Breakthroughs in Bioscience

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INSIDE this issue

Individualized Medicine: Genetically Fine-Tuning Prevention, Diagnosis, and Treatment of Disease

In search of the gene
1
On the cutting edge
4
Spelling out the human genome
7
A decade of progress
8
Next generation sequencing
10
The future of individualized medicine
11
Acknowledgments

Individualized Medicine: Genetically Fine-Tuning Prevention, Diagnosis, and Treatment of Disease

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COVER: Individualized medicine, also known as personalized medicine or genomic medicine, is a medical paradigm offering customizable medicine based on one’s genes that can be used to prevent, diagnose, and treat disease. Innovations in individualized medicine come from technological advances that make it both feasible and affordable to decipher a person’s complete genetic make-up. By exploring answers to basic questions about microbes, cancer, the immune system, and other biological processes, scientists have fostered the current genetic revolution in medicine that is helping physicians find the right treatment for the right patient at the right dose. Image credits: Lonely/shutterstock (DNA), r.classen/shutterstock (medication); Designed by Corporate Press.
Individualized Medicine: Genetically Fine-Tuning Prevention, Diagnosis, and Treatment of Disease

When Milwaukee geneticist Elizabeth Worthey first saw her 5-year-old patient, he was so stunted by malnourishment she thought he was half his age. By then the child had undergone dozens of operations and extensive hospitalizations, almost died in intensive care, and had been given several courses of intravenous drug treatments for persistent inflammatory bowel disease, which was first diagnosed when he was a baby.

Nothing was working.

Suspecting he was born with a genetic defect that caused his severe illness, Worthey searched for all known genetic flaws in the boy’s DNA, but none of the genetic tests showed any likely culprits. Finally, in 2010, Worthey took an unprecedented step that ended up saving the boy’s life and changing the practice of medicine—she deciphered the exact makeup of all of the boy’s thousands of genes that determine the proteins his cells make. Proteins are the body’s workhorses that execute all of its functions. By doing a complete analysis of the boy’s protein-making genes (exome), Worthey discovered a defect in a specific gene that explained why his immune system went overboard and attacked gut microbes that are usually harmless and critical for digestion of food. Discovery of this genetic defect led to the boy undergoing a stem cell transplant that provided him with a normal immune system and cured his life-threatening bowel disease.

Worthey’s ability to zero in on her patient’s medical ailment and tailor therapy so effectively is an example of “individualized medicine” (also called “personalized medicine” or “genomic medicine”). This groundbreaking approach to predicting, diagnosing, and treating disease is dramatically changing how many cancers and other diseases are managed, preventing deadly side effects from prescription drugs, and avoiding drug resistance in patients being treated for infections.

In search of the gene

This revolution began in the middle of the 19th Century when the Austrian monk Gregor Mendel conducted his famous pea-breeding experiments and demonstrated that physical traits, such as plant height and pea color, are passed from one generation to the next via units of inheritance that later came to be called genes. But it was not until 1944 that Rockefeller University bacteriologist Oswald Avery showed genes were comprised of...
DNA. Avery realized this while pursuing research to discover why some strains of pneumonia are more deadly than others.

Avery’s finding drove basic researchers from all over the world on a competitive chase to determine the precise structure of DNA and how it worked to pass on traits. This race ended in 1953 when Rosalind Franklin at King’s College in London discovered that DNA contains two helically twisted strands connected to each other by a series of chemical rungs. That same year, James Watson and Francis Crick, then at Medical Research Council laboratories in Cambridge, England, correctly surmised each rung was composed of one of two chemical base pairs: adenine (A)-thymine (T) or guanine (G)-cytosine (C). Watson and Crick realized that it was the order of those A, T, G, and C bases on the DNA strand that spelled out the genes in every living organism and is the source of variation in physical traits. They also recognized that the two strands could be separated for copying—a simple way to pass on genetic information from one generation to the next.

A few years after Watson and Crick clarified the structure of DNA, biochemists Marshall Nirenberg, at the National Institutes of Health (NIH), and Har Gobind Khorana, at the University of British Columbia, deciphered the genetic code used by all living cells to translate the series of bases in their DNA into instructions for the production of thousands of proteins that determine cell structure and function. Nirenberg and Khorana discovered that the precise sequence of A, C, G, and T bases on a DNA strand is the formula that encodes the ordering of amino acids.

**Figure 1 – In search of the gene:** Gregor Mendel (left) showed with his plant breeding experiments that physical traits, such as the height of pea plants, were inherited. Later, Oswald Avery (right) discovered that genes were comprised of DNA. Photo credits: National Library of Medicine.

**Figure 2 – The structure of DNA:** Rosalind Franklin (top) was the first to create an image of a crystal of DNA. This image revealed that DNA is comprised of two helically twisted strands connected to each other by a series of chemical rungs. Then James Watson and Francis Crick (bottom) recognized that specific pairing between the bases A:T and G:C make up those rungs through hydrogen bonds that can be broken to peel apart the strands for precise replication, a critical property of DNA. Photo and image credits: National Library of Science/Science Source (Franklin), From the Linus Pauling and The Race for DNA Collection, Special Collections & Archives Research Center, Oregon State University (x-ray diffraction), A. Barrington Brown/Science Source (Watson/Crick).
acids linked together to create a protein. If the sequence has extra, misspelled, or deleted bases, the cell can make the wrong protein or too much or too little of the correct protein.

These mistakes, called mutations, can result in disease, although in some cases, mutations can actually protect people from developing specific disorders. Mutations in certain genes also play a role in making people more susceptible to the harmful effects of smoking or other environmental causes of disease, and in making microbes able to cause infections. (See “Knowing the Enemy” box insert.) In addition, genes shape how our bodies break down the drugs we take to cure disease or relieve its symptoms. (See “Finding the Right Dose” box insert.) Sometimes these variations are a result of ancestry, not actually representing mutations but natural variation.

In some cases, merely one misplaced base on a strand of DNA is sufficient to cause a disease, such as sickle cell anemia. Diseases caused by mutations in a single gene tend to be rare, however. More commonly, several variations in multiple stretches of DNA work together to increase the risk of developing a specific disorder. Many diseases, including certain cancers, heart disease, and diabetes, are caused by a combination of mutations in multiple genes, as well as by environmental influences, such as diet and exposure to tobacco

**Figure 3 – The genetic code:** Marshall Nirenberg (top) and Har Gobind Khorana (bottom) discovered that the precise sequence of bases on a DNA strand is a formula that encodes the ordering of amino acids linked together to create a protein. Each triplet of bases on a DNA strand codes for a specific amino acid, and the entire formula for a protein is passed via messenger RNA to cellular machinery, which translates it into the specific protein. Photo credits: Ferald V. Hecht/National Institutes of Health (Nirenberg), UW-Madison Biochemistry MediaLab (Khorana); Designed by Corporate Press.

**Figure 4 – Genetics of sickle cell anemia:** The change of just a single A to T in the gene that codes for the hemoglobin protein causes a different amino acid to be incorporated into the protein, which disrupts its structure. Red blood cells that contain the mutated hemoglobin take on a sickle shape instead of the more normal disc shape. Although this hemoglobin variant is responsible for sickle cell anemia, it also renders the red blood cells resistant to malaria infection. Image credits: Adapted from University of California Museum of Paleontology’s Understanding Evolution (http://evolution.berkeley.edu), Alila Medical Media/shutterstock (vessels); Designed by Corporate Press.
smoke. By comparing the DNA of those who develop a specific disease to those who don’t, researchers expect to discover telltale variations that would not only explain the causes of diseases, but suggest ways to diagnose and treat them.

The majority of human cells contain about six feet of DNA molecules made up of three billion base pairs. If printed out, those base pairs would fill 200 1,000-page New York City telephone directories. So how does one sift out a thimbleful of disease-fostering changes from the barrelful of DNA housed in each person’s cells? Researchers needed a way to divide, duplicate, detect, and contrast large quantities of the same small segments of DNA from people with and without certain disorders.

On the cutting edge

Developing the tools to carry out these feats hinged on a number of seemingly obscure discoveries in basic research labs, often decades before they were put to use. For example, in the late 1960’s, Hamilton Smith, a Johns Hopkins University biologist who was trying to determine how some bacteria are able to resist invasion by viruses, serendipitously discovered that enzymes produced by the bacteria cut DNA at specific well-defined sites. This finding paved the way for dividing long strands of DNA into more manageable snippets for study.

Finding the Right Dose

The way in which our bodies respond to medications varies from person to person. For example, you may become exceptionally drowsy in response to taking the pain reliever codeine, while your friend will not experience any sleepiness when taking the same dose. And five out of one hundred people don’t get any pain relief from codeine at all.

Our reactions to codeine and other drugs depend on the types and amounts of metabolizing enzymes we produce that break down these compounds. This metabolic “stew” is largely genetically determined. By comparing the genetics of people who have had bad reactions to a drug to those who have not, researchers uncovered key variations in drug metabolism that are rapidly changing how medicines are prescribed. This should help reduce the risk of serious side effects, which is one of the leading causes of hospitalization and death in the U.S.

At the forefront in this new revolution in drug prescribing is clopidogrel (Plavix), a drug commonly given to prevent blood clots in patients with heart disease. Some people are unable to metabolize this blood thinner, which is needed for the drug to be effective. A blood test analyzing seven genetic variants can indicate within one day whether a patient will benefit by taking this drug. In 2010, the Food and Drug Administration changed clopidogrel’s label to indicate this finding, and many clinics are altering their prescribing practices accordingly. The University of Florida, for example, uses the genetic blood test for clopidogrel metabolism for every patient who undergoes a cardiac catheterization, a procedure that involves passing a thin tube into arteries in the heart to look for blockages. If the test indicates the drug will not be effective, they are given a different blood thinner.

“This helps us prescribe the right medication the first time,” said Dr. R. David Anderson, Director of the cardiac catheterization laboratory at the University of Florida.

More than 100 drugs on the market, including codeine, contain genetic information on their labels regarding how individuals process these drugs, although not all are related to drug metabolism and adverse reactions. Some, including many new cancer drugs, specify which genetic tests should be run on tumor samples to indicate whether a drug is likely to work. Others can predict whether someone is likely to have a severe allergic reaction to a medication.

The new genetic tests that predict how people will respond to various treatments are also making drug development and testing more efficient and likely to be successful. Most drugs tested in clinical trials do not make it to the market. Many fail clinical tests because they are effective in only in a small percentage of patients who have the molecule the drug targets. Genetic tests can enable drug developers to screen out and test their experimental drugs only in those likely to respond to them. Such prescreening of clinical trial volunteers should allow smaller, faster, and less expensive clinical trials, which hopefully will translate into lower cost drugs and bring drugs to market more rapidly.

Prescreening with genetic tests may also enable more drugs to make it to the market by lessening or avoiding serious side effects that occur during clinical trials. One third of all experimental drugs fail clinical trials because they cause liver damage, though often in only a small subset of subjects. For example, if researchers could determine a genetic predisposition to liver damage, they could limit the testing and subsequent prescribing of the drugs to only those who are able to metabolize it without damaging their livers or risking their lives.
Basic research into radioactivity and fluorescence provided methods for labeling and piecing together the order of thousands of these overlapping snippets of DNA. These technical advances allowed scientists to study individual genes as well as their order along the DNA molecule. Detection of the proteins made by culprit DNA sequences also became possible thanks to years of research on the immune system and the structure and function of antibodies. Scientists developed methods to use animal cells to produce “designer” antibodies that could detect normal or abnormal proteins. Using these tools, highly specific probes were developed for identifying diseases in blood samples or cancer subtypes in tumor samples. Investigators developed tests in the 1980’s and 1990’s using these probes that indicated whether breast cancer tumors were likely to respond to estrogen-blocking therapy or the drug Herceptin.

Aiding these endeavors were basic researchers who developed methods to detect base sequence abnormalities in certain stretches of DNA shared by members of families who had specific

**Knowing the Enemy: Sequencing Pathogens**

The first genome sequence to be completely deciphered was that of a bacterium, *Haemophilus influenzae*, which can cause pneumonia and meningitis. Since that publication in 1995, researchers have generated close to 2,000 complete bacterial genome sequences, with improvements in sequencing technology now enabling investigators to produce a draft sequence of a bacterial genome containing 4 million base pairs in only one day. Genome sequences are also known for close to 3,000 viruses. For some, such as the human immunodeficiency virus (HIV), researchers have partially sequenced more than 300,000 different strains.

Basic genetic research on microbial genomes has had numerous life-saving applications. By comparing the genetic similarities of microbes that have afflicted patients, genetic sleuths have tracked the origin and transmission of various diseases, including antibiotic-resistant staph infections, cholera epidemics, and swine flu. Fully deciphering the genetic components of deadly diseases has also led to new drugs and vaccines, including many of the medicines used to treat HIV and widely-used vaccines for meningitis and cervical cancer.

Genetic tests can also indicate whether microbes possess genetic “weapons” that enable them to resist drugs. Physicians often use these tests to detect drug-resistant strains of the microbes that cause tuberculosis, staph infections, and HIV. The standard of care for HIV is to select an initial drug cocktail based on the genetic profile for HIV-drug resistance that is derived from the genetic sequence of the precise strain that the patient harbors. These genetic tests are cheaper and faster than the previous standard test for drug resistance, which was to measure the ability of the virus to grow in the presence of antiviral drugs.

Microbes frequently produce drugs that protect them from other microbes. Genetic analyses are also allowing for more effective mining of this resource for new drugs. Researchers discovered many antibiotics that have been used in the clinic by detecting them in the lab cultures of the microbes that produce them. But many antibiotics may not be generated under typical lab conditions, so they often elude researchers. However, some of these disease-fighting molecules can now be detected by searching for genes in microbes that are similar in sequence to those known to code for antibiotics. Once these genes are identified, researchers can develop compounds similar to the proteins coded for by those genes.
disorders. Such linkage studies combined with DNA sequencing led investigators to develop the first genetic tests for cystic fibrosis and susceptibility to early-onset breast or colon cancer in the 1990’s.

All genetic tests hinge on a key technique that was made possible because Indiana University microbiologist Thomas Brock went to Yellowstone National Park in 1966 to study the microbial ecology of the thermal springs that make Yellowstone famous. Scientific dogma at the time held that life could not occur at temperatures above 160 degrees Fahrenheit. To his astonishment, Brock and his student, Hudson Freeze, found a bacterium that survived in the scalding waters of Mushroom Spring.

Studying how this bacterium survives led to the discovery of an enzyme called Taq polymerase that can synthesize a duplicate strand of DNA at high temperatures. This polymerase enzyme is needed for the powerful DNA copying method known as polymerase chain reaction (PCR) developed by Kary Mullis of Cetus Corporation in the 1980’s. Such automated DNA duplication dramatically sped up gene sequencing and testing for specific genes.

Even with PCR, many of the early genetic tests based on sequencing DNA were time consuming, labor intensive, expensive, and used hazardous radioactivity, rendering them out of reach for most clinical
applications. That was changed by Leroy Hood, an immunologist at the California Institute of Technology. He was initially stymied in his attempts to figure out how the immune system makes so many different types of antibodies. So, he set his sights on developing a tool that would not only accelerate the progress of his own research, but make inexpensive and rapid sequencing of a person’s entire DNA (genome) a reality.

**Spelling out the human genome**

To solve the puzzle of antibody diversity, Hood needed to analyze the large and complex family of genes that permit a wide variety of antibodies to be produced. Teaming up with a chemist, an engineer, and a biologist with knowledge of computer science, Hood developed a method for automating DNA sequencing to make it more efficient. The team invented a DNA sequencer prototype that took three years to build and debuted in the mid-1980s. This technique relied on four different fluorescent dyes, which labeled each of the DNA bases, enabling large stretches of DNA to be read in sequence letter by colorful letter. At this point scientists realized the dream of being able to sequence the entire human genome could become a reality if enough funds and researchers were devoted to that task.

Hood and other researchers began discussing this possibility, and by 1990, the Human Genome Project (HGP), funded predominately by NIH and the U.S. Department of Energy, was formally launched. In all, the project included more than 2,000 researchers from 20 centers in six different countries. One private company called Celera, led by Craig Venter, was deciphering the human genome independently from NIH. Celera ultimately collaborated with this massive government undertaking, which was already churning out 1,000 letters of DNA every second, 24/7.

Venter and NIH Director Francis Collins, who led the HGP (during his directorship of the National Human Genome Research Institute), appeared in June of 2000 with President Bill Clinton to publically announce the completion of the first rough draft of the human genome, which was published on the Internet and permanently placed in the public domain without constraints on its use for further scientific study. Comparing the HGP to Lewis and Clark, President Clinton said: “Today the world is joining us here in the East Room to behold a map of even greater significance. We are here to celebrate the completion of the first survey of the entire human genome, the most important, most wondrous map ever produced by humankind….With this profound new knowledge, human kind is on the verge of gaining immense new power to heal. Genome science will have a real impact on all our lives—and even more, on the lives of our children. It will revolutionize the diagnosis, prevention, and treatment of most, if not all, human diseases.”

Three years later, the final completed sequence of the human genome was announced—almost exactly 50 years after Watson and Crick described the helical structure of DNA. The final sequence was of higher quality and had better coverage than the draft sequence. But the...
best was yet to come, including surprising discoveries about the causes of various diseases and innovative ways to treat them.

A decade of progress

In addition to the reference human genome HGP provided (which is actually a composite of multiple human genomes), dozens of other human genomes were soon sequenced and published, including those of Venter, Watson, and the Archbishop Desmond Tutu of South Africa. Researchers can comb through sequenced genomes base by base for clues to the causes and possible treatments for diseases.

Initially, to save on time and expense, investigators only sampled hundreds of thousands of single bases scattered throughout the genome that frequently vary between individuals. These highly variable sites, known as single nucleotide polymorphisms (SNPs – pronounced “snips”), are the base letters that in one person’s genome often differ from those in another at the same spot. SNPs can occur within genes, where they lead to a gene variant encoding a different version of the protein, or they can serve as landmarks for nearby (linked) stretches of DNA that vary between individuals and are inherited along with the SNPs. Comparison of the SNPs between a control population (i.e., no disease) and a patient population (i.e., have disease) are called genome-wide association (GWA) studies. These studies define a correlation between a particular SNP and the risk of a particular disease.

The first GWA study was published in 2005 and identified a genetic risk factor for an eye disorder called age-related macular degeneration, which is the leading cause of vision loss in the elderly. Subsequent studies identified four other genetic risk factors that, when combined with the first, double the chance a person has of developing the disorder when their sibling has it as well. Unexpectedly, two of these risk factors occur in genes associated with inflammation, suggesting that inflammation plays a significant role in causing age-related macular degeneration.

GWA studies have been especially effective at detecting the genetic causes of “Mendelian” diseases, which are caused by a single gene mutation. In 1990, the genetic and molecular basis was understood for fewer than two percent of the estimated 7,000-suspected Mendelian diseases. However, by 2011, researchers had uncovered the molecular basis of roughly 40 percent of these diseases.

Additional GWA studies have identified unexpected causes of other conditions. They have shown that some disorders that do not resemble each other at all (e.g., heart disease and melanoma; Parkinson’s disease and inflammatory bowel disease) share some of the same genetic risk factors and might consequently benefit from similar treatments. For one type of inflammatory bowel disease,
called Crohn’s Disease, GWA studies have identified dozens of genetic risk factors that have been used to develop animal models in which researchers are now testing promising new drugs.

Other early success stories stemming from the HGP and GWA studies include the development of genetic tests that can predict a person’s response to dozens of drugs and that are expected to help curtail deadly or ineffective responses to commonly prescribed medications. Other genome-wide tests on tumor samples can predict if women with early stage breast cancer will benefit from chemotherapy, suggest new targeted treatments for other types of cancers, and identify which patients are likely to benefit. (See “Finding the Right Cancer Treatment” side bar.) Another study found that African Americans with a specific variant of a gene experience 88 percent less risk of developing heart disease than Caucasians. This variant reduces cholesterol to extremely low levels and is avidly being pursued by drug companies that are clinically screening molecules that mimic the effects of the altered gene.

Despite these significant advances, GWA studies have been underwhelming in their ability to predict accurately the risk factors or causes for mental disorders or more common diseases such as diabetes, heart, or Alzheimer’s disease. For example, despite screening more than 10,000 people for more than two million SNPs, researchers have only uncovered 18 SNPs linked to type 2 diabetes, and these combined only explain six percent of the heritability of the disease. The poor performance of GWA studies in these cases is likely because complex disorders like diabetes can be caused by duplication, deletion, or mutation of multiple genes that can involve as many as one million base changes.

Figure 10 – Genome wide association studies: GWA studies compare single nucleotide polymorphisms (SNPs) between a control population (i.e., no disease) and a patient population (i.e., have disease). Peaks in the simulated plot identify SNPs associated with the disease. Image credits: Jane Ades/NHGRI (chromosomes); Designed by Corporate Press.
and be heavily influenced by environmental factors. The statistical methods necessary to establish correlations simply do not work well in these situations. It may also be that much disease is caused by rare variants that are not detected by GWA studies.

**Next generation sequencing**

Thanks to technological advances, genetic sequencing continues to become faster and less expensive. Researchers are developing new miniaturized systems that can sequence up to 100 million base pairs in less than a day and for under $1,000. Generating the same information in 2002 would have required months of work by a laboratory team at a cost of more than $500,000. Innovative “parallel sequencing” methods that simultaneously sequence multiple areas of the genome also now make it both time-efficient and economically feasible to sequence all the regions in the genome responsible for dictating the production of proteins. It was this type of exome sequencing that Worthey used to detect the cause of the severe inflammatory bowel disease that was affecting her pediatric patient.

Sequencing of all the portions of DNA that code for proteins (whole exome sequencing) or of the entire DNA molecule (whole genome sequencing) is increasingly being used to detect “mystery” disorders for which no known genetic tests can identify the cause. By 2012, NIH had funded whole exome or whole genome sequencing of samples from roughly 70,000 individuals participating in clinical research studies.

However, physicians are still a long way from submitting their patients’ full genomes for sequencing, not necessarily because the price is too high, but because the data are difficult to interpret, Varmus noted. Ways to access, compile, and analyze the reams of data piling in from genomic studies, while maintaining patient confidentiality, have not kept pace with the rate of discovery.

At present, there are still limits to our ability to apply genomic findings directly to clinical medicine. Most genetic analyses do not take into account environmental and other factors that influence the “turning on or off” of genes to make proteins, nor do they fully consider dynamic interactions between genes and proteins. Molecular bypasses (backup pathways) often crop up when a main molecular route to creating a specific protein is blocked; turning off one gene and production of its protein may prompt another gene to turn on such that the missing protein is ultimately produced.

But as is often the case in biomedical research, one answer usually raises additional fascinating questions that need to be explored to take findings one step closer to being clinically useful. Recognizing this, the federal government is funding major research initiatives aimed at interpreting genomic studies, including those focused on assessing the network of genes involved in specific cancers and how they interact, environmental
and other “epigenetic” factors that affect gene expression, and the influence of genes of microbes in the gut that can also influence human health. (See FASEB’s Horizons in Bioscience article Epigenetics: Looking Beyond Our DNA.)

Aiding genomics research and the quest to find causes and cures for diseases is the sequencing of the mouse and dozens of other animal genomes, including several species used to model diseases and basic biological processes. This research has revealed the remarkable conservation of genetic sequences. Consequently, genetic studies in mice and even flies can give researchers insight into human diseases. Moreover, scientists can also introduce genetic alterations in animals to model human disorders, from arthritis to Alzheimer’s disease.

The future of individualized medicine

Hopefully one day soon, a fully deciphered genome will be part of a patient’s medical chart. The prevention or early stemming of disease will become the main goal of medical care rather than treating the symptoms and damage already done to the body. As Francis Collins envisions it, we will go from a “sick care” system to a health care system. In his book, The Language of Life, Collins notes, “The genie is out of the bottle and large amounts of information about the genome will become part of the medical care most of us receive in the not very distant future.”

On a more personal note, Collins added that a genetic test, which unexpectedly indicated he had an increased risk for diabetes and macular degeneration, prompted him to shed 15 pounds and improve his diet to help prevent these disorders.

As it is, the new genetic landscape is already causing a paradigm shift in how cancer is diagnosed and treated, with molecular diagnosis adding to or replacing traditional pathological diagnosis based on microscopic features of tumors. (See the “Finding the Right Cancer Treatment” side bar.)

Due to finer genetic distinctions, other common diseases, such as Alzheimer’s disease and diabetes, may soon be seen as a compilation of numerous disorders due to an individual’s unique combination of genetic defects. The improved genetic landscape is also showing us that some seemingly different disorders may benefit from the same molecular treatment, while other superficially similar disorders may require dramatically different molecular cures.

None of the advances in individualized medicine would have come about if curious researchers weren’t trying to answer fundamental questions, such as, what makes some bacteria more resistant to viral infections or more infectious than others? What enables our immune system to generate a wide array of antibodies? How can microbes survive high temperatures? These researchers, in diverse disciplines and supported by public funding, enabled the revolution in individualized medicine that is taking place today.
Finding the Right Cancer Treatment

Individualized medicine has made the most progress in the treatment of cancer, where, for many common tumors, it is improving diagnosis, prognosis, and treatment. Traditionally, the diagnosis and prognosis of cancer is based on the physical traits of tumors that can be seen under the microscope. But decades of basic research has revealed that the type of cancer and its degree of aggressiveness depends on molecular traits not detected by microscopy.

For example, many types of breast cancer were typically lumped together because they looked the same. But research on breast tumors revealed new subtypes, including tumors whose growth is fueled by the hormone estrogen and consequently, are highly responsive to hormonal therapy. Other tumors are activated by the growth factor known as HER-2 and respond to the targeted breast cancer drug called trastuzumab (Herceptin). (See the Breakthroughs in Bioscience article Breast Cancer, Tamoxifen and Beyond: Estrogen and Estrogen Receptors.) Today, all breast tumors undergo molecular scrutiny that determines the course of treatment. As researchers continue to discover more molecular subdivisions of breast cancer, physicians will be able to predict which treatments are likely to be most effective in their patients.

Similarly, researchers have identified other subtypes of cancers, including a small percentage of lung cancers, that respond well to inhibitors of their main molecular driver of growth, the epidermal growth factor (EGF), as well as colon tumors unlikely to respond to EGF inhibitors. A large study found that patients with lung cancers fueled by EGF have a 71 percent response rate to EGF inhibitors compared to only a 1 percent response rate for those whose cancer does not grow in response to EGF. Scientists have also discovered that many patients with melanoma, kidney, or liver tumors have a genetic defect that causes them to generate a faulty protein called BRAF. These patients tend to respond well to new treatments on the market that block the action of BRAF.

Eventually, all cancers, which are usually categorized based on their tissue of origin, will have defined molecular profiles that should aid not only the diagnosis and prognosis of the tumors, but also facilitate targeted treatments that are individually suited to the unique tumor subtype a patient harbors. This is becoming more feasible given technological improvements in DNA sequencing enabling complete genetic profiles of tumor samples for just a few hundred dollars.

One recent study at M.D. Anderson Cancer Center in Texas genetically screened the tumors of patients with advanced cancers not responsive to treatment and found that about 40 percent of tumors had a genetic defect that could be targeted with an experimental or currently-marketed drug. When these patients were enrolled in a clinical trial, they had a four-fold higher response rate (28 percent) than similar patients who were given treatment that did not specifically target their genetic defect.

A large government funded undertaking is aimed at furthering such basic molecular discoveries on tumor types and is likely to lead to more targeted and effective treatments for a wide range of cancers. NIH’s Cancer Genome Atlas is currently collecting and genetically analyzing more than 25,000 tumor samples from 50 different cancer types to generate a more complete catalogue of cancer-causing molecular changes on which new pharmaceuticals can be based.

Even without revealing the main drivers of tumor growth, new genetic tests are able to detect the aggressiveness of breast cancer, and physicians and their patients are increasingly relying on these tests when deciding whether to pursue toxic chemotherapies for early-stage breast cancers. For example, Oncotype Dx is a test done on tumor samples that searches for 21 genetic abnormalities linked to aggressive breast tumors. Based on the results, patients with early-stage, hormonally responsive breast cancer that hasn’t spread to their lymph nodes are grouped into low, intermediate, and high risk categories of having a tumor recurrence. Results of this test have frequently changed the treatment recommendations of physicians, as well as reduced patient anxiety levels. Similarly, there is a 12-gene test that predicts recurrence of colon cancer that may help define more accurately those patients who will not benefit from chemotherapy.
Additional suggested reading:


Biographies:

**Margie Patlak** writes about biomedical research and health from the Philadelphia region. She has written for *Discover, Glamour, Physician’s Weekly, Consumer Reports on Health, The Washington Post, Los Angeles Times, Dallas Morning News*, and numerous other publications. She has written frequently for the National Institutes of Health and the National Academy of Sciences and currently works with a number of trade journals, such as *Endocrine News* and the *Journal of the National Cancer Institute*. This is her ninth article in the Breakthroughs in Bioscience series.

**Howard P. Levy, MD, PhD**, is an Assistant Professor in the Department of Medicine at Johns Hopkins University. He is board certified in Internal Medicine and Clinical Genetics. His interests include primary care of adults with genetic conditions, genetic risk assessment for common complex diseases, and integration of genetics into primary care medicine. He provides medical services for adults with a wide variety of genetic disorders as well as general primary care patients, with whom he emphasizes genetic principles to improve routine care and preventive medicine. He is also interested in the use of electronic health records to improve patient engagement, facilitate collection of family history and genetic testing information, and enhance overall quality of care.

The Breakthroughs in Bioscience series is a collection of illustrated articles that explain recent developments in basic biomedical research and how they are important to society. Electronic versions of the articles are available in html and pdf format at the Breakthroughs in Bioscience website at: www.faseb.org/breakthroughs