Personalizing PRECISION MEDICINE

A Global Voyage from Vision to Reality

Kristin Ciriello Pothier

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Introduction

It was the spotted lung scan day.

My old friend Heather[1] said this to me, matter of fact, over pizzas one evening as she described one of many pivotal moments in the last 2 years of her life with cancer.

Her statement, on a day memorialized in her mind by a diagnostic test, is a small window into the life of a cancer patient. Her life pre-cancer was busy, successful. She managed her own design business and ran hard and spirited, traits we were all envious of in college and that stuck with her. There was no time for anything other than her business, her husband, and her zest for life. A nagging, mild tender breast that just didn't go away prompted her to go to the doctor more out of annoyance than anything else. She was slated to meet her husband abroad at the end of the week for a European vacation; this was 1 appointment out of 20 she needed to check off her list. She hadn't even had a routine mammogram because she had barely reached her 40s and hadn't gotten around to it yet. That European trip never came.

Heather watched curiously as the administrator of her mammogram went from calm to concerned to alarmed. The administrator called her boss. Her boss's face also did not hide the alarm. Heather was scheduled for a biopsy immediately.

The days after the diagnosis were filled with research and calls to any friends that could help, from a medical point of view and from a support point of view. Thankfully, Heather's support system also included a childhood friend who was a cancer researcher at one of the top institutions in the United States and could get her to the right physicians in her own city.

And then the treatment began.

Her days, which before were measured in her meetings with clients to restore their historic homes, her long dinners with her husband, and her energetic throes into SoulCycle, were now measured differently. Days measured in test

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1 All previously unpublished patient names have been changed.

results, in exhaustion from the drug regimens, in pain from the surgeries, and in desperate hope for the next day highlighted in her support systems surrounding her. She did everything right. Her physicians personalized her treatment for her with drugs that would work on her specific cancer. The cancer looked like it was gone. And then, a follow-up scan suggested a suspected relapse and potential spread of the cancer to the lung. Her lungs looked, well, "spotted." And it started all over again.

Indeed, as much as this experience was personal to Heather, we are only starting to personalize cancer treatment in the truest sense. "I did certain things to 'hack' my experience specifically for me ... both medically and psychologically. But I understand it is difficult for doctors to do this with thousands of patients," Heather said. The ability to tailor a drug regimen to a specific genetic code that is truly personalized to that specific DNA double helix has been a dream of researchers, physicians, and patients alike. Advances in precision medicine, specifically around the genome and the helices embedded, are making this dream a reality.

Patients struggle with "chemo," drugs that indiscriminately kill both cells in their tumors and normal cells like their hair follicles, the lining of their throats and stomachs, and their sperm and eggs in their reproductive systems. According to Christopher Cutie, a urologist by training and the current chief medical officer of the innovative bladder cancer company Taris, "With any therapy that hasn't been tested for a lifetime of a patient, there is risk of what the body may do. The body craves homeostasis. When we expose it to insult, even if correcting one part of the body, it may manifest itself differently in another part."

Today, biomarkers directly connected to drugs or to crucial outcomes in the human body allow physicians to identify drugs that are most likely to help a patient, and those drugs can be used to target cancerous cells only, which reduces the side effects that the patient experiences. 28% of all drugs approved by the FDA today have biomarker information, with more in the pipeline to come. But while new advances in precision medicine hold so much promise, many challenges must be overcome before precision medicine can truly transform healthcare. For example, former President Obama's Precision Medicine Initiative aims to collect genetic and metabolomic profiles, medical records, and other health information for at least one million people, and the wealth of data will help researchers advance their understanding of diseases. "Wearables," which are devices like watches or chest monitors worn on a person, will also aid in the collection of tremendous amounts of health data. However, fundamental questions must first be addressed, such as how to store these sensitive data, how to share the data, and how to use these data to create value for patients.

Furthermore, access to healthcare remains a global challenge. Targeted therapies are among the most sought-after and most expensive therapies in the

world, and market access and payment issues must be solved to ensure that precision medicine benefits all patients, not just a select few. Here in the United States, we have built some of the most prestigious cancer centers in the world, and the likes of the University of Texas MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Massachusetts General Hospital, and Mayo Clinic provide some of our best demonstrated examples of precision medicine from vision to reality. But not all regions of the world, or even regions of the United States, have complete access to these types of institutions although they each continue to enhance and broaden their reach, and I admittedly spend more time in this book analyzing the global challenges we are facing when access is not yet achieved.

The power of precision medicine also opens the door to controversy given that the most advanced techniques can be used to do far more than cure disease. Many fear that new technology will enable the creation of designer babies or the elimination of diversity. While many scientists have discussed limitations on this type of human engineering, biomedical research is global, and there is no single authority that can limit how technologies are used.

This book explores the advances that have been made in precision medicine and discusses the global implications for companies, payers, researchers, physicians, and patients who are translating precision medicine from vision to reality. The research and one-on-one discussions with pioneers in precision medicine, day-to-day caregivers, and patients and their supporters worldwide provide firsthand experience into the reality behind the hype and demonstrate the raw emotion in building an entirely new discipline that not only brings so much good to our patients in need but also introduces many challenges. We have truly hit a new frontier, and the goal here is to bring clarity to the progress we have made, to begin a discussion of the complexities and challenges we face, and to inspire hope in the future we are building by **personalizing precision medicine**.

Methodology

This book is based on my experience in working in precision medicine strategy for products and services across diagnostics, life sciences, and therapeutics companies, investor groups, and medical institutions for over 20 years, extensive secondary research, and over 100 primary interviews with key stakeholders worldwide.

The secondary research included drug pipeline research to uncover both current and future precision medicine drugs and the diagnostics that fuel them, scientific and clinical literature reviews on existing and emerging technologies within precision medicine, and website searching to verify the most cutting edge products, services, and offerings that fuel this industry.

The primary research included detailed one-on-one interviews with industry executives, laboratorians, physicians, payers, patients, and their caregivers in the United States, Europe, South America, Central America, the Caribbean, India, China, Japan, and the Middle East who gave their feedback, insights, and detailed views in order to promote education of precision medicine and to show the diverse impact of precision medicine among a range of stakeholders and regions around the globe.

About the Author

Kristin Ciriello Pothier is the global head of Life Sciences for the Parthenon-EY practice of Ernst & Young LLP. She has over 20 years of experience in business strategy and medical research in the life sciences industry. She is a noted international speaker, workshop leader, and writer in life sciences. She is also a clinical laboratory and medical innovation expert, helping develop and implement product and service strategies worldwide for investors, corporations, and medical institutions. Prior to EY, Kristin was a partner at Health Advances, a healthcare consulting company, and a research scientist and diagnostics developer at Genome Therapeutics, a commercial company sequencing for the Human Genome Project and at Genzyme, developing pioneering noninvasive prenatal tests and numerous other precision medicine-based diagnostics tests and algorithms. She earned an undergraduate degree in biochemistry from Smith College and a graduate degree in epidemiology, health management, and maternal and child health from the Harvard School of Public Health. She is also a founding director of BalletNext, a ballet company based in New York celebrating the convergence of innovative dance, music, and art. Kristin lives in Massachusetts with her husband and their two lively children.

Contents

Part 1

The History

1

The Right Drug, the Right Patient, the Right Time

Foundations of Precision Medicine

Eight-year-old Caleb Nolan faced an uncertain future when he was born. At 3 weeks old he was diagnosed with cystic fibrosis (CF), an inherited, devastating, incurable genetic disease that causes a buildup of mucus in various organs, including the lungs, pancreas, liver, and intestines. This results in poor weight gain, infertility, and chronic lung infections that can lead to respiratory failure. While antibiotics are used to treat infections, many CF sufferers eventually require a lung transplant, and few used to live beyond the age of 50. However, Caleb now lives a full life and will probably die of old age instead of CF [1].

CF is caused by an abnormality in the CF transmembrane regulator (CFTR) gene that prevents the normal movement of chloride ions across membranes and currently afflicts about 30,000 children and adults in the United States and 70,000 people worldwide [2]. As with all people, CF patients have two copies of the CTFR gene, one from each parent, but for them both copies are harmfully mutated. There are people who are "carriers" for the mutation who have one normal and one mutant copy, and while they do not have symptoms of CF, they can pass the gene to their children. At this moment, there are about 10 million carriers in the United States.

One of the most common mutations causing CF is called the deltaF508 deletion mutation, which can be detected using a number of molecular techniques. Akin to an error in the blueprints for building a cabinet that misses a shelf support, this means that the CTFR protein made from the blueprint of the mutated CTFR gene is defective due to a deletion at the 508th place along the protein code (see Figure 1.1). This kind of mutation can be tested by DNA amplification—making many copies of parts of someone's DNA CFTR gene and looking for the mutations that cause CF. There are three ways to assess CF: "carrier screening" of parents-to-be or pregnant women determines their CFTR gene status and helps families adequately prepare for the results. Testing is also done on amniocentesis samples to directly assess CF status in the unborn child. Finally, newborns are screened in all 50 states to assess CF status [4].

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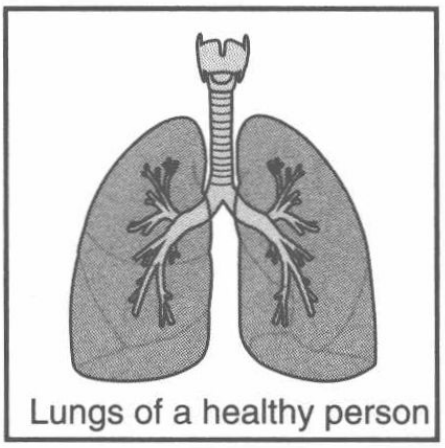

Normal CFTR sequence

Nucleotide:	ATC	ATC	TTT	GGT	GTT
Amino acid:	Ile	Ile	**Phe**	Gly	Val
Position:	506		**508**		510

Deleted in Delta F508

Delta F508 CFTR sequence

Nucleotide:	ATC	ATC	GGT	GTT
Amino acid:	Ile	Ile	Gly	Val
Position:	506			

Figure 1.1 The CFTR defect in cystic fibrosis. Source: Data from Pothier et al. [3].

Did You Know?

DNA stands for *d*eoxyribo*n*ucleic *a*cid, and it is the hereditary material in humans and virtually all other organisms. The information that DNA carries is stored as a "code" that is made of four different chemicals called bases—adenine (A), guanine (G), cytosine (C), and thymine (T). The sequence of the bases dictates how that organism is made and, although there are around three billion bases in humans, the sequence is 99.9% identical.

DNA bases pair up, with adenine (A) pairing with thymine (T) and guanine (G) pairing with cytosine (C). A sugar molecule and a phosphate molecule also attach to each base to create a nucleotide, and these nucleotides are then arranged into the DNA double helix (see Figure 1.5). The DNA is arranged into 46 structures called chromosomes that are arranged into 23 matching pairs, which include one sex pair. A female has 2 X's as the sex pair, and a male has an X and a Y. The entire collection of 46 chromosomes is called a karyotype.

DNA is made of building blocks called nucleotides, and as a highly dynamic and adaptable molecule, it can suffer many types of mutations. Some are harmless, some are helpful, and some can harm the DNA and, ultimately, the organism. These mutations can arise by chance or through environmental factors such as exposure to chemicals and can occur in somatic cells (nonreproductive cells) or germ cells (reproductive cells such as sperm and egg). Diseases like cancer largely affect somatic cells, while mutations in germ cells lead to inherited diseases like cystic fibrosis. Various types of mutation exist.

There are nucleotide substitutions, where one nucleotide is swapped for another; insertions and deletions (indels), where nucleotides are added or deleted; and frameshift mutations, which are insertions or deletions of more than one nucleotide that result in the complete alteration of the sequence of a protein [6].

However, CF sufferers have new hope for treatment. This is due to a revolutionary treatment approach that was approved by the FDA in 2012. The drug Kalydeco is the first to target the underlying genetic cause of the disease. Kalydeco is one of a new generation of medicines that are specifically tailored to treat a disease based on the genetic makeup of an individual. In the case of Kalydeco, rather than just treating the symptoms of the disease, the drug acts on the gating defect associated with the defective CFTR protein, helping to open up the blocked chloride channels (see Figure 1.2). This allows for a clearing of the mucus buildup from the inside out. These drugs are part of a new age in medicine, "precision medicine," which strives to provide the right treatment for the right patient at the right time.

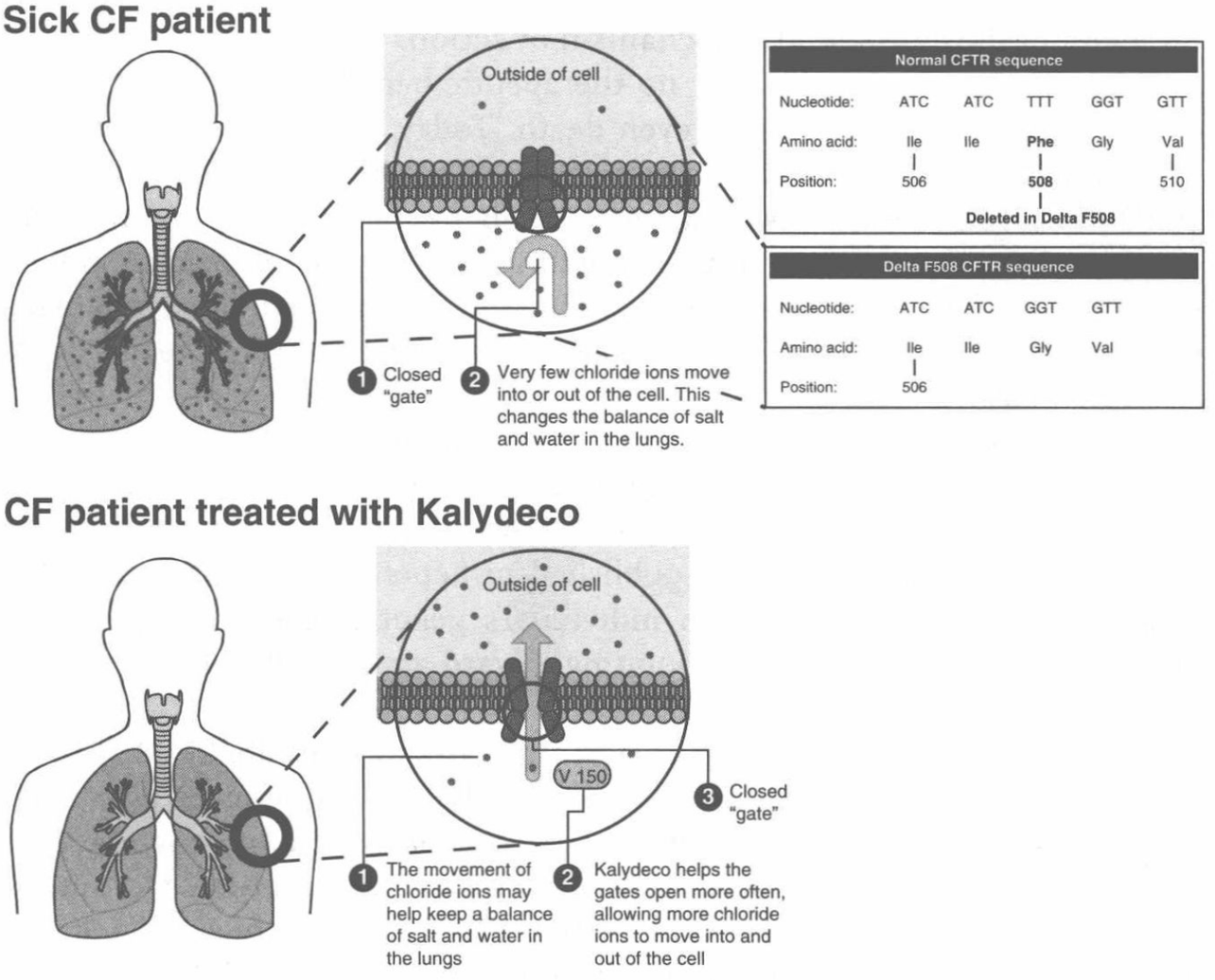

Figure 1.2 Kalydeco's mechanism of action. The drug acts to open up the protein gate that regulates the movement of chloride ions between the outside and the inside of the cell. Source: Adapted from Kalydeco [7].