

The Case for
**Personalized
Medicine**

Today:

A patient has late-stage non-small cell lung cancer (NSCLC). She has gone through a number of treatments, but none were able to arrest the cancer's spread. The mother of four has progressive disease and precious little time to waste on treatments that do not work. Her physician read reports of a newly approved drug called Xalkori® (crizotinib) that might offer hope. However, only about five percent of NSCLC patients whose tumors have the anaplastic lymphoma kinase (ALK) gene rearrangement can potentially benefit. A newly approved diagnostic test determines that the patient has the gene rearrangement and that the drug is a treatment option for her. After starting to take Xalkori®, the tumors begin to respond.

The Future:

Imagine a physician sitting down with his laptop and a morning cup of coffee. On a website that he uses to help manage his practice, an alert pops up. It tells him that a series of studies have demonstrated a connection between multiple rare mutations found in 10 percent of people and the likelihood that they might convert to type 2 diabetes. Nearly all of his patients have had their entire genome sequenced and entered into their electronic medical record – a process that takes only a week, costs a few hundred dollars, and is reimbursed by insurance companies because of the many benefits it provides to lifelong health management. He conducts a quick search of his 2,000 patient database and finds about 80 who are at risk. To half of those patients, he sends a strong reminder and advice on diet and lifestyle choices they can take to avoid the disease. To the other half, whose medical records reveal pre-diabetic symptoms, he sets up appointments to consider more proactive treatment with drugs that can prevent the onset of disease.

Introduction

For more than two millennia, medicine has never wavered from its aspiration of being personalized. In ancient times, Hippocrates would combine an assessment of the four humours – blood, phlegm, yellow bile and black bile – to determine what was then considered the best course of treatment for each patient. Today, the sequence of four chemical building blocks of DNA in the genome, together with telltale proteins in the blood, enable more accurate predictions of whether an individual will develop an illness many years in the future or is developing it now, will respond positively to treatment, or will suffer a serious reaction to a drug. 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.

Patients with melanoma, metastatic lung, breast, or brain cancers, and leukemia are now being routinely offered a “molecular diagnosis” in some clinical centers, allowing their physicians to select tailored treatments that can greatly improve their chances of survival. Melanoma is no longer just melanoma, but can now be sub-classified by its genetics (*e.g.*, *BRAF* positive). Non-small cell lung cancer can be *EGFR* positive or *ALK* positive. Treatments targeting *BRAF*, *ALK* and other gene mutations are remarkable improvements over standard therapies and the point at which most cancer cases are given a targeted course of treatment based on their molecular designation will not be far off (Figure 1).¹

The genotyping of drug-metabolizing enzymes has led to improved dosing of drugs for conditions as wide-ranging as depression and anxiety, coronary and peripheral artery disease, inflammatory bowel disease and cancer, thereby helping patients avoid harmful side effects, drug interactions or ineffective treatment.



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)

Thousands of patients have already seen dramatic benefits, yet examples of personalized medicine in action remain sporadic, occurring mostly at well-funded academic medical centers, or prompted by a well-informed patient or a technologically-savvy physician.

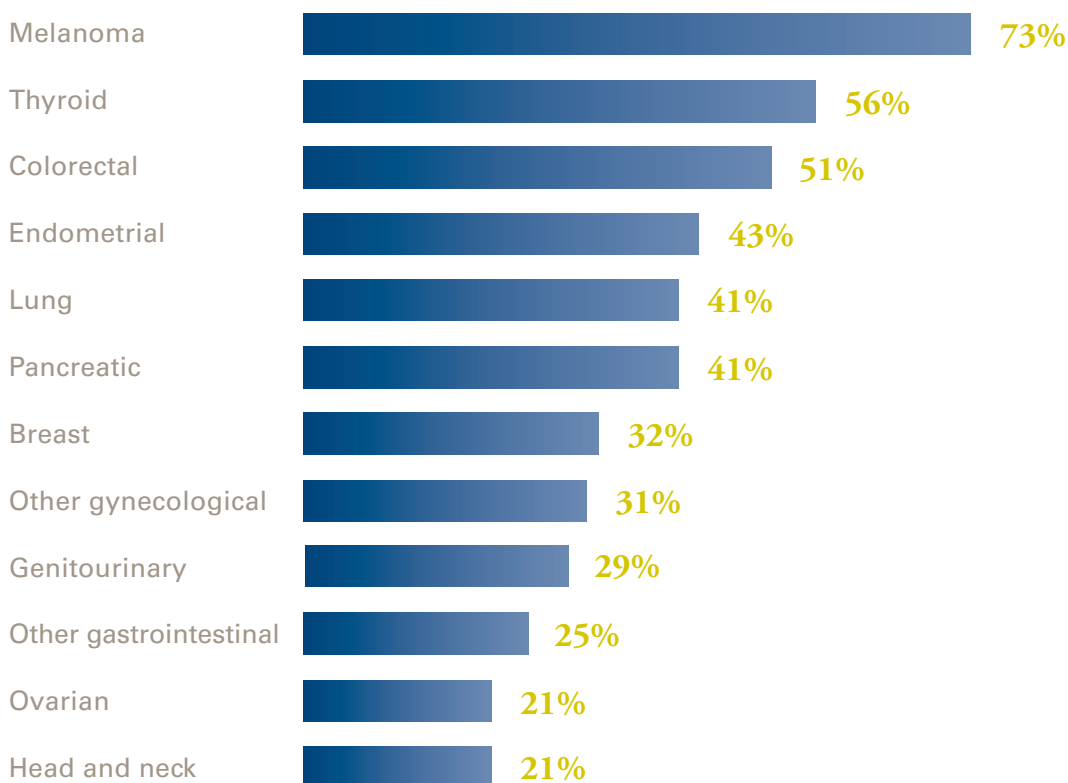
In the future, personalized medicine will become embedded in every

hospital, clinic and medical practice, supported by electronic health records, a clinical decision support system, tailored blood and tissue tests aimed at very early and precise diagnosis, and a personal genomic sequence linked to every patient’s medical record. It is a scenario that seems all the more plausible with the plunging costs of genomic sequencing, emerging epigenetic and

FIGURE 1. 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 type of cancer



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proteomic technologies and a strong commitment by the federal government to support full implementation of electronic health records.

With such rapid developments, it is imperative for the health care system and society to co-evolve with the technology.

Additional laws must be enacted to protect citizens from discrimination

based on their genetic makeup; new systems of insurance payment must account for future disease risks as well as present conditions; and payment systems must provide flexibility for clinicians to tailor care to individuals based on genetics and other factors.

Regulatory guidelines must adapt to the coupling of diagnostics and drugs that target genetically defined

populations and professional education must be modernized to prepare the next generation of doctors and other health care professionals to administer personalized medicine.

There is momentum toward these goals, but much remains to be done to stay ahead of a very steep technology curve.

Building a Track Record

In 1902, Sir Archibald Garrod made the first connection between genetic inheritance and susceptibility to a disease – alkaptonuria;² and in 1956, the first discovery of a genetic basis for selective toxicity was made – for the antimalarial drug primaquine.³ 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 it is perhaps only in the few years since the complete sequencing of the human genome in 2003 that personalized medicine has begun in earnest and is now moving beyond the genome into the entire spectrum of molecular medicine, including the proteome, metabolome and epigenome.

The historical precedents for modern personalized medicine stretch back several decades, but clearly momentum is building now for a more rapid transformation. Segmenting populations into groups of patients who have a greater likelihood of responding to a particular treatment or avoiding side effects is changing the dynamic of drug development and the practice of medicine, and creating opportunities to introduce new business and health care economic models. These changes are beginning to take place as the field builds a solid track record, demonstrating that it can:

- Shift emphasis in medicine from reaction to prevention;
- Select optimal therapy and reduce trial-and-error prescribing;
- Make drugs safer by avoiding adverse drug reactions;
- Increase patient adherence to treatment;
- Improve quality of life;
- Revive drugs that failed in clinical trials or were withdrawn from the market;
- Help control the overall cost of health care.

Shift 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 a 36 to 85 percent lifetime chance of developing breast cancer, compared with a 13 percent chance among the general female population,^{4,5,6} and a 16 to 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.

More than 1,600 genetic tests exist that signal inherited susceptibility to conditions ranging from hearing loss to sudden cardiac arrest.⁷ A subset of these tests that offer a predictive capability, spotting the potential disease before symptoms appear, may be considered to be “personalized.” While not every test is linked to a therapeutic option, a genetic

diagnosis often permits targeted prevention or mitigation strategies. A patient with inherited cardiomyopathy, for example, can be identified and lifestyle changes and disease monitoring implemented to avoid the risk of sudden death.⁸

Select 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 2).⁹ Studies have linked differences in response to the differences in genes that code for the drug-metabolizing enzymes, drug transporters, or drug targets.^{10,11,12} The use of genetic and other forms of molecular screening allows the physician to select an optimal therapy the first time and to avoid the frustrating and costly practice of trial-and-error prescribing.

One of the most common applications 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 these women, standard therapy is not effective,



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

but an antibody drug called Herceptin® (trastuzumab) can reduce the recurrence of a tumor by 52 percent when used in combination with chemotherapy, compared to chemotherapy alone.^{13,14} 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).

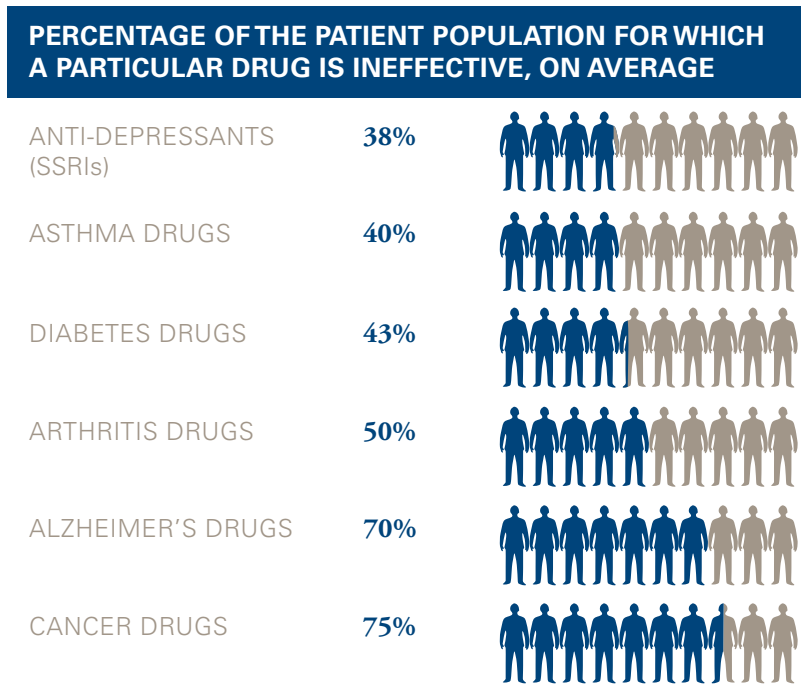
Two complex diagnostic tests, Oncotype DX® and MammaPrint®, use genetic information to help physicians chart the best course of treatment for breast cancer patients. Oncotype DX® can determine whether women with certain types of breast cancer are likely to benefit from chemotherapy.^{15,16,17} MammaPrint® can determine which early-stage breast cancer patients are at risk of distant recurrence following surgery.¹⁸ Both tests place patients into risk categories that inform physicians and patients whether their 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.

A growing number of drugs have become available for the treatment of colon cancer, some of which are best selected using a genetic test. 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.¹⁹ 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.²⁰

Meanwhile, new targeted therapies, paired with genetic tests, are providing 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, cobas® 4800 BRAF V600 Mutation Test and Vysis ALK Break Apart FISH Probe Kit.

Outside oncology, the blood clot-preventing drug Plavix® (clopidogrel) presents another case for using genetic testing to select the best course of treatment. Plavix® can have a very 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®, relative to other patients.²¹ A genetic test costing a few hundred dollars can reveal the risk and allow physicians to craft an alternate course

FIGURE 2. One Size Does Not Fit All



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

Building a Track Record Continued

of treatment, such as administration of the drug Effiant® (prasugrel).

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 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.²²

Make drugs safer by avoiding adverse drug reactions. According to several studies, about 5.3 percent of all hospital admissions are associated with adverse drug reactions (ADRs).²³ Many ADRs are the result of variations in genes that code for the family of cytochrome P450 (*CYP450*) enzymes and other drug-metabolizing enzymes.^{24,25} These variants cause a drug to be metabolized either faster or slower than is true in the general population. As a result, some individuals have trouble inactivating a drug and eliminating it from their bodies, leading to “overdose toxicity,” while others eliminate the drug too rapidly, before it has had a chance to work. The consequences range from unpleasant to fatal if these genetic variations are not considered when dosing.

The U.S. Food and Drug Administration (FDA) has approved the Amplichip® *CYP450* test, a microarray device that can detect 29 variations in two important *CYP450* genes, *CYP2D6* and *CYP2C19*. These genes are linked to the metabolism of about 25 percent of all drugs prescribed.²⁶ Follow-on multiplex assays from Autogenomics (*CYP2C19*) and Luminex (*CYP2D6*) have also been approved by the FDA. These tests are especially useful for comprehensive polypharmacy management, prevalent in the elderly and seriously ill.

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 need to get warfarin dosing right the first time to avoid serious and possibly fatal adverse effects led the FDA to recommend genotyping for all patients before warfarin treatment.²⁷

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, which metabolizes the drug more slowly and is found significantly more often in African than in European-based populations.²⁸ Lowering drug dose in individuals with this allele can help reduce adverse effects and increase treatment compliance.

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.

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 will 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.

Inherited forms of hypercholesterolemia (high cholesterol) can increase the risk of myocardial infarction before the age of 40 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.²⁹

Improve quality of life. A molecular diagnostic test that simply requires a blood sample can replace invasive and uncomfortable tissue biopsies. Allomap® is a multi-gene expression test that can detect whether the immune system of a heart transplant recipient is rejecting the new organ.³⁰ Approximately 25 percent



We are on the tipping point of a whole new game in how we develop drugs [for cancer].”

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



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.”

Margaret Hamburg, M.D.
Commissioner, U.S. Food and Drug Administration

Francis Collins, M.D., Ph.D.
Director, National Institutes of Health

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 for several years. This invasive procedure requires inserting a tube into a vein in the neck which is then threaded to the heart to obtain the biopsy. Allomap[®], FDA-approved in 2008, requires only a blood sample to measure the expression level of 11 genes – data that can determine the likelihood that the patient is experiencing a rejection. A recent study suggests that outcomes may be equivalent for patients who are monitored using Allomap[®] and those who receive endomyocardial biopsies, which several major health insurance companies deem medically necessary.³¹

Revive drugs that failed in clinical trials or were withdrawn from the market. A failing drug or drug candidate can be revived by limiting its use 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. 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 has won approval as a first line treatment for that patient population in the United Kingdom.

Bucindolol is a beta-blocker that was being tested for the treatment of heart disease, but was dropped by its maker several years ago after it failed to demonstrate effectiveness over placebo.³² Since then, scientists have developed a diagnostic test, called the Beta-blocker Evaluation of Survival Test (BEST), which can predict which patients will benefit from the drug. A study using BEST provided much clearer evidence of bucindolol’s effectiveness in a subpopulation (about 50 percent) of heart patients; the drug reduced heart disease deaths by 48 percent and hospitalizations for heart failure by 44 percent.³³ As a result, bucindolol may be resurrected to treat patients for whom it will work.

Help control the overall cost of health care. The cost of health care in the United States 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 treatments. As such, it can also play an important role in the implementation of Accountable Care

Organizations set up under the Affordable Care Act to coordinate patient care and reduce costs. One model estimated that genetic testing to target dosing of the blood thinner drug warfarin could prevent 17,000 strokes in the U.S. and could avoid as many as 43,000 visits to the emergency room.³⁵

Mayo Clinic and the pharmacy benefits manager Medco put the warfarin 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.³⁶

An economic analysis of the Oncotype Dx[®] test looked at the real costs of treating women with breast cancer in a two million member health plan. If one-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).³⁷ Another study found that \$604 million could be saved annually among all patients if Vectibix[®] (panitumumab) or Erbitux[®] (cetuximab) were limited to those patients with metastatic colorectal cancer whose *KRAS* gene is not mutated, because those are the only patients who benefit from the drugs.³⁸

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.

It took \$3 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 described by Moore's Law, the same rule that has predicted reliably the exponential increase in performance of computer technology for the past 40 years; whole-genome sequencing costs fell from \$100-300 million in 2001 to about \$10 million in 2007, a price that still confined such sequencing within the purview of only well-funded laboratories or government initiatives.

By 2008, as second-generation DNA sequencing instruments were taken up broadly by the research market, Moore's Law was no longer relevant – the ability to sequence entire genomes accelerated at a rate far exceeding that ever experienced by the semiconductor and computer industries. By 2009, the cost and duration of sequencing an entire genome decreased significantly, to \$50,000 in two months.³⁹ In May 2011, Illumina announced that it had lowered the price for sequencing whole human genomes to \$5,000 per genome.⁴⁰ Additional costs and time may be added for analysis and annotation in a clinical setting.



Today, one of our biggest goals is to cut the cost of sequencing an entire human genome to \$1,000 or less. This advance will pave the way for each person's genome to be sequenced as part of the standard of care, leading to a revolution in the practice of medicine."

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

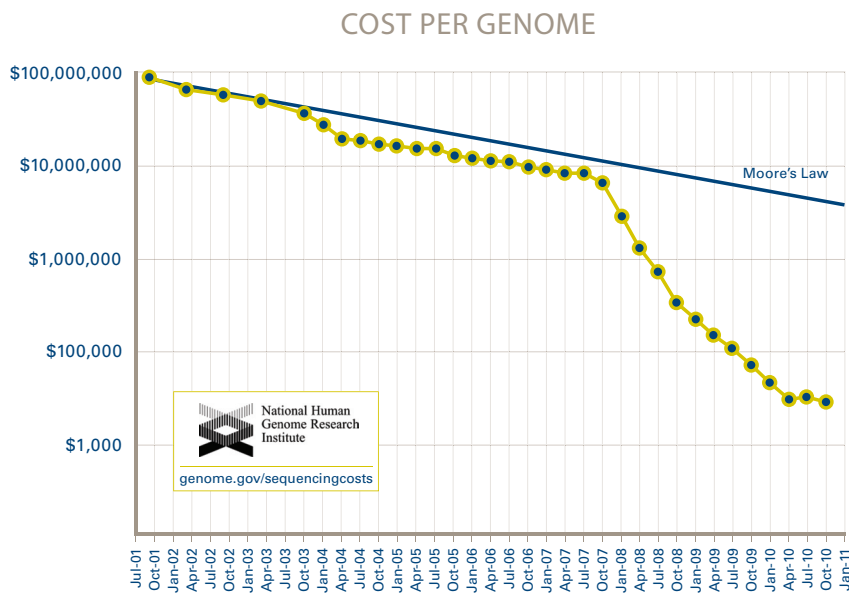
The National Human Genome Research Institute (NHGRI) has funded a number of projects aimed at developing technology to sequence an entire genome for less than \$1,000, and has tracked the performance for those projects over time. The results reflect a general trend in the industry and an important transition around mid-2007 brought on by next-generation sequencing technology (Figure 3).

As the cost and duration of genomic sequencing continues on a sharp downward curve, many scientists believe that, with the help of private and public investment, the \$1,000 genome will arrive within a few years.⁴¹ 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.⁴² Costs of full genomic sequencing have already fallen to the point that such sequencing has been employed in certain cases to resolve difficult diagnoses, with insurers determining that the approach was cost-effective enough to be reimbursed.^{43,44}

Capturing individual genomes of entire populations will be a tremendous boon to research. When thousands and ultimately millions of complete (de-identified) genome sequences are made available to researchers, a tremendous gap in human genetic variation data will be filled. It is thought that many common human

FIGURE 3. The Rapidly Decreasing Cost of Sequencing Complete 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 January 2011, which have since reached \$5,000 per genome.

ailments, such as heart disease, diabetes, and cancer, are actually the result of numerous rare genetic variations, and that even for the same disease, one person might not carry the same set of variants as another. Personal genomes will provide both a powerful tool for identifying those rare genetic variants as well as more accurate means to predict disease susceptibility and response to treatment. These rare variants are, as National Institutes of Health 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 genome-wide disease association studies.

As mass sequencing efforts are underway, a third generation of sequencing technologies is preparing for its debut.

These budding technologies include reading off base pairs of DNA strands as they thread through nanopores,⁴⁵ 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.⁴⁶

Advances are occurring not only in sequencing technology. There is a growing understanding of the changes that occur to the genome that alter its chemistry and structure 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 the environment and lifestyle, 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 National Institutes of Health (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 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, would allow physicians to develop a more holistic, proactive health care strategy based on the patient’s susceptibility to different diseases and 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 managing patients with specific genetic and other characteristics, genomic sequencing and health information technology will transform the practice of medicine.

Regulatory Policy

Clear and appropriate regulation of personalized medicine products and services can enable the development of personalized medicine by providing innovators with a stable, predictable means for bringing new technologies to market, and providing a foundation for fair coverage and payment decisions that ultimately allow research and development costs to be recouped.

Personalized Medicine Tests. The emergence of personalized medicine tests to inform clinical decision-making, along with tests to guide drug selection and dose, has led the FDA to publish guidance documents related to the regulation of these products. Traditionally, diagnostic tests have fallen into two main categories, 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. Use of LDTs often requires more extensive sample and reagent preparation than is required for the diagnostic kits, as well as specialized laboratory equipment and the services of skilled technicians. Both

the Centers for Medicare and Medicaid Services (CMS) and FDA claim jurisdiction over LDTs, but the FDA has taken a hands-off approach, leaving the laboratories that perform these tests to be regulated by CMS's authority under the Clinical Laboratory Improvement Amendment (CLIA) rules.

Recent developments in personalized medicine, in particular the proliferation of complex diagnostic tests and services linked to major health decisions and targeted directly to consumers, have prompted concerns in some sectors about the safety of these new products. The concept of test "safety" comes into play when one considers the consequences of misinterpretation: an ineffective therapy, an unnecessary preventive surgery, or any number of suboptimal,

and sometimes irreversible, medical decisions. Many 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.

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 regulatory approval. Due to the sheer volume and long-term outcomes of many of these tests, 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 suffice for laboratories performing most LDTs. In addition, to provide some transparency around the quality and regulation of hundreds of molecular tests offered by clinical laboratories, the National Institutes of Health is launching a voluntary national registry to catalog available tests.

In general, the protean state of molecular testing regulation has created uncertainty for companies, which have no way of knowing how much they will need to invest, in terms of clinical, economic, or comparative studies, to get their products on the market and to keep them there.

“Promoting personalized medicine means making sure the FDA medical product centers work together as a team to get safe and effective new treatments to patients as quickly as possible.”

FDA Innovation Report, October 5, 2011



Recently, the development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common... These technologies are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect.”

Draft Guidance for Industry and FDA Staff – In Vitro Companion Diagnostic Devices, July 14, 2011

Pharmaceuticals. While the clinical regulation of genetic testing is debated, the FDA’s Voluntary Exploratory Data Submissions (VXDS) program (introduced in 2004 as the Voluntary Genomic Data Submission program) continues to have a positive impact on drug and biologic development. The program enables companies and the FDA to work together to better understand pharmacogenomics before issuing regulatory standards. The informal communication and the agency’s policy of supporting “adaptive” clinical trials that can genetically “enrich” a study population helps companies to integrate genomics into their product development.⁴⁷ As a result, most development projects are accompanied by data on the effects of genetic variation or other biomarkers on 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.⁴⁸ 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).⁴⁹

Companion Diagnostics. The need for a clear regulatory path for “companion diagnostics” has been a great concern ever since the first therapeutic/diagnostic product pair (Herceptin®/HercepTest™) was approved six months apart in 1998. Definitive guidelines have not been published, but regulatory agencies, including the FDA and European Medicines Agency (EMA), have shown signs of addressing the issues. In 2011, the FDA released its Draft Guidance for *In Vitro* Companion Diagnostic Devices, which has helped to clarify the agency’s intention to conduct simultaneous reviews of a drug and its corresponding companion diagnostic.⁵⁰ 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 either mandated or recommended in several cases that biomarker testing be performed prior to prescribing certain drugs. Recognizing that the class of companion therapeutics/diagnostics is likely to grow, the FDA began publishing a table of genomic biomarkers that it considers valid in guiding the clinical use of approved drugs.⁵¹

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, signaled by the creation of a new position for Director for Personalized Medicine in the Office of *In Vitro* Diagnostic Evaluation and Safety, as well as its partnership with Medco to mine data on prescriptions, genetic tests, and clinical outcomes, may ultimately lead to more definitive regulatory guidelines.

Payment

Regulatory approval of personalized medicine products and services is only half the battle on the road to adoption; coverage and payment by CMS or a patient's insurance policy is also needed. Both public and private insurers recognize the benefits of molecular testing in patient management but payers also require *evidence* of its clinical, if not economic, value.

Payers stress that to justify coverage, prognostic tests will have to be subjected to a more rigorous assessment of their cost-effectiveness and impact on health outcomes than is currently the case.⁵² However, if the tests are not reimbursed and not widely used in practice, it is difficult to gather sufficient evidence to supply proof of cost-effectiveness. To date, the scarcity of clinical data on personalized medicine products able to satisfy these assessments has kept payers from fully embracing them. This conundrum was perhaps most clearly illustrated by the rejection of genetically-guided warfarin dosing by Medicare (due to studies that cast some doubt on benefit claims),⁵³ despite the fact that the genetic tests were recommended by the FDA.⁵⁴

Clinical trials for personalized drugs and companion diagnostics have been funded under government grants and programs. Examples include the TAILORx study of Oncotype DX® funded by the National Cancer Institute, the **W**arfarin **A**dverse **E**vent **R**eduction for **A**dults **R**eceiving **G**enetic **T**esting at **T**herapy **I**nitiation (WARFARIN) Study approved by CMS, and the Clarification of Optimal Anticoagulation through Genetics (COAG) trial.⁵⁵ Although these multi-million dollar studies complement industry-funded efforts, they do not provide a sustainable solution to closing the evidence gap for supporting reimbursement and adoption of personalized medicine.

Pharmacy benefit managers (PBMs) have stepped in to provide what might be a more viable business model for adoption. Because they are responsible for processing and paying prescription drug claims, developing formularies and managing drug benefits for more than 210 million Americans, PBMs have a significant interest in getting the best economic value from prescribing practices. Along with their clients (private insurers, employers and Medicare), they also have extensive access to data on patient outcomes and the use of drugs and diagnostics.

Rather than conduct expensive randomized controlled trials, PBMs offer clinically-validated diagnostic tests to patients and then use “real-world” observational data – from actual clinical encounters, not a controlled trial – to establish the clinical utility and cost effectiveness of the test. With these data, molecular tests can then be introduced to insurers with a greater chance of reimbursement and adoption. The use of observational data avoids the “Catch 22” of having to establish proof of utility before most people can even use the tests. By partnering with PBMs, the costs to the diagnostic company to obtain the required evidence for reimbursement are much lower than if they conducted studies on their own, although questions about the significance of observational studies compared with randomized, controlled clinical trials remain.

Two of the largest PBMs, CVS Caremark and Medco, have launched initiatives to

assess the contribution of genetic testing toward patient outcomes and health care savings. Medco has presented data from a real-world observational study of warfarin, recruiting more than 900 patients for genotyping and comparing genetically-guided dosing of the anticoagulant to patients dosed without the benefit of a genetic test.⁵⁶ The study established clinical utility and cost-effectiveness of genotyping at a significantly lower cost than the traditional approach of conducting clinical trials. CVS Caremark is evaluating a number of other pharmacogenomic drug/test combinations, including Pegasys® (peginterferon alfa-2a) and Copegus® (ribavirin) for hepatitis C; Gleevec® (imatinib mesylate), Tasigna® (nilotinib) and Sprycel® (dasatinib) for chronic myeloid leukemia; Tarceva® (erlotinib) for non-small cell lung cancer; and Tykerb® (lapatinib) for breast cancer.

The model also works for diagnostic tests that guide therapy with generic drugs, and there are ongoing studies through Medco's “Genetics for Generics” program to assess azathioprine (an immunosuppressant), tamoxifen for breast cancer, carbamazepine for epilepsy, abacavir for HIV, and clopidogrel for preventing stroke and heart attack.

PBM involvement in promoting personalized medicine for both branded and generic drugs is a natural fit: since anywhere from 20 to 80 percent of initially prescribed treatments fail, the payer community has an incentive to ensure that medicines are prescribed



Comparative effectiveness should complement the trend in medicine to develop personalized medicine – the ability to customize a drug and dose based on individual patient and disease characteristics. One of the advantages of large comparative effectiveness studies is the power to investigate effects at the sub-level that often cannot be determined in a randomized trial. This power needs to be harnessed so personalized medicine and comparative effectiveness complement each other.”

Federal Coordinating Council for Comparative Effectiveness Research, June 30, 2009

correctly the first time so that money is not wasted by trial and error.

As diagnostic and drug developers struggle with establishing evidence for safety and efficacy for regulatory approval, as well as clinical utility and cost effectiveness for reimbursement, insurers and policymakers have raised the bar further by calling for studies that establish the *comparative effectiveness* of the new products and services against established standards of care.

In 2010, the newly enacted health care reform law established the independent Patient-Centered Outcomes Research Institute (PCORI), tasked with conducting studies on the comparative risks and benefits of marketed drugs and devices. The law specifically directs the institute to conduct comparative effectiveness research (CER) in subpopulations differentiated by race, ethnicity, gender, and age, as well as genetic and molecular subtypes, an approach advocated by the Personalized Medicine Coalition. This shift would be the first time such studies are conducted with a focus on subpopulations. As such, it will require consideration of how to conduct them in a way that facilitates rather than inhibits development of personalized medicine tests and drugs.

Even if the economics and evidence requirements for personalized medicine studies can be demonstrated, reimbursement

policies of government and private insurers will still have to be modified to make full use of personalized medicine diagnostics. Specifically, CMS’ policies, often replicated throughout the insurance industry, need to be updated to permit screening when it is cost-effective.

For a new era of medicine that relies on predicting and preventing disease before it occurs, the CMS rules for Medicare are outmoded. They state “tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute.” Such a policy has placed significant limits on the adoption of personalized medicine practices that offer value by predicting disease risk *precisely in the absence of* signs or symptoms. Although Medicare generally does not cover tests that are prognostic or predictive, there are some notable exceptions, including Pap tests, colorectal cancer screening tests, mammograms, and PSA screening.

Even if CMS covers a predictive test, the way it is paid for can hinder its adoption. New molecular tests are typically categorized under the current procedural terminology (CPT) codes, which often do not account for the technical complexity of the tests and their interpretation. Many of the services provided by genetics specialists required to interpret the tests are not

reimbursed, or are undervalued by current payment policies. Although research and development costs for molecular diagnostic tests are significantly higher than those for conventional laboratory tests, due to extensive genomic research and clinical validation, CMS generally pays for the innovative molecular tests based mostly on materials cost and performance steps, and at the same level as older laboratory tests.

There are indications, however, that the payment policies of both public and private insurers are beginning to move toward supporting personalized medicine:

- The American Medical Association CPT Editorial Board is developing a multi-tiered set of CPT codes for molecular diagnostics that will identify and describe the technology and services of these tests.⁵⁷
- CMS announced that it was considering opening a National Coverage Determination (NCD) process for pharmacogenetic testing in 2009, allowing payment for “investigational” products (such as genotyping for warfarin) in order to facilitate a path to reimbursement and adoption.⁵⁴
- Several large private insurers, including Aetna, United Healthcare, and Kaiser Permanente, have instituted progressive coverage policies that pay for molecular tests identifying pre-symptomatic high-risk populations (*e.g.*, *BRCA1/2* for breast cancer) or that guide optimal therapy (*e.g.*, *Oncotype Dx*[®]).

Health Information Technology

Health information technology (Health IT) helps power personalized medicine, but personalized medicine will not reach its full potential or widespread adoption until nearly every hospital, clinic and physician's office incorporates Health IT into its organization and practice. It will be difficult to manage the large volume of information generated from tens of thousands of human genes and proteins to understand their relationship with disease risk and treatment response. It will be hard to create an instant...and molecular data to better understand disease correlations and allow health care providers to make timely, sound clinical decisions based on a body of scientific knowledge that may be beyond the training, experience or memory of a single practitioner. Nevertheless, these are the features that will be required to enable personalized medicine in the new Health IT infrastructure.

Government support for Health IT is strong. The Obama administration has made implementation of Health IT a top priority by including \$44 billion in funding as part of the Health Information Technology for Economic and Clinical Health Act, or HITECH Act. A section of the American Recovery and Reinvestment Act of 2009 (ARRA), HITECH formalized the Office of the National Coordinator for Health Information Technology and offers funding for infrastructure and incentive payments to providers who adopt and use Health IT at an evolving standard of implementation termed "meaningful use." It is important to note that after 2015, hospitals and physicians face penalties for *not* using Health IT, such as electronic health records (EHRs), in a meaningful way, which should include molecular information.

Many hurdles to implementing an interoperable system of EHRs nationwide remain, but many are being overcome not only by the pressing need for change, but also by the commitment from the federal



[W]e must ensure that new systems are capable of handling, sharing and analyzing the genetic and outcomes data needed to promote the continued development of personalized medicine."

Darrell M. West, Ph.D.

Vice President, Governance Studies, The Brookings Institution

government to complete the transition to EHRs as an essential part of health care reform. 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: creating a "learning health care system" that links clinical outcomes to new research on genetic and other molecular variation,

encourages a team-based approach to health care, provides the physician with clinical decision support, engages patients in their own health maintenance and provides data on personalized diagnostics and treatments to support a rational basis for insurance coverage. Health IT will thereby become a powerful enabler in the realization of personalized medicine.

Genetic Non-Discrimination

As the role of genetics in medicine becomes more prominent, genetic privacy has also come into sharper focus. The knowledge of a person's susceptibility to disease, even before he or she shows signs or symptoms, can be either a powerful tool in improving health and quality of life, or a means to discriminate in the workplace, and 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.



We are in a new era of the life sciences...but in no area of research is the promise greater than in the field of personalized medicine.”

Senator Edward M. Kennedy

Remarks on the Senate's Consideration of the Genetic Information Nondiscrimination Act, April 24, 2008

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 its access. However, the rules only applied to federally-funded institutions and gaps remained in privacy protections with respect to employers and insurance providers.

In 2008, the *Genetic Information Nondiscrimination Act (GINA)* was signed into law, explicitly prohibiting employers and health insurers from discriminating against individuals on the basis of their genetic risk factors. The federal law remains to be tested but it 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. Such confidence may open the door to greater participation in research as well as acceptance of genetic information as part of medical records. In November 2010, the Equal Employment Opportunity Commission stepped in to provide greater clarification on its interpretation of GINA, generally strengthening its provisions (although some employers, such as the military, are exempt).

Recognizing that GINA does not sufficiently 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 Governor 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.⁵⁸ 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.

While laws on genetic privacy evolve to meet the needs of patients, current law, HIPAA in particular, can also make it harder to collect and analyze aggregated clinical data for the development of new personalized treatments and diagnostics. The public's expectation of protecting privacy and the need to encourage research must be properly balanced so that medical care can continue to improve.

Medical Education

As personalized medicine becomes a reality in mainstream medical practice, physicians and other health care providers will have to administer or advise on the application of growing numbers of molecular and genetic tests and pharmacogenomically-guided 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 arise from molecular and genetic testing. The adoption of personalized medicine technology and approaches will depend 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.

Many studies have documented the deficit in genetics education for the health care professions and the barriers it presents to full integration of genetics into medical practice.⁵⁹ Such studies have uncovered several reasons for the continuing absence in medical educational programs: 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 integrated into basic science curricula, genetics instruction is usually left out of clinical training.

The lack of genetics curricula has prevented new genetic knowledge from widespread clinical adoption. A recent survey of physicians regarding hereditary breast, ovarian and colorectal cancer revealed limited knowledge and a lack of confidence in incorporating key genetic concepts into their practice.⁶⁰ For example, only 37.5 percent of respondents understood correctly that hereditary breast cancer linked to *BRCA1* and *BRCA2* genes could be transmitted through fathers. A survey

of psychiatrists found that although 83 percent believed it was their responsibility to discuss genetics with patients, only 58 percent actually did so, and only 25 percent felt able to do so competently.⁶¹ Other studies pointed to physicians' lack of awareness of the newly passed genetic anti-discrimination law,⁶² inappropriate referrals to genetic testing and counseling,⁶³ and shortcomings in their ability to pass on key genetic information relevant to their patients' conditions.⁶⁴ A recent survey by Medco and the American Medical Association found that 98 percent of physicians are aware that patient genetic profiles can and will influence therapy, but only 10 percent believe they have the knowledge required to use genetic information in practice.⁶⁵

Taking 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 specific programs have emerged to provide an example for what medical education could look like in the future.

Harvard Medical School has one of the longest standing 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, as well as clinical laboratory rotations and specialty clinics in cardiovascular, cancer, renal, pulmonary and endocrine genetics. A number of other leading medical education institutions including, but not limited to, Duke University School of Medicine, Ohio State University and Stanford University have made significant commitments to combine classroom and clinical training in genomic approaches for internal and pediatric medicine.

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) and in colleges of pharmacy.⁶⁶

The Emergence of Participatory Medicine

The expanding use of Health IT in the clinical setting, as well as the potential to connect patients to their own medical records from their homes and smartphones, creates an entirely new scenario where patients can become active participants in their own medical care. Such participation will become an essential component of personalized medicine, completing the loop between doctor, patient and medical research. There are several ways in which patient participation enables and magnifies the benefits of personalized medicine.

First, the scale of studies required to pinpoint multiple rare genetic mutations that may be responsible for common chronic conditions will make such studies prohibitively expensive unless the data are collected nationwide from real-life clinical encounters. These “observational data” will become major currency for the discovery of gene-disease associations and the variable response to drugs and treatment. Patients’ willingness to contribute data from their medical records, including entire genomic sequences, will drive both observational and formal clinical studies.

Second, environment, lifestyle, diet, family history, and the patients’ observations of their own symptoms will need to be combined with molecular data to provide a comprehensive view of the factors that influence disease risk, progression and treatment outcomes. The personal health record, essentially a patient-owned portal into his/her electronic health record, will enable patients not only to record observations of their own health or conditions into their record, but to manage their treatment and make appropriate lifestyle changes to slow progression or prevent onset of disease.

Third, in an environment where the medical establishment has been slow

to take on the practice of personalized medicine, the engaged patient will play an important role in driving adoption of personalized medicine.

A survey of 1,000 U.S. residents in 2010 found that public support for personalized medicine remains strong. About 58 percent of respondents saw the value in using genetic information to help identify which drugs would work

best for them during treatment, and 65 percent would like to use genetic data to determine whether they might suffer unwanted adverse reactions to a drug.⁶⁷

As patients continue to accept and even demand personalized medicine products that yield better health outcomes, their active participation in contributing data to research will accelerate the discovery of new diagnostics and treatments.



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
Founder and Chairman, Proventys

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 using evidence well beyond what is visibly obvious into categories that presage the course of disease and its likely response to treatment, 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 some day a genomic sequence in every medical record. The implications of this transition are that we will 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.

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.

The enabling technologies of personalized medicine, in particular genomic sequencing and its interpretation, will have to be further developed and standardized for routine clinical practice.

Medicare and private insurers must establish a path toward evaluating the clinical and economic utility of personalized medicines in order to facilitate their reimbursement.



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

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

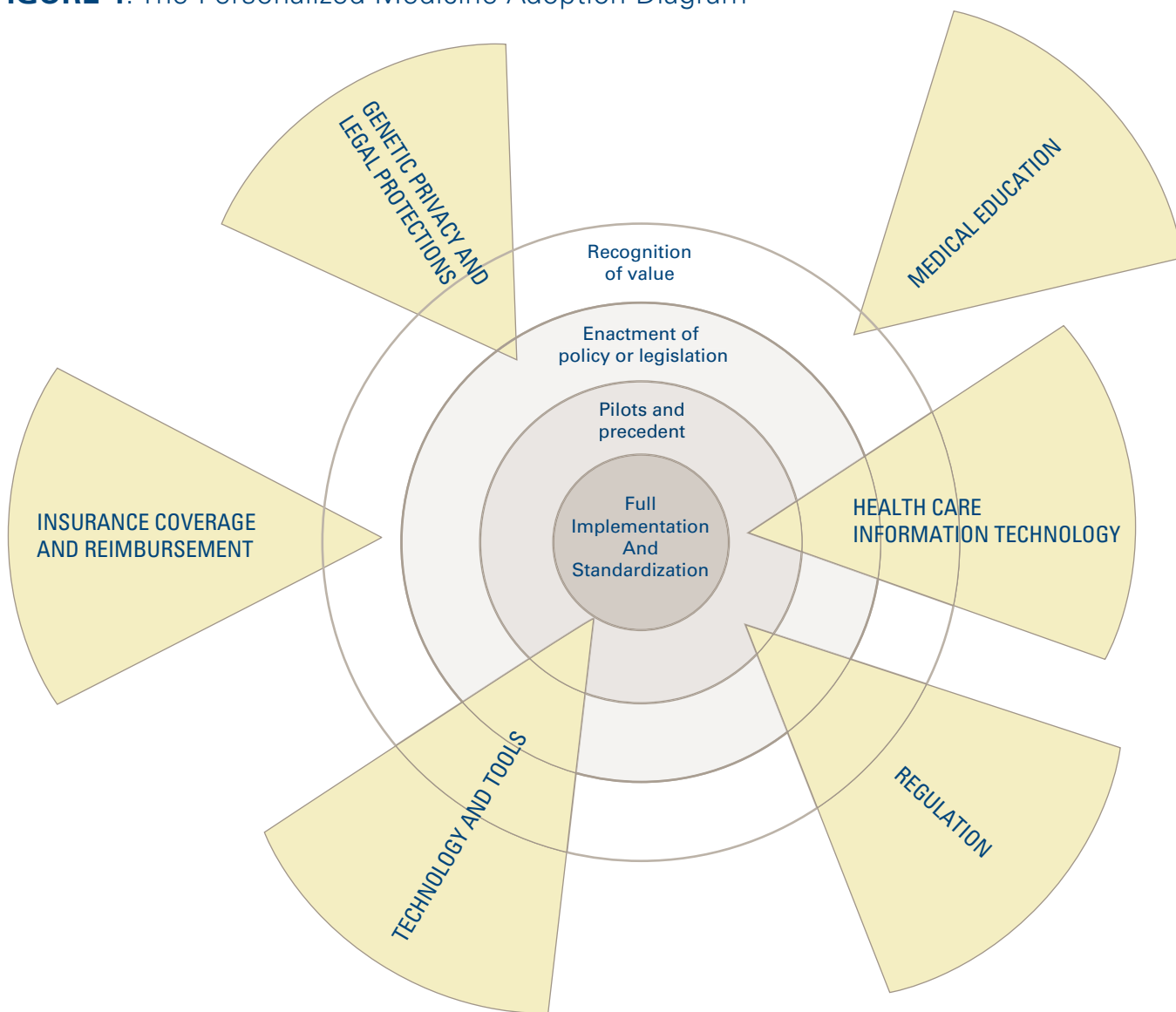
Educational institutions must now prepare the next generation of physicians for the inevitable arrival of personalized medicine, and hospitals and physician practices must adopt electronic health records.

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. A diagram illustrating

the degree to which each of these sectors has progressed is presented in Figure 4.

Hippocrates warned us over 2,400 years ago that “the art 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 opportunity from a wave of data headed our way—and to realize the full health and economic benefits of matching the right treatment or prevention to each and every patient.

FIGURE 4. The Personalized Medicine Adoption Diagram



The implementation of personalized medicine requires a confluence of several sectors (represented by wedges in the diagram). Concentric circles represent stages of implementation. Full implementation of personalized medicine can only be achieved when all sectors converge toward the center.

Table: Selected Personalized Medicine Drugs, Treatments and Diagnostics as of September 2011*

Indications in quotes and otherwise unattributed, are cited from the therapeutic or diagnostic product label.

Therapeutic product labels contain pharmacogenomic information as:

Information only

Recommended

Required

Unhighlighted products have no pharmacogenomic information, recommendations or requirements in the label.

Therapy	Biomarker/Test	Indication
Mivacron® (mivacurium)	Cholinesterase gene	Anesthesia adjunct: “Mivacron 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.”
Ansaid® (flurbiprofen)	CYP2C9	Arthritis: “ <i>In vitro</i> studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite, 4'-hydroxy-flurbiprofen.”
Depakote® (divalproex)	UCD (NAGS; CPS; ASS; OTC; ASL; ARG)	Bipolar disorder: “Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders [UCDs]...particularly ornithine transcarbamylase deficiency [OTC].”
Aromasin® (exemestane) Arimidex® (anastrozole) Nolvadex® (tamoxifen)	Estrogen Receptor (ER)	Breast cancer: Exemestane is indicated for adjuvant treatment of post-menopausal women with ER-positive early breast cancer. Anastrozole is for treatment of breast cancer after surgery and for metastases in post-menopausal women. Tamoxifen is the standard therapy for estrogen receptor-positive early breast cancer in pre-menopausal women.
Chemotherapy	Mammostrat®	Breast cancer: Prognostic immunohistochemistry (IHC) test used for postmenopausal, node negative, estrogen receptor expressing breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy.
Chemotherapy	MammaPrint®	Breast cancer: Assesses risk of distant metastasis in a 70-gene expression profile.
Chemotherapy	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.
Chemotherapy	CompanDx® 31-gene signature	Breast cancer: The test predicts “time to event” for metastasis of breast cancer, following surgery or biopsy.
Faslodex® (fulvestrant)	Hormone Receptor (HR)	Breast cancer: Fulvestrant is indicated for the treatment of hormone receptor positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy.
Herceptin® (trastuzumab) Tykerb® (lapatinib)	HER-2/neu receptor	Breast cancer: “...for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER-2 [Human Epidermal growth factor Receptor 2] protein and who have received one or more chemotherapy regimens for their metastatic disease.” High levels of HER-2 expression have been associated with increased disease recurrence in breast cancer, but show a better response to trastuzumab.
Pharmaceutical and surgical prevention options and surveillance	BRCA 1/2	Breast cancer: Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer.
Nolvadex® (tamoxifen)	Breast Cancer Index SM (HOXB13, IL17BR)	Breast cancer: Calculates a combined risk analysis for recurrence after tamoxifen treatment for ER-positive, node-negative breast cancer.

THERAPY	BIOMARKER/TEST	INDICATION
Bidil® (isosorbide and hydralazine)	<i>NAT1; NAT2</i>	Cardiovascular disease: Prescribed for heart failure, the “mean absolute bioavailability of a single oral dose of hydralazine 75 mg varies from 10 to 26%, with the higher percentages in slow acetylators.”
Coumadin® (warfarin)	<i>CYP2C9</i>	Cardiovascular disease: Detects “an increased bleeding risk for patients carrying either the <i>CYP2C9</i> *2 or <i>CYP2C9</i> *3 alleles.” “The lower initiation doses should be considered for patients with certain genetic variations in <i>CYP2C9</i> and <i>VKORC1</i> enzymes.”
Coumadin® (warfarin)	<i>VKORC1</i>	Cardiovascular disease: “Certain single nucleotide polymorphisms in the <i>VKORC1</i> gene (especially the 1639G>A allele) have been associated with lower dose requirements for warfarin.”
Coumadin® (warfarin)	PGx Predict™: Warfarin	Cardiovascular disease: Determines <i>CYP2C9</i> and <i>VKORC1</i> genotypes to predict likelihood of adverse events with warfarin therapy.
Coumadin® (warfarin)	Protein C deficiencies	Cardiovascular disease: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has been associated with tissue necrosis following warfarin administration.
Lipitor® (atorvastatin)	<i>LDLR</i>	Cardiovascular disease: “Doses should be individualized according to the recommended goal of therapy. Homozygous Familial Hypercholesterolemia (10-80mg/day) and heterozygous (10-20mg/day).”
Pharmaceutical and lifestyle prevention options	Familion® 5-gene profile	Cardiovascular disease: Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Plavix® (clopidogrel)	<i>CYP2C19</i>	Cardiovascular disease: “ <i>CYP2C19</i> poor metabolizer status is associated with diminished response to clopidogrel...Pharmacogenetic testing can identify genotypes associated with variability in <i>CYP2C19</i> activity.”
Statins	SINM PhyzioType™	Cardiovascular disease: Predicts risk of statin-induced neuro-myopathy, based on a patient’s combinatorial genotype for 50 genes.
Camptosar® (irinotecan)	<i>UGT1A1</i>	Colon cancer: “Individuals who are homozygous for the <i>UGT1A1</i> *28 allele... are at increased risk for neutropenia following initiation of Camptosar® treatment...A reduction in the starting dose...should be considered for patients known to be homozygous for the <i>UGT1A1</i> *28 allele.”
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.
Erbix® (cetuximab) Vectibix® (panitumumab)	<i>BRAF</i>	Colon cancer: A mutation in <i>BRAF</i> identifies 12-15 percent of metastatic colorectal cancer patients who fail to respond to TKI’s. Non-mutated forms of <i>BRAF</i> and <i>KRAS</i> genes are required for response.
Erbix® (cetuximab) Vectibix® (panitumumab)	EGFR expression	Colon cancer: “Patients enrolled in the clinical studies were required to have... evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit.” EGFR positive individuals (high expression) are more likely to respond to the drug than those with reduced EGFR expression.
Erbix® (cetuximab) Vectibix® (panitumumab) Iressa® (gefitinib) Tarceva® (erlotinib)	<i>KRAS</i>	Colon cancer: <i>KRAS</i> mutations are associated with poor response to the anti-EGFR antibody cetuximab. The FDA suggests use of cetuximab and panitumumab is not recommended for the treatment of colorectal cancer patients with <i>KRAS</i> mutations.”Retrospective analyses of metastatic colorectal cancer trials have not shown a treatment benefit for the <i>EGFR</i> inhibitors in patients whose tumors had <i>KRAS</i> mutations in codon 12 or 13.”
Erbix® (cetuximab) Vectibix® (panitumumab) 5-fluorouracil (5-FU) Camptosar® (irinotecan)	Target GI™	Colon cancer: Provides information of the expression of key molecular targets— <i>KRAS</i> , <i>TS</i> , and <i>TOPO1</i> —to guide therapy.

THERAPY	BIOMARKER/TEST	INDICATION
Camptosar® (irinotecan) Platinum therapies 5-FU Gemzar® (gemcitabine) Alimta® (pemetrexed) Erbix® (cetuximab) Vectibix® (panitumumab)	ResponseDx:Colon™	Colon cancer: Expression profiles and mutations in <i>ERCC1</i> , <i>TS</i> , <i>EGFR</i> , <i>BRAF</i> , <i>KRAS</i> provide information for the selection of various therapies.
Tegretol® (carbamazepine)	<i>HLA-B*1502</i>	Epilepsy and bipolar disorder: Serious dermatologic reactions are associated with the <i>HLA-B*1502</i> allele in patients treated with carbamazepine. “Patients with ancestry in genetically at-risk populations should be screened for the presence of <i>HLA-B*1502</i> prior to initiating treatment with Tegretol®. Patients testing positive for the allele should not be treated with Tegretol® unless the benefit clearly outweighs the risk.”
Immunosuppressive drugs	AlloMap® gene signature	Heart transplantation: Monitors patient’s immune response to heart transplant to guide immunosuppressive therapy.
Pegasys® (peginterferon alfa-2a)	<i>IL28B</i>	Hepatitis C: “A single nucleotide polymorphism near the gene encoding interferon-lambda-3 (<i>IL28B</i>) was associated with variable SVR [sustained virological response] rates.”
Selzentry® (maraviroc)	CCR5 receptor	HIV: “Selzentry®, in combination with other antiretroviral agents, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1...”
Ziagen® (abacavir)	<i>HLA-B*5701</i>	HIV: “Patients who carry the <i>HLA-B*5701</i> allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the <i>HLA-B*5701</i> allele is recommended.”
Entocort® (budesonide)	Prometheus® IBD Serology 7	Inflammatory bowel disease: Identifies subset of patients who will benefit from budesonide.
Busulfex® and Myleran® (busulfan)	Philadelphia Chromosome/ <i>BCR-ABL</i>	Leukemia: “Busulfan is clearly less effective in patients with chronic myelogenous leukemia who lack the Philadelphia (Ph1) chromosome.”
Gleevec® (imatinib)	Philadelphia Chromosome/ <i>BCR-ABL</i>	Leukemia: “Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult and pediatric patients with Philadelphia chromosome positive [indicated by presence of <i>BCR-ABL</i>] chronic myeloid leukemia (CML) in chronic phase.”
Purinethol® (mercaptopurine) Tabloid® (thioguanine) Imuran® (azathioprine)	TPMT	Leukemia: Guides adjustment of dose in treatment of acute lymphoblastic leukemia: “Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe Purinethol® toxicity from conventional doses...It is recommended that consideration be given to either genotype or phenotype patients for TPMT.”
Sprycel® (dasatinib)	Philadelphia Chromosome/ <i>BCR-ABL</i>	Leukemia: “Dasatinib is indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.”
Tasigna® (nilotinib)	<i>UGT1A1</i> , Ph+	Leukemia: “Tasigna® is...indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML)...” in adults resistant to imitinab. <i>UGT1A1*28</i> patients have a high risk of hyperbilirubinemia.
Trisenox® (arsenic trioxide) Vesanoid® (tretinoin)	<i>PML/RARα</i>	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 <i>PML/RAR-alpha</i> gene expression.”
Bexxar® (tositumomab)	CD20	Lymphoma: “Bexxar...is indicated for the treatment of patients with CD20 antigen expressing...non-Hodgkin’s lymphoma.”
Ontak® (denileukin diftitox)	CD25	Lymphoma: “Ontak® is 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.”

THERAPY	BIOMARKER/TEST	INDICATION
5-fluorouracil (5-FU) Gemzar® (gemcitabine)/ carboplatin Erbix® (cetuximab) Vectibix® (panitumumab) Iressa® (gefitinib) Tarceva® (erlotinib)	ResponseDx:Lung™	Lung cancer: Expression profiles and mutations in <i>ERCC1</i> , <i>TS</i> , <i>EGFR</i> , <i>RRM1</i> , <i>KRAS</i> , and <i>EML4-ALK</i> provide information for the selection of various therapies.
Gemzar® (gemcitabine) Daraplatin® (carboplatin)	<i>RRM1</i>	Lung cancer: Gemcitabine interferes with the DNA synthesis function of ribonucleotide reductase through its active subunit (<i>RRM1</i>). Low levels of <i>RRM1</i> gene expression are associated with improved response to gemcitabine/platin therapy.
Iressa® (gefitinib) Tarceva® (erlotinib)	<i>KRAS</i>	Lung cancer: <i>KRAS</i> is mutated in about 30 percent of lung cancers, which exhibit resistance to EGFR-directed drugs used in NSCLC therapy. However recent evidence suggests the role of <i>KRAS</i> mutation status in choosing EGFR TKI or anti-EGFR monoclonal antibodies is unclear.
Tarceva® (erlotinib)	<i>EGFR</i> expression and activating mutations	Lung cancer: <i>EGFR</i> activating mutations occur in approximately 10 percent of Caucasian patients with NSCLC and up to 50 percent of Asian patients. Data from multiple studies indicate a predictive role for <i>EGFR</i> activating mutations with respect to response rate and progression-free survival with TKI therapy, particularly in the first-line setting.
Xalkori® (crizotinib)	<i>ALK</i>	Lung cancer: “Xalkori® is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (<i>ALK</i>)-positive as detected by an FDA-approved test.” The <i>ALK</i> abnormality occurs in 1-7% of NSCLC patients.
Xalkori® (crizotinib)	Vysis <i>ALK</i> Break Apart FISH Probe Kit	Lung cancer: The Vysis <i>ALK</i> Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the <i>ALK</i> 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 Xalkori® (crizotinib).
Aralen® (chloroquine)	<i>G6PD</i>	Malaria: “The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency.”
Monitoring and prevention strategies	<i>p16</i>	Melanoma: Anyone with the inherited gene mutation in <i>p16</i> is at higher than average risk for melanoma—up to 50 percent by age 50, or 50 times the risk of non-mutation individuals.
Zelboraf™ (vemurafenib)	<i>BRAF V600E</i>	Melanoma: “Zelboraf™ is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with <i>BRAF V600E</i> mutation as detected by an FDA-approved test.” The <i>BRAF V600E</i> mutation is found in about half of melanoma patients.
Zelboraf™ (vemurafenib)	cobas® 4800 <i>BRAF V600</i> Mutation Test	Melanoma: The cobas® 4800 <i>BRAF V600</i> Mutation Test detects the <i>BRAF V600E</i> mutation in formalin-fixed, paraffin-embedded (FFPET) human melanoma tissue. It is designed to help select patients for treatment with vemurafenib, an oral medicine designed to treat patients whose melanoma tumors harbor a mutated form of the <i>BRAF</i> gene.
Chemotherapy	CupPrint™	Multiple cancers: Determines cancer classification for tumors of unknown primary origin.
Chemotherapy	CancerTYPE ID®	Multiple cancers: Classifies 39 tumor types from tumors of unknown primary origin, using a gene expression profile.

THERAPY	BIOMARKER/TEST	INDICATION
5-FU Gemzar® (gemcitabine) Alimta® (pemetrexed)	<i>TS</i>	Multiple cancers: Colon cancer: High levels of <i>TS</i> gene expression correlate with colorectal tumor resistance to 5-FU. Gastric cancer: <i>TS</i> gene expression in primary adenocarcinoma of the stomach has an inverse relationship to response (e.g., high expression, low response) for patients treated with 5-FU. Lung cancer: Patients with high levels of thymidylate synthetase (<i>TS</i>), a DNA synthesis enzyme, in their tumors tend to respond less favorably to <i>TS</i> inhibitors such as 5-FU.
Elitek® (rasburicase)	<i>G6PD</i>	Multiple cancers: “Rasburicase administered to patients with glucose-phosphate dehydrogenase (G6PD) deficiency can cause severe hemolysis. ...Do not administer <i>ELITEK</i> to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency...Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting <i>ELITEK</i> .”
Pharmaceutical and surgical treatment options and surveillance	<i>MLH1, MSH2, MSH6</i>	Multiple cancers: Guides surveillance and preventive treatment based on susceptibility risk for colon and other cancers.
Platinum therapies Camptosar® (irinotecan)	<i>ERCC1</i>	Multiple cancers: Colon cancer: In a study of advanced colorectal cancer treated with 5-fluorouracil/oxaliplatin, low <i>ERCC1</i> expression is associated with longer survival. High expression of <i>ERCC1</i> is associated with response to irinotecan therapy. Gastric cancer: Patients treated with FOLFOX (5-fluorouracil/leucovorin/oxaliplatin) regimen or first-line cisplatin-based regimens respond significantly better if they show lower levels of <i>ERCC1</i> expression. Lung cancer: Enzyme excision repair complementing factor 1 (<i>ERCC1</i>) helps repair DNA damage caused by platinum-based therapy. Low <i>ERCC1</i> is a favorable indicator for response to platinum therapy.
Xeloda® (Capecitabine)	DPD	Multiple cancers: “Rarely, unexpected severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. ...XELODA is contraindicated in patients with known [DPD] deficiency.”
Drugs metabolized by Cytochrome P450 2C19: carisoprodol, clopidogrel, dexlansoprazole, diazepam, drospirenone & ethinyl estradiol, esomeprazole, modafinil, nelfinavir, pantoprazole, prasugrel, rabeprazole, ticagrelor, voriconazole 2D6: aripiprazole, atomoxetine, carvedilol, cevimeline, chlordiazepoxide & amitriptyline, citalopram, clomipramine, clozapine, codeine, desipramine, desloratadine & pseudoephedrine, dextromorphan & quinidine, doxepin, fluoxetine, fluoxetine & olanzapine, fluvoxamine, galantamine, gefitinib, iloperidone, imipramine, metoprolol, modafinil, nefazodone, nortriptyline, paroxetine, perphenazine, pimozide, propranolol, propafenone, protriptyline, quinidine, risperidone, terbinafine, tetrabemazine, thioridazine, timolol, tiotropium, tolterodine, tramadol & acetomenophen, trimipramine, venlafaxine	Amplichip® <i>CYP2D6/ CYP2C19</i>	Multiple diseases: FDA classification 21 CFR 862.3360: “This device is used as an aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information.”

THERAPY	BIOMARKER/TEST	INDICATION
Gleevec® (imatinib)	<i>PDGFR</i>	Myelodysplastic syndrome: Imatinib is indicated for “Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with <i>PDGFR</i> (platelet-derived growth factor receptor) gene re-arrangements.”
Revlimid® (lenalidomide)	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.”
Celebrex® (celecoxib)	<i>CYP2C9</i>	Pain: “Patients who are known or suspected to be <i>P450 2C9</i> 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.”
Immunosuppressant Therapies	ImmuKnow®	Post-Transplant Immune Status: ImmuKnow® is an immune cell function assay that detects cell-mediated immunity in an immunosuppressed population.
Enbrel® (etanercept) Remicade® (infliximab)	PsoriasisDx™	Psoriatic arthritis: This sequencing-based assay detects the presence of gene variant <i>MICA-A9</i> , indicative of an increased risk of psoriatic arthritis. Identification of risk could guide monitoring and early treatment with TNF-alpha antagonists.
Psychiatric drugs	GeneSightRx®	Psychiatric disorders: Genetic variants (<i>CYP1A2</i> , <i>CYP2D6</i> , <i>CYP2C19</i> , serotonin transporter gene <i>SLC6A4</i> , serotonin 2A receptor gene <i>5HTR2A</i>) in this test may affect a patient’s ability to metabolize, tolerate or respond to 26 psychotropic medications.
Risperdal® (risperidone) Zyprexa® (olanzapine)	PhyziType PIMS	Psychiatric disorders: Predicts risk of psychotropic-induced metabolic syndrome, based on a patient’s combinatorial genotype for 50 genes.
Efudex® (5-FU)	DPD	Skin cancer: “Efudex® should not be used in patients with dihydropyrimidine dehydrogenase (DPD) deficiency.”
Gleevec® (imatinib)	<i>c-KIT</i>	Stomach cancer: “Gleevec® is also indicated for the treatment of patients with Kit (<i>CD117</i>) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).”
Herceptin® (trastuzumab) Tykerb® (lapatinib)	HER-2/neu receptor	Stomach cancer: Patient survival was significantly improved with Herceptin®+ chemotherapy versus chemotherapy alone in the treatment of gastric cancer.
Herceptin® (trastuzumab) Platinum therapies 5-FU	ResponseDx:Gastric™	Stomach cancer: Expression profiles and mutations in <i>ERCC1</i> , <i>TS</i> , and <i>HER2</i> provide information for the selection of various therapies.
Rifadin® (rifampin) Nydrazid® (isoniazid) Pyrazinamide	<i>NAT</i>	Tuberculosis: “Slow acetylation may lead to higher blood levels of the drug, and thus, an increase in toxic reactions.”

* This list is not intended to be comprehensive but reflects commonly used or available products as of September 2011. 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 website (<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 websites and public announcements.

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Note: all websites were accessed as of September 8, 2011.

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