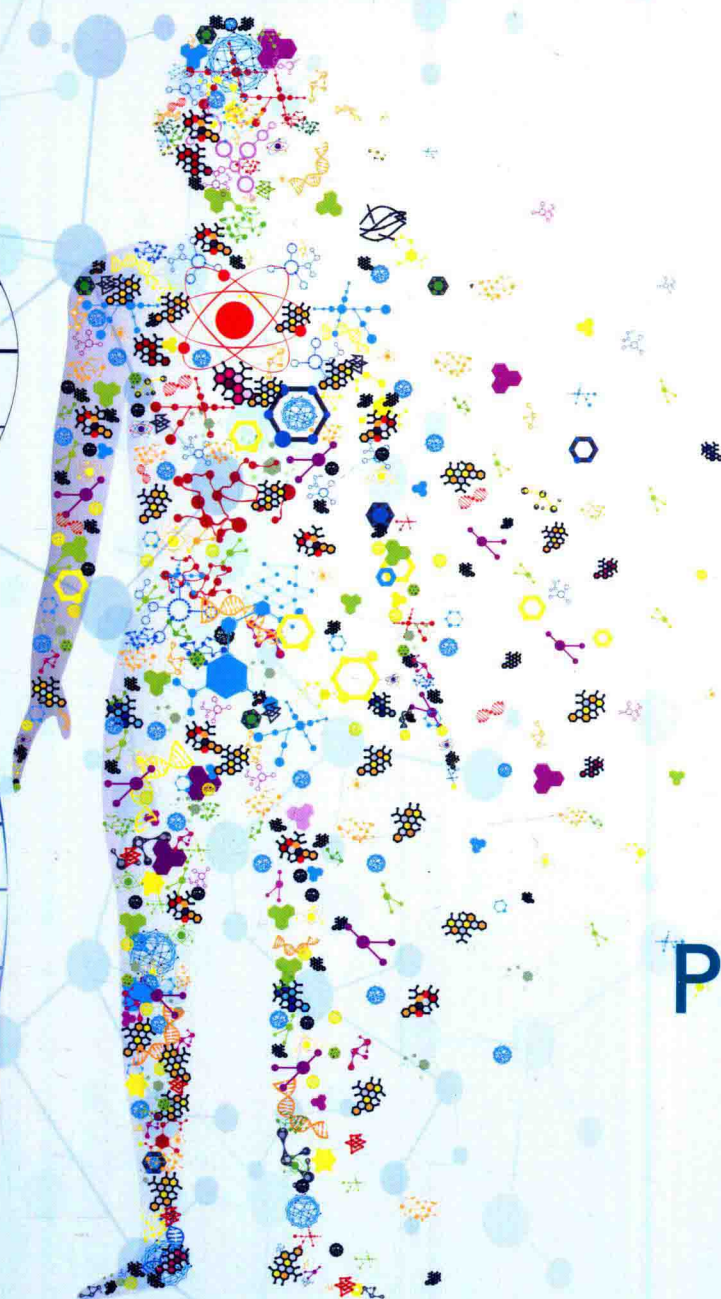


Advancing Healthcare Through Personalized Medicine



Priya Hays



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Advancing Healthcare Through Personalized Medicine

For Shreyas, Tejas, Sahil, and Rohan
Four Treasures

Preface

Medicine as a field in the early twentieth century was based on the humoral hypothesis, positing that an excess or deficiency of any of four distinct bodily fluids in a person—known as humors or humours—directly influences his or her temperament and health. The humoral hypothesis was based on early Greek and Roman physiology. The humoral hypothesis was replaced in the 1900s by the sciences of microbiology, biochemistry, and biology. A paradigm shift took place that entirely transformed medicine into the way it is practiced today.

Similarly, a new paradigm shift at hand in healthcare is based on the emerging field of personalized medicine, a disruptive innovation that will profoundly change our thinking of medicine. Personalized medicine concerns targeted patient treatment; in other words, rather than pursuing a “one-drug-fits-all” approach, personalized medicine providers in healthcare focus on tailoring drugs to the specific needs of each patient through stratification. Personalized medicine focuses on using biomarkers identified through genetics, proteomics, and metabolomics for prevention and therapy. With the advent of genomic technologies, personalized medicine will have the capability to proactively predict and diagnose disease efficiently. Personalized medicine has already led to significant advances in cures for cancer, including treatment for breast, colon, lung, and blood cancers. It has the potential to revolutionize healthcare, as have other “revolutions” in medicine that have improved the quality of life for Americans, for example, insulin for diabetics and the polio vaccine for all individuals. It is crucial that people become familiar with personalized medicine, the science behind it, its economic effects, its effects on patients, and its overall implications for society.

As medicine is practiced today based on the pathophysiology of disease, clinicians focus on acute episodes of chronic disease. Chronic illness grows over time: the genome and environment lead to development of disease, once reaching a point where it will manifest clinically. The more the patient waits, the less reversibility and greater costs there are, constituting very little awareness into the root causes of chronic disease and “backwards-looking medicine.” Many physicians were looking at improving this paradigm and creating fundamentally new ways of practicing medicine. Personalized medicine arose under this backdrop of developments. Emerging technologies would now target disease based on early molecular detection leading to earlier clinical detection. Medicine began to evolve in this direction as early as 2002, from reactive medicine to patient-driven proactive medicine, with coinvolvement of patients and physicians in healthcare.

I became interested in personalized medicine by attending my first conference on the subject, the 2013 Personalized Medicine World Conference held by Silicom Ventures. Funding from the company I was working at at the time, Affymetrix, allowed me to attend the conference. I was fascinated by the advances, treatments, and changes to medicine brought about by the implementation of personalized medicine. I learned about companion diagnostics, the economics of personalized medicine, and recent Food and Drug Administration advances to change clinical trials brought about by personalized medicine (used interchangeably with precision medicine).

This interest did not come naturally as the result of my work. I have written two books: *Molecular Biology in Narrative Form*, based on the dissertation I conducted in the Department of Literature at University of California, San Diego, and *Science, Cultural Values and Ethics*, based on my

postdoctoral research fellowship in hematological research at Dartmouth Medical School. However, these books were more in the areas of biomedicine and society, rather than reviews of the state of scientific advances. Through the course of my academic career, I published articles in such prestigious journals as *L'Esprit Createur*, a preeminent French studies journal, and the *Bulletin of Science, Technology and Society*, a tour de force in presenting articles on science, technology, and society studies. I even had an article on the state of interdisciplinarity in the journal *Interdisciplinary Literary Studies*, extolling the intellectual accomplishments of the humanities.

Yet, my work was considered abstract and theoretical. After observing members of my family suffering from Huntington's disease, a fatal neurodegenerative illness, I turned a page.

After hearing about clustered regularly interspaced short palindromic repeats (CRISPR) technologies and how gene editing had the potential to cure or reverse inherited disease, I began to see the merits of biomedical progress and how it can affect patient lives, and wanted to devote my writing efforts to making a difference in patient lives and helping physicians navigate through the complex maze of personalized medicine. Thus, this book is the outcome of numerous interviews, conference presentations, patient narratives, research, and painstaking literature surveys. Even though the experience of writing this book has challenged my ideals and attitudes, I still remain positive about the outcomes that precision medicine can bring about for patients, physicians, and the public in general.

The gains in healthcare through personalized medicine have been varied, and the current state of affairs remains as follows. Technology has been breathtaking through the development of proteomics and metabolomics and the capacity to analyze big data moving rapidly. We have made some advances in predictive and diagnostic tools in terms of companion diagnostics. Cancer therapeutics have constituted a paradigm shift; however, other areas of diseases have not progressed far enough. Reimbursement remains a barrier, not supporting the culture of proactive medicine. Chronic disease mitigation also receives poor grades. Each of these areas is addressed in this book, accompanied by a fair assessment of progress and challenges.

By chronicling the most recent advances in personalized medicine, *Advancing Healthcare through Personalized Medicine* aims to inform healthcare providers, scientists, industry and government

leaders, and members of the business community, and perhaps even the general public, of the coming revolution in healthcare. Beginning with President Barack Obama's Precision Medicine Initiative (now also known as the All of Us Research Program), which he unveiled at the 2015 State of the Union, to look at targeted treatment approaches such as Gleevec, a widely used cancer drug, the book delves deeply into the promise of personalized medicine, how it will drive innovation in biomedicine, and the challenges to its implementation. Personalized medicine will have broadly reaching effects on society, both financially and ethically, and the economic and moral implications of personalized medicine remain at the forefront of the stakeholder interviews, discussions, examples, case studies, and patient narratives in the book. The book uses jargon-free descriptions and describes how targeted genomic medicine and its accompanying companion diagnostics will constitute the future of healthcare. In short, I explain how the current healthcare crisis can be mitigated through the emergence of personalized medicine.

As I have found through my research, personalized medicine means many different things to people depending on position—clinician, patient, payer, or drug developer, among others—and within these roles, there are even more perspectives. Public ventures such as the Precision Medicine Initiative, which aims to have a cohort of volunteers sequenced in a shared database, still compete with private ventures such as Craig Venter's Human Longevity Institute, which aims to determine any individual's omics, resulting in a secured database. Privacy issues remain paramount, along with data integrity and storage. Personalized oncology has made the greatest gains, but cardiovascular disease and the central nervous system are quietly progressing. The value of companion diagnostics still remains to be determined, and venture capital is still not incentivized completely toward it. Gene panels remain active for tumor biology, but there are advocates for next-generation sequencing. These issues are discussed in more detail in this book. Perhaps I have raised more questions from this monograph than provided answers, but I hope to have enlightened the reader on one of the greatest advances in the twenty-first century: personalized and precision medicine.

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Acknowledgments

This book on personalized medicine has benefited greatly from the contributions of many people through interviews, presentations, case studies, patient narratives, and scientific and medical articles. Through conferences on personalized medicine, I have collected information from presentations to present the latest in leading-edge treatments for prevention and cures of diseases through personalized medicine. These presenters served as outstanding sources for state-of-the-art material on genomic technologies, pharmacogenomics, and basic research in personalized medicine. Interviews took place with individuals who are at the forefront of implementing personalized medicine. Many others facilitated these interviews by supporting my attendance at conferences and by suggesting people to interview.

I wish to give special thanks to the following individuals, whose expertise make up this book and who have been instrumental in the advancement and implementation of personalized and precision medicine: Edward Abrahams and his staff at the Personalized Medicine Coalition, whose exemplary efforts in the implementation of personalized medicine remain at the forefront of biomedicine; Angel Anaya; Retta Beery, who provided firsthand insight into the medical journey of her extraordinary twin son and daughter; Carol Berry of Asuragen for her information on molecular diagnostics of thyroid cancer; Trevor Bivona of the University of California, San Francisco, who provided an informative interview on the gains of personalized medicine; Erwin Bottinger of Mount Sinai School of Medicine, who provided his time on the efforts of Mount Sinai in biobanking; Wylie Burke of the University of Washington, a premier bioethicist; Robert Califf of the Food and Drug Administration for his presentation on the regulatory landscape;

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This book is dedicated to my nephews Shreyas, Tejas, Sahil, and Rohan, whose love and affection have brought great joy to my world.

Finally, this book is written for the patients, families, and communities who have faced life's impediments because of disease, illness, and sickness, and for physicians who have met with frustration in traditional trial-and-error medicine. If this book can provide hope to them in any form through personalized and precision medicine, then its main purposes have been met.

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CHAPTER 1

Introduction: Biomedical innovation and policy in the twenty-first century

The question is not whether personalized medicine is here to stay; it is how fast is it going to be implemented.

Raju Kucherlapati, PhD

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The development of Xalkori, also known as crizotinib, a small molecular inhibitor encoded by the ALK gene targeted to treat non-small-cell lung cancer (NSCLC), began several years ago. Analysis of a cDNA library Japanese patient with lung adenocarcinoma identified a novel fusion between the EML4 and ALK genes with the ability to transform 3T3 fibroblasts. Analysis of a series of biopsies from NSCLC patients revealed that ~5% of patients carry this fusion protein (Ranade et al., 2014). After this initial finding in 2007, crizotinib was discovered to be an effective targeted therapy for patients whose NSCLC tumors harbored the ALK gene. According to Ranade et al., it caused tumors to shrink or stabilize in 90% of 82 patients carrying the ALK fusion gene, and tumors shrank at least 30% in 57% of people treated. These promising clinical results led to phase II and a phase III trials, which selectively enrolled NSCLC patients with ALK fusion genes. Astonishingly, within four years of the initial publication by Soda et al. (2007), the Food and Drug Administration (FDA) approved crizotinib for the treatment of certain late-stage (locally advanced or metastatic) NSCLC patients whose tumors had

ALK fusion genes, as identified by a companion diagnostic that was approved simultaneously with the drug, as Ranade et al., noted.

When the FDA approved the cancer drug known as Gleevec in 2001 for treatment against chronic myeloid leukemia (CML), the agency did so after one of the shortest drug review processes on record. Novartis, the maker of Gleevec, also known as imatinib mesylate, had sponsored the clinical trials behind the drug. The FDA approved the drug within 10 weeks of reviewing three separate studies on 1000 patients. On May 10, 2001, at the press conference announcing the FDA approval of Gleevec, Health and Human Services (HHS) secretary Tommy Thompson declared:

Today I have the privilege of announcing a medical breakthrough. Like most scientific breakthroughs, this one is not sudden, nor does it stand alone. Rather, like most scientific advancement, it is a culmination of years of work and years of investment, by many people in many different institutions, and even

in different fields of medicine. We are here to announce one dramatic product of all those efforts. But we believe many more products will follow, based on years of scientific groundwork. So this is the right time to acknowledge those efforts, to recognize that our investments in research are paying off, and to praise the teamwork that has brought us here. It's also the right time to talk about what this can mean for our future—a future that promises a new level of precision and power in many of our pharmaceutical products. Today the Food and Drug Administration has approved a new drug, Gleevec, for treatment of chronic myeloid leukemia—or CML. Let me just say that it appears to change the odds dramatically for patients. And it does so with relatively low occurrence of serious side effects.

With the details of the effectiveness of Gleevec and its implications, Thompson's announcement quickly gained the news media's attention. CNN cycled the story every half hour throughout the day of the press conference. The Associated Press wrote and updated the story several times, and the news made the front page of newspapers nationwide. In the weeks following the announcement, extraordinary coverage was given to Gleevec and its effects on cancer, including a cover story in *TIME* magazine (May 28, 2001) and reports in the *New York Times*, *USA Today*, and *Newsweek*.

Gleevec was proven to be effective not just against CML, but also against another cancer, gastrointestinal stromal tumor (GIST). Three days after Thompson's press conference, during the annual meeting of the American Society of Clinical Oncology in San Francisco, Dr Charles Blanke announced that the so-called "leukemia pill" had stunning results against GIST (<https://liferaftgroup.org/wp-content/uploads/2012/09/May2001newsletter.pdf>).

According to a website for a GIST patient advocacy group a dozen years after its approval, Gleevec is a relatively unknown pill. Why all the attention focused on one orange pill against two relatively rare cancers (CML affects 4500 patients annually, while GIST is even rarer)? Although primarily addressing CML rather than GIST, Thompson broadly answered the question at the HHS press

conference: Gleevec is targeted therapy—it kills leukemia cells while sparing normal white blood cells. Unlike other more strenuous chemotherapy regimens, Gleevec has relatively few side effects. Gleevec targets the signal in the cell that causes cancer, acting as a molecular switch. Gleevec is now the prototype of cancer drugs, and cancer research laboratories around the world are trying to mimic the effects of Gleevec on other types of cancers.

As reported by the National Cancer Institute, most of the 4500 Americans diagnosed with CML each year are middle-aged or older, although some are children. In the first stages of CML, most people do not have any symptoms of cancer, as disease progresses slowly. Bone marrow transplantation in the initial chronic phase of the disease is the only known cure for CML. However, many patients are not young or healthy enough to tolerate transplantation; of those expected to tolerate transplantation, many cannot find a suitable donor, and the procedure can cause serious side effects or death. For these patients, treatment with the drug interferon alfa, introduced about 20 years prior to Gleevec, may produce remission, restoring a normal blood count in up to 70% of patients with chronic-phase CML. If interferon alfa is ineffective or patients stop responding to the drug, the prognosis is generally bleak.

Gleevec has produced higher remission rates in three short-duration, early-phase clinical trials. In the results of one clinical trial, reported in April 2001 in the *New England Journal of Medicine*, Gleevec restored normal blood counts in 53 out of 54 interferon-resistant CML patients, a response rate rarely seen in cancer with a single agent. Fifty-one of these patients were still doing well after a year on the medicine, and most reported few minor side effects. Imatinib mesylate was invented in the late 1990s by scientists at Ciba-Geigy (which merged with Sandoz in 1996 to become Novartis), in a team led by biochemist Nicholas Lydon, and its use to treat CML was driven by oncologist Brian Druker of Oregon Health & Science University. Druker led the clinical trials confirming its efficacy in CML (Gambacorti-Passerini, 2008). The scientific story of Gleevec, which became known as targeted therapy, a medical breakthrough that was a result of years of research, heralds back to the discovery of the BCR-ABL mutation in chromosomes 9 and 22 by Janet Rowland at the University of Chicago, and the pioneering work of researchers

at Johns Hopkins University who discovered that cancer cells harbor this mutation. Gleevec is targeted therapy, designed to attack cells with this BCR-ABL mutation (also known as translocation, when pieces of chromosomes detach from one or more chromosomes and move to another chromosome). This BCR-ABL mutation affects a growth pathway in the cell known as the tyrosine kinase pathway, which leads to a cancerous state.

For the first time, cancer researchers now have the necessary tools to probe the molecular anatomy of tumor cells in search of cancer-causing proteins," said Richard Klausner of the National Cancer Institute. "Gleevec offers proof that molecular targeting works in treating cancer, provided that the target is correctly chosen. The challenge now is to find these targets (<http://www.cccbiotechnology.com/WN/SU/gleevecnews.php>).

There are hundreds of known mutations for cystic fibrosis (CF), an inherited disease that affects the lung leading to complications such as pneumothorax. In 2012, the FDA approved a new therapy for CF called Kalydeco (known generically as ivacaftor), which was approved for patients with a specific genetic mutation—referred to as the G551D mutation—in a gene that is important for regulating the transport of salt and water in the body. The G551D mutation is responsible for only 4% of cases in the United States (approximately 1200 people). In these patients, Kalydeco works by helping restore the function of the protein that is made by the mutated gene. It allows a proper flow of salt and water on the surface of the lungs and helps prevent the buildup of sticky mucus that occurs in patients with CF and can lead to life-threatening lung infections and digestive problems.

The FDA's profile of personalized medicine chronicles the development of Herceptin (Simoncelli, 2013):

The story of trastuzumab (Herceptin, made by Genentech, Inc.) began with the identification by Robert Weinberg in 1979 of "HER-2," a gene involved in multiple cancer pathways. Over the next two decades, UCLA researcher Dennis Slamon worked to understand the link

between HER2 and specific types of cancer. Slamon observed that changes in the HER2 gene caused breast cancer cells to produce the normal HER2 protein, but in abnormally high amounts.

Overexpression of the HER2 protein appeared to occur in approximately 20%–25% of breast cancer cases, and seemed to result in an especially aggressive form of the disease. These observations made it clear that HER2 protein overexpression could potentially serve as both a marker of aggressive disease as well as a target for treatment. In May 1998, before an audience of 18,000 attendees of the annual meeting of the American Society for Clinical Oncology (ASCO), Slamon presented evidence that Herceptin, a novel antibody therapy he had developed in collaboration with researchers at Genentech, was highly effective in treating patients with this extraordinarily aggressive and intractable form of breast cancer. What was so revolutionary about Herceptin was that it was the first molecularly targeted cancer therapy designed to "shut off" the HER2 gene, making the cancerous cells grow more slowly and without damaging normal tissue. This precision also meant that patients taking the new treatment generally suffered fewer severe side effects as compared with other cancer treatments available at that time.

In September 1998, FDA approved Herceptin for the treatment of HER2 positive metastatic breast cancers. On that same day, the Agency granted approval to DAKO Corp for HercepTest, an in vitro assay to detect HER2 protein overexpression in breast cancer cells.

Four stories, four drugs. Each of these highlights certain aspects of personalized medicine and positive lessons learned: the discovery of driver mutations that drugs could target, rapidly facilitated clinical trials that lessen FDA approval time for breakthrough drugs, and codevelopment of drug and companion diagnostics that lead to effective predictive treatment for patients. Raju Kucherlapati's statement is telling of the coming revolution in biomedicine ahead of us.

One of the most remarkable changes has occurred in the landscape of clinical trials in the wake of personalized (physician approaches) and precision (pharma approaches) medicine. By identifying driver mutations in heterogeneous tumors that could serve as targets for therapy, drug companies could save time and money in drug development by “designing small but highly effective trials targeted to those patients more likely to benefit from the therapy” (Ranade et al., 2014). In a study led by researchers at Weill Cornell Medical College in 2015, results identified 684, or 8%, of eligible trials as precision cancer medical trials that were significantly more likely to be phase II and multicenter; involved breast, colorectal, and skin cancers; and required 38 unique genome alterations for enrollment. The proportion of precision cancer medicine trials compared with the total number of trials increased from 3% in 2006 to 16% in 2013 (Roper et al., 2015).

In July 2015, oncologists will start enrolling patients in a clinical trial with 20 or more arms, each testing different agents against different molecular targets and each including patients with different cancers. In design, the trial itself couldn't be more different from the classic clinical trial.

Instead of focusing on one cancer, as trials have for decades, the National Cancer Institute's NCI-MATCH (Molecular Analysis for Therapy Choice) trial will include patients with any solid tumor or lymphoma who have one of many genomic abnormalities known to drive cancer. Patients will be matched with a targeted agent that has shown promise against their abnormality, regardless of what cancer they have. Known as a basket trial, the new design highlights the rapidly growing number of potential targets and agents in oncology and the urgency of finding more efficient ways to evaluate them in trials (McNeil, 2015).

According to a review published by the National Cancer Institute, recent advancements in cancer biomarkers and biomedical technology have begun to transform the fundamentals of cancer

therapeutics and clinical trials through innovative adaptive trial designs. The goal of these studies is to learn not only if a drug is safe and effective, but also how it is best delivered and who will derive the most benefit (Heckman-Stoddard and Smith, 2014). Heckman-Stoddard and Smith (2014) cite two trials under way: I-SPY and BATTLE:

I-SPY 1 is a neoadjuvant trial of women with locally advanced breast cancer, which are assessed for estrogen receptor (ER), progesterone receptor, human epidermal growth factor 2 (HER2), and Mammprint, a 70-gene predictive signature of distant recurrence prior to treatment (or randomization). The trial evaluates molecular biomarkers of treatment and response and breast imaging to guide “adaptive” (i.e., subsequent optimal treatments). Initial studies were used to develop and validate optimal metrics of treatment response in I-SPY1.

In I-SPY 1, chemotherapy was administered before surgery, and biomarkers were compared with tumor response on the basis of magnetic resonance imaging (MRI), pathologic residual disease at the time of surgical excision, and 3-year disease-free survival. The study found that pathologic complete response (pCR), defined as no invasive tumor present in either the breast or axillary lymph nodes, differed by molecular subset; hormone receptor-positive/HER2-negative carcinomas were associated with the lowest pCR (9%) and hormone receptor-negative/HER2-positive had the highest pCR (45%). I-SPY 1 also indicated that pCR was predictive of recurrence free survival within a molecular subset. The study showed that MRI volume was the best predictor of residual disease after chemotherapy. This study established the infrastructure to integrate biomarkers and imaging with shared methods and real-time access to study data which will be leveraged for I-SPY 2....

The phase II Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE)

program is a second example of a clinical trial to determine regimes for precision or personalized medicine. Biomarkers have emerged as an important factor in planning treatment for non-small cell lung cancer (NSCLC) because of knowledge that specific epidermal growth factor receptor (EGFR) mutations lead to improved outcomes with EGFR tyrosine kinase inhibitors (TKI). The BATTLE program consists of an umbrella trial plus four phase II protocols. These phase II protocols used agents directed against promising molecular targets at the time the study began in 2005. The targets included EGFR (erlotinib), KRAS/BRAF (sorafenib), retinoid-EGFR signaling (bexarotene and erlotinib), and vascular endothelial growth factor receptor (VEGFR) (vintorelin). The primary endpoint of the study was the 8-week disease control rate (DCR) defined as complete or partial response or stable disease via Response Evaluation Criteria in Solid Tumors (RECIST). A 30% DCR in similar patients was used as a control, with treatment efficacy defined as a greater than 80% probability of achieving greater than 30% DCR.

Patients enrolled in the umbrella trial underwent tumor biopsy and biomarker analysis for 11 biomarkers: mutations in EGFR, KRAS, and BRAF; copy numbers of EGFR and the Cyclin D1 gene (CCND1); and protein expression level of VEGF, VEGF-2, RXRs α , β , and γ , and Cyclin D1. The biomarker analysis was completed with day 14 biopsy; patients and investigators were blinded to biomarker results until the patient went off study. The results of the biomarker analysis were used to classify patients into one of five groups: (1) EGFR mutation and/or amplification; (2) KRAS or BRAF mutation; (3) VEGF and/or VEGF-2 overexpression; (4) RXRs α , β , and γ , and/or Cyclin D1 overexpression and/or CCND1 amplification; or (5) negative for biomarker panel. Those patients who were positive for more than one marker were

assigned to a treatment group based on the marker with highest predictive value. During the first part of the study patients were enrolled randomly to each of the four phase II studies except for patients with prior erlotinib treatment who were excluded from the erlotinib-containing study arms. The results of this randomized portion of the study were used to assess the association between a given marker group and disease control. For example, patients with an EGFR mutation and/or amplification had a certain probability of disease control with each of the treatment regimens. For the second part of the trial this probability was incorporated into a Bayesian adaptive algorithm to randomly assign patients to an optimally predicted treatment arm. The probability of disease control was updated throughout the trial based on accumulating data.

Efficacy outcomes for these biomarker-driven trials have also been demonstrated in one study published in the *Journal of the National Cancer Institute* led by investigators at the Moores Cancer Center at the University of California, San Diego:

In order to ascertain the impact of a biomarker-based (personalized) strategy, outcomes were compared between US Food and Drug Administration (FDA)-approved cancer treatments that were studied with and without such a selection rationale. The results: fifty-eight drugs were included (leading to 57 randomized [32% personalized] and 55 non-randomized trials [47% personalized]). Trials adopting a personalized strategy more often included targeted oral and single agents and more frequently permitted crossover to experimental treatment. In randomized registration trials (using a random-effects meta-analysis), personalized therapy arms were associated with higher relative response rate ratios compared with nonpersonalized trials. Analysis of experimental arms in all 112 registration trials (randomized