2

KEYS TO WELLNESS

Biological Markers That Govern Your Health

Since the epic moment when the first sequencing of the human genome was announced, genetic research has become exponentially faster, cheaper, and more revealing. In fact, decoding complete genomes has now become routine for today's genetic researchers, laying bare an embarrassment of riches in genomic data. So, you may wonder, does it make sense to have your own personal genome mapped in an effort to find markers for inherited diseases? Or, could a complete genetic profile provide indicators that will help you optimize your health? We've made it to first base in answering such questions, so in this chapter we'll go deep to center field for more specifics.

So far we've learned that whole-genome mapping for identical twins is not very predictive for the health issues that will

befall them later in life. Instead, factors such as diet, exercise, exposures to toxins, and the balance of bacteria in our gut biome have much more bearing on your health prospects. On the other hand, gene tests can tell us if we have inherited an irreversible rare disease, and they can alert us about genetic vulnerabilities that *can* be modified through correct health practices or proper medical interventions. But then again, some diseases don't even result from genes we can map; for example, cancer often arises from mutations that can form at any time. In other words, not discovering a cancer gene in a genome test doesn't mean that you won't develop this disease later on because of your choices.

Since these points have been made earlier, you may wonder why I seem to harp on this issue. I do so because of the all-pervading presence of the mechanistic, "disease-care" paradigm of medicine. In the face of the profound findings of the epigenetics revolution that I report on in this book, this older model of human biology still remains dominant in medical schools, drug companies, regulatory agencies, most other scientific establishments, and in the mass media. As a result, too much genetic research is focused on identifying gene variations that may be linked to particular diseases. This data can be useful, of course, but such knowledge cuts both ways. As we saw in the case of Angelina Jolie, gene-test results can be misleading if treated in isolation from the more essential factors. And among these factors is the discovery that we shape our *epigenome* each day by our decisions, and further, that this sensitive and malleable biological "script"

governs the vast number of our health outcomes. In addition, our personal epigenesis leaves behind crucial biomarkers we can detect and modify—a key topic of this chapter.

Incidentally, I've just described the precision medicine of the future. For now, the medical establishment will continue to favor the simplicity of gene hunting, perhaps because of our cultural bias toward the technological quick-fix. But if we combine this lazy attitude with the ravages of today's biological reductionism, much can go wrong. An inevitable result will be the overdetection and overtreatment of "genetic" diseases based on nearly useless tests that arise from an outdated biological paradigm. Perhaps the most disturbing modern example of the abuse of testing technology comes from an earlier era of medicine when we witnessed the excessive use of the misleading PSA test for prostate cancer. (PSA stands for *prostate specific antigen*.) Sadly, *Scientific American* recently reported that "millions of men have gotten unnecessary biopsies, surgery, and radiation as a result of taking the PSA test."[10] Could such gross examples of malpractice based on genetic testing be in our future?

Ultimately, the usefulness of your medical test depends on the truthfulness of your scientific paradigm and the maturity of your research based on it. Research into the nature of the epigenome and the gut biome is progressing at an exponential rate, and the more advanced paradigm of systems biology that supports this research is leading to a new era of testing

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10 John Horgan, "Why I Won't Get a PSA Test for Prostate Cancer," *Scientific American* (June 14, 2017).

that relies on the *biological assay*. The comprehensive gene tests of the past are now being *repurposed* within this broader "systems" context. Indeed, the rich data these newer tests supply us can be reframed to support health optimization—rather simply feeding today's obsession with the treatment of disease in isolation from its true causes!

These tests of the future will be far more targeted than the broad-brush DNA assays that are produced today. Gene tests will be linked with data from other biological measures and "crunched" with the help of advanced software. Most importantly, this sophisticated biological information will be framed within a holistic model of human health in which our daily health practices will occupy center stage.

The Search for Modifiable Genetic Biomarkers

You'll recall that certain genes are penetrant—they dictate irreversible gene expressions such as eye color, height, hair texture, or rare diseases. There is no "high court of appeal" when it comes to such deterministic genes; you can't change the gene expression that produces your hair color, no matter how rigorously you pursue a healthy lifestyle. Because researchers now know the locations of such genes, their "loci" (and that of other nonmodifiable DNA material) is set aside in the typical gene test. Instead, they target a smaller set of genes or DNA regions that matter to human health, throwing their resources at finding variants that code for disease with

high probability. As we've seen, those ahead of the pack seek out epigenetic or biomic markers that point to opportunities for health optimization.

Assuming such technical feats can be accomplished efficiently, the next logical step is to get proactive and ask better questions. For example, how do we run tests to locate crucial factors that we can manage *before* serious disease sets in? What are the *modifiable* biomarkers that govern the major processes in the body that are the most critical for health? A vivid example is *C-reactive protein*. An excess of this biomarker in our blood is a solid indicator of general inflammation; an unknown genetic process in the liver produces it, but all agree that its presence is a useful indicator of this disease condition. A simple blood test gives doctors a reliable measure of this marker.

As a clinician, I believe that the best use of today's epigenetic research is to narrow down the markers that are the *most* predictive. Once we have a selection of these most useful biomarkers, we should do further research to reduce this list down to a critical few—therefore providing an inexpensive basis for a very different kind of biological assay than we have seen in the past. My colleagues and I believe that we will eventually reduce this key list of modifiable biomarkers down to approximately 30-40 total, or even fewer. These crucial biomarkers should be the focus of today's epigenetic research, since, by definition, they will point to those gene expressions—those epigenetic markers—that influence the most vital biochemical pathways in the body. As we will see in Chapter 3, at least seven such

biological pathways determine which major diseases or states of health we will experience in our lives.

When gene expressions exert their influence on these important pathways, they leave behind biochemical tracers of their activity. But isolating and studying these traces has not proved easy. Locating them is like finding the tracks of an animal after a fresh snowfall. Identifying the diseases that "tracks" in our body might signify is like reading footsteps in the snow to determine which sort of animal has passed through, where it was headed, and when it was on this section of the trail. In the same way, biological tracks in our body give us a sense of the direction, speed, and intensity of the influence exerted in us by the function of biochemical pathways.

In addition, no one marker or "footprint" can ever tell the whole story. In fact, no single biomarker has decisive meaning all by itself. It is the *pattern* of "the footsteps on the trail" that must be interpreted by highly trained doctors, often working with genetic counselors.

Further, researchers are not in precise agreement as to which combination of markers point to specific health or illness outcomes. At a minimum, many varieties of data points will be needed to get there. I believe that these must include specialized genetic and epigenetic tests; the results of advanced blood tests; and the data from *biomic assays* (tests based on a sample from the gut microbiome)—along with other measures still to be determined. In theory at least, all of the biomarkers in each of these categories are modifiable. This mass of data can then be correlated using advanced software

algorithms to produce a series of diagnoses and treatments consistent with the goals of personalized medicine.

It will not be easy to narrow things down to a small set of biomarkers and patterns among this vast range of data. According to one estimate, there are thousands of epigenetic markers; hundreds of indicators in a complete blood count test or CBC (a blood test used to evaluate your overall health); and hundreds of markers in a *biomic assay*. The permutations of these elements are in the millions!

Biological Tests of the Future

Today's exclusive focus on data-intensive gene testing will gradually become a thing of the past. The coming era of precision medicine will also give rise to *epigenetic* mapping—and we're fortunate that an international effort to profile complete human epigenomes is now under way. One of its first findings, for example, revealed that people with Alzheimer's disease had epigenetic changes related to their immune system, opening up a surprising new avenue of research. This clinically significant finding is just one of the many results of the work of the International Human Epigenome Consortium (IHEC), which was launched officially in 2010 in Washington, DC. IHEC says that it aims to produce over one thousand "reference epigenomes" and make them available to the international scientific community. Mastering this highly complex challenge will require another decade or two to be realized.

In the meantime, the hype regarding gene mapping will persist for a few more years. During the transitional period, government regulators are responding to the growing number of companies who market direct-to-consumer gene testing. As far back as 2012, the Government Accounting Office (GAO) purchased genetic tests for identical DNA samples from four of the most prominent companies in this field, and compared the test results for 15 common diseases. The reports varied greatly between the companies. A GAO spokesperson stated, "We found that 10 of the 15 companies engaged in . . . fraudulent, deceptive, or otherwise questionable marketing practices. . . . In general, [direct-to-consumer] testing is of little to no medical value."[11]

To further illustrate the "wild west" state of the genetics testing market, in 2013 the FDA ordered 23andMe—an early leader in the field—to suspend its operation. Its testing services assessed the risk for more than 250 diseases; consumers simply ordered a $99 kit directly from the company. Among their many worries, FDA regulators were concerned that false positives from the assay could cause some patients to receive excessive or unneeded medical care.[12] Thankfully, 23andMe has reformed itself and moved on, as we'll see in Chapter 6.

The next generation of biological tests is almost here. The

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11 Associated Press, "Gene Mapping for Everyone? Study Says Not so Fast," http://www.dailyherald.com/article/20120402/business/704029816/ (Apr. 2, 2012).

12 Alberto Gutierrez, "Warning Letter, 23andMe, Inc.," Inspections, Compliance, Enforcement, and Criminal Investigations of the U.S. Food and Drug Administration, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm (Nov. 22, 2013).

science of epigenetics is fostering a new regime of advanced tests for biomarkers across many biological systems, including the epigenome and biome. These test results will help you focus on how your life choices condition your gene expression. It is this element of choice that is lost amid today's hype about genome mapping.

Junk DNA: Shedding Light on the "Dark Genome"

To better understand how today's confusion among biomedical paradigms has come about, allow me to backtrack into what today seems like ancient times in genetic research.

To get started, let's return to the cozy scene of our DNA coiled up in the cell's nucleus in the form of 46 chromosomes. Next, let's isolate one of these chromosomes and magnify it under a very powerful microscope. What we'll discover is that thousands of genes are interspersed like Christmas-tree decorations along each DNA strand. The function of the genes found along this expanse, it was once thought, was to code for proteins that do the work of cell metabolism. By the year 2000, scientists had identified roughly 100,000 types of proteins in the human body; and because of their simplistic model of the genome, researchers expected to find about the same number of protein-coding genes. In other words, because of their mechanistic picture of human biology, scientists believed that there was always

a direct relationship between a single gene and a single protein, and that the work of these proteins alone determines our health and longevity.

That's why they were truly startled to learn from the results of the Human Genome Project that the actual gene count is only about 20,000. Additional research went on to show that the protein-coding regions of human DNA (the locations where we find actual genes) account for *less than three percent* of the entire genome! Scientist were dumbfounded. Could the rest of our DNA really be useless junk, or remnants of the past that no longer contribute to cell metabolism? The puzzled genetics research community coined the term *dark genome*, a direct allusion to the concept of dark matter used by astrophysicists to designate the invisible and mysterious form of matter that makes up about 90 percent of the universe.

Significant technical progress began to point the way out of this conundrum. By about 2003, geneticists could trace all of the steps in the process of coding (or synthesizing) a protein. First, the code has to "go mobile," so to speak; special protein messengers have to be created from the raw genetic code that sits in a fixed position in the cell's nucleus. Serving this function is DNA's famous chemical cousin, *ribonucleic acid* (RNA), and scientists have become increasingly impressed in the years since by how versatile and clever this molecule can be. It's been long known that RNA literally "unzips" the coiled-up DNA strand, identifies a discrete portion of it, and attaches itself to this region in a kind of

one-night stand. The RNA then "copies" the exposed gene instructions in that DNA region, which it treats as a template. The RNA zips back up the location it is working with, and then (typically) carries these orders outside the nucleus to the cell's "protein factories" that are located in the *cytoplasm* (the term for everything else in the cell other than the nucleus and the cell membrane). Here the RNA's copy of a portion of the gene code goes to work, specifying the amino-acid sequence required for a particular form of protein synthesis. These highly specialized proteins go on to perform any one of thousands of routine biological functions. And while the general outline of this picture was understood by scientists in the early days of the genetics revolution, better research tools have allowed them to fill in details down to the smallest molecular components.

Protein synthesis was now well understood, but what about the much longer patches of "junk DNA"—that mysterious portion of the genome that seems to sit there quietly filling in the space between (and even within) genes? It was known that these regions do not code for proteins, so how could they possibly be useful?

If all the kinks and folds of the DNA helix were stretched out instead of being curled up inside the cell's nucleus, this string would be about nine feet long. At this point, science knew what only *three inches* of this strand was doing when it interacted with RNA—a rather humbling situation considering that this embarrassing state of affairs was the case only about a decade ago. And further, what about the other sorts

of RNA molecules that were now being identified, thousands of them in fact, that do *not* create proteins but seem to have other and unknown roles in cell physiology?

For better illustration, imagine that the unfurled helix was straightened out and magnified so that it extended the entire length of the Pacific Ocean, forming a bridge from California to Japan. At this level of magnification, our identifiable 20,000+ genes would look like thousands of dots of land—tiny islands that resemble stepping-stones across the great expanses of the ocean. Imagine tiny cargo ships hauling proteins out of the little ports on these islands. This archipelago of protein commerce would be like hundreds of little versions of the Hawaiian or Fijian islands, whereas the vast majority of the rest of the expanse would be very long tracts of water with a DNA double-helix bridge running over it. What was happening along this vast DNA bridge running over these open stretches of water to connect the bitty little islands of genes?

There's a big reason why this mystery eluded us for so long: cell metabolism is utterly complex and nonlinear. In other words, our metabolism is, as we noted in Chapter 1, the result of a vast network of diverse biochemical influences—a stark contrast with the image that is invoked by a machine-like correspondence of one gene with one protein.

More specifically, studies have now confirmed that the so-called dark genome contains vast DNA regions that *code for RNA*, doing so not to synthesize a protein but to create *other* types of RNA; indeed, many unexpected varieties of RNA

were identified. And the plot gets even thicker. We've long known that RNA plays a big role in gene regulation and other cellular functions, but there are *also* long stretches of the DNA helix that do not encode RNA at all. These "empty spaces" in the Pacific Ocean actually regulate gene expression in yet *other* ways we are now learning about.

Along most of these stretches, and very often directly on and around the genes as well, chemical markers get imprinted in response to that "cloud" of multiple influences—that huge network of biochemical actors that are always impinging on the cell's environment. These influences carry out our epigenetic programming, utilizing a special epigenetic language for directly switching on or off, or up and down, the expression of specific genes or the other essential regions of our DNA that code for RNA or other molecules.

The ENCODE Research Project and Junk DNA

To better understand these frontier spaces in our DNA archipelago, big things have had to happen. "Big data" that was not derived from previous studies of actual genes had to be collected. This means that scientists had to penetrate the "darkness" of the *intergenetic* spaces in the DNA strand. And they finally did so in the form of a massive project called ENCODE ("Encyclopedia of DNA Elements").

This heroic endeavor was undertaken by an international consortium of 32 research institutes organized by the

International Human Epigenome Consortium, an umbrella organization we touched on in the last section. These scientists pooled their efforts to answer the long-standing mystery as to what was hidden in the 97 percent of the total human genome we knew almost nothing about.

Because most of the results of this project are in, we can cut to the chase. In September 2012, the study reported three major findings:

First, the "junk DNA" designation was starkly incorrect. According to ENCODE's findings, "about 80 percent of the genome is biochemically active"—far beyond what was ever imagined to be the case.

Second, the researchers discovered that four million intergenic "spaces" on the DNA strand actually act as switches that control gene expression through RNA and by other means, and these switches are called *regulatory DNA*. This finding also made it abundantly clear that the biochemical regulation of genes is more intricate than anyone ever expected. Because of this complexity, predicting specific diseases turns out to be more difficult than anticipated due to the staggering number of variables.

A third major insight from the ENCODE project is that disease usually occurs when a *structurally normal gene suffers from abnormal regulation*. This means that

> searching for a single, abnormal gene is usually beside the point. It would be more expedient to research the vast stretches of the helix strand for receptor sites for specialized molecules that control gene expression.[13]

In short, most of what we once called "junk DNA" is actually a complex intergenic system that regulates genes; it's not the only epigenetic system hosted in the cell, but this once-mysterious domain of regulatory DNA is one of the several major types of epigenetic modifiers that help all living things adapt to their life conditions.

Further, this discovery has big implications for human health. The original ENCODE researchers found epigenetic switches spread across these regulatory DNA regions that are linked with cancer, multiple sclerosis, lupus, rheumatoid arthritis, Crohn's disease, and celiac disease, and their successors are going much further. Dr. Eric Lander, a leader in the Human Genome Project and now the president of a joint research endeavor of Harvard and MIT, has observed that the newly emerging understanding of intergenic DNA is a "stunning resource."

ENCODE results are also transforming cancer research. As the ENCODE team focused on cancer began determining the DNA sequences of cancer cells, they realized that most of the thousands of DNA mutations in cancer cells were not

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13 E. Pennisi, "ENCODE: Project Writes Eulogy for Junk DNA," *Science* (Sept. 7, 2012): 337:1159. See also J. R. Ecker et al., "Genomics: ENCODE Explained," *Nature* (Sept. 6, 2012): 489:52.

occurring in the genes of these cells. *Instead, these mutations are to be found only in the epigenome*. The challenge now becomes figuring out which instances of epigenetic mutation actually drive a particular cancer's growth. Within this cancer team, one subgroup examined prostate cancer genes that, it was already known, are not readily attacked by drugs. They showed which regions of the epigenome control those genes, giving doctors an alternate way to go after them: by targeting the associated epigenetic switches.

Because the epigenome is stunningly complex, the ENCODE project was technically daunting. Its advances were only possible because of major advances in DNA sequencing and computational biology; these researchers generated 15 trillion bytes of raw data, and analyzing the data required the equivalent of more than 300 years of computer time.

ENCODE and related developments offer great hope for the future of mapping an individual's epigenome and tracking the influences that shape it. For example, at different points over a person's lifetime, we will be able to create a picture of that person's changing "epigenetic state." Or, epidemiologists will be able create "epigenetic maps" of groups of people in a specific locale to help explain their biological relationship with their immediate environment. The upshot is that our genes are swimming in an ocean of influences that determine their expression through a rich variety of epigenetic regulatory mechanisms. Mapping that complexity and finding clinical applications for this knowledge is the challenge before us.

A More Advanced Look: Gene Variants as Disease Biomarkers

A fly ball is going deep into the outfield, so let's return for a second look at an important fundamental: the problem of gene variants. We've noted that certain of these mutations, such as the gene for Huntington's disease, are inescapable; there's no stopping the expression of such rare genes short of physically "editing" them out of the DNA strand—a topic we cover in Chapter 6. Fortunately, almost all of these dangerous "one-trick" variants are known to science. Thanks to ENCODE and other efforts, research has now moved toward the wild-cat world of big data—a forbidding place in which computationally sophisticated scientists look for groups of genes or regions of the epigenome that are only indirectly associated with diseases. These studies are generally known as "gene associations." Such associations are useful factors in the equation that don't necessarily lead us to the causes of diseases, but instead can be correlated with more complex patterns or "clouds" that ultimately tell the whole biological story. These genetic or epigenetic associations can, however, act as *biomarkers* for those disease-creating patterns.

Targeting such general associations may sound less glamorous than discovering single-gene diseases, but this difficult research is still an important contributor to the era of personalized medicine. Such linkages can lead us to more customized strategies that are an incremental improvement on the current one-size-fits-all approach to much of medical care. In

addition, if a patient does become ill, knowledge of gene associations can help doctors select the treatments most likely to be effective and least likely to cause adverse reactions.

The good news is that in some cases, these genome-wide association studies (GWAS), which we touched on before, have identified very specific markers that seem to have statistically significant connections with particular conditions.

The GWAS approach begins with the *reference human genome sequence* that was first produced by the Human Genome Project and has been refined ever since with the new data sets made available by ENCODE and other research projects. Using certain advanced tools, scientists search the whole genomes of thousands of people with particular diseases or traits in search of small gene variations that stand out when compared to the reference data. The scientific name of these variants is *single nucleotide polymorphisms* or SNPs (pronounced "snips"). Generally speaking, specific SNPs are found more frequently in people with a particular disease or trait than in people without these characteristics.

Here is a representative list from among the many exciting findings that have recently been reported by GWAS researchers around the world. These may seem "far afield," but they represent possible solutions to a great deal of human suffering.

1. Some SNP variants are located in proximity to sites in the genome that contain regulatory DNA. As a reminder, these DNA sequences are not genes; instead, they act as epigenetic regulators on the vast intergenic

portions of the DNA strand. The teams discovered many disease associations to mutations (i.e., SNPs) found at specific regulatory locations.

2. A targeted GWAS has provided important clues about the genetic basis of age-related macular degeneration. Five major gene variants are now associated with this condition, and the presence of each is associated with up to triple the amount of risk for this eye disorder.

3. Another genome-wide association focused on a specific disease was able to identify more than thirty variants related to Crohn's disease. In particular, three of these SNPs are both very common and are directly associated with increased risk for Crohn's.

4. Important advances have been made in the genetics of autism because of a well-designed Chinese study. This effort was not at the scale of a GWAS, but it was equally ambitious. It found very strong evidence that the autistic children had mutations in at least three specific genes. This study represents progress, but the researchers pointed out that the work of sorting out the complexities of this mysterious disease is still in its infancy.[14]

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14 In this study, three teams independently studied 549 families in which one child suffered from autism but the child's parents or siblings did not. Each team sequenced every gene in each individual (i.e., the autistic child, its parents, and some unaffected siblings). All three groups independently came up with the same basic finding.

5. GWAS researchers, also in China, have found strong gene associations to major depression in people who have endured excessive stress. Scientists previously knew that the degree of a person's stress and life adversity is linked to the incidence of two important genetic factors. Researchers conducted a GWAS called CONVERGE to look further into this association, and discovered that these same two biomarkers are also associated with the incidence of major depression in women.[15]

6. Several genome-wide association studies have identified genetic links between disease conditions that were previously thought to be unrelated. For example, an unlikely link between macular degeneration and inflammatory bowel disease was discovered in one GWAS. Other GWAS-inspired discoveries of diseases that share genes with ostensibly unrelated illnesses include type II diabetes, melanoma, Crohn's disease, Parkinson's disease, and prostate cancer. Finding these common pathways also underscores the potential for developing drugs or nutrients that may be effective in treating such formerly unrelated conditions.

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15 The two genetic factors involved here were (1) the increased presence of mitochondrial DNA (energy-conversion structures outside the nucleus of a cell that host tiny amounts of DNA) and (2) shortened telomere "caps"—biochemical entities at each end of a chromosome that protect it from deterioration. CONVERGE was a GWAS of 5,864 women with recurrent depression who were compared to 5,783 women without depression histories. In this connection, it is interesting to note that the same telomere and mitochondrial changes can be reproduced by the administration of a naturally occurring stress hormone.

7. A GWAS's can help match an individual's overall genetic profile to the likely effect of particular drugs. In some instances, a person's genetic makeup can predict the occurrence of toxic side effects from a specific drug. Further, GWAS researchers have found that the presence of particular mutations in tumors can predict whether or not specific drugs will work or not as an effective treatment for that tumor.[16]

Nearly 600 genome-wide association studies covering 150 distinct diseases and traits have been published, and some observers have questioned their cost-effectiveness. But I believe that these findings reveal the increasing importance of computational biology to personalized medicine, both because of the uniqueness of each person's genome and also because meaningful biomarkers can now be discerned across large groups of people.

16 For example, researchers at Sloan-Kettering have found that it can be better to base cancer treatments on the genetic mutations generated by a cancer than on the organ system where that cancer originated. Conventional treatments might yield a response rate to chemotherapy of 10 or 20 percent, but the newer drug targeted according to the type of mutation has an amazing response rate of 50 or 60 percent. The National Cancer Institute is now doing an advanced research program along the same line.

Biomarkers and the Era of Personalized Medicine

Centuries of evolution in the medical profession have delivered us to the brink of truly personalized medicine. We now live in an era in which high-tech methods will soon yield cost-efficient ways to test for those biochemical markers that matter most to each individual's health. We'll interpret this test data by using for reference the results of thousands of studies of the impact of diet, drugs, stress, and exercise; the results of routine gene tests that indicate vulnerabilities; the new reference models of epigenomes and gut biomes coming out of universities; the results of genome-wide studies; and data from many other kinds of other advanced methodologies.

I have mentioned previously that—as our own contribution to precision medicine—my colleagues and I have been compiling a small number of what we believe are accurate, predictive, and inexpensive biomarkers. We began this process several years ago when we realized that no single laboratory test existed for all of the blood biomarkers we then believed should be tracked; to test for all of them, we realized we would need to send blood samples to five or six labs. So, several of my medical colleagues and I tried this awkward approach as an experiment. It cost us approximately $8,000 to test one of us, and the results were unimpressive. Every lab measured by a different standard, so a test of the same gene or biomarker at different labs inevitably yielded conflicting

recommendations. Even the trained geneticists on our team found it difficult to piece together a cohesive interpretation.

This experience increased our determination to create a single laboratory that will focus on a small but meaningful set of markers, which I report on fully in Chapter 6. According to our protocol, the test result from that single source would be used to create a highly personalized plan that covers all the bases: diet, exercise, meditation, stress management, and other lifestyle recommendations. Then, at the end of 12 weeks, we would retest. Most of the markers should show improvement at this point. We would continue to make adjustments based on feedback received at regular intervals. Such personal fine-tuning at the level of genetic expression is unprecedented in human history. Will it give us radical new levels of health? Time will tell, but I am hopeful.

We can anticipate that the science will improve as we go. Right now, for example, there are five good markers for inflammation, but as we make progress, we may find that we only need to test for one of these. So, instead of testing for 30–40 markers overall, we may even find a way to reduce the list of markers to 15 and cut the cost even further.

As clinicians, we are also hopeful that patient compliance will improve as more evidence comes in with each new assay. But let's be honest. If you have to give up unfermented soy and a long list of other foods or habits you like "for the good of your health," the odds are you'll change only a few behaviors at first; then you can move on and improve your choices the next time as you begin to see useful results and feel better.

Our lifestyle choices may hold the key to our health, but habits are notoriously difficult to change.

We can also expect inevitable resistance from the conventional medical community itself. It takes years, sometimes generations, before any major innovation becomes widely accepted. Throughout history, scurvy (a vitamin C deficiency) has cost millions of lives. Yet its cure had been repeatedly discovered and forgotten for more than 400 years. Implementation of personalized medicine on a large scale will require a major reform of the healthcare infrastructure. Such a shift is bound to require years, if not decades. But such a transformation is a virtual necessity because of the profound implications of the epigenetics revolution and its related disciplines.