Personalizing PRECISION MEDICINE

A Global Voyage from Vision to Reality

Kristin Ciriello Pothier

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Boston, MA, USA

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This edition first published 2017

Registered Office
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

Editorial Office
111 River Street, Hoboken, NJ 07030, USA

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Library of Congress Cataloging-in-Publication Data

Names: Pothier, Kristin Ciriello, 1974– author.
Title: Personalizing Precision Medicine: A Global Voyage from Vision to Reality / Kristin Ciriello Pothier.
Description: Hoboken, NJ : John Wiley & Sons, Inc., 2017. | Includes bibliographical references and index. |
Identifiers: LCCN 2017020345 (print) | LCCN 2017021066 (ebook) | ISBN 9781118792179 (pdf) | ISBN 9781118792124 (epub) | ISBN 9781118792117 (pbk.)
Subjects: | MESH: Precision Medicine–trends
Classification: LCC R733 (ebook) | LCC R733 (print) | NLM WB 300 | DDC 610–dc23
LC record available at https://lccn.loc.gov/2017020345

Cover Design and Image: Courtesy of Diana Saville.

Set in 10/12pt Warnock by SPi Global, Pondicherry, India

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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Acknowledgments

This book would not have been completed without the support of my loving family—Bryan, Olivia, and Luke—and our parents and dear friends and the support of Ernst & Young LLP. I would like to give special thanks to my *Personalizing Precision Medicine* life sciences lead editorial team in the firm's Parthenon-EY practice, led by Mahala Burn, Brian Quinn, Joe Zaccaria, Jessica Lin, and Jay Canarick. Additional thanks goes to our team of Parthenon-EY consultants who contributed to the research in the book, including Alasdair Milton, Jay Buckingham, Jessica Bernheim, Alex Chen, Glenn Engler, Will Janover, Ankit Goel, Eric Haskel, Ryan Juntado, Hayley Kriman, Harish Kumar, Chen Liu, Melissa Maggart, Armelle Sérose, Hanu Tyagi, Eleonora Brero, Shushant Malhotra, Derek Matus, Amy McLaughlin, Will Poss, Melanie Gaynes, Chris Bravo, Gillian O'Connell, Jeremy Rubel, Hamza Sheikh, Mark Sorrentino, Yuan Wang, Maxine Winston, Gary Yin, Ike Zhang, and Scott Palmer. Also, thanks for the support of my Ernst & Young leadership teams worldwide, my quality, legal, graphics, and marketing teams; my cover illustrator Diana Saville; and external copy editor and oldest, most honest friend, Kristin Walker Overman. Also incredible thanks to my publisher Wiley and its team led by Jonathan Rose for having the patience to wait for the completion of this book. And finally, thanks to my friends, family, and trusted colleagues affected by cancer, who generously devoted their time and support to help me make this book a reality.

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

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.

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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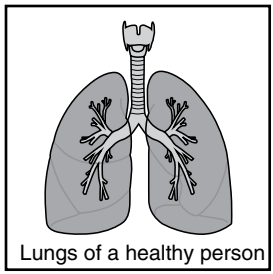
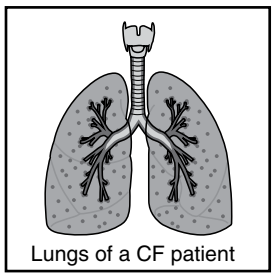


Normal CFTR sequence					
Nucleotide:	ATC	ATC	TTT	GGT	GTT
Amino acid:	Ile	Ile	**Phe**	Gly	Val
Position:	506		**508**		510

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.

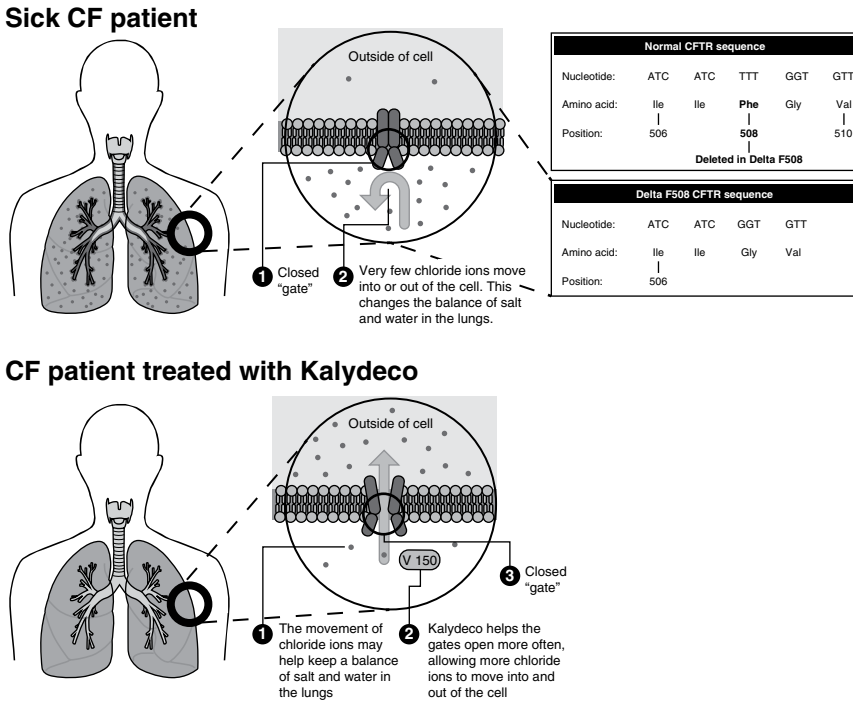


Figure 1.2 Kalydeco's mechanism of action. The drug acts to open up the protein gate that regulates the movement of chloride ions between the outside and the inside of the cell. Source: Adapted from Kalydeco [7].

The Origins of Precision Medicine

The 1990s was a golden age for the pharmaceutical industry. This was the original "blockbuster" era, when the focus was on developing broad-spectrum drugs for large "primary care" indications like high cholesterol, asthma, and depression. Adopting a "one-size-fits-all" approach meant that companies could generate billions of dollars in sales by targeting the largest patient populations, spending hundreds of millions of dollars on marketing campaigns, and having large sales forces focusing on doctors. Even drugs that were fourth, fifth, or sixth to market could achieve stellar sales performance using this approach, with insurance companies willing to cover these products.

Drug development strategies used by many companies during the 1990s were crude and rudimentary compared with those commonly utilized today. When hunting for a new multibillion-dollar drug, companies screened huge libraries of compounds against a target to look for a suitable candidate that was then tested in clinical trials. The companies searched without assessing whether certain people would be nonresponders or would have an adverse reaction. In some cases, researchers didn't even fully understand the compound's mechanism of action.

This often resulted in little or no therapeutic benefit and, in some cases, caused serious side effects and even death. Today, less than half of people prescribed an antidepressant achieve remission with the first therapy [8], while patients treated for asthma, type II diabetes, arthritis, and Alzheimer's all have differing responses to their medications [1] that can lead to limited therapeutic outcomes or serious side effects. Overall, it is estimated that many of the leading drugs in the United States today only benefit between 1 in 25 and 1 in 4 patients [9].

Warfarin, a common blood thinner, can cause major bleeding and death due to the fact that patients respond to the drug in different ways, driven by genetic variations on a person-to-person basis. However, an analysis of a number of independent studies published in September 2014 showed that dosing of warfarin based on an individual's genetics could reduce major bleeding episodes by over 50%, pointing toward a personalized approach to treatment with the drug [10].

The rigid drug development approach of the past has resulted in the termination of a number of compounds late in the clinical trial process, as companies fail to find a therapeutic signal or, worse still, uncover a major safety issue. On many occasions, this is due to the heterogeneous nature of the patient populations that are used in the trials, with researchers never fully understanding the genetic, environmental, or lifestyle factors that can influence drug response in these large population-wide studies [9].

The impact of this approach to drug development was highlighted in 2005 when Tysabri, an immunosuppressant drug used to successfully treat multiple sclerosis, was removed from the market following three cases of a rare neurological condition called progressive multifocal leukoencephalopathy (PML). Two patients subsequently died [11].

Tysabri was returned to the market in 2006 with a black box warning—a statement of serious risks required by the FDA—and a risk management plan. As part of this, the drug's manufacturer, Biogen Idec, worked with a lab to develop a test that helped stratify patient risk based on the specific presence in the patient's body of the John Cunningham (JC) virus, which can cause PML in patients with compromised immune systems. Biogen had therefore developed a precision approach to treatment with Tysabri.

These examples highlight the complex, multifactorial nature of drug response. Often, biomarkers or molecular pathways that scientists think are involved in disease turn out only to be associated with the disease, rather than to be the root cause (see Figure 1.3). The result can be billions of dollars in wasted R&D spend and drugs that either have limited therapeutic benefit or, in worse case scenarios, can actually cause serious harm to patients. This is why precision medicine promises to be revolutionary for the field of medical science.

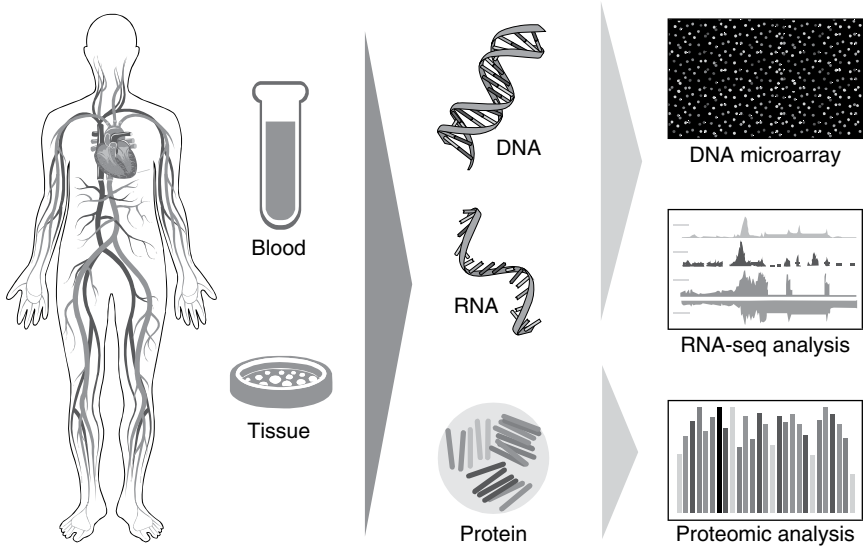


Figure 1.3 Molecular diagnostics examine the molecules in the cell, that is, the DNA, RNA, or proteins, and their role in human biology and disease. Source: Data from Pothier et al. [3].

The idea of tailoring medicine to an individual is not new. Hippocrates, the "Father of Western Medicine," said that "it is more important to know what sort of person has a disease, than to know what sort of disease a person has." [12] However, it would be another 2500 years before precision medicine became a reality.

The scientific underpinnings of precision medicine began in the late 1860s when Swiss chemist Friedrich Miescher stumbled across a new molecule as he was trying to isolate proteins from white blood cells. Instead of successfully isolating proteins, he discovered a substance in the cell nucleus that had chemical properties that were different from those of proteins.

He named this new molecule "nuclein," deducing that it consisted of hydrogen, oxygen, nitrogen, and phosphorus, and, believing that he had discovered something important, he stated that "it seems probable to me that a whole family of such slightly varying phosphorous-containing substances will appear, as a group of nucleins, equivalent to proteins" [13]. Miescher, who was largely forgotten after his death, had discovered DNA (Figure 1.4).

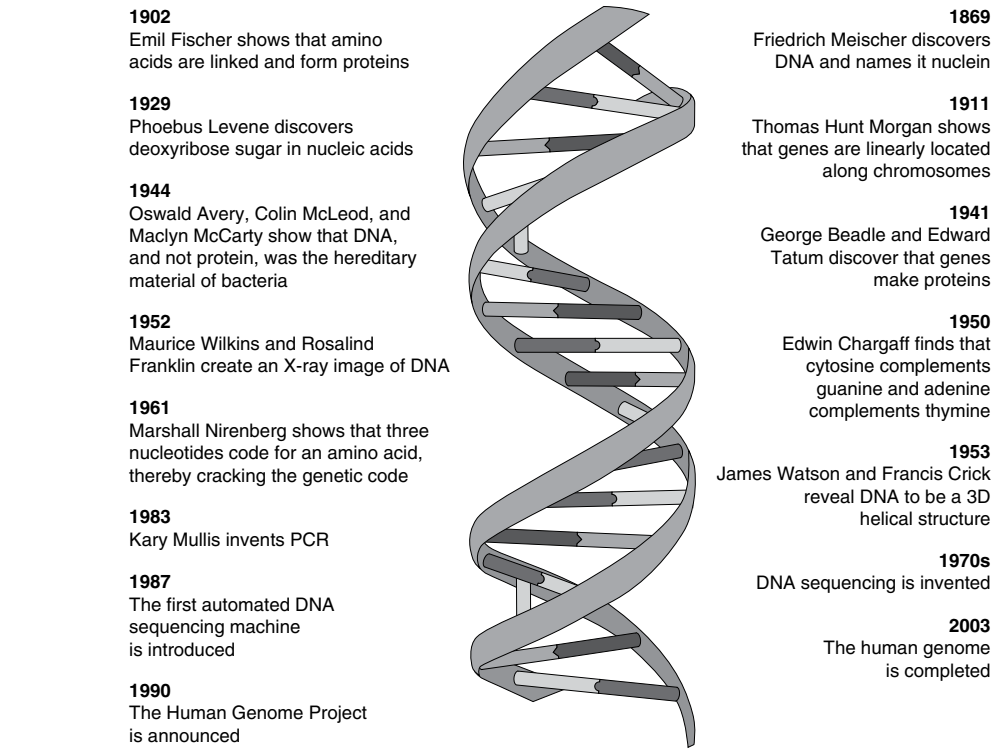


Figure 1.4 The history of DNA.

Russian scientist Phoebus Levene, Austrian biochemist Erwin Chargaff, American scientist Oswald Avery, and English chemist Rosalind Franklin played major parts in linking Miescher's original discovery of nuclein in 1869 to the 1953 announcement by James Watson and Francis Crick that DNA exists as a three-dimensional double helix (Figure 1.5). Watson and Crick won the Nobel Prize in Physiology or Medicine in 1962 for their discovery. Sometimes forgotten is their colleague in this research, Rosalind Franklin, a chemist who also made the discovery with the team but died of ovarian cancer before the Nobel Prize was awarded. Unfortunately, Nobel Prizes are not given posthumously.

Although they had now discovered the "blueprint" for a human being, scientists in the 1950s still didn't know how the information held in our DNA was translated to the 20-letter alphabet of amino acids, the building blocks of proteins, which are the functional units that ultimately drive cellular processes. In 1939, the role of another nucleic acid, RNA, had been linked to protein synthesis, but it wasn't until the 1950s that the various types of RNA that are

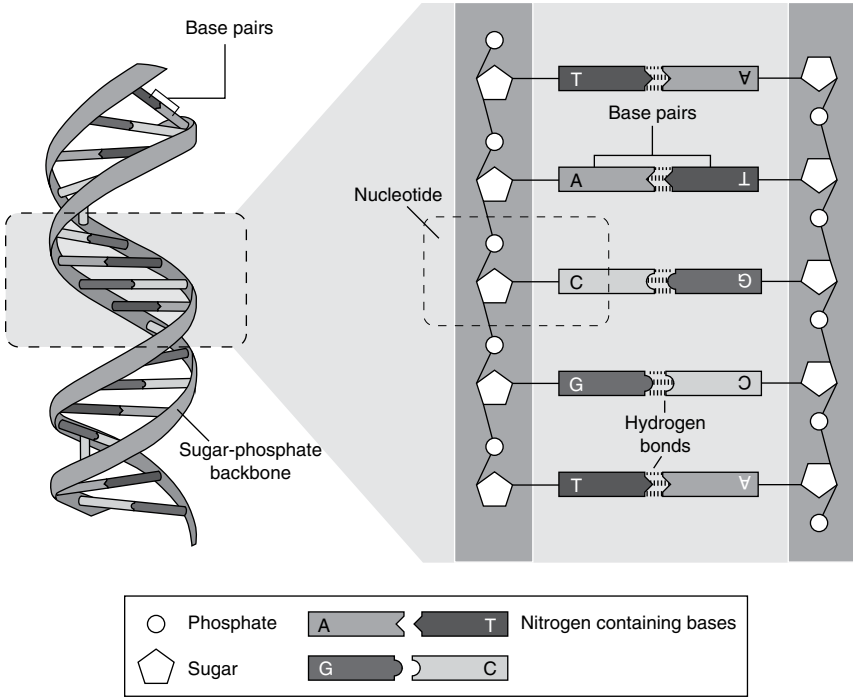


Figure 1.5 The double-helix structure of DNA. The molecule consists of four bases—adenine (A), guanine (G), cytosine (C), and thymine (T) and a sugar-phosphate backbone. Adenine always binds to thymine (A–T) and guanine always binds to cytosine (C–G). Source: Adapted from Encyclopædia Britannica [5].

essential in turning the DNA code to protein were identified. It's now known that when DNA is replicated, it's translated to single-stranded messenger RNA (mRNA), with the thymine base (T) replaced with uracil (U). The process of converting the mRNA to protein happens on a molecule called a ribosome. Another type of RNA called transfer RNA (tRNA) can bind to the free amino acids and bring them to the ribosome, where the tRNA reads the mRNA code and starts to build out the protein. In his groundbreaking paper in 1961, Marshall Nirenberg presented results from an experiment that showed that three nucleotides coded for an amino acid. With this discovery, the genetic code had finally been cracked (see Figure 1.6) [15].

In the 1970s, a technique was invented that would revolutionize the field of molecular biology and would prove to be essential to the future of precision medicine—the development of DNA sequencing. Until the advent of DNA sequencing, molecular biologists could only examine DNA indirectly through protein or RNA sequencing [16]. What scientists lacked was the ability to sequence, analyze, and interrogate the building blocks of life in order to locate gene sequences and identify mutations in the genetic code.

Sequencing was quickly followed by the introduction of the polymerase chain reaction (PCR) in 1983, which allowed researchers to quickly amplify a specific target sequence [17]. PCR is now considered a workhorse in molecular diagnostics, with Kary Mullis receiving a Nobel Prize in Chemistry in 1993 for its invention. PCR is a powerful tool for locating short segments of a gene where known critical mutations or variances can lead to altered cell functions associated with disease. PCR tests for the presence of a portion of DNA that has a known base sequence, employing

Did You Know?

The PCR process is elegant in its simplicity. There are four components—the template (sequence of DNA to be amplified), DNA polymerase (enzyme that adds new nucleotides to a growing DNA strand), primers (small segments of DNA that bind a specific region on either side of the target DNA and start replication of the DNA at that point), and a salt solution called the buffer that stabilizes the reaction components. The DNA is denatured (hydrogen bonds holding the double helix are broken, creating single-stranded DNA) by heating to more than 90°C. As the mixture cools to between 40 and 60°C, the primers bind to their target sequence on the template. The reaction is then heated to around 72°C, which is the optimal temperature at which DNA polymerase operates. The polymerase extends the primers, adding the nucleotides onto the primer in the correct order, based on the sequence of the template. This process is then repeated over and over again. Because the DNA made in the previous cycle can also serve as a template, the resulting amplification of DNA is exponential [3].