

## Genomics: Changing Medicine and More

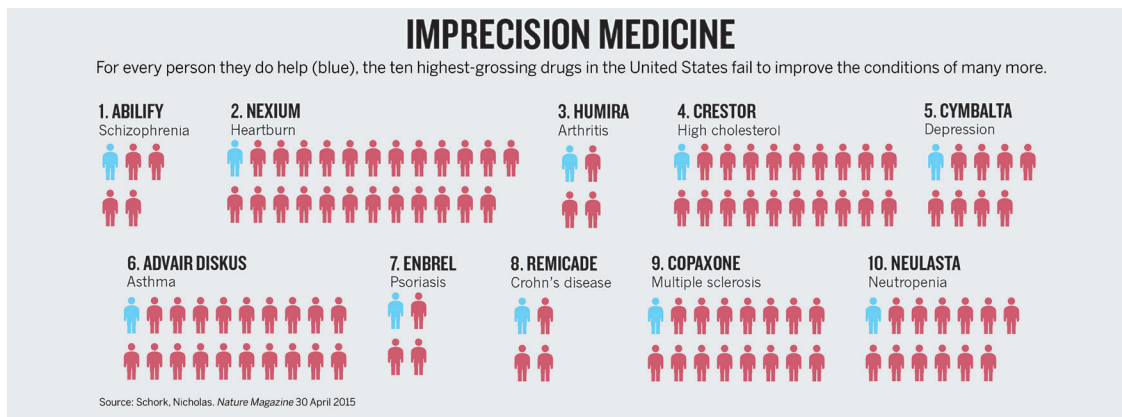
As thematic investors, we study secular trends, disruptive innovations and economic forces with the potential to reshape the world. Personalized medicine is a case in point.

The Human Genome Project and developments it has spawned are transforming our understanding of each person's unique molecular and genetic profile. More important, as more whole human genomes are sequenced, over 1.5 million to date, increased data is yielding new knowledge linking genetic profiles to specific diseases. This is advancing the frontiers of diagnosis and treatment.

While many medications today activate or suppress the immune system, cell and gene therapies operate at a more granular level, introducing live cells or altering a person's genetic code. Rather than manage the symptoms of a condition, cell and gene therapies can address the root cause, offering the potential to treat previously untreatable, and even cure previously incurable, diseases.

### A Well-Timed Pivot to Rare Diseases

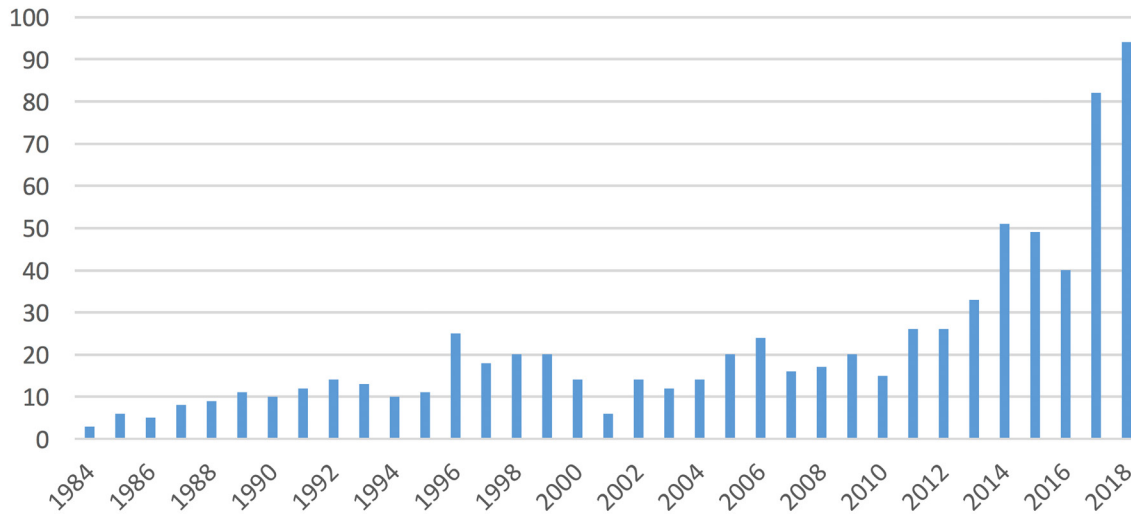
Concurrent with the rise of genomics, traditional drug development has reached a choke point. Bringing a new drug to market now takes on average 15 years with a cost of \$2.6 billion. Large-cap biopharma companies in 2018 earned only 1.9% on their research and development investment, down from 10.1% in 2010. At the same time, late-stage pipeline assets have fallen by 23%. Compounding and confounding this slowdown, drugs that do reach the market often prove ineffective for many patients.



Drug developers have been shifting attention to rare diseases. Defined as conditions that affect fewer than 200,000 people, rare diseases include conditions such as Leber congenital amaurosis, an eye disorder that only affects two to three newborns per 100,000, and spinal muscular atrophy, which affects one per 8,000 to 10,000 people worldwide. In recent years, approvals of "orphan" drugs that treat these rare diseases have increased dramatically.



## Orphan Drug Approvals



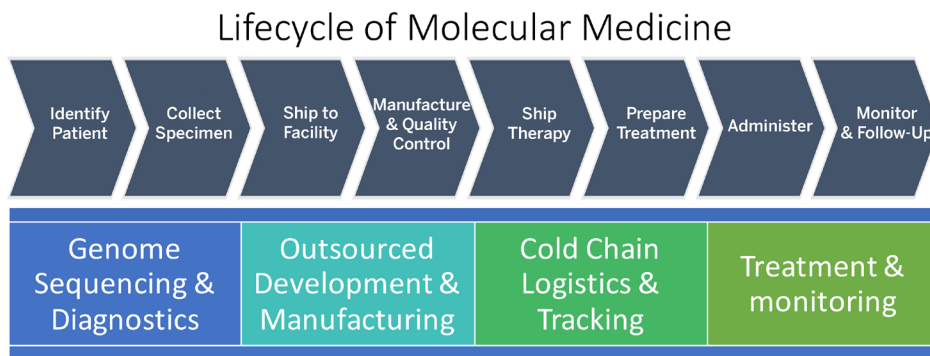
Source: www.fda.gov, Chevy Chase Trust

As over 80% of rare diseases have a known monogenic (single-gene) cause, rare diseases are particularly good candidates for personalized medicine. Our research estimates there are approximately 1,700 cell or gene therapies in various stages of clinical trials. From an investment standpoint, this shift to molecular/genomic medicine is opening up areas of opportunity beyond the drug therapies themselves.

### Focusing on Genomic Enablers

It's difficult to predict whether a drug in development will come through the pipeline, which of those that do will be commercially viable, much less which might become blockbusters. The technologies that facilitate development and logistics have more certainty and are the growth engines of a nascent field.

The processes and infrastructure used in cell and gene therapies are fundamentally different than those used in traditional medicine. We believe that a historic opportunity in personalized medicine lies less in identifying the next blockbuster drug and more from researching and understanding contributors in the genomic supply chain.



Source: Chevy Chase Trust



## Identifying the Picks and Shovels of a New Frontier

As genomics disrupts the pharmaceutical and healthcare industries, the evolving ecosystem presents opportunities for infrastructure companies along the supply chain. Here are three very different facilitators – one in diagnostics, one in development and one in distribution.

**Illumina** is the global leader in DNA sequencing. The firm provides an integrated range of instruments, consumables and services that are essential in the identification and understanding of genetic variations.

Led by Illumina, the cost of sequencing the human genome has declined faster than Moore's Law, from \$13 billion in 2003, to \$1,000 in 2014, and broaching a \$100 genome today with the recent introduction of Illumina's NovaSeq sequencer. At a lowering cost of accessibility, genome sequencing should have broad application in clinical diagnostics, particularly oncology and reproductive health.

We believe Illumina operates with a strong moat, owning 70% of the sequencing market and having generated over 90% of the world's sequencing data. Illumina is to DNA sequencing what Google is to Internet search, but in its early stages with virtually no alternatives. A person only needs to have his or her whole genome sequenced once during a lifetime. But, if a genetic test can diagnose cancers before symptoms appear, healthy people might get a liquid biopsy as part of annual exams. We are at a tipping point in genomic sequencing as it moves from science to discoveries to applications to routine consumer genetic tests.

**Horizon Discovery** is the global leader in the design, manufacture and application of gene editing and gene modulation. Horizon Discovery creates genetic models of human disease that biopharma companies and labs use in drug development. Once these models are created, they become part of Horizon Discovery's library of cell lines, currently the largest in the world at over 23,000. Customers are provided cells in pairs, one with genetic change attributable to a disease and one a normal version. Adopting gene editing to identify and validate biological targets for precision medicine offers faster, cheaper and more effective drug development.

On average, drugs now take 15 years to develop and cost \$2.6 billion. The main component of the \$2.6 billion is funding the cost of previous drug candidate failures, estimated to be 90% of the total. Horizon Discovery's products help pharma and biotech companies fail poor drug candidates earlier in development. Horizon Discovery's cell engineering platform allows these companies to understand the exact effect that genetic differences within a disease or patient will have on the efficacy of a drug.

Horizon Discovery should benefit from long-term trends to rationalize drug R&D, develop more personalized medicines and outsource components of drug development. This is particularly true of gene engineering where outsourcing is quicker and cheaper than developing resources and capabilities in-house.

**Cryoport** provides temperature controlled logistics solutions for the shipment of cell and gene therapies. Use of dry ice packing is no longer suitable for many new therapies because temperatures only average -80° Celsius with standard deviation up to 14 degrees. Samples used to develop CAR-T therapies must



be kept below -136° Celsius and within a stable range of two to eight degrees. This requirement exists whenever therapies involve the shipment of living cells. Cryoport packaging can keep samples as low as -190° Celsius.

Cryoport's competitive advantage includes a proprietary cloud-based tracking system that receives pings from cryogenic packages every seven minutes to report temperature, pressure, orientation, shock and humidity. It also includes chain of custody and compliance information providing end-to-end traceability of cellular drug products. This technology assures a very low failure rate giving confidence to shippers and receivers.

Since rare diseases by definition only affect a small number of people in any given region, shipping globally adds cost and complexity. Cryoport has worked in over 100 countries. Its first mover advantage, industry leading technology and global reach position it well in a growing market for cell and gene therapies requiring commercial transportation.

Molecular/genomic drug development should accelerate exponentially. As traditional drugs continue to take more time and money to produce, personalized medicine is coming of age in a favorable regulatory environment. Incentives in the Orphan Drug Act include market exclusivity for seven years, tax credits up to 25%, waiver of prescription drug user fees and grant programs. Further, because of the interconnected nature of the human genome, biopharma companies are able to leverage investment in one drug into the development of others. All of this helps ensure the growth of a robust industry infrastructure as more genomes are sequenced, more data is gathered, more diseases become treatable and new and better drugs come to market.