

# Personalized Medicine – Practice and Prevention in Oncology

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## Summary

The future of medicine, particularly oncology, is personalized medicine. This is the use of genetically based testing to identify either patient or tumor characteristics of a disease to target treatment. Genetic-based oncology diagnostics includes tools for diagnosis and stratification, drug selection, dose selection, and patient monitoring. Many of these tests are currently being used, but could be better used to both improve quality of care and reduce costs secondary to inappropriate medication use.

## Key Points

- Personalized medicine is the use of diagnostic testing to identify specific characteristics of a disease in a patient to help determine targeted treatment.
- Personalized medicine is not the same as genetics.
- Genetic-based oncology diagnostics includes tools for diagnosis and stratification, drug selection, dose selection, and patient monitoring
- In the realm of oncology, most of the focus in personalized medicine is on companion diagnostics: tests whose results are paired to specific therapies or course of treatment.
- The use of personalized medicine can help managed care save money by targeting the most appropriate therapy for the most appropriate patients.

PERSONALIZED MEDICINE REFERS TO THE use of diagnostic testing to identify specific characteristics of a disease in a patient or a specific patient pre-condition that is used to help determine the best treatment – often the choice and dose of medication to better fit the patient’s expected physiologic response. Doctors who use a personalized medicine approach do not treat empirically based on a broad diagnostic label such as breast cancer but based on specific characteristics such as human epidermal growth factor receptor (HER2) positive breast cancer for which targeted anti-HER2 therapy would be indicated. The use of a trial-and-error approach, or population-based approach, to treatment for a presumed disease is not personalized medicine.

Personalized medicine is a term that has been used broadly to describe use of pharmacogenomics, companion diagnostics, consultative diagnostics, and interpretive counseling services. Pharmacogenomics is the study of genetic variations related to drug metabolism differences among people for more effective dosing or to forewarn of potential toxicity. Pharmacogenomic tests do not specify if a medica-

tion will be effective. Companion diagnostics are tests that predict likely response to specific therapies or course of treatment. These also are known as predictive tests or DxRx tests. In oncology, most of the focus in personalized medicine is on companion diagnostics. Consultative diagnostics are interpretations of complex tests that may be used together to achieve a diagnosis or subclassify a disease to assist the treating physician. Interpretive counseling services are personalized interpretations of tests for patients that may face difficult personal choices based on these results (e.g. genetic counseling).

Personalized medicine is not the same as genetics. Genetics is the key to the door of personalized medicine, but is not a synonym. Information related to genetics and genetic technology has changed the way we can study and treat disease, but genetics is not the only way medicine is personalized. Genetic variation is at the root of physiologic variations in patients and diseases, which must be considered in the context of treatment decisions to derive more effective care and better outcomes.

Genetics is related to oncology. People are born

with certain genetic characteristics. Gene variations (or genetic alleles) are present in each gene and each cell, and usually are derived from each parent or may arise de novo. Heritable variations are known as germline variations. Certain genes related to cell growth or death may acquire deletions, replications, or mutations after birth that alter their function within a group of cells that grow abnormally forming a cancerous tumor. These acquired genetic changes are called somatic variations.

Pharmacogenomic tests look for germline variations in cell metabolism that are present in every cell

of the patient and remain the same for the life of the patient. Predictive or companion diagnostic tests look for somatic variations in tumor cells that may differ in one cancer from that of another related cancer – hence they differ for each patient but are acquired, not inherited. In the case of companion diagnostics, the genetic information obtained is limited to the tumor rather than the patient per se. Exhibit 1 contains some examples of companion diagnostic tests in oncology. For any given category of tumor there are several tests that can lead one to decisions that will impact therapy (i.e., a more ag-

**Exhibit 1: Today's DxRx Connections for Cancer**

Cancer Type	Diagnostic Tests	Therapy Options
Acute Myeloid Leukemia (AML)	CD33 FLT3 Inv16 T(8;21)	Mylotarg®, multiple chemotherapies
Acute Promyelocytic Leukemia (APL)	PML-RARA t(15;17)	ATRA, chemotherapy
Breast Cancer	HER2 by IHC or FISH ER & PR Oncotype DX®, MammaPrint®	Herceptin®, hormonal therapies, risk/adjuvant therapy
Chronic Lymphocytic Leukemia (CLL) ? Small Lymphocytic Lymphoma (SLL)	CLL-MRD by Flow Cytometry IgVH P53 Mutation Analysis P53 by FISH (17p-)3 CD20	Campath, Fludara®, Rituxan®, multiple therapies
Chronic Myelogenous Leukemia (CML)	BCR-ABL by RQ-PCR ABL Kinase Mutation Analysis	Gleevec, Sprycel, Tasigna
Colorectal Cancer (CRC)	EGFR PharmDx KRAS Mutation Analysis UGT1A1 Molecular Assay Thymidylate synthase (TS) MSI, IHC (hMLH-1, hMSH-2, hMSH-6, PMS-2)	Camptosar, Erbitux, Vectibix, 5FU, multiple therapies
Myelodysplastic Syndrome (MDS)	Deletion 5q Analysis	Dacogen®, Revlimid, Vidaza®
Myeloproliferative Neoplasms (formerly MPD)	JAK2 Mutation Analysis	Agrylin®, Hydrea®
Multiple Myeloma	Flow Cytometry, IHC, FISH	Alkeran®, Revlimid, Thalomid®, Velcade®, Zometa®
Non-Hodgkin's Lymphoma (NHL)	CD20	Bexxar®, INTRON® A, Rituxan, Zevalin®
Non-Small Cell Lung Cancer (NSCLC)	EGFR Mutation Analysis KRAS Mutation Analysis EGFR Amplification by FISH IHC tumor analysis ERCC1, RRM1 Expression Analysis	Avastin, Iressa, Tarceva, platinum therapies

**Exhibit 2: Genetics has changed Oncology Diagnostics  
Providing Tools to Personalize Therapy**

	Clinical decision being made	Dx-Rx Examples
1) Diagnosis & Stratification	What is the most accurate diagnosis? How severe is their disease? Are they at risk for disease?	BCR-Abl for CML- Gleevec® ER/PR for breast ca – Tamoxifen 5Q deletion for MDS – Revlimid®
2) Drug selection	What Rx is appropriate for this patient? What drug will they respond to? Will they have an adverse reaction?	HER2 expression – Herceptin® EGFR expression – Erbitux® EGFR mutation – Tarceva®, Iressa® BCR – Abl mutation – Gleevec®
3) Dose selection	What dose is appropriate for this patient?	UGT1A1 polymorphism – Camptosar® CYP450 polymorphism – Multiple
4) Patient monitoring	Is this patient responding to therapy?	BCR-Abl RT-PCR – Gleevec® CLL MRD – Campathe®

**Exhibit 3: Need for Personalized Medicine**

US drug spending \$250+B per year and growing fast

50% of drugs not efficacious as prescribed

US diagnostics spending decreased since 1984

Adverse drug reactions 6th leading cause of death

FDA interested in biomarkers and diagnostic algorithms

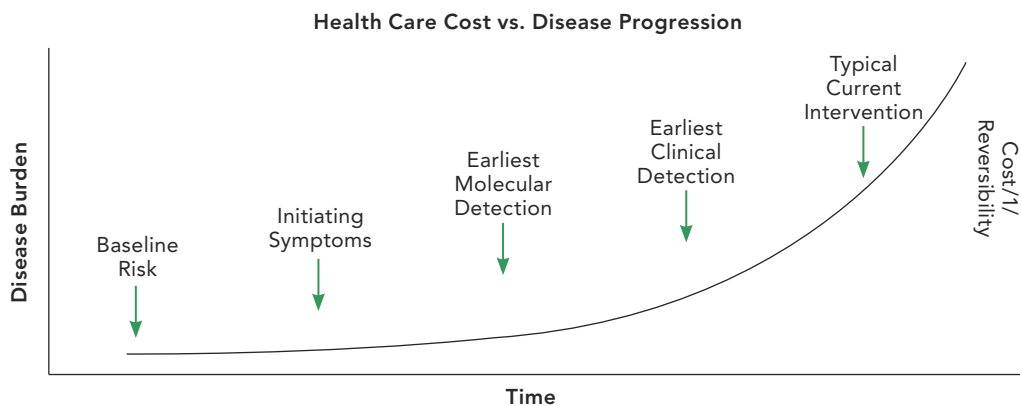
**Room for Improvement**

gressive tumor type, a tumor with a particular receptor).

It is important to note that personalized medicine tests are not absolute. Tumors are heterogeneous so not all cells behave the same or have the same receptors or proteins. A companion diagnostic test may predict that a patient will respond to a particular medication, but it does not guarantee response.

Genetic information is changing oncology practice by providing tools to personalize therapy. This includes tools for diagnosis and stratification, drug selection, dose selection, and patient monitoring (Exhibit 2). For example, chronic myeloid leukemia (CML) tumor burden can be measured and followed after chemotherapy using BCR-A BL (a fusion pro-

**Exhibit 4: Need for Change: Current Intervention is often late**



Source: Model by Ralph Snyderman, Duke University

tein) levels to gauge response to therapy.

There is a need for personalized medicine (Exhibit 3). The spending on medications continues to increase, yet it is estimated that 50 percent of medications are not efficacious as prescribed. Additionally, adverse events related to medications are a significant cause of morbidity and mortality. Increasing the use of pharmacogenomic and companion diagnostic tests should help manage these issues.<sup>1</sup>

In addition, in the current health care system, disease intervention is often late (Exhibit 4). In oncology, many times the patient already has significant disease burden at the time of diagnosis. Because patients have a large disease burden, they do not have time in terms of survival for trial and error with various therapies. Without predictive tests, chemotherapy overall is only 25 percent effective.<sup>2</sup> A test that could predict efficacy of a particular chemotherapy may give the patient a survival advantage.

As various cancers have been better defined, the ability to identify specific genetic alterations that occur with specific types of disease has evolved. For example, 70 years ago all cancers of the blood were basically lumped together and treated similarly. Today, 38 different leukemias and 51 lymphomas have been identified. Survival for leukemias and lymphomas has improved over that time from 0 percent to 70 percent.<sup>3</sup>

The wave of personalized diagnostic testing is having an impact on drug development. The number of diseases that can be precisely diagnosed and then treated with a highly specific therapy is certain to increase dramatically within the decade. In the past five years, oncology drugs for patients with specific genetic characteristics have soared from about 10 percent to more than 40 percent of those in clinical trials.<sup>4</sup>

Personalized medicine is a business model challenge. New test development is complex and expensive, at an estimated \$100 million per test. Although there are issues with the FDA approval of new genetic tests, the door needs to remain open for CLIA laboratory developed tests to be available as stimulation for the marketplace. If these tests have to go through the FDA approval process, their launch to the market is delayed by many years.

In addition to development costs, there are some barriers to wide-spread adoption of personalized medicine. Four barriers have been identified as hindering the transition from trial and error medicine to personalized medicine in the United States and, to varying degrees, the rest of the world.<sup>4</sup> First is the pharmaceutical industry's historically successful blockbuster model, which focuses on developing and marketing drugs for as broad a patient group as pos-

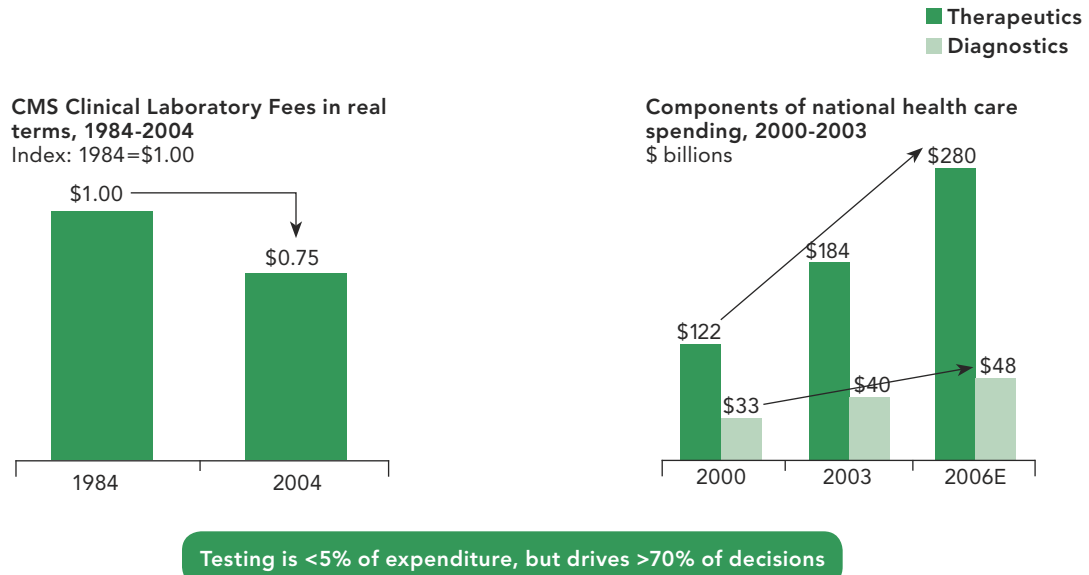
sible and discourages the development of therapies aimed at smaller subpopulations and the diagnostic tests that can identify them. Next is a regulatory environment that causes too many resources to be devoted to phase-three clinical trials (the "final exams" of a new drug's efficacy and safety) and too few to monitoring and assessment after the FDA has approved a drug. Third are the perverse economics of a dysfunctional payment system, which rewards physicians for activity (completing procedures and prescribing drugs) rather than for early diagnosis and prevention. The final barrier is physician behavior that is deeply rooted in trial-and-error medicine.

A fifth barrier could be described as a general lack of knowledge and concern about the use of genetic testing, particularly the distinction of "genetic" information related to inherited conditions versus "genetic" information of acquired somatic changes related to cancer. There are privacy concerns about inherited genetic information impacting a patient's health care status from an insurance point of view. These privacy concerns, whether valid or not, affect patients, physicians, regulatory agencies, and payers.

Because many of these tests are developed within individual laboratories, concerns have been raised about the validity and reproducibility of these tests. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, established by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, supports the development and implementation of a rigorous, evidence-based process for evaluating genetic tests and other genomic applications for clinical and public health practice in the United States. An independent, multidisciplinary expert panel (EGAPP Working Group) that select topics, oversees the systematic review of evidence, and makes recommendations based on that evidence.<sup>5</sup> EGAPP Working Group defines a genetic test as involving the analysis of chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, or gene products (e.g., enzymes and other proteins) to detect heritable or somatic variations related to disease or health. Whether a laboratory method is considered a genetic test also depends on the intended use, claim or purpose of a test. There are questions whether one group can examine all the tests being conducted around the country. For example, Genzyme Genetics conducts greater than one million tests annually.

The American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) have developed or are developing proficiency testing and usage guidelines for various personalized medicine tests. For example, ASCO and CAP collaborated to develop evidence-based guideline for

Exhibit 5: Diagnostics Provide Valuable Information at Modest Cost



Reference 6

optimal HER2 testing for invasive breast cancer and released recommendations in December 2006. Before the guidelines, 20 percent of HER2 results were false positives and 10 percent were false negatives.

Results of personalized medicine tests and managed care data can be used to improve care and save money. Diagnostic testing provides valuable information at a modest cost (Exhibit 5).<sup>6</sup> Testing accounts for less than 5 percent of expenditure, but drives more than 70 percent of decisions. United Healthcare found that 12 to 15 percent of their trastuzumab (Herceptin<sup>®</sup>) orders were for women who tested negative for HER2 overexpression, even though the medication is only effective in HER2 positive patients. They implemented a system using the ASCO/CAP guidelines to only pay for Herceptin<sup>®</sup> for patients with appropriate HER2 results. This plan resulted in a decrease in inappropriate medication use and an estimated cost avoidance of \$4 million per year.<sup>7</sup>

Another example of a companion diagnostic test that may provide financial benefits in the overall cost of care is KRAS (or K-ras) mutation analysis in colorectal cancer. KRAS is among the most commonly mutated oncogenes in cancer. About 40 percent of patients with colorectal cancer have mutations. If KRAS is mutated in a patient with colorectal cancer, there is no response to epidermal growth factor receptor (EGFR) inhibitors, either large monoclonal antibodies like cetuximab (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>®</sup>), or small molecule inhibitors like erlotinib (Tarceva<sup>®</sup>).<sup>8-10</sup>

KRAS mutations turn on tumor cell growth regardless of EGFR. Ninety percent of pancreatic cancer patients have KRAS mutations, which is one of the reasons that disease is so aggressive and difficult to treat. Significant cost savings could be achieved by targeting EGFR therapy to only those patients with colorectal cancer without mutations who advance to second line treatment.

Another example where therapy can be targeted for most cost effective use is EGFR mutations in non-small cell lung cancer. EGFR mutations are found in 10 to 20 percent of all patients and in greater than 85 percent who clinically respond to EGFR tyrosine kinase inhibitors TKIs.<sup>11</sup> These mutations correlate with clinical characteristics of patients likely to respond to EGFR TKIs (female, non-smoker, adenocarcinoma, Asian).

### Conclusion

Personalized medicine has arrived in the form of both predictive companion diagnostic tests and pharmacogenomic tests. In oncology, predictive companion diagnostic tests result in substantial improvements in treatment efficacy and substantial cost savings for common diseases such as breast cancer, colon cancer, lung cancer, and leukemia. Reference laboratory testing achieves a high level of diagnostic accuracy and reduces costs related to inappropriate therapy in patients unlikely to benefit from expensive targeted therapies. A close relationship between diagnostic testing laboratories and managed care organizations can lead to better patient outcomes and

reduced health care costs. **JMCM**

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