



Investing in Disruptive Change: Personalized Medicine

As thematic investors, we look for phenomena that are transforming economic prospects across multiple industries. Then, we seek to identify companies that will benefit, are investable through public equities with ample liquidity, and are likely to pay off within three to five years. One of these phenomena is the emerging field of personalized medicine.

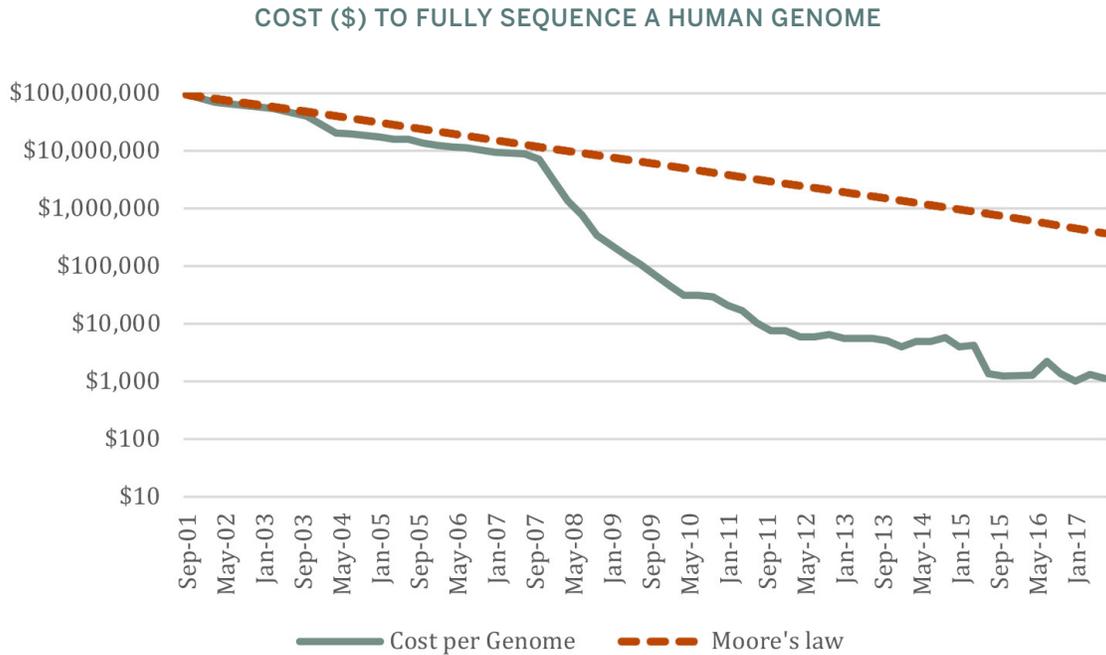
Many industries have long made personalization the gold standard of service and delivery. Medicine is entering the early stages of personalization. Most medical treatments still focus on the average symptom of the average ailment for the average patient. Unfortunately, average can be far less than average when it comes to healthcare. Breakthroughs in our understanding of the human genome have been occurring with accelerating frequency. While these breakthroughs have made personalized medicine a limited reality, a fuller reality is yet to be realized. As a result, personalized medicine today is a niche market. In our view, we are at an inflection point in the evolution of healthcare with the potential to disrupt current models of patient care, drug development, pricing and insurance.

The New Frontier: Putting Personalized Medicine in Perspective

To put this pending transformation in perspective, consider the discovery of germ theory in the 19th century. It found that many diseases are caused by specific microorganisms and led to the 20th century development of antibiotics to treat bacterial infections and vaccines to prevent viral infections. As a result, major infectious diseases such as polio, cholera, and bubonic plague were eradicated. In the 21st century, the new medical frontier is genomics. It offers the possibility of conquering genetic-based diseases.

One driver of rising health care costs is the rapidly increasing percentage of the population over age 65. The Center for Disease Control predicts that 25% of the population now 50 years old will live into their 90s. The World Health Organization estimates that the number of cancer cases will increase 70% over the next two decades as people live longer. Aging populations with their higher propensities for genetic-based diseases will result in an increasing number of people taking genetic tests. The tests will help medical professionals provide early warning and early diagnosis, optimizing treatment plans and fueling further growth in the genetic testing market.

An expanding market is possible because the cost of sequencing a human genome has rapidly declined. At the turn of the millennium, the Human Genome Project cost nearly \$3 billion and took 13 years to sequence the first draft of the human genome. Since then, the cost of sequencing an entire genome has declined at a rate that far exceeds Moore's law (the observation that the processor industry doubles computing power for the same price every two years), as shown on the next page.



Source: National Institute of Health

Now at a cost of about \$1,000, gene sequencing is comparable in price to many other routine medical tests. New innovations continue to drive costs down, with today's fastest machines able to sequence a genetic sample in an hour at a cost of about \$100. Lower costs will lead to new applications and more widespread use.

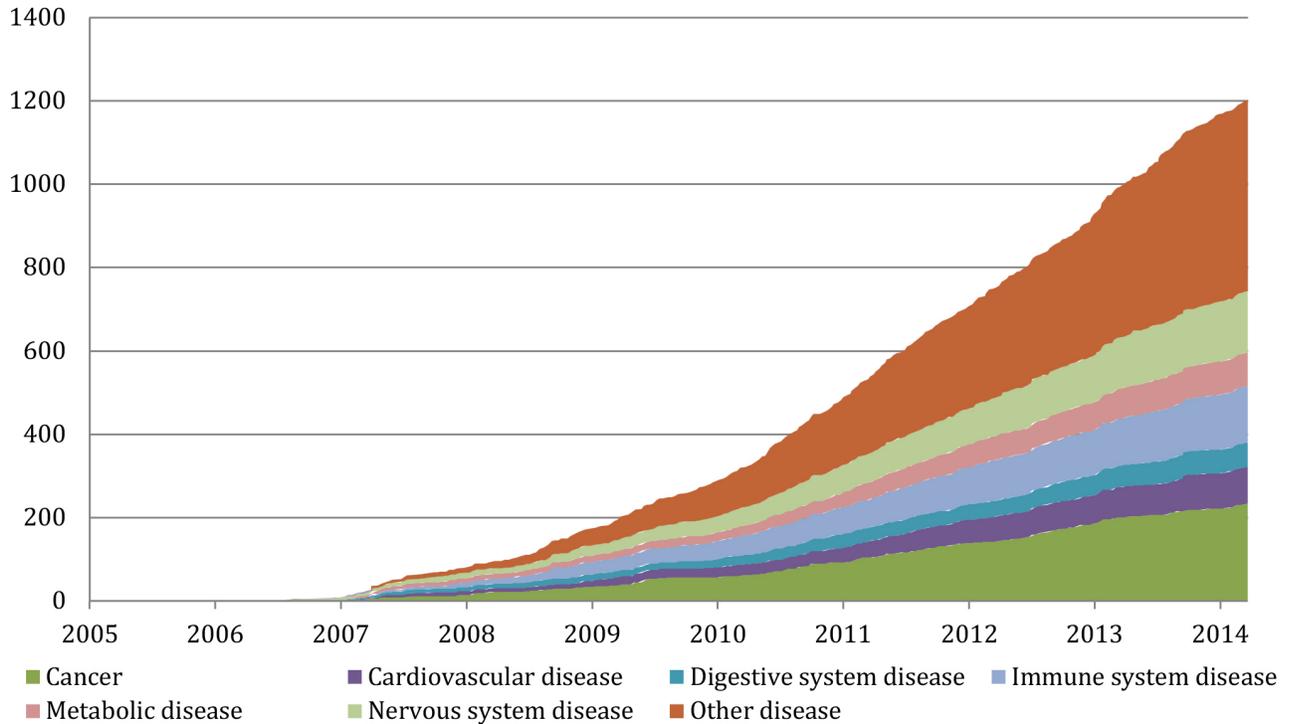
As important as cost reduction, speed improvements have made sequencing clinically useful—meaning tests can be completed before patient treatment decisions need to be made. Cheaper and faster sequencing has enabled large-scale studies, to the point where entire countries are investing in genomic studies of their populations. To date, 1.5 million human genomes have been sequenced. However, we still understand less than 1% of the variants of the human genome and have tested less than 0.02% of the human population. There are currently 50 large-scale population studies underway, each ranging from tens of thousands to millions of people. Understanding genetic makeup and genetic differences has barely scratched the surface.

Each human genome has roughly 3 billion base pairs of DNA and potentially as many genetic traits, so genetic analysis requires computing power and data storage comparable to other “big data” fields. For example, sequencers produced by Illumina, the market leader in sequencing equipment, have generated 225 petabytes of data over the past five years. That is equivalent to the amount of data in 765 years of continuous high definition video. GRAIL, a pioneer in early cancer detection, generates one terabyte of data (the equivalent of around 130,000 digital photos) from each liquid biopsy they perform. The improving capacity of processors and the development of statistical tools for analyzing large and unstructured sets of data are unlocking the value of this information, helping researchers uncover previously unknown genetic relationships by comparing patients and diseases across massive and growing databases.

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DISEASES WITH IDENTIFIED GENETIC LINKAGES



Source: National Human Genome Research Institute Catalog of Published Genome-Wide Association Studies, iamB Consulting

Personalized medicine has been made possible by scientific breakthroughs in our understanding of how a person's unique molecular and genetic profile makes them susceptible to certain diseases. This same research is increasing the ability to predict effective treatments for individual patients. New diagnostic tests and the biological markers they measure can help medical professionals evaluate the likelihood a patient will develop a disease, diagnose a disorder, evaluate the severity of a disorder and determine an optimal treatment.

Personalized medicine has potential in both clinical research and patient care. For example, a 34% reduction in chemotherapy use could occur if women with breast cancer receive a genetic test of their tumor prior to treatment. Over \$600 million in annual health care cost savings could be realized if patients with metastatic colorectal cancer received a genetic test for the KRAS gene prior to treatment. Some 17,000 strokes could be prevented each year if a genetic test is used to properly dose blood thinners.

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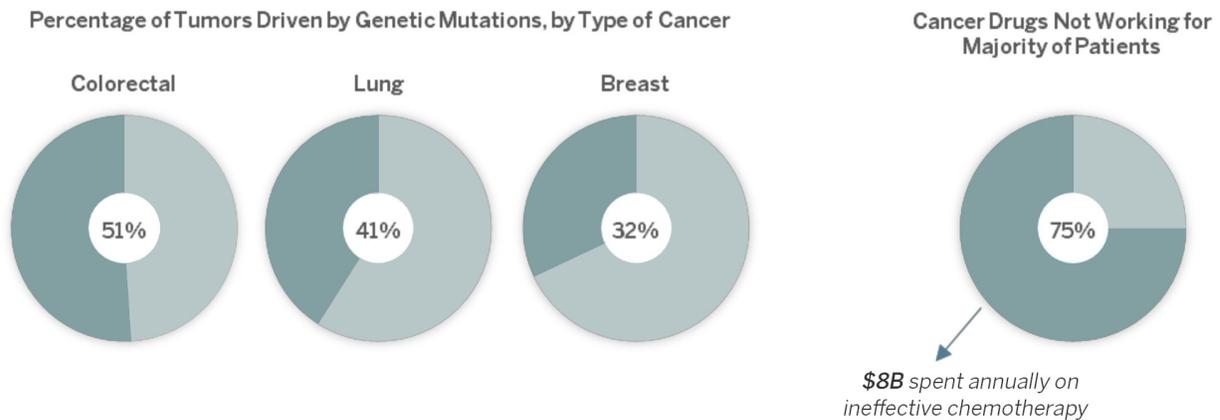


New Diagnostic Tools Lead to More Precise Treatments

A significant portion of the \$3 trillion Americans spend annually on healthcare is for treatments of little demonstrated value. In fact, over 4 billion prescriptions were written in the United States last year representing close to \$500 billion in spending, yet only 50% of prescribed drugs are effective.

The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Several high-volume cancers can benefit from genetic testing, as shown here.

HIGH-VOLUME CANCERS RIPE FOR TARGETED APPROACH



Source: The Advisory Board

In 2017, the FDA approved the first and, to date, only broad panel of genetic-based diagnostic tests for various kinds of cancer and The Center for Medicare and Medicaid Systems issued comments favoring insurance reimbursement, important steps toward commercial adoption. Today, companion diagnostics, in which physicians use individual genetic profiles to identify drugs most likely to successfully treat specific cancers, are used in only 15% of advanced-state cancer patients. Currently, there are 75,000 genetic tests on the market, representing approximately 10,000 unique conditions (up 12-fold from five years ago).

Understanding genetic codes and genetic predispositions for various diseases has enormous consequences, with new tests for celiac disease, Parkinson's disease, macular degeneration, early-onset Alzheimer's, hemophilia and many other chronic diseases, including several types of cancer. About 40% of adults today will be diagnosed with some type of cancer during their lifetime. It is estimated that 73% of cancer medicines in the pipeline will target specific genetic biomarkers.

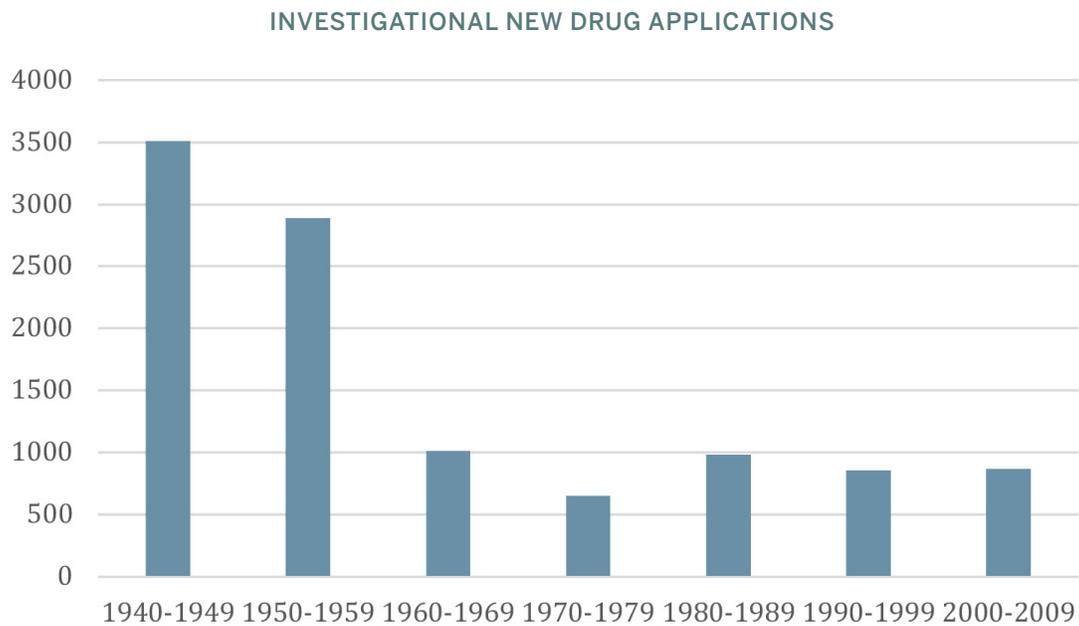
The genetic testing market was \$10.6 billion in 2017 and is expected to grow almost 12% annually from 2018 to 2024. Diagnostic testing is the largest segment with revenue of \$5.7 billion, followed by the prenatal and newborn test market. The continued availability of new tests will fuel further demand for genetic testing.

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A Pill a Day: No Longer the Prescription of Choice

Over the past 50 years, we have seen stagnation in new drug development. The table below highlights the number of new drug applications received by the Food and Drug Administration between 1940 and 2009. More drug applications were filed between 1940 and 1950 than in the four decades after 1970.



Source: <https://www.fda.gov/AboutFDA/History/ProductRegulation/ucm2006085.htm>

While the methods for treating chronic illness have not changed in decades, the costs have. Adjusted for inflation, cancer drug prices have increased more than 100 fold in the last 50 years. Twenty years ago, an extra year of life cost approximately \$50,000 in cancer treatment. Today this figure is closer to \$250,000.

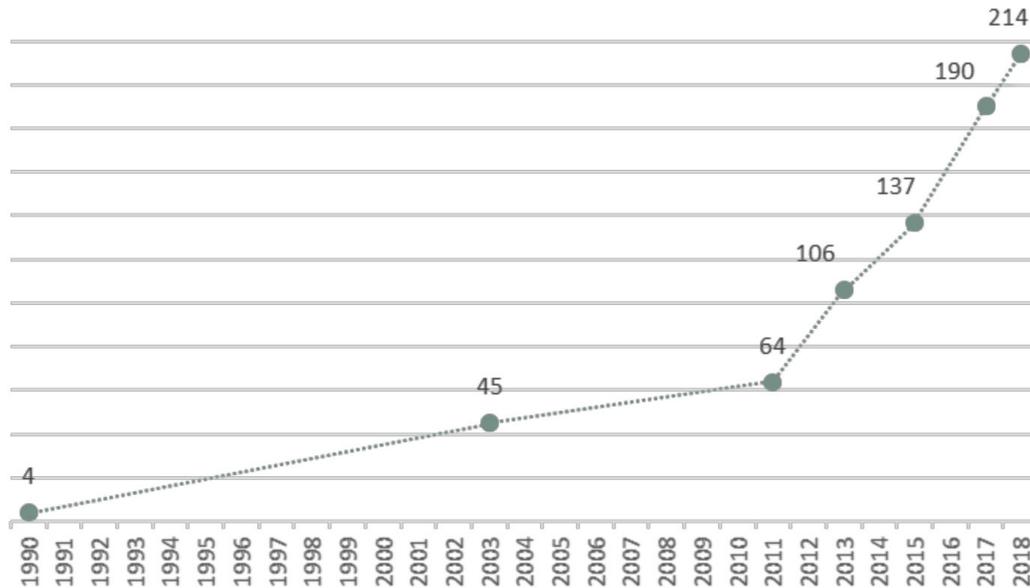
Per dollar spent, cancer drugs are delivering less and less value. For example, Gleevec, a leukemia drug manufactured by Novartis, was initially priced at \$26,000 per year when introduced in 2001. Price increases resulted in the same formulation costing \$120,000 per year at the time of patent expiration.

The exception to this trend is in personalized medicine. Hundreds of targeted therapeutics are now in Phase I, II, and III trials. During the past four years, an average of 25% of new drug approvals were personalized medicines, meaning that an individual's biomarkers help determine their use. The FDA is now approving personalized medicines based on fewer and smaller clinical trials. In April 2018, former FDA Commissioner, Scott Gottlieb, expressed the Agency's goal to further streamline the approval process for small-scale genomic-based treatments. Against a backdrop of slowing overall drug development, the number of drugs associated with patient specific genetic information is accelerating, as shown on the next page.

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THE NUMBER OF DRUGS THAT REQUIRE PATIENT SPECIFIC GENETIC INFORMATION HAS MORE THAN DOUBLED OVER 4 YEARS



Source: FDA, iamB consulting

Even as aggregate new drug development slows, rare drug designations that treat orphan illnesses, defined as those with fewer than 200,000 cases in the U.S., are increasing—up from 320 in 2016 to 459 in 2017. Worldwide sales of rare disease drugs are forecast to grow at an annual rate of 11.3% from 2018 to 2024, roughly double the growth rate for the non-rare market.

Some of the most promising genetic-based treatments may require a single dose compared to a regimen of daily maintenance medications. Single-dose therapies customized to an individual's genetic makeup are designed to provide a one-time cure versus a lifetime of managed care. This will present challenges to an industry accustomed to sustained cash flows from drugs with large user populations, prescription renewals and long-term patent protection. New and different payment models are being evaluated today. Companies such as Novartis and Spark Therapeutics have implemented novel payment approaches that include rebates if the therapy is not effective. A recent example of this new payment paradigm is Spark's Luxturna, which treats progressive childhood blindness related to a defective gene. The one-time treatment is administered as a single dose and gives patients a working copy of the gene, potentially saving a child from a lifetime of blindness. The treatment carries an \$850,000 list price. However Spark has explored an outcomes-based reimbursement policy where the company is paid fully only if the drug works. Legacy payment models are ripe for disruption.

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Given their current investments in blockbuster drugs and manufacturing platforms geared toward large-scale production, major pharmaceutical companies are showing an inclination to invest in personalized medicine through acquisitions. Companies that have acquired genomic-based drug capabilities include Bristol Myers, with its acquisition of Celgene; Eli Lilly, with its acquisition of Loxo Oncology; Novartis, with its purchase of AveXis; and most recently, Roche, with its acquisition of Spark Therapeutics. This trend of large pharmaceutical companies acquiring gene-therapy focused companies should continue.

Some of the most promising work is in the areas of cell and gene therapy. Cell and gene therapies deliver benefits through use of a patient's cells or genome. Gene-editing tools like CRISPR-Cas9 repair defective genes and also impact the genes that will be passed on to future generations. CAR-T is a type of treatment in which a patient's cells are changed in the lab so, when reintroduced, they will attack cancer cells. These are highly personalized treatments that re-engineer a patient's own cells to combat certain cancers.

The pace of innovation in cell and gene therapy is accelerating. In August 2017, the first cell therapy was approved by the FDA to treat a rare form of blood cancer. Just two months later, the second cell therapy was approved. At the end of 2017, the FDA approved the first gene therapy to treat a form of progressive blindness. Innovation continued in 2018 as multiple gene editing therapies were approved to begin clinical trials. Recently, the Medicare Hospital Inpatient Prospective Payment System Proposed Rule for FY 2019 and Medicare National Coverage Analysis for CAR-T-cell Therapy for Cancer, redesigned policies and payment rates to improve access to personalized CAR-T-cell therapies. This is a precursor to more investment in research and development and, ultimately, wider adoption and use.

Personalized medicine is approaching an inflection point that we think is underappreciated. Decades of work in academia and research labs is translating into new drug development. We see three evolving catalysts:

- **Data.** A fast-growing database of genomic information is facilitating discovery and understanding of genomic targets. The more we understand about the human genome, the better we are able to identify the unique genes responsible for chronic illness. As more genetic targets for drug therapies emerge, personalized alternatives will replace traditional treatments.
- **Delivery.** An understanding of genetic linkages with cancer and other chronic diseases is only the first step in mitigating disorders. Doctors need a way to both deliver a therapy to the source of the illness and a mechanism through which to correct the defect. Until recently, there were few vehicles with which to introduce therapeutic changes. Now, there are a growing number of biological and chemical options to deliver cures, such as viral vectors and lipid nanoparticles.
- **Manufacturing.** Biotech companies now have the expertise to cultivate biological products at scale. Leveraging that expertise into a manufacturing capability will convert what is a current bottleneck into broader commercial adoption.

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Investment Insights

Our initial thematic research started with the possibilities created by the Human Genome Project. It expanded to encompass molecular science, personalized medicine and technologies that enable broader adoption of breakthrough developments.

Our goal is not to focus on the science of the next century. Our focus is on how technology and medicine can be leveraged to benefit people in the next decade. Our first job is to understand the possibilities. Our second is to understand when they will be relevant and what industries will be affected. Here are some of our thoughts.

- By 2022, the total addressable market opportunity for genomic therapies has been estimated to be \$4.8 trillion. We think the opportunity is much larger and extends well beyond the healthcare sector.
- Pioneering companies in biological engineering and manufacture will be winners. Companies with intellectual property rights for genetic model testing and the first to build cell manufacturing facilities will have meaningful advantages.
- As fast as the time and cost have come down to sequence the human genome, it currently takes roughly eight hours to interpret the results of a single person's sequenced whole genome. With large population studies underway and as sequencing of newborns becomes commonplace, new and improved parallel processing chips, graphic processing units and purpose built chips will be essential.
- Demand growth for genomic sequencers from medical researchers has been augmented by demand from healthcare providers as applications have expanded from research labs to clinical providers. Governments and consumers will be the next source of strong demand growth. This is a technology with high barriers to entry where market leaders will continue to gain market share.
- The advent of personalized medicine will force pharmaceutical companies to reconsider their current business model. The blockbuster model will give way to drug therapies tailored to individual patients. This will require that drugs move through the pipeline faster, are more effective, safer and less costly to develop.
- Personalized medicine is in essence precision medicine and predictive medicine. Companies that produce the tools and technology, such as companion diagnostics, that facilitate better information, better outcomes and lower costs will become increasingly valuable.

Reading the human genome was a comparatively recent breakthrough. The Human Genome Project was officially completed less than two decades ago. Scientists are now developing new and sophisticated ways to not only read the genome, but interpret genetic code, edit genetic code and replace genetic code. Genomics, personalized medicine and associated technologies should prove to be one of the major investment themes for the next decade and beyond.