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INVESTORS

Disruption in Healthcare

Disease treatment is changing rapidly, leading to new therapies and better long-term results for patients. Portfolio Manager Andy Acker and Research Analyst Dan Lyons discuss how these exciting advances are leading to new investment opportunities in healthcare.

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Q What do you think are some of the most revolutionary changes happening in drug development?

The old way of drug development involved modifying chemical compounds, testing them and empirically looking for whether the drug had a desired effect. Now we're doing more targeted development. Here is a gene that we know is defective and here is the protein that it makes. So let's go after that directly. In doing so, medicine becomes more personalized and far more effective.

One of the most revolutionary aspects is the massive scale at which you can do DNA sequencing (the process of determining the order of the chemical building blocks, or bases, that make up DNA). In the past, we could only sequence a single DNA fragment at a time. Today, technology has made it possible to sequence millions of fragments simultaneously and to analyze the data with vastly improved, lower-cost computing power. That's led to the discovery of new genetic targets, which is the key to understanding and treating disease.

This new way of sequencing – called next-generation sequencing – has done for biomedicine what the semiconductor did for the computing industry. We've set off down this path of Moore's Law in medicine, and we believe it is just getting started. (Moore's Law is the principle named for Intel co-founder Gordon Moore, who observed that computing power essentially doubles every two years.)

Q How are researchers harnessing this knowledge to treat disease?

It's a one-two punch. Computing power has made it much faster and cheaper to interpret genetic information. At the same time, there are more modalities for treating patients. In the old days, we treated disease with pills, which are small-molecule chemical compounds. Over time, that advanced to biologics and antibodies, which do a much better job of addressing the underlying cause of illness. Now we can actually manipulate genetic material.

For example, with gene therapy we can create a functional copy of a gene and deliver it into a patient's cells. That gene is now producing a protein that previously may have been missing. With a single infusion, we're essentially turning the body into a factory that produces the correct protein and potentially cures the disease. So not only do we have a better understanding of what's causing disease, but we have all these new modalities for treating the problem.

Q Does technology play a pivotal role?

We've made a lot of advances in medicine by understanding and manipulating genetic material, but we're also benefiting from advances in the tools that researchers use. X-ray crystallography is a good example. With this imaging technique, scientists can see, at an atomic level, how well a drug binds to its protein target. As a result, even small-molecule drugs are becoming more targeted and effective, with fewer safety issues. That makes it easier for companies to get regulatory approval, which can improve the risk/reward opportunity for investors.

We're also seeing advances in medical devices and robotics. Last year, the U.S. Food and Drug Administration (FDA) approved the first integrated continuous glucose monitor, or iCGM, for diabetes management. This device is a patch that contains a sensor. When applied to the skin, the iCGM transmits real-time glucose readings to a compatible device, like a smartphone. It can also be integrated with an insulin pump that will automatically release insulin, if needed. All of this is possible only because of advances we've made in sensors, algorithms, wireless transmission and mobility. It's transforming the way diabetics manage their disease, and we expect to see more examples like this across healthcare.

Q What's the potential market size for some of these new therapies?

To take one example, scientists so far have identified approximately 7,000 genetic diseases, but less than 5% have treatments today. Knowing exactly which genes are defective and correcting them with a one-time gene therapy treatment would add tremendous value to the healthcare system and dramatically improve the lives of these patients. We still have a long way to go.

For example, heart disease is one of the biggest killers, with one in every four deaths caused by it each year in the U.S. New therapies are helping reduce the risk of someone suffering a serious event, such as heart attack, stroke or death. But even if you reduce the odds of those events by 30% – a significant amount – there's still a lot of room to improve, given the numbers.

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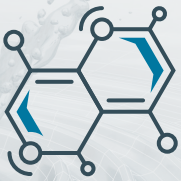
> **Mr. Acker**

Milestones in Modern Medicine



1972

Paul Berg creates DNA molecules from combined genes, the foundation of modern genetic engineering.

1977

Frederick Sanger's chain-termination sequencing method for DNA – the process of determining nucleotide bases in DNA – is developed. This method is later used to help map the human genome.

1985

Kary Mullis develops polymerase chain reaction (PCR), a technique that makes it possible to generate millions of DNA copies from a single strand of DNA. PCR goes on to have multiple medical and forensic applications.

1986

The first monoclonal antibody, Orthoclone OKT3, is approved by the U.S. Food and Drug Administration (FDA) to reduce organ transplant rejection. Monoclonal antibodies will become important tools for biomedical research and the treatment of complex diseases, including cancer, rheumatoid arthritis, asthma and Crohn's disease.

Q What about the regulatory hurdles that must be cleared in order to bring new products to market?

The FDA is mindful of the many advances taking place in medicine. So it is taking a pragmatic approach and collaborating with companies to lower the cost of drug development. The FDA has also created new pathways for firms to achieve regulatory approval and bring products to market faster. So, companies have an incentive to focus on truly innovative new therapies, which in theory leads to more competition and better treatments for patients while potentially rewarding the companies that succeed.

This mindset is not limited to the U.S. Regulators in Europe have similar goals while China is making a big push to add more therapies to the country's National Reimbursement Drug List. China has also introduced reforms to encourage innovation and reduce the backlog of drugs waiting for approval. China is the second largest pharmaceutical market in the world, so these changes are significant.

The same is true for medical devices. The FDA really wants to lower the time and cost of bringing new devices to market. In 2018, for example, the agency created a way for devices related to iCGMs to come to market without clinical trials or other time-intensive steps. These types of initiatives should shorten product cycles and create more competition, helping drive down costs for the healthcare system. And while competition can be bad for incumbents, it can be good for start-up companies that want to bring something to market that's differentiated.

Q Does competition also pose a risk for investors?

It means investors have to be mindful of what's becoming an increasingly competitive marketplace. It is one reason why we also invest in private companies. We want to be aware of not just the companies that are leaders today but also the firms that could disrupt tomorrow. Research shows that 90% of drugs that enter human clinical trials never make it to market. So, we think it's important to cast a wide net and rigorously apply fundamental research.

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1992 & 1996

PD-1 and CTLA-4 identified as immune checkpoints, proteins that suppress immune system responses to cancer. This marks a foundational step for the development of immunotherapies.

2000

Human Genome Project: A first draft of the human genome is completed, the culmination of a decade of work by scientists worldwide using a version of the Sanger sequencing method.

2003

Iressa, the first targeted therapy for the treatment of non-small cell lung cancer, is approved. By targeting cancer cells specifically, medicines such as Iressa can potentially delay cancer progression with fewer side effects than chemotherapy.

2005

Next-generation sequencing (NGS) technology is developed. NGS makes it possible to sequence DNA more quickly and at considerably lower cost than the Sanger method, revolutionizing genetic research and making personalized medicine possible.

2011

The FDA approves Yervoy, the first immunotherapy to target and block an immune checkpoint, enabling the immune system to identify and kill cancer cells.

Novel Therapies Defined

Small-Molecule Drug
A medicine with a low molecular weight, enabling it to easily enter cells and effect change. Most small-molecule drugs are taken as pills, and new tools such as x-ray crystallography have helped to make the drugs more targeted and effective.

Monoclonal Antibody
Man-made versions of immune system proteins that can be programmed to bind to specific targets and initiate an immune system response.

Immunotherapy
Therapies that activate or strengthen the immune system to combat cancer. These therapies include:

Checkpoint Inhibitor: These medicines essentially take the "brakes off" the immune system, helping it recognize and fight cancer cells.

CAR T-cell Therapy: A process by which T-cells (a type of immune cell) are extracted from a patient's blood, genetically engineered to target and kill cancer cells, multiplied, and reinserted into the body.

Targeted Anti-Cancer Therapy
These medicines interfere with specific molecules involved in the growth, progression and spread of cancer. Targeted therapies can be either monoclonal antibodies or small-molecule drugs.

RNA Interference
A mechanism that uses a gene's own DNA sequence to turn off expression of a malfunctioning gene, a process known as gene silencing.

Gene Therapy
A method by which healthy genes are inserted into cells via a viral delivery vehicle to correct a genetic defect.

Gene Editing
The insertion, deletion or replacement of DNA at a particular location in the genome using revolutionary molecular tools such as CRISPR-Cas9.

2012

Europe grants first regulatory approval for a gene therapy, Glybera, a treatment for hereditary lipoprotein lipase deficiency, a rare genetic disorder in which the breakdown of body fats is disrupted.

2012

CRISPR-Cas9 is shown to be an effective methodology for cutting precise DNA sequences and inserting replacement DNA, marking a significant leap forward for gene editing.

2017

The FDA approves the first CAR T-cell therapies, one for the treatment of B-cell acute lymphoblastic leukemia, the most common childhood cancer in the U.S., and another for certain types of non-Hodgkin lymphoma. According to the Cancer Research Institute, there are now 753 CAR T-cell therapies under development, with half already in clinical trials.

2017

The first gene therapy is approved in the U.S. The medicine, Luxturna, treats children and adults with a rare form of inherited vision loss that can lead to blindness.

2018

The FDA approves the first RNA interference drug to treat a peripheral nerve disease caused by hereditary transthyretin-mediated amyloidosis.

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Concentrated investments in a single sector, industry or region will be more susceptible to factors affecting that group and may be more volatile than less concentrated investments or the market as a whole.

The healthcare industries are subject to government regulation and reimbursement rates, as well as government approval of products and services, which could have a significant effect on price and availability, and can be significantly affected by rapid obsolescence and patent expirations.

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