



INVESTMENT INSIGHTS SERIES

From Treatment to Cure

The Acceleration of Health Care Innovation and Investment Opportunity

We believe the health care sector is in the early stages of a multiyear growth cycle – full of important discoveries unlike anything seen since the earliest days of modern medicine. For investors that can capitalize on these advances, the opportunity could be enormous.

IN OUR VIEW

- ▶ There are dramatic changes occurring in the health care sector.
- ▶ These changes are driving strong underlying growth and creating significant winners and losers.
- ▶ The challenge of discerning the winners from the losers offers opportunity for differentiated research.

Consider the sequence of advances in the pharmaceutical industry: modern chemistry brought a golden age of small molecule drugs in the 1970s and 1980s with new therapies for heartburn, cholesterol, and hypertension. Modern biotechnology in the 1980s and 1990s led to the availability of safer and more potent therapeutic proteins, enhancing treatments for cancer and autoimmune disease. Today, with the cost of genetic analysis cut by several orders of magnitude, scientists can get to the very root of genetic and acquired diseases like hemophilia and cancer. We expect this to lead to an even more profound age of therapeutic advance, potentially underpinned by the advent of direct gene therapy and targeted pharmaceuticals, generating “functional” cures for our most serious diseases.

So, what is the impact for investors? In this paper, we review a number of factors contributing to the acceleration of innovation in life sciences and the potential commercial impact. We also look at why revolutionary advances occurring today, coupled with supportive secular demographic trends, could make health care an exciting sector for investment.



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READ INSIDE

- ▶ Revolutionary Advancements in Life Sciences
- ▶ Ongoing Commercial Power of Health Care Innovation
- ▶ Demographic Trends Providing a Long-Term Secular Tailwind
- ▶ Identifying Opportunities: “The 90/90 Rule”

Even as decades of scientific progress are poised to deliver huge gains to medicine, we believe the life sciences boom is still not fully appreciated by many investors. Consider the question: What is currently the most innovative sector of the global economy? And where is innovation leading to outsized gains for investors?

Judging by news headlines one might conclude that it's consumer technology. However, is Google's self-driving car more important than a potential cure for cancer? Which is the more valuable innovation: the Apple Watch or Gilead Science's new therapy for hepatitis C, a highly effective treatment for a disease that takes the lives of more than 1,000 people each day? Consider that Gilead's hepatitis C therapy earned the company more than \$12 billion in sales in its first year alone. With over 90% gross margins and patents that extend to 2030, the value creation could be substantial.

The life sciences innovation and growth boom has been driven by advances in medicine, computing power, imaging, and engineering, supported by secular demographic trends toward higher health care spending worldwide. Markets for novel breakthrough therapies are potentially measured in the tens of billions, and companies across the sector are delivering levels of growth and return difficult to find in the current slow growth market environment. Given these factors, we believe investors should closely examine the opportunities emerging from the dynamic change taking place in the sector.

The Dawn of a New Era in Life Sciences

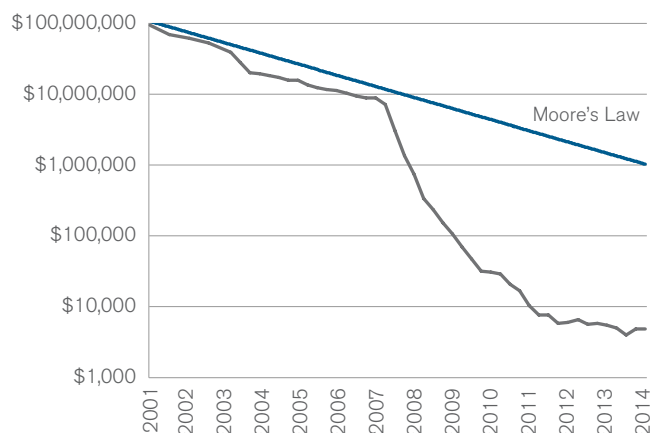
The acceleration of innovation in the life sciences has been dramatic. Many decades of advanced R&D in biology, chemistry, genetics, and computer technology have come together to deliver revolutionary new health care treatments. The result is a wave of novel therapies to address a number of chronic and/or fatal diseases, in some cases even offering the promise of cures. The companies delivering such revolutionary advances are also providing significant value for shareholders across the health care sector – from pharmaceuticals to biotech to medical devices.

The pace of these groundbreaking advances has been accelerating, thanks to rapid reductions in development time and costs that are improving the productivity of research. Consider the field of human genetics. In 1999, the "Human Genome Project," a global collaboration to sequence the first human genome (the "book of life"), successfully sequenced the human genetic code after 13 years and at a cost of \$3 billion. Since then, by combining revolutionary chemistry with radical semiconductor design, scientists have made

dramatic improvements in the efficiency of genetic analysis. Today, scientists can sequence a human genome in just a few days, at a cost of a few thousand dollars (see Exhibit 1). In early 2015, researchers for the first time broke the \$1,000 cost barrier.

EXHIBIT 1: COST PER GENOME

Cost of Sequencing Down 20,000 Fold in 13 Years



Source: National Human Genome Institute. As of 7/31/2014.

Improved genetic analysis has led to an improved understanding of the underlying causes of many diseases, allowing scientists to target them more directly. Targeted therapies for specific populations are resulting in more effective therapies with a better risk/reward, and a greater number of these innovative therapies are advancing in clinical development and ultimately making it to market. Many such treatments are superior to what came before, revolutionizing the care, and potential cure, of a variety of diseases from hepatitis C to cancer, from multiple sclerosis to psoriasis, and from hemophilia to Alzheimer's disease.

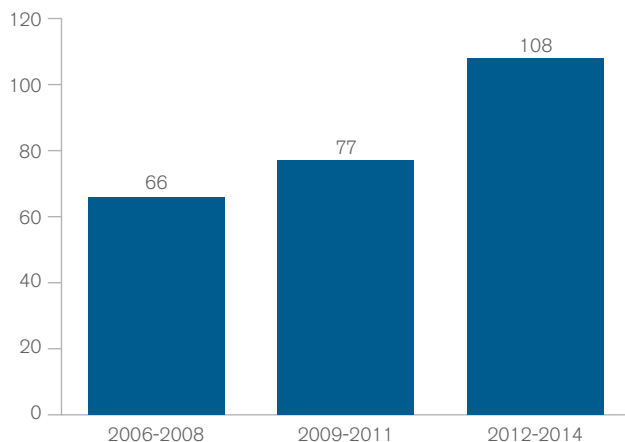
Drug therapies, for example, have seen a rapid evolution in delivery mechanisms. Small chemical compounds delivered in pill form dominated medicine for most of the 19th and 20th centuries (think of companies such as Merck and Pfizer). Then the industry moved to biologics, including engineered proteins (Amgen, Biogen, and Genentech). Now we are moving to more advanced treatments that involve manipulating genetic information to directly target RNA or DNA. New cancer treatments, for example, can remove cells from the body, reprogram their DNA, and reinsert them into the body to kill cancer cells. New therapies for cystic fibrosis for the first time can target the underlying genetic defect for the majority of patients.

In cardiovascular medicine, a new class of drugs can lower levels of cholesterol by an additional 50% to 60% over the best available treatments today. Early clinical data is suggesting potential for a substantial reduction in major cardiac events such as heart attack, stroke, and death. New therapies are moving into late-stage clinical development for Alzheimer's disease – with a demonstrated ability to remove the plaques in the brain believed to be the cause of Alzheimer's progression. New treatments were recently approved for lung and skin cancer, which for the first time, can unleash the power of the immune system to help find, attack, and kill cancer cells. We believe that a wave of such radical new cancer therapies holds the promise of long-term functional cures for previously incurable cancers.

As the rate of innovation increases, the health care sector has seen rising approval rates for new therapies. Between 2012 and 2014, for example, the industry witnessed the approval of 108 new drugs in the U.S. – a 50% increase over the average of the previous six years (see Exhibit 2). In 2014 alone, 41 new drugs were approved in the U.S., the most in 16 years.

EXHIBIT 2: NUMBER OF DRUGS RECEIVING FDA APPROVAL

**108 New Drugs Approved from 2012 to 2014
(>50% Above the Average Over the Previous 6 Years)**



Source: Washington Analysis, FDA, 2014.

Health Care Innovation Is Not Limited To Biotech

Biotech and pharmaceutical companies have grabbed headlines, but they are not the only companies making exciting progress within the health care sector; medical device companies are also delivering promising improvements.

As society has upped its focus on cost containment, the device industry has responded by developing transformative products addressing areas like cardiovascular and neurological diseases. This stands in contrast to the incremental changes the industry had made historically, such as improving battery life or device profiles.

For example, Boston Scientific recently introduced the world's first subcutaneous implantable defibrillator. This product protects patients from life threatening arrhythmias while avoiding complications of earlier technologies, such as infections. St. Jude Medical now markets CardioMEMS, a miniature implanted pressure monitor that alerts caregivers of the potential for an acute worsening of heart failure that could lead to hospitalization. Another medical device company, Medtronic, just launched a leadless pacemaker in Europe, and recently launched a wireless heart monitor about the size of a matchstick that can be inserted in a matter of minutes at a doctor's office. Additionally, Edwards Lifesciences, Medtronic, and Boston Scientific now market valve replacement products that can be implanted without the need for open heart surgery.

The Commercial Power of Health Care Innovation

From a commercial standpoint, revolutionary therapies have strong pricing power and often see rapid adoption in the marketplace – where they are addressing significant unmet medical needs. The U.S. spends more than \$200 billion annually on treating Alzheimer's patients, \$850 billion on heart disease management, and hepatitis C kills over 1,000 people each day worldwide. But eradication of hepatitis C, for example, is now within reach, and new treatments for the leading causes of death (heart disease and cancer) are becoming a reality.

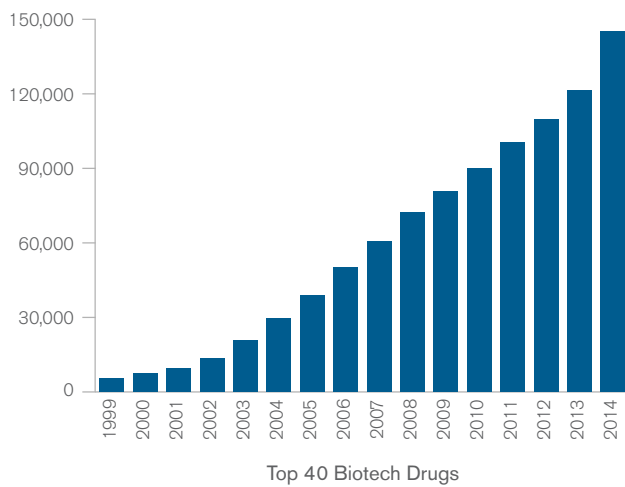
In fact, all seven of the largest biotechnology companies are in the early stages of major new product launches. As decades of medical and technology advancement come to fruition, successful companies are seeing an explosion of blockbuster drugs and medical devices. Moreover, given the long development timeline and massive investments required, many of these new therapies earn long-term patent protection

lasting 10 years or longer, giving their companies significant insulation from competitive forces.

For example, in 1999 there were only a few blockbuster biotech drugs with over \$1 billion of sales, such as Amgen's Epogen and Neupogen. Today there are more than 40 such blockbusters, and that number continues to increase every year. From an investment standpoint, such revolutionary products create tremendous growth opportunities. In fact, with these advances, biotech sales have increased more than 25-fold since 1999 (see Exhibit 3).

EXHIBIT 3: BIOTECHNOLOGY SALES

Sales Up 25x Since 1999

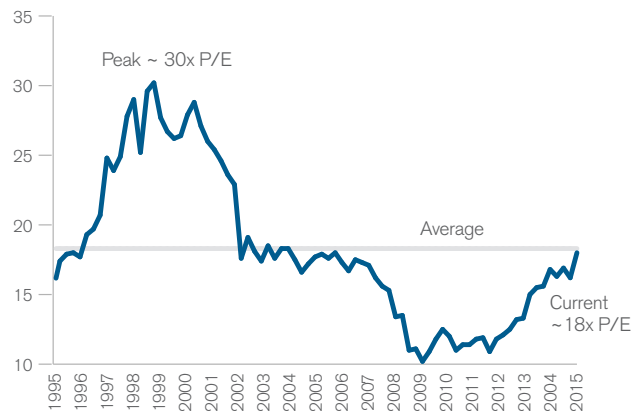


Source: ISI Group and Janus Capital Group.

Investors should also note that even as we are seeing years of R&D translate into meaningful revenue, earnings, and cash flow for these companies, we believe the health care sector as a whole is still trading at reasonable valuations. In fact, the sector underperformed for seven out of eight years between 2003 and 2010, and the rally of the last few years has only driven the sector back to average valuation levels of the last 20 years. As of the end of Q1 2015, the sector traded at a forward P/E of approximately 18x earnings, well below the prior 30x peak reached in 1999 (see Exhibit 4).

EXHIBIT 4: MSCI WORLD HEALTH CARE INDEX VALUATION (FORWARD P/E)

Valuation Still Significantly Below Prior Peaks



Source: Datastream, FactSet. As of 3/31/15.

GILEAD SCIENCES: A Case Study in Growth and Reward

Just a few years ago, the standard-of-care for hepatitis C required a year of weekly injections of a drug called Interferon, which caused significant flu-like side effects. Even after a year of poorly tolerated therapy, the drug only cured about 40% of patients, so few chose to begin treatment. The field changed in late 2011, when Gilead bought a company called Pharmasset to combine both companies' hepatitis C drugs into a single treatment. It was an audacious move, with Gilead paying \$11 billion for a company with no revenues and only one key pipeline asset.

As it turned out, Gilead's move enabled the company to develop the first well tolerated, "all oral" treatment for hepatitis C, with the potential to cure over 90% of patients in as little as 12 weeks. Nevertheless, a year before the launch, the consensus estimates for first-year sales were only about \$1 billion. However, the company earned more than \$12 billion in first-year sales, and Gilead saw its earnings quadruple in one year. Despite dozens of analysts following the company, the consensus estimates were off by a factor of 12.

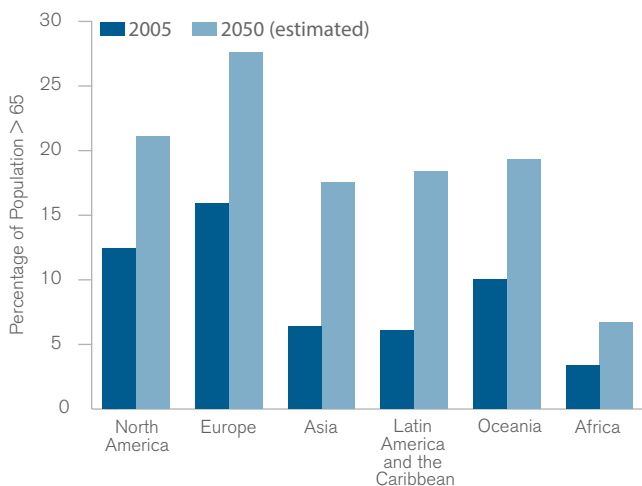
Despite average valuation levels, we believe fundamentals for the sector have never been better. And while some growth is being priced in, valuations still look reasonable given our view of the strong growth potential. As an example, Gilead Sciences, the company highlighted in the case study on the previous page, currently trades at a P/E multiple of 12, well below the S&P 500 Index's P/E multiple of 18. For companies in the earliest stages of blockbuster launches, new products could drive revenue and earnings growth for many years to come, thanks to patent protection that can extend for 10 to 15 years.

Demographics: A Long-Term Secular Tailwind

In life sciences, the growth opportunity is further supported by positive long-term trends in demographics and the increased wealth of populations in developing economies. The U.S. alone should see an average of 10,000 baby boomers reaching retirement age each day for the next 18 years. Globally, we expect this trend to drive significant demand increases throughout Asia, Europe, and Latin America. As summarized in Exhibit 5, the over-65 population is expected to double or triple in every major region of the world over the next 40 to 50 years. Importantly, the elderly spend more than three times as much on health care as the rest of the population (see Exhibit 6). This increased spending results from serious diseases affecting the elderly (such as cancer, heart disease, and Alzheimer's), which also drive higher rates of hospitalization and four times the medication use as the rest of the population. The fact that innovative therapies and breakthroughs are being made specifically for a number of these age-related conditions provides significant growth opportunity as this demographic trend continues.

EXHIBIT 5: POPULATION OVER THE AGE OF 65

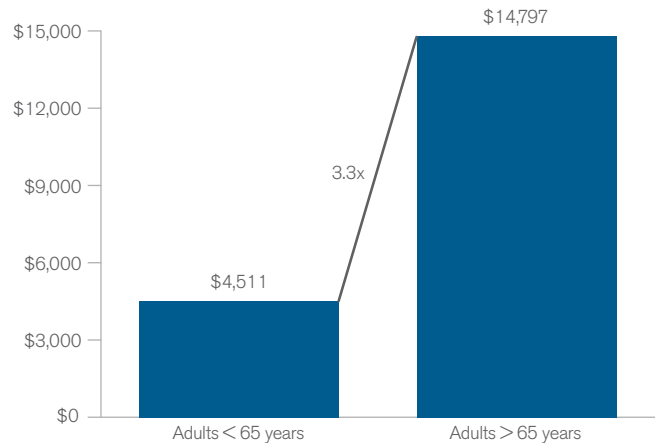
Significant Increases Expected Across the World



Source: United Nations.

EXHIBIT 6: HEALTH CARE SPENDING PER CAPITA

Elderly Spend >3x on Health Care Compared to General Population

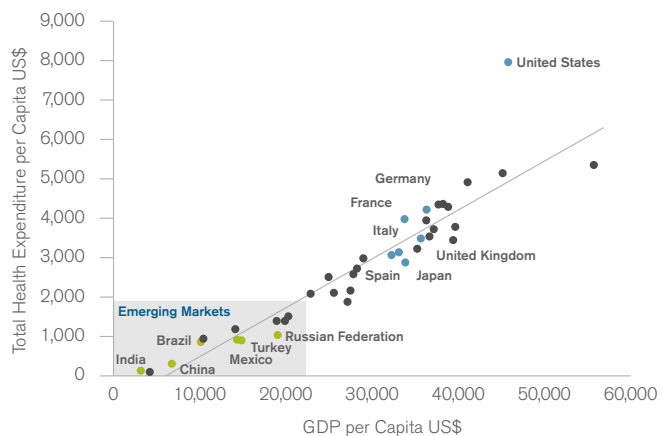


Source: Center for Medicare and Medicaid Services, 2006. Health Care Spending per Capita, 2004.

In the emerging world, health care spending is also on the rise, but for different reasons. Historical data shows a high correlation between the wealth of a country and its health care expenditures. Generally, as countries get wealthier, they tend to spend a higher percentage of GDP on health care (see Exhibit 7). Currently, emerging countries spend just a fraction of what developed countries do on health care, but emerging countries are growing more quickly and are expected to see economic growth well above the global average. We expect this rapid economic growth to be a big driver of health care spending in many emerging countries. For example, China alone is planning to invest over \$1 trillion on health care infrastructure in the coming years.

EXHIBIT 7: GDP AND HEALTH EXPENDITURE

GDP Growth Drives Growth in Health Care Spend



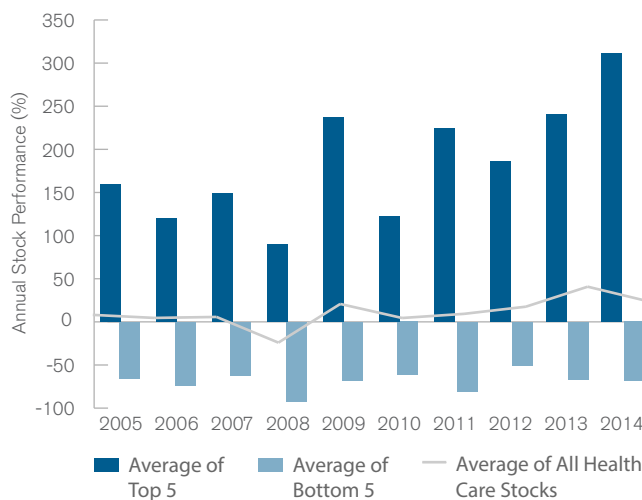
Source: OECD Health Data 2011; WHO Global Health Expenditure Database as of 10/28/11.

Identifying Opportunities: “The 90/90 Rule”

We believe the numerous opportunities emerging from life sciences are best managed from a bottom-up perspective. Long-term themes and trends are well-known and observable by many, and timing them is nearly impossible. Additionally, converting long-term trends to investment opportunities at the company level is a very difficult task. Therefore, we advocate for thorough fundamental analysis in the sector. This is especially critical given the complexity of individual treatments and the binary nature of drug development, which often results in extreme outcomes and a large disparity between the winners and losers (see Exhibit 8). In fact, while a single successful drug can drive billions of dollars in revenue, a single failed product can cause the price of a stock to fall 50% or even 70% in a single day.

EXHIBIT 8: AVERAGE PERFORMANCE OF TOP 5 AND BOTTOM 5 HEALTH CARE STOCKS

Significant Disparity Between Winners and Losers



Source: Wilshire 5000 Index. Includes average performance of stocks over \$500M in market cap.

We believe health care companies follow what we call “the 90/90 rule.” Historically, 90% of the treatments that move into human clinical testing never make it to market; and of those that do, in our experience, the consensus street estimates are wrong 90% of the time. Analysts have a tendency to vastly over- or under-estimate the market potential of new products. As seen in the Gilead case study featured earlier in this paper, consensus sales estimates were off by a factor of 12.

Due to these challenges, we believe exhaustive fundamental research (including clinical and statistical analysis) is critical for investors to develop a better view of the intrinsic value of a company. A new product launch can be helped or derailed by any number of factors, from pricing, to medical need, to efficacy, to ease of prescribing, to patient receptiveness. For unmet medical needs, pricing can be higher than market estimates, with penetration and market share gains more rapid – but the reverse can also be true. In the first half of 2015 alone, multiple stocks suffered one day declines of over 70%, and a disappointing launch can even lead to bankruptcy.

To address the binary nature of risk in life sciences, we advocate for rigorous bottom-up analysis, as well as balanced portfolios managed with a disciplined “value-at-risk” framework. For example, one could actively manage position sizes to limit the potential loss from any single investment to no more than 1% of the total portfolio value. We believe that risk management should include balancing portfolios across regions, market caps, and the sub-sectors within health care (e.g., biotechnology, pharmaceuticals, health care services and medical devices). Life sciences are also sufficiently diverse that one could balance the portfolio with varying degrees of growth (e.g., dominant players with strong market positions and free cash flow; emerging growth companies with new products that can drive an acceleration of revenue and earnings; and contrarian investments that may be suffering from short-term market misperceptions of future growth prospects).

In Summary

Innovation in life sciences is life-changing and life-saving. We believe the health care sector is at the early stages of a multiyear growth cycle, with many important breakthroughs still to come. This growth should be further supported by demographic trends of an aging global population and the rise of the middle class in emerging markets, which should continue to drive higher health care spending across the world. In the current low interest rate, low return environment where high return opportunities are difficult to come by, we feel the health care sector offers many compelling investment options at reasonable valuations. We believe we are at the forefront of an unprecedented era in the life sciences, and we encourage all investors to examine the merits and opportunities of this exciting sector.

About the Author

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Andy Acker is Portfolio Manager of the Janus Global Life Sciences strategy and all related portfolios, a position he has held since May 2007. He also serves as an equity research analyst and sector team leader of the health care sector research team. Mr. Acker served as Assistant Portfolio Manager of the Life Sciences strategy from April 2003 to April 2007 and as Co-Portfolio Manager of the Janus Aspen Global Life Sciences portfolios from October 2004 to April 2007. Mr. Acker joined Janus in August 1999 as an equity research analyst, focusing on companies in the biotechnology and pharmaceutical industries. Prior to Janus, he worked as a strategy consultant for the Boston Consulting Group and as a health care analyst for Morgan Stanley Venture Partners. Mr. Acker received his bachelor of science degree in biochemical sciences from Harvard University, graduating *magna cum laude* and Phi Beta Kappa. He also earned an MBA from the Harvard Business School, graduating with honors. Mr. Acker holds the Chartered Financial Analyst designation and has 19 years of financial industry experience.

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