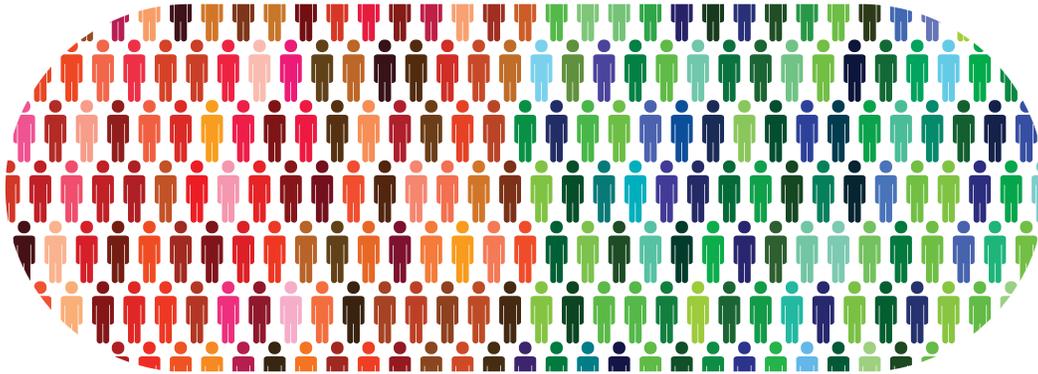


# The Value of Personalized Medicine

A Series by [REALWORLDHEALTHCARE.org](http://REALWORLDHEALTHCARE.org)



“Personalized Medicine offers an increasing number of patients the ability to live longer, healthier lives. But who are the researchers behind these advances and why are they excited about their work and the future it may bring? While their data is often published, presented, and discussed, their passion is rarely shared.

The Value of Personalized Medicine is a recently published series of articles that brings you the stories behind the research and celebrates researchers as heroes for their commitment to improving medicine. Please accept this complimentary copy as our way of thanking you for your commitment to advancing medicine and improving patients’ lives.”



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## Personalized Medicine & Companion Diagnostics: What You Need to Know

By Emily Burke, Ph.D., Director of Curriculum Development, BiotechPrimer.com



Personalized medicine – also referred to as precision or stratified medicine – is already changing the way we diagnose and treat disease. As our ability to obtain and analyze large amounts of genetic data increases, so too will the range and power of these personalized tools.

The idea of personalized medicine is not new. Physicians have long known that patients vary in their responses to medicine, and have sought to optimize individual responses. The father of medicine, Hippocrates, writing more than two millennia ago, said “It is more important to know what sort of person has a disease,” wrote Hippocrates, “than to know what sort of disease a person has.” But today, for the first time in human history, we have the tools available to make it personalized medicine a reality.

Twenty years ago, there were only four medicines on the market with genomic information on their label. Today, there are more than 100. These breakthroughs were made possible first by the completion of the Human Genome Project in 2003, and accelerated by advances in technology that have made sequencing individual patient genomes a realistic possibility. These new medicines and their accompanying diagnostics have increased both safety and efficacy by targeting specific patient populations most likely to benefit.

In this Real World Health Care series, we’ll examine specific examples of personalized medicines and diagnostics, and explain the technology that has made them possible.

### Helpful Terms

Companion Diagnostic: A companion diagnostic is the test or measurement intended to assist physicians in making treatment decisions for their patients, usually by determining the efficacy and/or safety of a specific drug for a targeted patient group. For a list of all FDA-approved companion diagnostics, [click here](#).

DNA Sequencing: Determines the order of every single base pair in a given gene (gene sequencing) or in an entire genome (whole genome sequencing).

Epidermal Growth Factor Receptors (EGFR): EGFR is found on the cell surface and is activated by growth factor binding. Once activated, EGFR activates enzymes inside the cell that drive the cell forward into cell division. EGFR overexpression is associated with a number of cancers, including lung cancer, anal cancers, and glioblastoma multiforme.

Gene Expression: The process cells use to read genetic information to make proteins. Because each cell in our body has the same genetic information, it is the differences in gene expression that determine what proteins a cell will end up producing. Gene expression differences are also associated with disease. For example, a type of cell or tissue may make too much or too little of a particular protein, which is the basis for many genetic disorders.

Monogenic Diseases: Changes in one gene cause the disease. Examples: sickle cell anemia, cystic fibrosis, and Huntington's disease.

Personalized Medicine: Implies the development of medicines for an individual, based on their unique genetic, metabolic, microbiomic and other "signatures."

Pharmacodynamics (PD): How a drug affects the body.

Pharmacokinetics (PK): How the body affects a drug.

Polygenic Disease: Caused by the interactions of many different genes. Examples: cancer, heart disease, Alzheimer's disease and Parkinson's disease. Polygenic diseases often have susceptibility genes associated with them, which increase the likelihood of the person developing the disease, but do not absolutely predict its development.

Precision Medicine: Dividing patient groups into specific populations and designing new drugs for those subtypes.

Prodrug: A drug given to patients in an inactive or less than fully active form.

Single Nucleotide Polymorphism (SNP): A one base difference in the DNA sequence of a gene when compared to the sequence found in the majority of the population. Many SNPs have no significant impact on an individual's health, but others are associated with disease susceptibility.

Check back soon for the next article in our series on personalized medicine and companion diagnostics: an interview with Joshua P. Cohen, Ph.D., Research Associate Professor, Tufts Center for the Study of Drug Development.

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To read this on the RWHC blog, [click here](#).

## Personalized Medicine & Companion Diagnostics: Speaking with Dr. Joshua Cohen, Tufts Center for the Study of Drug Development

**Editor's Note:** In August, the [Tufts Center for the Study of Drug Development](#) (CSDD) hosted a [roundtable](#) of R&D leaders focused on development of companion diagnostics that can show their use in conjunction with personalized therapeutics that will lead to positive health outcomes. We spoke with [Joshua P. Cohen](#), Ph.D., Research Associate Professor, Tufts CSDD about the promises and challenges in the field of personalized medicine.

**Real World Healthcare:** According to Tufts CSDD, 20 percent of new drugs winning approval in the U.S. last year were considered personalized medicines. What do you think is driving the growth you expect to see?

**Joshua Cohen:** More investment in the science of biomarker identification and validation, and more investment in the commercialization of personalized medicines and diagnostics.



**RWHC:** What reimbursement problems, if any, do you see for companion diagnostics?

**JC:** There are two challenges concerning companion diagnostic pricing and reimbursement. The first is coding. Traditionally, diagnostics have been code-stacked — coded for each individual activity involved in the preparation and use of a diagnostic. Each code is then assigned a price and, when taken together, the prices of individual codes make up the price that diagnostic manufacturers get reimbursed. Code-stacking does not, however, reflect the value of a diagnostic. It only reflects the price of individual components.

The value of a diagnostic is reflected by the second pricing and reimbursement challenge: clinical utility — the linkage between a companion diagnostic and positive health outcomes. The more clinical utility a diagnostic has the greater the chance it will be reimbursed and the higher price it can command. If a diagnostic differentiates between likely responders and non-responders, the value of that differentiation should be reflected in the diagnostic's price.

**RWHC:** What can drug and diagnostic companies do to accelerate the development of biomarker efficacy and remove this key hurdle to the development of personalized medicine?

**JC:** Identification of biomarkers early in development. Coordination and communication with regulators early in development, as the regulatory processes for diagnostics and therapeutics are different. Also, use of next-generation sequencing to develop diagnostics, in which biomarkers with predictive claims undergo rigorous clinical (cross) validation.

**RWHC:** When it comes to personalized medicine, even high R&D success rates may not mean much if physicians won't prescribe it and payers won't reimburse it. Are you aware of any hesitancy to entering the space by the industry?

**JC:** There may be some hesitancy on the part of the biopharmaceutical industry because personalized medicine alters the blockbuster model. This said, many newly approved personalized medicines have high price tags. In some cases, these high price tags have made them blockbuster drugs (e.g., Herceptin, Gleevec). Physicians will prescribe personalized therapeutics as long as evidence suggests it does a good job at differentiating between likely responders and non-responders to a particular therapeutic, or indicates which sub-group is at risk for certain adverse effects. Similarly, payers will reimburse personalized therapeutics and companion diagnostics if evidence supports their effectiveness and safety. An issue has come up with respect to awareness on the part of the physicians about personalized medicine, and specifically the role that diagnostics play. In cases in which there is less awareness of the need to employ a certain diagnostic, less clinical adoption will occur.

**RWHC:** What fields of medicine are furthest along in development of personalized medicines?

**JC:** Oncology dominates. There is a better understanding of the science behind targeted therapies and the role that biomarkers play.

**RWHC:** Why do you like this field?

**JC:** It represents the promise of individualizing treatments, rather than relying on an iterative, trial-and-error method.

To read this on Real World Health Care, [click here](#).

## Targeting Breast Cancer: The Subtypes of Breast Cancer

By Emily Burke, Ph.D., Director of Curriculum Development, BiotechPrimer.com

Editor's Note: Based on an article originally published in [Biotech Primer Weekly](#)

Hearing your doctor utter the words HER2-positive, HR-positive, triple-negative or BRCA mutation can be devastating — even for the most resilient person. Simply put, all are linked to breast cancer. Breast cancer is complex, and a diagnosis can be caused by all, some, or even none of the factors listed above.



In fact, the [National Cancer Institute's annual report to the nation](#) outlined four molecular subtypes of the disease. Each subtype is categorized by the cancer's hormone receptor (HR) status and the level of expression from the HER2 gene. These cellular distinctions lead patients on different treatment journeys because the cancer subtype determines the drugs used in a treatment plan.

### HER2-Positive

HER2-positive (HER2+) breast cancer patients — about 20% of all breast cancer cases — have the most highly effective therapies available on the market. HER2+ cancer cells produce, and therefore present, larger than normal numbers of the HER2 receptors on their cell surface. These HER2 receptors capture growth factors, which trigger the cell to grow and reproduce more rapidly than normal. Mutations are more likely with rapid reproduction and thus, a tumor is born.

Overexpression of the HER2 receptor is the result of having extra copies of the HER2 gene, known in the world of genomics as gene amplification. Gene amplification events are thought to be caused by mutations that occur after a person is born — it is not an inherited form of cancer.

Certain monoclonal antibodies can bind to and block the activity of the HER2 receptor on cancer cells. When the HER2 receptor is blocked, the HER2 growth factor can no longer bind and send a growth signal to the cell, so the cancer cells stop dividing. The presence of an antibody on the surface of HER2+ breast cancer cells also signals the patient's immune system to attack the cell.

Another available treatment comes in the form of an antibody-drug conjugate — a monoclonal antibody that delivers a highly toxic drug directly to HER2+ breast cancer cells. As a normal part of the cell's lifecycle, cell-surface receptors get internalized or "taken up" by the cell on a regular basis. When the

antibody-drug conjugate is attached to a receptor that gets internalized, the toxic payload is released from the antibody and kills the cancer cell internally.

### **HR-Positive**

About 70% of breast cancer diagnoses involve a significant number of receptors for either estrogen or progesterone, making them hormone receptor positive (HR+). HR+ cancers may respond positively to treatments that block either the action or the production of estrogen. In some cases, these treatments may continue to be used for up to five years after initial treatment to prevent recurrence.

Two common type of medications for HR-positive breast cancers are tamoxifen and aromatase inhibitors. Both types of drugs may also be prescribed as a preventative treatment in women who are at high risk for breast cancer. In fact, tamoxifen is named on the [World Health Organization's List of Essential Medicines](#), a list of the most important medications needed in a basic healthcare system.

Tamoxifen works by inhibiting the estrogen receptor. On the other hand, aromatase inhibitors block the production of estrogen by inhibiting an enzyme whose activity is required for estrogen production.

In February of this year, the FDA approved a new treatment for estrogen-receptor positive, HER2-negative breast cancer: a small molecule inhibitor of cellular enzymes known as cyclin-dependent kinases (CDKs). CDKs promote the development and division of cancer cells, and inhibiting CDKs helps to arrest cancer growth.

### **Triple-Negative**

Triple-negative breast cancers lack receptors — they are estrogen-receptor negative, progesterone-receptor negative, and HER2-negative. Since there are no receptor drug targets, this subtype is challenging to treat, and to date there are no targeted therapeutics. If detected early enough, triple-negative breast cancer may respond well to chemotherapy.

### **The BRCA Gene**

BRCA stands for “**B**Reast **C**Ancer susceptibility gene” and everyone has the BRCA1 and BRCA2 genes. The job of BRCA is to scan cellular DNA for damage and trigger DNA repair processes when mutations are found. BRCA genes are passed down from one generation to the next — a good thing, unless the version passed down is a mutated version.

Mutated BRCA1/2 genes are non-functioning, so they cannot locate DNA damage, nor can they enlist DNA repair. Testing positive for BRCA1/2 mutations may indicate there is an accumulation of DNA damage, which may eventually lead to cancer. BRCA is normally active in breast and ovarian cells, which is why certain mutations in BRCA1/2 are associated with a significantly increase risk of developing breast or ovarian cancer. It must be stressed that BRCA1/2 mutations in and of themselves do not cause cancer; they simply make it more likely to occur.

A new class of drugs known as PARP1 inhibitors gives hope to patients whose breast cancer is associated with non-functioning BRCA genes. PARP1 is a second type of DNA repair protein. By inhibiting this

pathway, DNA damage becomes so extensive that the cancer cells commit “cell suicide” (or apoptosis). When the cell in question is a cancerous cell, apoptosis is a very good outcome.

Not all triple-negative breast cancers are BRCA associated, but many BRCA associated cancers are triple-negative. For this reason, triple-negative breast cancer patients may find hope in PARP1 inhibitor drugs.

To read this article on Real World Health Care, [click here](#).

## Personalized Medicine & Companion Diagnostics: Speaking with Keith Stewart, Director of the Mayo Clinic Center for Individualized Medicine

**Real World Health Care:** Why was the Center for Individualized Medicine formed at the Mayo Clinic? What were its initial goals and how have those goals changed?

**Keith Stewart:** The Center was formed in 2012 with the idea that it would harness the power of the human genome to improve health care for our patients. It was considered to be one of three transformative initiatives for the future of the Mayo Clinic and a discipline in which Mayo Clinic should be a leader.



**RWHC:** How has personalized medicine and the work you're doing at the Center for Individualized Medicine helped the Mayo Clinic to improve health outcomes?

**KS:** By using the genome as a lifetime resource and not just a "one and done" test, we believe we will lower the costs of health care. For example genomic knowledge will improve the precision of diagnosis, reduce unnecessary testing, allow the right drug at the right time and ultimately improve health outcomes.

**RWHC:** What types of companion diagnostics are being conducted at the Center for Individualized Medicine to identify the best therapy for individual patients?

**KS:** Many. One good example is pharmacogenomics where we have created 18 drug alerts in the electronic health record already. But we have many other examples: cancer gene panels in prostate cancer, glioblastoma, myeloma, sarcoma, and colorectal cancer. Panels in cardiac disease and neurology, for example in peripheral neuropathy, epilepsy, and movement disorders. And, of course, whole genome sequencing for families with rare diseases.

**RWHC:** In your opinion, what is the most exciting translational research being conducted at the Center for Individualized Medicine?

**KS:** I am very excited about our work in the microbiome and how that will impact human health and how we might use genomic sequencing in infectious disease to identify pathogens that are hard to culture. But there are many such areas. We will be sequencing the pharmacogenomes of 10,000 of our patients and launching clinical trials in the areas of organ transplant and immune-oncology next year.

**RWHC:** Where do you see the future of blood cancer-related personalized medicine and companion diagnostics heading?

**KS:** As an example we have built and are launching a gene panel in myeloma which identifies mutations but will also call common translocations. If successful this should replace the era of conventional cytogenetics and FISH testing. The same will be true in acute leukemias and lymphomas. A major area of interest is in immune-oncology and we will be launching trials in this area next year to understand how genomics can select for patients most likely to respond.

**RWHC:** When full-genome sequencing becomes routine, what sort of information do you envision healthy people obtaining and applying as a result of having their genome sequenced?

**KS:** I think the answer may not be what most people expect. Yes, we will find medically actionable things such as carrier status and pharmacogenomics, but to me, the most important thing might end up being what is negative. As an example, when I had my genome sequenced, it struck me that I would never again have to have any other genetic testing done for the rest of my life. So, if I have a blood clot, cancer, or develop Parkinson's or dementia, I already know I am negative for the currently understood genetic risk factors.

## Personalized Medicine & Companion Diagnostics: Speaking with Dr. Razelle Kurzrock

Real World Health Care recently sat down with [Dr. Razelle Kurzrock](#), Director, [Center for Personalized Cancer Therapy](#) & Clinical Trials Office, University of California San Diego [Moore's Cancer Center](#), to discuss the present state and future direction of genomics and immunotherapy.

**Real World Health Care:** Why was the Center for Personalized Cancer Therapy formed at Moore's Cancer Center? What was its initial goal and has that goal changed?

**Razelle Kurzrock:** The strategy for the Cancer Center really began to evolve with the arrival of Director [Scott M. Lippman](#). We worked together at [MD Anderson Cancer Center](#), and we both had an interest in moving into the precision medicine and personalized cancer medicine field. Based on our experience, we thought the Center could be transformative for patients with cancer. So, we started with a business plan that focused on the Center's essential components: vigorous clinical trials, researching hereditary predispositions in cancer, genomics and immunotherapy. That plan and those components became the cornerstone for what we wanted to build and who we wanted to recruit.

The only change since then is that our scope has continued to grow. The field of genomics and immunotherapy has become more exciting. We also realized we needed a strong educational component, primarily because physicians were not overly familiar with genomics and immunotherapy, so we added a fellowship in personalized cancer therapy. We also opened a rare diseases clinic. Because some rare cancers don't have an FDA-approved therapy, we look at these patients from a genomic or immunotherapy standpoint right from the start.

**RWHC:** How are patients selected to participate in your Experimental Therapeutics program?

**RK:** We have clinical trials and therapies for patients in all disease groups. But in addition, we have early clinical trials and genomically targeted or immunotherapy trials within Experimental Therapeutics. These trials are not disease based. Included in the Experimental Therapeutics trials are phase I studies that do not concentrate on a particular cancer. In the past, Phase I trials were considered as dose-finding trials. Today, these Phase I trials are more exciting and have therapeutic impact. Even the FDA is now occasionally approving drugs after Phase I testing. Included in Experimental Therapeutics are basket or umbrella trials, which look at cancer from immune or genomic points of view, instead of as "breast" or "colon" cancer. Both early-stage and umbrella trials don't always fit well into the disease site program, so we developed our Experimental Therapeutics program.



We also wanted to develop a new way of looking at cancer. We choose patients for Experimental Therapeutics based on what we think is best for the particular patient at hand. Our tumor board reviews patients, and if they feel a trial in a disease-based program is warranted, that's what is recommended. However, if biological characteristics indicate that patients would do best with a genomic or immune approach that is not disease based, the patients are funneled into our Experimental Therapeutics program.

**RWHC:** Can you give an example of a type of experimental immunotherapy that is being tested?

**RK:** While there are a number of novel molecules to talk about, I think it is our overall approach that is of interest. Immunotherapy is exciting...but it's so exciting that the tendency is to give these therapies to everyone. Instead, we investigate the biomarkers that identify the patients who will respond well to a particular therapy. We know there are certain patients who will have a wonderful response to a particular immunotherapy drug, but other patients won't. So we try to apply the personalized medicine approach to immunotherapy. We are now starting to identify biomarkers that will tell us which patient is best for immunotherapy and which may not benefit.

**RWHC:** Since creating the Center for Personalized Cancer Therapy, has Moores Cancer Center seen an increase in positive patient outcomes? If yes, can you please explain to our readers?

**RK:** It certainly generates a lot of buzz when you have patients who were expected to die soon, but thanks to personalized cancer therapy, they are alive and doing well a year or two later. While these individual cases are important, we cannot rely on anecdotes. We therefore also analyze data on patient outcomes in a systemic way, with a protocol that lets us evaluate patient outcome data on more than a case-by-case basis. This is our PREDICT program. In fact, we just submitted a paper on the first 450 patients to go through our program. The data shows improved outcomes in almost every parameter, so that good buzz we're sensing is corroborated by solid data.

**RWHC:** What types of companion diagnostics is the Center for Personalized Cancer Therapy conducting to identify the best course of treatment for each individual patient?

**RK:** We certainly take advantage of FDA-approved companion diagnostics, based on label indications. However, we're also very involved in working with different molecular diagnostic assays and looking at patients to see what those assays tell us about the patient. We want to know if those assays help us predict the best drugs for the patient.

**RWHC:** What type of enhancements might we see in the future of personalized medicine if researchers can use genomics on blood samples to predict patient outcomes or response to treatment?

**RK:** This is a really exciting area that we are working on within the Center's liquid biopsy program. These are "biopsies" that look at DNA in the blood stream. In effect, one can do the analysis on a small tube of blood. And, it goes beyond the blood stream. We are also looking at genomics of DNA shed by tumors into the urine. These assays are still in a young phase and under development. But it's amazing that we

can take a blood or urine sample and use the genomic information in those samples to better understand response even before the patient gets a CAT scan. It can take months before a CAT scan shows response, but our research is beginning to suggest that urine or blood tests can give early information about both responses and resistance to treatment. We still have a lot work to do to prove the accuracy of the correlations, but when that happens, it will be revolutionary for the field.

**To read this interview at Real World Health Care, [click here](#).**

# The State of Cystic Fibrosis and Precision Medicine

By Emily Burke, Ph.D., Director of Curriculum Development, BioTech Primer Inc.

EDITOR'S NOTE: This article is reprinted with permission from [BioTechPrimer.com](http://BioTechPrimer.com).

During President Obama's State of the Union address earlier this year, a cystic fibrosis patient named Bill Elder sat beside First Lady Michelle Obama. Diagnosed with the disease at 8 years old, Mr. Elder is "healthier now than ever before" at age 27, thanks to ivacaftor. As a third-year medical student, he is not only surviving but thriving. Receiving an invitation to be the guest of honor at the presidential speech of the year is the exclamation mark to an extraordinary story.



Mr. Elder is an example of the success of modern medicine. His cystic fibrosis (CF) treatment derives from an understanding of the underlying molecular causes of the disease. This approach, referred to by the President as *precision medicine*, is the focus of new federal investments to speed the development of targeted therapeutics — drugs designed for a subset of patients with a specific genetic defect rather than for the "average" patient.

## Personalized Medicine vs. Precision Medicine

Personalized medicine implies the development of medicines for an individual, based on their unique genetic, metabolic, microbiomic and other "signatures." Think of a breast cancer patient getting a genetic test for the BRCA gene to determine their specific genetic mutation and subsequent personalized course of treatment — not just a therapy for all BRCA-induced cancers. As large scale, full-genome sequencing becomes more efficient and common, we may start to see truly personalized medicines

But for now, a better term is "stratified" or precision medicine — dividing patient groups into specific populations and designing new drugs for those subtypes.

## What is Cystic Fibrosis?

Cystic fibrosis is a genetic disease caused by one of several possible mutations in the gene encoding the "cystic fibrosis transmembrane conductance regulator" (CFTR) protein. The CFTR protein is critical for the production of sweat, digestive fluids and mucus. It affects around 70,000 people globally and is prevalent in America, Europe and Australia.

The CFTR protein is classified as a *channel protein* — a category of proteins that create a channel, or tunnel, across the cell membrane. This specialized gateway allows things to pass through the cell that will otherwise be denied entry or exit.

