

THE CASE FOR PERSONALIZED MEDICINE

We present a case for personalized medicine, shedding light on its demonstrated benefits and limitations, and outlining a realistic scenario for its evolution.

In considering whether personalized medicine has a viable future, a look into the past reveals that it has always been here in some form. But in its modern manifestation, which relies on molecular analysis and proactive care, personalized medicine will require an extensive system of support. This system will include new regulatory approaches, revamped medical education curricula, integrated health information systems, legislation to protect against genetic discrimination, insurance coverage for sophisticated molecular diagnostic tests, and a reimbursement system that encourages proactive care. Because of the many hurdles before it, some experts have questioned whether personalized medicine will become a dominant trend in healthcare, or just a passing phase. In this paper, we present the case for personalized medicine, shed light on its demonstrated benefits and limitations, and outline a realistic scenario for its evolution.

By using molecular analysis to achieve optimum medical outcomes in the management of a patient's disease or disease predisposition, personalized medicine promises to introduce a new standard of healthcare.

The molecular methods that make personalized medicine possible include testing for variations in genes, gene expression, proteins, and metabolites, as well as new treatments that target molecular mechanisms. Test results are correlated with clinical factors – such as disease state, prediction of future disease states, drug response, and treatment prognosis – to help physicians individualize treatment for each patient.

In a sense, physicians have always practiced personalized medicine. They routinely use diagnostic tests to determine a patient's disease. They also switch drugs or adjust dosages to optimize treatment or avoid harmful side effects. However, the traditional form of personalized medicine has been based on the observable manifestations of a disease or treatment, such as a tumor on a mammogram, the appearance of cells under the microscope, or a patient's complaints of dizziness in response to a drug. It is only recently that doctors can routinely incorporate a patient's molecular information, such as protein biomarkers in the blood that indicate an elevated risk of cardiovascular disease, the presence of prostate cancer, or inflammation, to guide treatment decisions.

Some diseases, such as the many forms of cancer, can now be characterized by their molecular profile. In the past, the diagnostic classification of a cancer was based on the organ or tissue location where it originated in the body – for example, breast cancer or liver cancer. Now, it is possible to classify a patient's cancer by the genes that it expresses, its cell surface proteins, and other molecular attributes. Such molecular characteristics provide new information on how rapidly the cancer might spread or how it might respond to specific treatments.

If widely adopted into clinical practice, genetic and other molecular diagnostic tests (including molecular-targeted imaging) could transform the delivery of healthcare. These tests could offer substantially more information about a patient's condition, including disease susceptibility and progression, and likely drug response. Due to

their predictive nature, the tests may form the basis of more preventive interventions. Moreover, since many of the tests focus on inherited genetic makeup, they may have implications not only for the patient but for the patient's blood relatives as well.

Molecular diagnostic tests challenge a healthcare finance system that has long depended on visible disease symptoms and gross clinical classification. At the same time, the ability to classify diseases into distinct molecular subcategories challenges traditional pharmaceutical business economic models that focus on “one-size-fits-all” drugs. As a result, the economic rationale for personalized medicine-driven healthcare decisions will be based increasingly on the cost savings realized through proactive

and preventive interventions. Such an approach will require a culture and policy shift in the way medicine is practiced and paid for today.

Genetic and other molecular tests raise ethical, legal, and societal questions as well. For example, if a genetic test determines that a patient has a propensity for developing breast cancer, should the healthcare professional advise family members to be tested for the same altered gene? How should test results be protected to



prevent employers from misusing the information and insurance companies from denying coverage?

The benefits of personalized medicine may well outweigh any drawbacks or challenges. Advocates of personalized medicine stress its potential to:

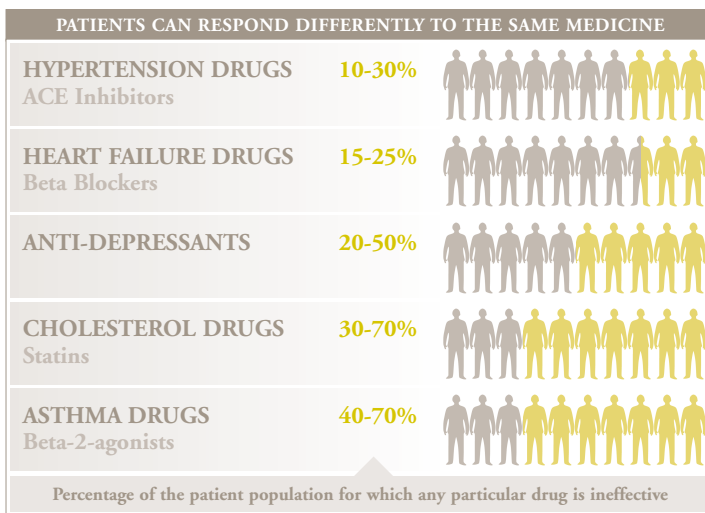
- Detect disease at an earlier stage, when it is easier to treat effectively
- Enable the selection of optimal therapy and reduce trial-and-error prescribing
- Reduce adverse drug reactions
- Increase patient compliance with therapy
- Improve the selection of targets for drug discovery
- Reduce the time, cost, and failure rate of clinical trials
- Revive drugs that failed clinical trials or were withdrawn from the market
- Avoid withdrawal of marketed drugs
- Shift the emphasis in medicine from reaction to prevention
- Reduce the overall cost of healthcare

To date, much of the promise and many of the challenges of personalized medicine remain untested, and projections for its future, based on this limited evidence, range from quite pessimistic (The Royal Society 2005; Williams-Jones *et al.* 2003) to markedly optimistic (Ginsburg *et al.* 2006). In this report, we present evidence that personalized medicine has already proven its value and will continue to grow in importance, while at the same time acknowledging that uncertainties remain about the full extent of its ultimate impact.

MOUNTING EVIDENCE

Select optimal therapy: Physicians have long recognized that patients can respond very differently to the same medication. For example, a statin drug used to lower cholesterol levels may work for only 30 to 70 percent of patients (Spear *et al.* 2001). Studies have linked differences in drug responses to differences in genes that code for the production of drug-metabolizing enzymes, drug transporters, or drug targets

(Mangravite *et al.* 2006; Rieder *et al.* 2005; Terra *et al.* 2005). Detection of these genetic differences provides the opportunity to use genetic or other forms of molecular screening to select optimal therapy the first time and avoid a trial-and-error approach to prescribing.



Women with breast cancer are among the first beneficiaries of the personalized medicine approach. About 30 percent of breast cancers are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor 2 (HER2). In normal quantities, HER2 promotes normal cell growth. But when a genetic mutation causes HER2 to be over-expressed on the cell surface, certain breast cells are prompted to multiply uncontrollably and invade surrounding tissue (Ménard *et al.* 2003).

Women with HER2-positive breast cancer do not respond well to standard therapies. Development of an antibody drug – Herceptin® (trastuzumab) – that specifically inhibits the HER2 receptor has greatly improved the survival rate of women with this deadly form of cancer (Piccart-Gebhart *et al.* 2005; Romond *et al.* 2005). Molecular diagnostic tests have been developed that measure either HER2 protein levels or gene copy numbers to identify patients who will benefit from receiving Herceptin.

Gleevec® (imatinib), another successful example of personalized medicine, is used in the treatment of chronic myelogenous leukemia (CML) and malignant gastrointestinal stromal tumors. CML is caused by a chromoso-

mal rearrangement that creates a fusion between two normal proteins, producing one abnormal protein called Bcr-Abl that promotes a rapid increase in the number of white blood cells. Gleevec binds specifically to Bcr-Abl and inhibits its action. Appropriate prescription of the drug can be confirmed by a diagnostic test that detects the presence of the *BCR-ABL* gene. Studies show vastly improved response rates and lower toxicity for CML patients receiving Gleevec compared with patients receiving standard chemotherapy (Druker *et al.* 2001). Over 90 percent of patients receiving Gleevec respond positively to initial treatment, and many experience complete remission.

Recently, a genetic test to monitor the emergence of Gleevec resistance has been introduced. Gleevec resistance occurs in about 4 to 5 percent of CML cases (Genzyme 2006). This new test could provide an additional tool for personalization of treatment.

Personalized medicine is also revolutionizing the treatment of acute lymphoblastic leukemia (ALL), the most common cancer among children and adolescents (Pui *et al.* 2006). In 1962, only 4 percent of children with the disease survived 10 years after diagnosis (the criterion for a “cure”). Today, due to the use of genetic screening technologies and improvements in treatments, the cure rate has increased to over 80 percent, while the five-year survival rate is approaching 90 percent. Using genetic analysis to determine ALL subtypes allows clinicians to choose the optimal drug and dosage for each patient and reduce the chances of toxicity and relapse. In some cases, chemotherapy or radiation may be avoided, limiting the possibility of major organ damage or secondary cancers. Clinicians can also identify patients for whom standard treatment would be inadequate and who, therefore, must be treated more aggressively. In some cases, the magnitude of benefit from a variety of standard treatment options can be determined for specific cancer patients (Burstein *et al.* 2006).

One of the first diseases to be addressed with a personalized medicine approach was HIV/AIDS. Twenty years ago, a diagnosis of HIV/AIDS was a virtual death

sentence. Now, by the use of phenotypic and genotypic resistance information, physicians can reject only those drugs to which the virus has become resistant, and preserve alternative therapies for future use. As a result, physicians can manage the patient’s HIV as a chronic disease over a long period of time. HIV genotyping has become an integral part of AIDS patient management since 1996, and could become a model for the implementation of personalized medicine in other areas (Blum *et al.* 2005).

Reduce adverse drug reactions: Studies estimate that over 2 million serious adverse drug reactions (ADRs) occur annually in the United States, causing as many as 137,000 deaths (Lazarou *et al.* 1998). Some of these deaths could be prevented by testing individuals for genetic variations indicating their susceptibility to toxic reactions.

Many adverse drug reactions are caused by variations in genes coding for enzymes. Enzymes are complex proteins that catalyze chemical reactions in the body, such as the metabolism of nutrients or drugs. About half of all drugs are metabolized by the cytochrome P450 family of enzymes present in the liver and gastrointestinal tract (BCBS 2004). There are over 30 different forms of these enzymes, each coded for by a different gene. Variations in these genes can lead to decreased or increased metabolism of certain drugs. As a result, some individuals may have trouble inactivating a drug and eliminating it from their body, while others eliminate the drug before it has a chance to work. For drugs that are metabolized too slowly, there is an increased risk for patients to be “overdosed” when given a typical dose, possibly resulting in serious toxicity.

The FDA has approved the Amplichip® cytochrome P450 test, which can detect variations in two important cytochrome P450 genes (Jain 2005). The information provided by Amplichip and similar tests will help physicians make better decisions about drug treatments and dosages. The UGT1A1 assay was also approved by the FDA to predict patients’ safety-related responses to irinotecan (used to treat colon cancer).

The test allows physicians to adjust the irinotecan dosage for the approximately 10 percent of patients who metabolize the active form of the drug too slowly.

Administration of the drug warfarin, used to prevent blood clots, is complicated by genetic variations in a drug metabolizing enzyme (CYP2C9) and a vitamin K metabolizing enzyme (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 adverse effects led an FDA advisory committee to recommend genotyping for all patients receiving warfarin (Womack 2005). An actual revision of the drug label awaits the results of a definitive clinical study.

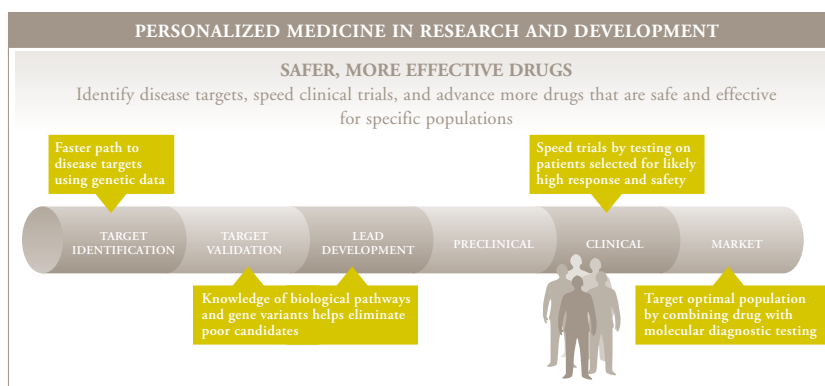
Thiopurine methyltransferase (TPMT) is another enzyme that has been studied from a personalized medicine perspective. TPMT is responsible for inactivating purine drugs used for treating ALL and other diseases (Wang *et al.* 2006). TPMT gene variations can cause variations in enzymatic activity and thus drug metabolism. One in 300 patients has both copies of their TPMT genes coding for an inactive form of the enzyme, a condition known as TPMT deficiency. In these patients, the normal dose of purine drugs results in an accumulation of active compound, which may cause a potentially fatal bone marrow reaction that results in an abnormal lowering of the white blood cell count. After a few cases of fatal toxicity in TPMT-deficient ALL children treated with a purine drug, physicians started screening for variations in the TPMT gene before administering the drug. When a TPMT deficiency is detected, the dose is lowered to 10 to 15 percent of the standard dose. This adjustment ensures that systemic levels of the drug are comparable to those found in patients with normal TPMT who have been given a standard dose.

Increase patient compliance: Patient non-compliance with treatment regimens leads to adverse health effects and increased costs. When personalized therapies prove more effective or confer fewer adverse effects, it

can be assumed that patients will more likely comply with their treatments. The impact could be greatest for the treatment of diseases such as asthma and diabetes, in which noncompliance commonly exacerbates the condition. As yet, there are anecdotal reports, but no definitive published studies on patient compliance as it relates to the use of personalized therapies.

Reduce time, cost, and failure rate of clinical trials:

Developing a new drug is a costly and lengthy process (DiMasi *et al.* 2003). Theoretically, the use of “pharmacogenomic” data, or information about how patients’ genes affect their drug responses, could reduce the time and cost of drug development. Using genetic tests, researchers could pre-select patients for studies, using those most likely to respond or least



likely to suffer side effects. “Enriching” the clinical trial pool, as this approach is called, could reduce the size, time, and expense of clinical trials. Moreover, use of pharmacogenomics early in the drug development process could reduce product failures by focusing resources on drug candidates most likely to be safe and effective. According to a report by the Boston Consulting Group (Tollman *et al.* 2001), drug companies could save as much as \$335 million per drug by incorporating this type of data into certain drug development programs.

Anecdotal evidence suggests that pharmacogenomics can cut the length of clinical trials as well. For example, a phase III clinical trial for the drug Tykerb (lapatinib) was terminated early due to the drug’s remarkable success in treating a genetically defined subset of patients with breast cancer (Pollack 2006). In the case

of Herceptin, both development time and cost were reduced when a diagnostic test was used to pre-select patients in a pivotal clinical study.

Rescue drugs that are failing in clinical trials:

The Herceptin story followed a pattern of adapting clinical trials to alter the fate of a new drug. Phase III trials in 1997 showed the drug to be ineffective in the overall population tested, but subsequent evaluation of trial results revealed that women who tested positive for HER2 over-expression had a significantly better response to the drug. In 1998, the U.S. Food and Drug Administration (FDA) was presented with clinical data suggesting that the HER2-positive subset, defined by a diagnostic test, would benefit from the drug (Cobleigh *et al.* 1999), and the FDA approved the drug/diagnostic combination.

Rescue drugs withdrawn from the market:

Currently, there are no examples in which a drug has been returned to market based on genetic or molecular diagnostics after having been withdrawn for serious adverse events. However, Iressa (gefitinib) is an example of a drug that is currently making an attempt at resurrection.

Approved in 2003 for the treatment of advanced non-small-cell lung cancer, the leading cause of cancer deaths in the U.S., Iressa dramatically reduced tumor size, but only in a small percentage of patients (Tamura *et al.* 2005).

Later, researchers identified the molecular marker that correlates with Iressa response. Since then, however, large phase III clinical trials showed that the drug did not improve survival in a general population of lung cancer patients. Faced with the paradox of remarkable success in a few, but failure among a broader popula-

tion, the FDA restricted use of the drug to a few thousand patients who had been using and benefiting from the drug prior to the results of the phase III clinical study. The drug’s manufacturer is currently attempting to develop a genetic test that might better define the subset of patients who respond to the drug.

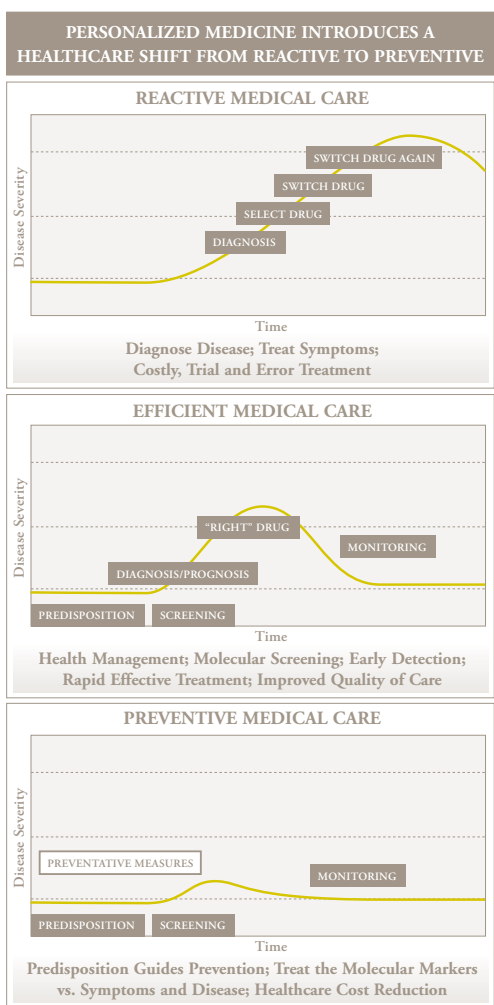
Shift emphasis in clinical practice from reaction to prevention:

Personalized medicine introduces the ability to use molecular markers that signal the risk of disease or its presence before clinical signs and symptoms appear. This information underlies a healthcare

strategy focused on prevention and early intervention, rather than reaction to advanced stages of disease. Such a strategy can delay disease onset or minimize symptom severity. Examples of prognostic molecular markers now being used in clinical practice include C reactive protein, indicating risk of cardiovascular disease, and LDL and HDL cholesterol indicating risk of atherosclerosis. Detecting abnormal levels of these markers may trigger steps aimed at preventing future disease.

Two genetic tests now on the market can identify disease susceptibility and guide preventive care. One is a test for BRCA1 and BRCA2 genetic variants that indicates hereditary propensity for breast and ovarian cancer (Nelson *et al.* 2005). Women with BRCA1 or BRCA2 genetic risk factors have a 36 to 85 percent lifetime chance of

developing breast cancer, compared with a 13 percent chance among the general female population. For ovarian cancer, women with certain BRCA1 or BRCA2 gene variants have a 16 to 60 percent chance of contracting the disease, compared with a 1.7 percent chance among the general population. Use of the BRCA1 and BRCA2



genetic test can be used to guide preventive measures, such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

The second currently available genetic test is the p16 test for melanoma (Begg *et al.* 2005). P16 accounts for up to 40 percent of hereditary cases of melanoma and has also been linked to pancreatic cancer. For those who test positive, several prevention options are available, including early detection, preventive surgery on suspicious lesions, and reduced sun exposure.

The treatment of early-stage breast cancer in women may be transformed by several assays in development that scan a panel of genes correlated with risk of disease recurrence and response to therapy (Paik *et al.* 2004; Cronin *et al.* 2004). One such assay now being used in clinical settings is *OncoType DX™*, which analyzes the expression of 21 genes (Hornberger *et al.* 2005; Paik *et al.* 2006). The information provided by this test supports both treatment and monitoring decisions based on the foreknowledge of disease progression, time to event, and likelihood of treatment benefit (Paik *et al.* 2006; Habel *et al.* 2006).

ECONOMIC STUDIES

It also appears that personalized medicine provides a new economic model of drug development that benefits both pharmaceutical companies and patients. For example, clinical trials of Herceptin and Gleevec leading to initial regulatory approval were conducted in a relatively small number of patients qualified by specific biomarkers. The use of these biomarkers permitted clearer results in clinical trials and faster, less expensive paths to FDA approval. Gleevec, originally approved for treating chronic myelogenous leukemia, was later approved for treating gastrointestinal stromal tumors, based on related molecular mechanisms. Encouraged by these success stories, several major pharmaceutical companies are targeting diseases with a smaller defined patient population in order to reduce the initial cost and duration of clinical trials, and then later expanding the drugs' indications to other related diseases (Penny *et al.* 2005).

A few studies indicate that molecular diagnostic tests might make healthcare more cost-effective.

Researchers from the Massachusetts Institute of Technology recently performed a study using insurance claims for asthma patients to determine the economic impact of a hypothetical diagnostic test used to predict drug response (Stallings *et al.* 2003). They found that the use of such a test would offset costs

“Some evidence suggests that personalized medicine could provide a new economic model of drug development that would benefit both pharmaceutical companies and patients.”

for payers, provided that the test was sensitive and not overly expensive. In addition, an examination of genetic testing for TPMT deficiency, which can lead to severe adverse reactions to purine drugs, has confirmed the cost-effectiveness of such testing under certain conditions (Tavadia *et al.* 2000; Marra *et al.* 2002). Recently, a pharmacoeconomic analysis model was published detailing the impact of applied genomics testing in cancer on cost savings in specific disease situations (Hornberger *et al.* 2005).

In general, personalized medicine therapies and diagnostic tests have not yet prompted widespread review and cost-effectiveness analysis, but a number of studies that have been conducted provide some interesting insights, as well as preliminary validation of the economic benefits of personalized medicine in the delivery of healthcare (Phillips *et al.* 2005).

PUBLIC POLICY CONSIDERATIONS

Although research and the steady progression of the science can make the case for personalized medicine, studies alone are insufficient to ensure its adoption into clinical practice. Factors such as regulation, reimbursement policies, legislative protections against misuse of genetic information, a healthcare information technology (HIT) infrastructure, and the education of healthcare professionals will influence the rate at which personalized

medicine is incorporated into the healthcare system. It will be imperative for the Personalized Medicine Coalition (www.personalizedmedicinecoalition.org) and other advocates to support the implementation of policies favorable to personalized medicine within the healthcare delivery system (Abrahams *et al.* 2005).

Regulation: The U.S. regulatory climate has been very supportive of trends in personalized medicine, and regulators are encouraging a personalized approach to drug and diagnostic development. In recent years, the FDA has:

- Acknowledged the relationship between genetic constitution and drug response in labeling guidelines (21 CFR 201.57) (more information is available at <http://www.access-data.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57>)
- Approved the first device for rapid characterization of cytochrome P450 genes
- Collaborated with other Federal agencies to improve cancer therapies through biomarker development and evaluation
- Published the “Guidance for Industry: Pharmacogenomic Data Submissions,” clarifying what type of genomic data needs to be submitted to the Agency and when, and encouraging the voluntary submission of exploratory genomic data (March 2005)
- Released its drug and diagnostic co-development concept paper (April 2005)
- Published guidance on the incorporation of genotypic and phenotypic resistance tests into the study of anti-viral drugs (June 2006)
- Issued “Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays” with request for public comment (September 2006)

From 2004 (prior to the publication of the guidance for pharmacogenomic data submissions) to the second quarter of 2006, the number of formal requests (consults) for genomic data review and voluntary genomic

data submissions to the FDA (as part of regular INDs, NDAs or BLAs) increased significantly, from a total of 5 in 2004, to 20 in 2005, and 29 in the first half of 2006 (Frueh 2006).

These actions by the FDA are helping to create a constructive regulatory environment that will foster the emergence of personalized medicine. A key regulatory building block still to come is a set of guidelines outlining requirements for the co-development of pharmacogenomic drugs and diagnostic tests (concept paper and other key documents and guidances are available at <http://www.fda.gov/cder/genomics>).

Reimbursement: Adequate and timely coverage and reimbursement by insurers are also critically important to the adoption of personalized medicine therapies. In many cases, reimbursement follows regulatory approval. For example, the joint FDA approval of both Herceptin and a diagnostic test for determining which breast cancer patients would benefit from Herceptin paved the way for reimbursement of both products by most third party payers. However, coverage and payment policies will need to adapt to keep pace with scientific progress. For example, Medicare reimbursement policy for diagnostic tests is usually based on confirming traditional diagnosis of existing signs and symptoms. Such an approach can discourage adoption of molecular tests, which may be more predictive in nature. Reimbursement policies will have to be realigned to support a more preventive, proactive approach to medicine. Medicare coverage of Herceptin/Herceptest and the gene expression profile *Onco type DX* portends an increasing awareness among payers of the value of personalized medicine. Keeping formulary policy up to date with personalized medicine will also be important to adoption by physicians and patients. Current one-size-fits-all approaches to listing drugs in formularies will have to be reconsidered as pharmacogenomics makes increasingly clear that one therapy will not be optimal for all patients (Reinhardt 2001).

HIT infrastructure: Widespread adoption of electronic health records (EHRs) will play an important role in preparing our health system for personalized medicine, providing rapid access to both clinical information

and molecular test results so patients and physicians can make optimal treatment decisions. EHRs will also accelerate the treatment discovery cycle by providing researchers with access to large databases of (anonymized) patient data. Several pieces of legislation have been introduced to promote the adoption of EHRs, while many states, private hospitals, and physician practices are moving ahead with their own HIT programs (Lohr 2006).

PRIVACY

Currently, federal and state laws offer only a patchwork of protection against the misuse of genetic information. To fulfill the promise of personalized medicine, basic genetic nondiscrimination legal protections need to be established in order to enable and encourage individuals to participate in research, and take full advantage of genetic screening, counseling, testing, and new therapies. Proposed legislation, such as the Genetic Information Nondiscrimination Act of 2005, suggests that most of the gaps in privacy protection can be covered. One survey (White *et al.* 2003) indicated that about half of the public (48 percent) is interested in using genetic information to understand and optimize their health. Although the public is generally supportive and anticipatory of personalized medicine, the fear of genetic discrimination in employment and health insurance (expressed by 68 percent of those surveyed) is a significant obstacle to full participation.

“ Although the public is generally supportive of personalized medicine, legal protections concerning genetic discrimination must be addressed in order to encourage participation. ”

MEDICAL EDUCATION

The degree to which physicians utilize personalized medicine will be limited by their knowledge of the subject and their awareness of available tests and treatments. Most medical education institutions have not incorporated personalized medicine into their curricula, which is likely to hinder acceptance of personalized medicine for

years to come (Frueh *et al.* 2004). On the other hand, medical professionals will be encouraged to adopt these personalized approaches due to their potential for improvements in patient safety, concerns for medical liability, and reimbursement policies. Educational programs will be necessary to prepare a healthcare workforce capable of administering personalized medicine.

CONCLUSIONS

Currently, the evidence establishing a clear-cut case for personalized medicine remains largely anecdotal rather than statistical, but that is to be expected for such a nascent field. In oncology, there are many proofs of principle for personalized medicine, and many more are emerging. Multiple examples have demonstrated the utility of personalized medicine in selecting optimal therapy, rescuing drugs from failed clinical trials, and shifting emphasis from disease treatment to disease prevention.

Many other claims remain untested, including the ability to rescue drugs that have been withdrawn from the market or the ability to reduce the time, cost, and failure rate of clinical trials. Furthermore,

little hard evidence is available on the impact of a personalized medicine approach on pharmaceutical industry productivity or healthcare economics.

Whether personalized medicine will “revolutionize” clinical care is uncertain. However, at least in some cases, a personalized medicine approach to treatment has led to cost savings in the administration of healthcare, demonstrated itself to be a viable business strategy for product development, and most importantly, proven its benefit to patients. In fact, there is some indication that the field is entering a new phase, marked by the emergence of treatments, now in clinical trials, for patients who develop resistance to a personalized medicine drug, such as Tykerb in place of Herceptin, or AMN107 in place of Gleevec. It is therefore reasonable to expect that many more successful examples of personalized medicine will be seen in the near future.

Selected Personalized Medicine Drugs, Treatments, and Diagnostics *

Therapy	Biomarker/Test	Indication
Anti-retroviral drugs	TruGene®-HIV 1 Genotyping Kit	Guides selection of therapy based on genetic variations that make the HIV virus resistant to some anti-retroviral drugs.
Cancer treatment regimens	Oncotype DX™ 21-gene assay	Quantifies the expression of 21 genes linked to the likelihood of breast cancer recurrence in women, and the magnitude of benefit from certain types of chemotherapy and hormonal therapy.
Camptosar® (irinotecan)	UGT1A1	Colon cancer: “Variations in the UGT1A1 gene can influence a patient’s ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects.” ¹
Drugs metabolized by cytochrome P450	Amplichip® CYP2D6/ CYP2C19	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.” ²
Gleevec® (imatinib mesylate)	BCR-ABL	Chronic myelogenous leukemia (CML): “Gleevec (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.” ³
Gleevec® (imatinib mesylate)	c-KIT	Gastrointestinal stromal tumor (GIST): “Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).” ³
Herceptin® (trastuzumab)	HER-2/neu receptor	Breast cancer: “. . . for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.” ⁴
Immunosuppressive drugs	AlloMap® gene profile	Monitors patient’s immune response to heart transplant to guide immunosuppressive therapy.
Pharmaceutical and surgical prevention options and surveillance	BRCA 1,2	Guides surveillance/preventive treatment based on susceptibility risk for breast and ovarian cancer.
Pharmaceutical and lifestyle prevention options	Familion® 5-gene profile	Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Pharmaceutical and surgical treatment options and surveillance	p16/CDKN2A	Guides surveillance/preventive treatment based on susceptibility risk for melanoma.
Purinethol® (mercaptopurine)	TPMT	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. . .” ⁵
Tamoxifen	Estrogen receptor	“The estrogen and progesterone receptor values [in breast cancer patients] may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.” ⁶

Entries in which diagnostic tests received formal FDA approval, or drugs that have a reference to pharmacogenomic selection in their label, are shaded yellow.

*This list is not intended to be comprehensive, but reflects commonly used products as of September 2006. Chart is based on research and industry sources.

BCR-ABL = breakpoint cluster region – Abelson

BRCA 1,2 = breast cancer susceptibility gene 1 or 2

c-KIT = tyrosine kinase receptor

CYP = cytochrome P450 enzyme

HER2 = human epidermal growth factor receptor 2

TPMT = thiopurine S-methyltransferase

UGT1A1 = UDP-glucuronosyltransferase 1A1

¹ U.S. Food and Drug Administration, *FDA Clears Genetic Test That Advances Personalized Medicine Test Helps Determine Safety of Drug Therapy* 22 August 2005, <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01220.html> (accessed 15 August 2006).

² U.S. Food and Drug Administration, *FDA classification 21 CFR 862.3360* 1 April 2005, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cf/fr/CFRSearch.cfm?fr=862.3360> (accessed 15 August 2006).

³ U.S. Food and Drug Administration, *FDA Oncology Tools Approval Summary for imatinib mesylate for Accel*. Approv 18 April 2003,

<http://www.accessdata.fda.gov/scripts/cder/onctools/summary.cfm?ID=326> (accessed 15 August 2006).

⁴ U.S. Food and Drug Administration, *FDA Oncology Tools Product Label Details in Conventional Order for trastuzumab*, <http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=Trastuzumab> (accessed 15 August 2006).


⁵ U.S. Food and Drug Administration, *Purinethol® drug label*, http://www.fda.gov/Medwatch/SAFETY/2004/jul_PI/Purinethol_PI.pdf (accessed 15 August 2006).

⁶ U.S. Food and Drug Administration, *FDA Oncology Tools Product Label Details in Conventional Order for tamoxifen* 28 October 1998, <http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=tamoxifen> (accessed 15 August 2006).

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