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Beyond the Scalpel: D(ata), N(ucleotides) and A(rtificial Body Parts)

- Innovations in medical technology offer tremendous promise in health care making prevention, diagnosis and treatment more personalized and effective
- Lines between science fiction and fact blur as genetic intervention, 3D-printed organs, surgical robots and data-based genome diagnostics slowly become reality
- Genomics, microbiome, artificial body parts and data analytics project rapid revenue growth and technological breakthroughs
- While still small relative to the $7 trillion global health care industry, medical technologies like genomics are growing twice as fast as other segments such as pharmaceuticals
- Along with direct medical interventions, improved data and analytics should be an important driver of efficiency, helping save research and development costs of $27 billion in the coming years, better targeting treatments and providing early warning of major illness
- The investment framework combines stages of care, prevalence of diseases and cutting-edge technologies to help explain a complicated field
- Medical technology and industries like biotech have exhibited short-term volatility tied to concerns about unproven technologies and regulatory uncertainty

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Imagine that human organs can be printed in machines as is done with documents. What if doctors had the ability to heal spinal cord trauma with cellular technology hours after an accident? Instead of expensive and lengthy diagnostic tests, is there a system that could provide reliable answers in minutes and at a fraction of the cost?

All of this is already reality. The first 3D-printed bladder was successfully transplanted into a patient in 2006. While still some time away, laboratories around the world are working toward printing human hearts, kidneys and livers. In 2009, the Federal Drug Administration (FDA) approved tests of stem cell treatments for people with spinal cord damage, and research published since has shown that a patient's motor skills improve following the procedure. A young man paralyzed from the neck down regained use of his arms and hands after a stem cell injection in 2016.

In 2011, a doctor at the Arizona State University biomedical informatics department noted that many of the sensors used in expensive medical tests could be acquired at a fraction of the price. After five years of development, he had created a machine that cost $600 and could run 33 diagnostic tests for just a few dollars per patient.

These cases sound like science fiction, but they are now science fact. Each represents an early case of innovation in a specific field of medical technology, or "med tech," but portends an exciting future for medicine. We identify four areas that we believe will have promising breakthroughs in the coming decades and provide some scientific explanation and cases that help justify our views.

Investors should recognize that industries and market segments most exposed to med tech can also be quite volatile. For example, 30-day volatility for the S&P 500 Health Care Index has averaged 13.9 during the past five years, whereas the growth-oriented NASDAQ Biotechnology Index has been much more volatile at 24.1. Investors in the biotech index also experienced four drawdowns of 15% of more—including a drop of almost 40% in 2015 and 2016. Returns for the NASDAQ Biotechnology Index have closely matched the S&P 500, underperforming by 1% over the past five years, meaning investors have received market returns but with more risk.

Even so, the growth opportunities and efficiency gains are significant, given the World Health Organization's last estimate of $7.2 trillion expenditure in global health care in 2015. The size and complexity of this market can often be overwhelming for investors unfamiliar with the technology, markets and regulatory policy.

To help investors navigate the rapidly evolving med tech field, the investment framework here focuses on the greatest growth opportunities, and those in which the technology is close to application. These opportunities are filtered by the underlying technologies, prominence of illnesses and stages of medical care. This helps identify advances that have the biggest addressable markets and helps to avoid highly speculative technologies or companies tied to a single exploratory product.

Revolutionary Technologies

The molecular biology that underlies genomic and nanotechnology research is basically as complicated as rocket science. We cover four broad areas in the evolving med tech field investors should consider from a high level: genomics, microbiome, robotics and artificial body parts, and data and analytics (see Exhibit 1).

Genomics

Genomics leverages DNA and RNA, the fundamental building blocks of life, to personalize treatment. DNA lies inside every cell's nucleus and is the blueprint for all living things. DNA consists of four molecules, called nucleotides, which are paired in a double helix. The nucleotides form sequences that encode what proteins and other molecules the body should produce. RNA is a single strand of nucleotides used when cells replicate.

After sequencing all of the nucleotides in the human genome in April 2003 biologists were able to accelerate identification of variations in genetic code that could cause disease. The next breakthrough was the ability to alter the sequence of these nucleotides using DNA and enzymes found in bacteria. Now that there is technology to edit a genome, modern genetic research can focus on recoding or blocking genes that lead to disease.

The genetics category includes gene editing, RNA interference, proteomics, recombinant DNA therapy, DNA vaccines, personalized medicine and mRNA inhibitors. The companies focused on this area are distinguished by the methods used to treat a special class of diseases. Given the complexity of the human genetic code, knowledge of the nucleic acid sequences or patterns and methods of delivering personalized treatments are defining factors in cost-effective therapies. Since the sequences of DNA found in nature are discoverable and not eligible for patent protection, this knowledge will proliferate. The methods developed for editing and delivery will likely prove critical.

How then do genomics companies differentiate themselves and maintain their value? One of the most difficult hurdles for gene therapy is delivering the treatment to the cells. Treatments are

either ex vivo (outside the body) or in vivo (inside the body). Ex vivo treatments take cells from the patient, inject them with a virus containing the gene correction and then return them to the patient. In vivo treatments inject the gene correction into the patient's tissue or blood stream. This is an easier delivery method for the patient and practitioner, but it can be difficult to get the therapy to the correct cells, so it may trigger an immune response. The delivery mechanism is a critical part of these companies' value, with some relying on the delivery technology alone as their marketable product. These companies are well positioned to become platforms for the delivery of many different gene therapies.

Stem cells represent another opportunity for healing damaged tissue. While much discussion focuses on embryonic stem cells that can easily adapt, there are other forms of stem cells as well, such as adult stem cells, currently being explored. Initial human stem cell research has focused on areas such as spinal cord injury, degenerative diseases and diabetes.

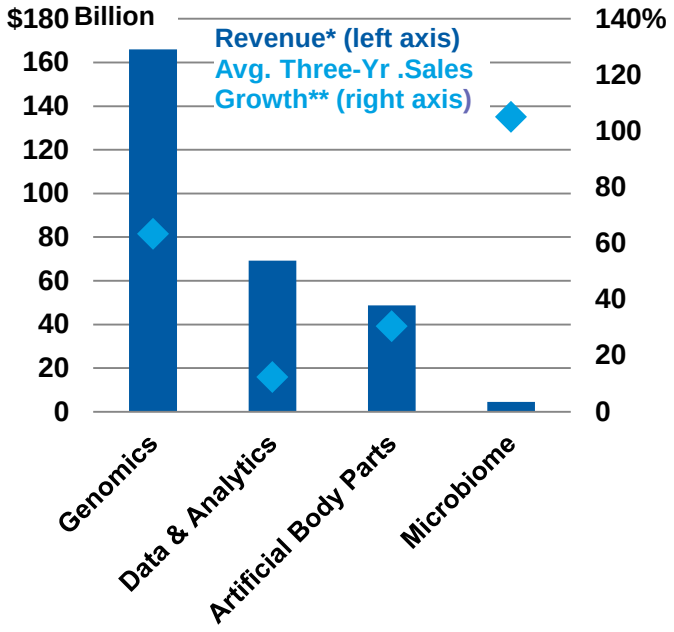
Finally, there is the technology that alters the genetic code. The one that has gathered most attention is "clustered regularly interspaced short palindromic repeats" (CRISPR), which is a sequence of bacteria genes than can be repurposed to cut or alter genomic sequences in host bodies. US researchers have published results on animal tests, and reportedly Chinese scientists have already used CRISPR on 86 human patients with cancer and HIV. While CRISPR is the most well-known, other methods of gene editing are gaining attention as well.

Microbiome

A second emerging medical technology is microbiome. Much smaller than the genomics field, microbiome research focuses on microbes such as bacteria, viruses and fungi that live inside and on humans. Microbes comprise about 1% to 2% of human body mass. Until recently, conventional wisdom suggested that exposure to bacteria, viruses and fungi should be minimized and microbes destroyed. The overprescription of antibiotics or the prevalence of hand sanitizer are examples of the emphasis on killing these foreign organisms.

Research suggests that these microscopic organisms may play a critical symbiotic role with human hosts. In fact, the Human Microbiome Project, a National Institutes of Health initiative, is creating a road map of the body's organisms. These microbes are now thought to be critical in keeping organs and other parts of the body in balance. Better understanding of this area may improve treatment for cancer, intestinal diseases and immune systems.

Exhibit 1: Genomics Is Largest and Fastest Growing Medical Technology



*Revenue is as of fiscal year end 2017. **Sales growth is the compound annual growth rate
Source: Bloomberg, Morgan Stanley Wealth Management as of fiscal year end 2017

Artificial Body Parts

A third area that offers potential is artificial body parts. This categorization includes any biologic or nonbiologic substance introduced into the body to mimic the functioning of a naturally occurring human organ, limb, valve or other object. This includes robotics, artificial hearts, 3D-printed organs, nanotech and autologous cell therapy—growing an individual's cells outside of the body as replacement tissue for the host.

One of the major challenges facing the health system is a shortage of replacement organs. Dr. Todd Pesavento, at Ohio State University notes that the number of transplanted organs was flat between 2006 and 2015. What's more, 100,000 people are awaiting a kidney, more than four times as many as all the other organs combined. Dr. Anthony Atala at Wake Forest University has led efforts merging biological tissue with bridging structures in 3D printers, that is overlaying or growing biological tissue on nonorganic printed foundations, in an attempt to generate organs such as kidneys. While this work remains experimental, advances

in robotic body parts are a reality. Hands and legs are the most common robotic prosthetics, but future advancements could include eyes and ears.

Data and Analytics

The final category in our medical technology theme is data and analytics. According to IDC Health Insights and Dell EMC, the amount of health data collected globally will increase 47.4% annually between 2013 and 2020, representing a massive opportunity for application of analytics in medicine. To wit, venture capital funding for applications of artificial intelligence in health care grew at 126.8% annually between 2012 and 2016, reaching $794 million, according to TM Capital.

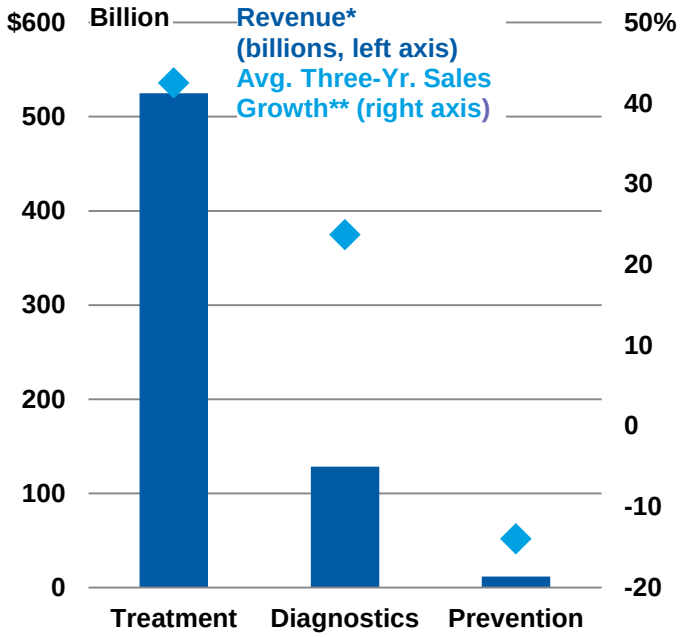
Improvements in drug development represent a significant opportunity. The California Biomedical Research Association estimates that a new drug spends 12 years in development and trial. Only one in 1,000 reaches market at an average cost of $359 million, according to PwC. Harvard University in 2017 estimated that these technologies could save the pharmaceutical industry $27 billion by 2025. Another area that requires tremendous processing power is genomic sequencing. The human genome is 3 billion letters long which would require 1.2 million single-sided printed sheets that would reach 424 feet high, so mapping and analyzing DNA requires both processing power and analytical tools.

Machine-assisted diagnoses are expected to grow significantly. One artificial intelligence algorithm has specifically been applied to improve cancer diagnosis. Computers can be loaded with data allowing inferences off a larger number of medical cases than a doctor could possibly remember or even see. Large companies are combining to simplify medical record-keeping, and ensure the right information flows to the right doctor. While many of the medical technologies discussed above are still experimental, transformative data and analytics are already here.

What Is the Opportunity and Size of the Market?

Health care is a significant part of the US and global economies. US health care spending was approximately $3.5 trillion—18% of GDP in 2017—and is expected to rise 5.3% in 2018, according to the Centers for Medicare and Medicaid Services. The Centers also estimate that through 2026, US health care expenditures could average 5.5% annual increases. The World Health Organization estimates that global health care spending reached $10 trillion in 2017. Alongside real estate and finance, health care is one of the largest industries in the US.

Exhibit 2: Largest Opportunity Is in Treatment



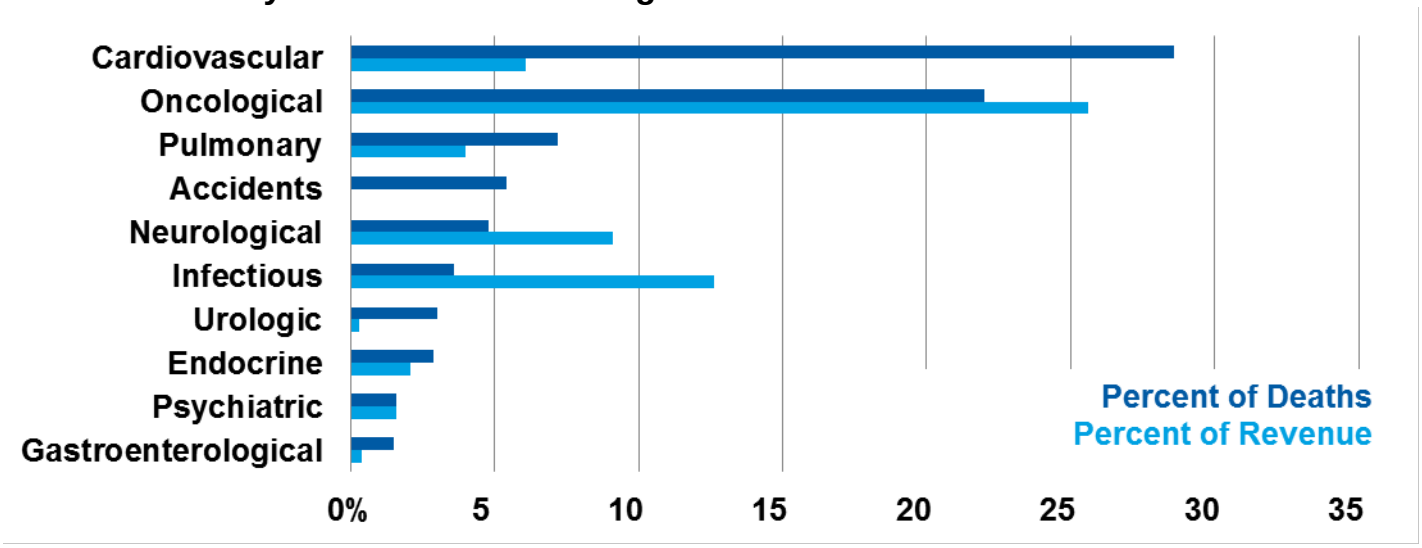
*Revenue is as of 2017 fiscal year. **Sales growth is the compound annual growth rate
Source: Bloomberg, Morgan Stanley Wealth Management as of 2017 fiscal year

Health care providers and services represent the largest component of the sector, totaling about 71% of revenue, or $1.4 trillion. While this business will likely benefit from the innovative technologies discussed above through improved efficiencies and outcomes, growth in this business has lagged areas like biotechnology and health care technology. Pharmaceuticals are the second-largest industry in the health care sector, 12% of revenue (see Exhibit 2). While this is nearly double the size of biotech, the pharmaceuticals are growing at a slower rate. Biotech's three-year average sales growth is 22%, nearly double that of pharmaceuticals and the fastest growing sector in the industry.

Prevention

The market for med tech is large and covers three stages of health care. The smallest segment at present is prevention, which is aimed at avoiding illness and more expensive medical care. Prevention generates only $11 billion revenue, but could see resurgence as medical data breakthroughs and cultural shift toward healthy lifestyles siphon spending from the other two areas.

Exhibit 3: Deadly Diseases Are the Largest Markets



Source: Percent of deaths from the Centers for Disease Control and Prevention *National Vital Statistics Reports* Vol. 66, No. 6, Nov. 27, 2017. Percent of Revenue from Bloomberg based on a compilation of relevant companies at fiscal 2017 year end. Morgan Stanley Wealth Management.

Diagnostics

The next phase in medical treatment is diagnostics, which is significantly larger than prevention and generated $124 billion in 2017. Diagnostics leverages a range of medical techniques including equipment and compounds. More advanced diagnostics may use genetic sequencing on cancerous growths, and viral and bacterial infections.

At the heart of this transformation are biomarkers, which are gene sequences or proteins that indicate disease or risk of disease. Biomarkers are transforming medical diagnostics for diseases like cancer. Many cancer patients who are detected early have a good prognosis. Existing techniques for early detection can be both expensive, intrusive and inconclusive.

Colon cancer is one such example. According to Healthcare Bluebook, a colonoscopy costs about $2,700 in New York City. On the other hand, a blood test that looks for high levels of a protein associated with prostate cancer is $60. If a similar biomarker blood test existed for colon cancer, many more people would likely be screened and cancers detected earlier.

Biomarkers are also aiding in the development of new treatments. Drugs that may have failed clinical trials because they produced too many side effects in a broad population may clear clinical hurdles with a genetically targeted subgroup. Testing could also identify populations most likely to respond to a specific treatment based on their genetic makeup or other biomarkers, increasing the efficacy of the drug and improving trial results. This targeting of treatments to a specific genetic sequence or protein is referred to as personalized medicine.

Treatment

The largest part of the medical sector lies in treatment of illness. That stage accounts for $523 billion in revenue, with the average company growing sales by 43% annualized in the past three years. Treatment, like prevention and diagnostics, includes conventional treatment and not solely comprised of med tech. That said, the vast majority of health care expenditure has been and will continue to be focused on treatment. Some of the more innovative methods include genetically customized drug treatments, gene therapy, surgical tools and robotics, genetic or nanotech delivery methods and lab-grown or artificial body parts.

In time, we expect the entire continuum of prevention, diagnostics, and treatment to merge into one. In the future when someone turns 18, their genetic makeup could be mapped from a swab of saliva. This may be compared against a database of genetic mutations and their associated diseases to determine if the person is at risk for developing any of them. The person who could then get a shot which replaces the high-risk mutations with healthy genetic code. The patient will be spared from the diseases they could have otherwise developed. Is the testing preventive or diagnostic? If a patient never had a disease, can they be considered treated for it?

Deadliest Diseases

Another way of thinking about opportunity in the health care sector relies on the most prominent and lethal medical conditions. Four of the six leading causes of death involve medical conditions that could see major breakthroughs in the next decade (see Exhibit 3). The first two leading causes of death in the US are cardiovascular and oncological illnesses, accounting for 27% and 22%, respectively. In one instance, replicated heart tissue could help identify what medications would be most effective against conditions. Med tech is similarly being applied to specialized cancer treatments.

The next causes of death are pulmonary disease and accidents. The first is largely preventable by lifestyle changes. Med tech is valuable to accident treatment in numerous ways such as spinal cord or transplant options. Neurological and infectious illnesses round out the other major causes. Patients with short-term memory challenges may be able to soon get a performance-enhancing implant. Scientists are also targeting infectious diseases with techniques ranging from genetically attacking resistant bacteria to fighting viruses with UV light.

In sum, we believe there is tremendous opportunity given the size of the medical industry and ongoing research that will likely create breakthrough technologies, allowing for more effective treatments, including those with no available cures. The total revenue in 2017 of companies involved in treating oncology, immunology, infectious, neurology and cardiovascular illnesses amounted to 66% of disease specific revenues or $222 billion. If these disease segments grow in line with the past three years, the revenue five years out would be $368 billion. This does not even count the remaining disease segments or technologies making up the med tech market. If med tech grows in line with prior revenue growth over the past three years, revenue three years forward would be more than $1 trillion.

What Are the Risks to Med Tech Growth?

Investors in next-generation med tech should see strong growth and profitability over time, but there are risks. Health care remains a highly regulated business, which creates uncertainty for companies making large investments to develop diagnostics and treatments.

Policy and regulatory risk in health care arises in a number of ways. The concern that continuously weighs on markets is the fear that government moves to curb private-sector power over drug prices. In the past decade, this issue has been raised in both Democratic and Republican administrations as well as finding a place in campaign platforms.

Part of the reason that policymakers have turned their attention to pricing is that a few companies relied on strategies that incorporated large price increases. The typical example is a company that buys a treatment for a rare disease that lacks any generic substitutes, and then drastically increases the price knowing that insurance companies and patients have little choice but to pay.

Most med-tech companies are not engaged in this kind of practice, but there are substantial research and development costs that go into methods like genome editing, personalized treatments and the growth of body parts. Government involvement in the sector increases the risks that companies investing in research will be unable to recover those costs if government can intervene to set prices. The risk of government intervention in pricing is likely to persist for some time, given the rapid growth in health care expenditures across the public and private sectors.

Some states have considered tying drug pricing with transparency in which companies would disclose research and development costs to prove to justify premium pricing. This measure targets those companies that levy large price increases on drugs that have been in the marketplace for some time and did not require the same type of investment. One challenge for the innovative companies is that disclosing costs could offer clues to the method of development and means by which a new medication works.

While drug and medical pricing face risks, there are others tied to policy. Health care is a tightly regulated industry and introduction of new treatments or methods can take a decade or more to reach market. The concept behind the regulatory regime is intended for patient safety, to ensure that new medicines achieve desired objectives and the potential side effects are well understood. Critics of the regulatory regime suggest that the system is overrun and the pace of innovation is moving more rapidly than the system can handle.

For investors, this means that potentially successful treatments might never make it to market if companies cannot self-fund or obtain external financing to operate in the face of a long approval process. Funding innovation could be even more acute as advances in data analysis and fabrication help fast followers close the gap on first movers caught up in regulatory slowdowns.

Another policy-related challenge, particularly relevant to genomics or microbiome, deals with patent and copyright law. Does a person own the copyright to their own genetic code simply because it is theirs? Can the genetic code of a microbe that could be centuries old be patented? Is decoding a genetic sequence sufficient to warrant intellectual property?

The current precedent established by the US Supreme Court in 2013 is that "DNA in its original form cannot be patented." A synthetically created gene that does not arise in nature could be patented, but this a fluid element of intellectual property law and increases the likelihood that some of this technology becomes commoditized and generic treatments will emerge.

A final risk comes in the form of ethical concerns over the use of technologies like stem cell treatments or genome editing. Stem cell research has been a political football in the US. The George W. Bush administration put stringent limits on use of stem cells, essentially eliminating public funding. The Obama administration reversed policy, allowing limited federal funding. Genome editing represents another set of ethical issues. Should parents be able to enhance the intelligence of an unborn child through genetic intervention or create designer children selecting eye and hair color? The power of gene editing extends in public safety and national security as scientists could create superviruses more dangerous than the Ebola virus. There are no easy answers to these questions, but the fate of some med tech firms will be caught up in these public debates.

What is the Investment Framework?

Med tech, and specifically biotech, have experienced boom and bust in public markets. The NASDAQ Biotechnology Index logged an annualized return of 8.8% in the five years ending Oct. 31, 2018, but there were also larger drawdowns and greater volatility than in the broader market (see Exhibit 4). Such boom-and-bust cycles are common in emerging technologies as exemplified by internet and hydraulic fracking stocks. As technologies mature, volatility typically declines, but investors should understand the risks when allocating to such rapidly evolving fields.

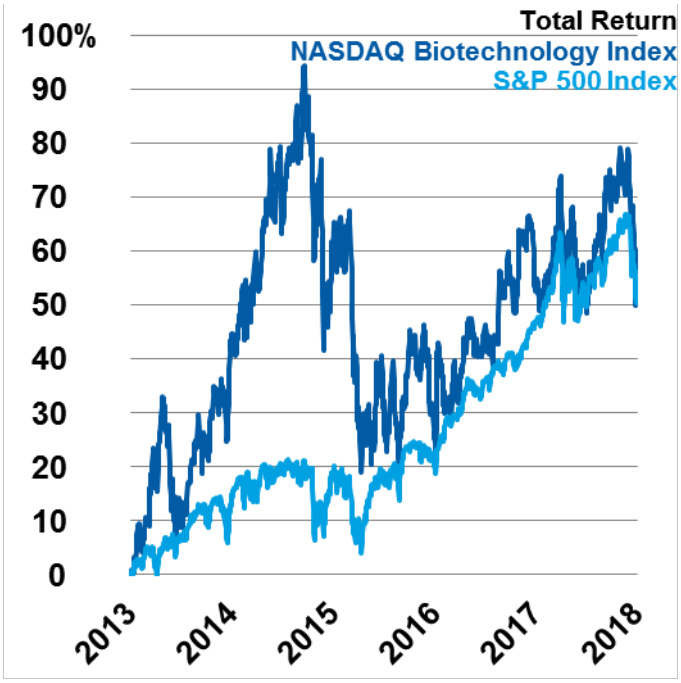
The investment framework developed here focuses on the highest growth opportunities within med tech while trying to dampen risk by focusing on technologies that can be used across different illnesses and stages of treatment. Exhibit 5 (see page 8) shows the systematic approach developed here. The analysis starts with the stages of medical care with largest being treatment; diagnostics is the second largest. While we believe prevention is an important and growing space, much of that market is tied to lifestyle like diet or fitness bands rather high tech medical breakthroughs.

The second filter relies on the technology used to address different illnesses and leverages the four categories described earlier: genomics, microbiome, artificial body parts, and data and analytics. Using our three-year growth estimates for revenue, genomics represents the largest opportunity followed by data and analytics. Interestingly, this pairs genomics, which involves high research and development costs, with data and analytics, which can leverage cloud infrastructure and potentially reduce the cost structure. The promising area of microbiome is currently the smallest opportunity and more speculative than the others.

The final factor that helps guide the investment framework looks at the prominence of illness in the US and as a result the addressable market. Diagnostics and treatment targeting oncology, immunology, infectious diseases, cardiovascular and neurology have the greatest demand for predefined illness. The nonspecific category captures medical conditions resulting from events like accidents, and as such, artificial body parts play a large role. It also includes diagnostic tools that can be used for a variety of diseases.

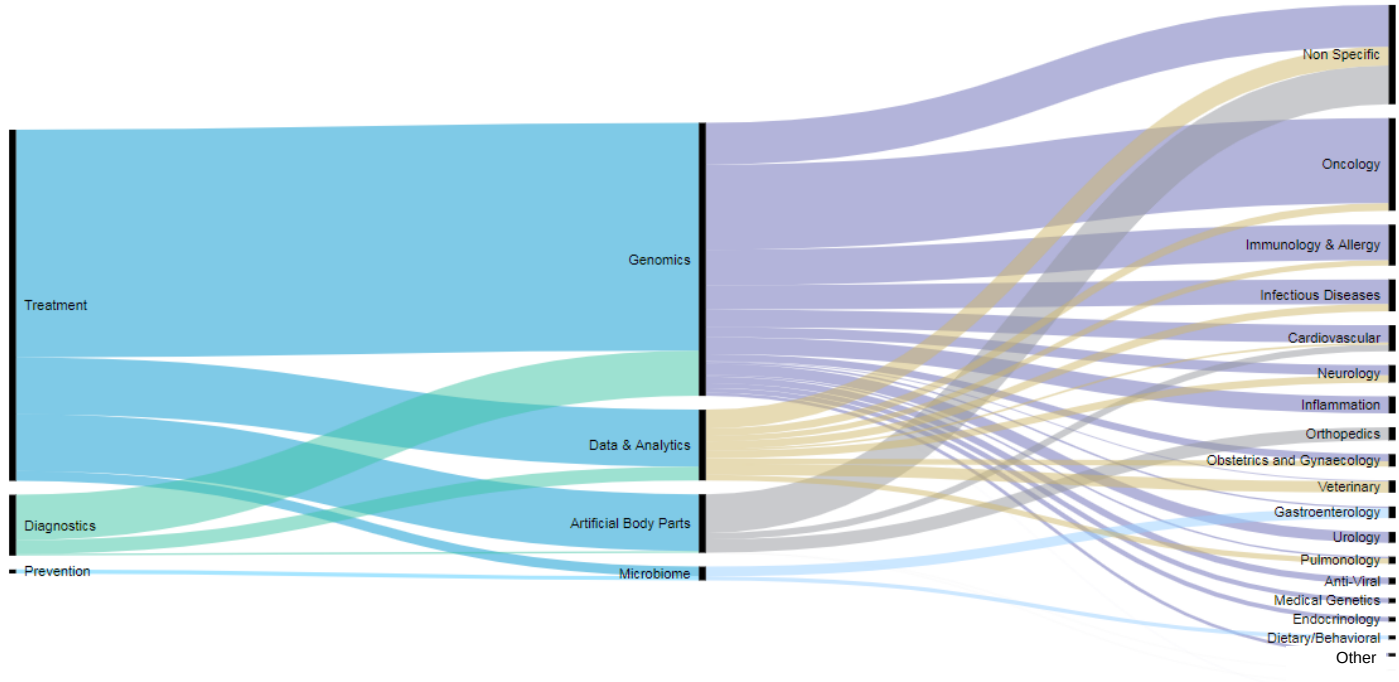
Using the framework developed here to identify opportunities, investors may consider companies focused on treatment and

Exhibit 4: Boom and Bust of Biotech



Source: Bloomberg, Morgan Stanley Wealth Management as of Oct. 31, 2018

Exhibit 5: An Investment Framework for the Medical Technology Market



Source: Bloomberg, Morgan Stanley Wealth Management. The forward revenue estimates assume the last three years' compound annual growth rate remains constant and is applied to current year revenues. The width of the strands represents magnitude of revenue. For perspective, the treatment/genomics branch is $228 billion and microbiome/dietary/behavioral branch is $4 billion. Other includes ophthalmology, rheumatology, dermatology and hematology.

diagnostics of cancer and immune disorders in genomics. Data and analytics played a key role in cancer treatment, infectious disease and neurological disorders. We believe that this revolution is still in the early stages. Some variables like prominence of illness are likely to persistent over time, but shifts in the technological landscape are highly variable. While many leading-edge firms utilize advanced technologies to address multiple illnesses, the goal here is to help understand the likely flow of resources based upon technology and need to guide investment.

Conclusion

While medical technology has made tremendous strides over the past 100 years with the development of solutions to once untreatable diseases, the next century may look more like science fiction than contemporary medicine. As new technologies emerge, society will have to confront a series of difficult ethical and policy issues. Nonetheless, the health care sector is prime for disruption as data analytics facilitate more rapid drug testing and personalized treatment, genomic diagnostics and editing enter mainstream, secrets of the microbiome are unlocked, and biological or robotic prosthetics help people live longer and more fulfilling lives. Investors should be on the forefront of this transformation while being mindful of the risks. ■

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Index Definitions

For indexes referenced in this report please visit the following: http://www.morganstanleyfa.com/public/projectfiles/id.pdf

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