may be treated successfully with hormone therapy alone. High-risk patients may require more aggressive treatment with chemotherapy.
	Oncotype DX® 7-gene signature	**Colon cancer:** The seven-gene signature (plus five reference genes) provides a risk score that indicates whether a patient is likely to have a tumor recurrence with stage II colon cancer. Risk levels guide treatment with adjuvant chemotherapy.
Panitumumab * (Vectibix®)	DAKO *EGFR* PharmDx Kit	**Colorectal cancer:** Identify *EGFR* expression in normal and neoplastic tissues and detects the *EGFR (HER1)* protein in *EGFR*-expressing cells. It is indicated as an aid in identifying colorectal cancer patients eligible for treatment with Panitumumab.
	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	Target GI™	**Colon cancer:** Provides information of the expression of key molecular targets—*KRAS, TS,* and *TOPO1*—to guide therapy.
	ResponseDx: Lung™	Lung cancer: Expression profiles and mutations in *ERCC1, TS, EGFR, RRM1, KRAS*, and *EML4-ALK* provide information for the selection of various therapies.
	Pathwork Tissue of Origin Test Kit—FFPE	Measure the degree of similarity between the RNA expression patterns in a patient's tumor and the RNA expression patterns in a database of fifteen tumor types (poorly differentiated, undifferentiated and metastatic cases) that were diagnosed according to then current clinical and pathological practice.
Pemetrexed * (Alimta®)	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
Pertuzumab * (Perjeta®)	HERCEPTEST	**Breast cancer:** To determine *HER2* protein overexpression in breast cancer tissues from patients with metastatic gastric or gastroesophageal junction adenocarcinoma. It is indicated as an aid in the assessment of breast cancer patients for whom Pertuzumab treatment is being considered.
	HER2 FISH PharmDx Kit	**Breast cancer:** Quantitatively determine *HER2* gene amplification in breast cancer tissue and patients with metastatic gastric or gastroesophageal junction adenocarcinoma. It is indicated as an aid in the assessment of breast cancer patients for whom Pertuzumab is being considered.
	MLH1, MSH2, MSH6	**Multiple cancers:** Guides surveillance and preventive treatment based on susceptibility risk for colon and other cancers.
	BRCA1/2	**Breast cancer:** Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer.
Platinum therapies *	ResponseDx: Colon™	**Colon cancer:** Expression profiles and mutations in *ERCC1, TS, EGFR, BRAF, KRAS* provide information for the selection of various therapies.
	ResponseDx: Gastric™	**Stomach cancer:** Expression profiles and mutations in *ERCC1, TS,* and *HER2* provide information for the selection of various therapies.
	PROGENSA PCA3 Assay	**Prostate cancer:** Detects Prostate Cancer Gene 3 (PCA3) messenger ribonucleic acid (mRNA) in male urine specimens to generate a PCA3 Score. The PCA3 Score is intended for use in conjunction with standard-of-care diagnostic algorithms as an aid in the diagnosis of prostate cancer.

Drug Name (Brand name)	Test/Kit	Indication
Tamoxifen * (Nolvadex®)	Breast cancer IndexSM	**Breast cancer:** Calculates a combined risk analysis for recurrence after tamoxifen treatment for ER-positive, node-negative breast cancer.
Tramatenib * (Mekinist®)	THxID™ *BRAF* Kit	**Melanoma:** Qualitative detection of the *BRAF* V600E and V600K mutations in human melanoma tissue. It is intended to be used as an aid in selecting melanoma patients whose tumors carry the *BRAF* V600E or V600K mutation for treatment with Trametinib.
Trastuzumab * (Herceptin®)	Bond Oracle *HER2* IHC System	To determine *HER2* oncoprotein status in **breast cancer** tissue. It is indicated as an aid in the assessment of patients for whom Trastuzumab treatment is being considered.
	HER2 CISH PharmDx Kit	Determine HER2 gene status in **breast cancer** tissue. It is indicated as an aid in the assessment of patients for whom Trastuzumab treatment is being considered.
	HER2 FISH PharmDx Kit	Quantitatively determine *HER2* gene amplification in breast cancer tissue from patients with metastatic gastric or gastroesophageal junction adenocarcinoma. It is indicated as an aid in the assessment of breast and gastric cancer patients for whom Trastuzumab treatment is being considered.
	HERCEPTEST	Semi-quantitative assay to determine *HER2* protein overexpression in breast cancer tissues. It is indicated as an aid in the assessment of **breast and gastric cancer patients** for whom Trastuzumab treatment is being considered.
	INFORM *HER-2/NEU*	**Breast cancer:** Determines the qualitative presence of Her-2/Neu gene amplification in human breast tissue. It is indicated for use as an adjunct to existing clinical and pathologic information currently used as prognostic indicators in the risk stratification of breast cancer in patients who have had a priori invasive, localized breast carcinoma and who are lymph node-negative.
	INFORM *HER2* DUAL ISH DNA Probe Cocktail	Intended for use in determining *HER2* gene status by enumeration of the ratio of the *HER2* gene to Chromosome 17. It is indicated as an aid in the assessment of patients for whom Trastuzumab treatment is being considered.
	INSITE *HER-2/NEU* KIT	Semi-quantitative detection of over-expression of *HER-2/NEU (I.E., C-ERBB-2)* in normal and neoplastic tissue. It is indicated as an aid in the assessment of breast cancer patients for whom Trastuzumab therapy is being considered.
	PATHVYSION *HER-2* DNA Probe Kit	To detect amplification of the *HER-2/NEU* gene human breast cancer tissue. It is indicated as an aid in the assessment of patients for whom Trastuzumab treatment is being considered.
	PATHWAY ANTI-*HER-2/NEU* (4B5) Rabbit mAb	Intended for laboratory use for the semi-quantitative detection of *C-ERBB-2* antigen in neoplastic tissue. It is indicated as an aid in the assessment of breast cancer patients for whom Trastuzumab treatment is being considered.
	ResponseDx: Gastric™	**Stomach cancer:** Expression profiles and mutations in *ERCC1, TS,* and *HER2* provide information for the selection of various therapies.
	SPOT-LIGHT *HER2* CISH Kit	Quantitatively determine *HER2* gene amplification in breast carcinoma tissue. It is indicated as an aid in the assessment of patients for whom Trastuzumab treatment is being considered.

Drug Name (Brand name)	Test/Kit	Indication
Vemurafenib * (Zelboraf®)	Cobas® 4800 *BRAF* V600 Mutation Test	**Melanoma:** Detects the *BRAF* V600E mutation in human melanoma tissue. It is designed to help select patients for treatment with Vemurafenib.
	Vysis CLL FISH Probe Kit	**B-cell lymphocytic leukemia:** Detect deletion of the LSI TP53, LSI ATM, and LSI D13S319 probe targets and gain of the D12Z3 sequence in peripheral blood specimens from untreated patients with B-cell chronic lymphocytic leukemia (CLL).
	Vysis *EGR1* FISH Probe Kit	**Acute Myeloid Leukemia:** Detect deletion of the LSI EGR1 probe target on chromosome 5q in bone marrow specimens and to be used, in addition to cytogenetics, other biomarkers, morphology and other clinical information, at the time of acute myeloid leukemia (AML) diagnosis as an aid in determining prognosis. Deletion of chromosome 5q has been associated with an unfavorable prognosis in AML patients.
	Vysis UroVysion Bladder Cancer Recurrence Kit	**Bladder cancer:** Detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via fluorescence in situ hybridization (FISH) in urine specimens from persons with hematuria suspected of having bladder cancer.
Psychology		
	GeneSightRx®	**Psychiatric disorders:** Genetic variants *(CYP1A2, CYP2D6, CYP2C19,* serotonin transporter gene SLC6A4, serotonin 2A receptor gene *5HTR2A)* in this test may affect a patient's ability to metabolize, tolerate or respond to 26 psychotropic medications.
Resperidone (Risperdal®) Olanzapine (Zyprexa®)	PhyzioType PIMS	**Psychiatric disorders:** Predicts risk of psychotropic-induced metabolic syndrome, based on a patient's combinatorial genotype for 50 genes.
Rheumatology		
Etanercept (Enbrel®) Infliximab (Remicade®)	PsoriasisDx™	**Psoriatic arthritis:** This sequencing-based assay detects the presence of gene variant *MICA-A9*, indicative of an increased risk of psoriatic arthritis. Identification of risk could guide monitoring and early treatment with TNF-alpha antagonists.

This list reflects commonly used or available products as of May 2014. Some products, for which the FDA recommends or requires pharmacogenomic testing or which have pharmacogenomic information in their label, are listed at the FDA's Web site (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Other listed products that are novel, and/or that address large populations, have been identified via web sites and public announcements.

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PMC
PERSONALIZED
MEDICINE COALITION

1710 Rhode Island Ave., NW
Suite 700
Washington, DC 20036

P: 202.589.1770
pmc@personalizedmedicinecoalition.org