ROCKEFELLER
CAPITAL MANAGEMENT

THE FUTURE OF DRUG PRICING

ROCKEFELLER CAPITAL INSIGHTS

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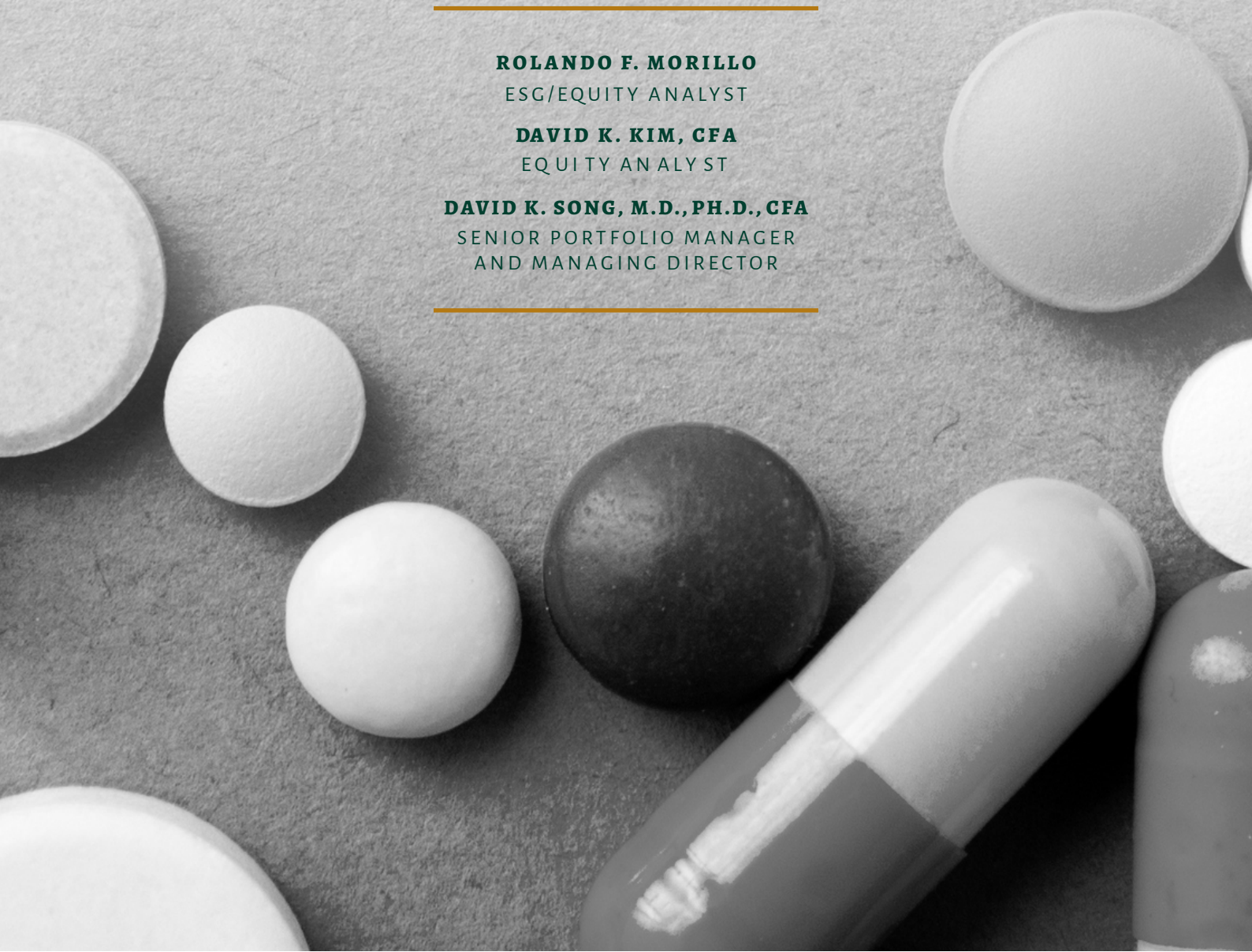


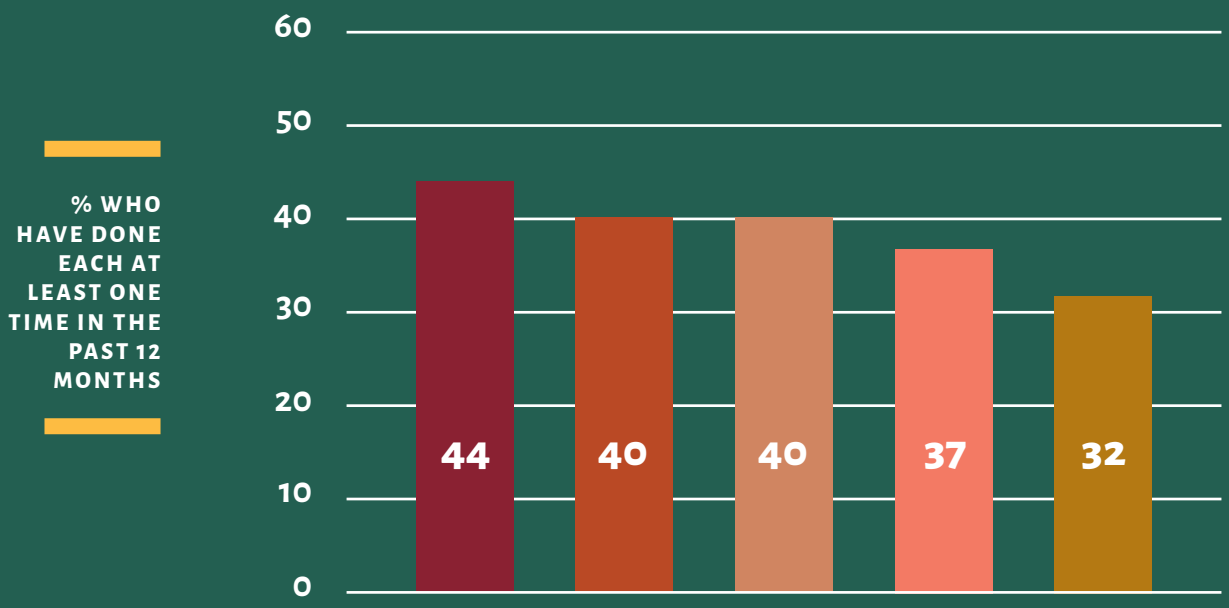
NEGATIVE **PERCEPTIONS**

have plagued the biopharmaceutical industry, relegating it almost to a status on par with the tobacco industry. Recent polls and surveys reveal the biopharmaceutical industry's reputation has been battered by a scrutinizing Congress, arbitrary industry price increases and lack of pricing transparency, not to mention the actions of a few bad actors. The cost of certain medications is so high that nearly one in 10 American adults are delaying or skipping treatment altogether according to a report published by the Centers of Disease Control (CDC).[1] With intense and growing pressure on drug companies from patients, legislators, and investors, we believe the biopharmaceutical industry is turning to value-based contracts, which link the price of a drug to its clinical and economic performance. But how did the biopharmaceutical industry get here? More importantly, are we in a nascent period of realization and inflection where the biopharmaceutical industry begins to counteract negative perceptions through the implementation of value-based care and outcomes-based drug pricing models? These are important issues we seek to understand through company engagement and research because we believe that the issue of drug pricing will have a fundamental impact on long-term biopharmaceutical business models and potentially even greater impact on society at large.

NOTE: 1 www.renalandurologynews.com/news/cdc-americans-can-not-afford-medications-eight-percent/article/395374/

QUESTION

THINKING MORE ABOUT THE COSTS OF HEALTHCARE, IN THE PAST 12 MONTHS, HOW OFTEN HAVE YOU DONE ANY OF THE FOLLOWING BECAUSE OF COST?



- DIDN'T GO TO DOCTOR WHEN YOU WERE SICK OR INJURED
- GONE WITHOUT A ROUTINE PHYSICAL OR OTHER PREVENTATIVE HEALTHCARE
- SKIPPED A RECOMMENDED MEDICAL TEST OR TREATMENT
- CHOSEN A LOWER COST OPTION FOR A RECOMMENDED TEST OR TREATMENT
- NOT FILLED A PRESCRIPTION OR TAKEN LESS THAN THE PRESCRIBED DOSE OF MEDICINE

Source West Health Institute/NORC poll conducted February 15-19, 2018, with 1302 adults nationwide

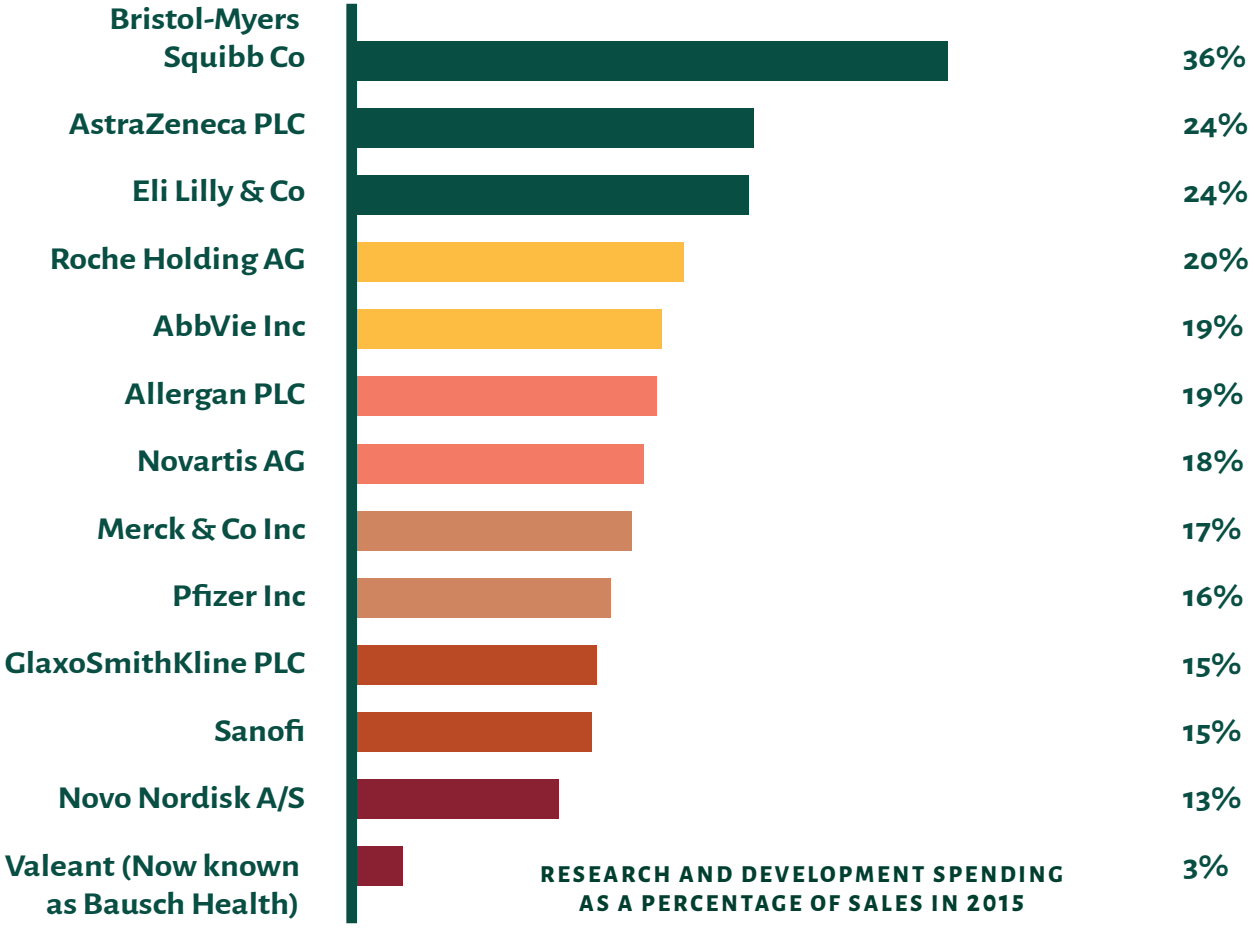
EXPLOITATION OF AN IMPLICIT **SOCIAL CONTRACT**

Valeant Pharmaceutical was solely focused on short-term shareholder returns, acquiring a myriad of companies then stripping down research and development (R&D) budgets and staff. Valeant intentionally spent only 3.6% of sales on R&D, while most of its industry peers spent around 15% or more. Valeant's strategy seemed like a breakthrough as the market kept rewarding the company until 2015, when increased scrutiny revealed accounting inaccuracies, restatements and a broader unsustainable long-term strategy.

Another company at the center of drug pricing criticism was Mylan; the price of its EpiPen increased over 500% over seven years. The price of the life-saving device for allergies provoked public outrage and led to a congressional hearing with Mylan CEO Heather Bresch. As a result of the criticism, Mylan increased its patient access program, developed a cheaper generic alternative to the EpiPen and agreed to pay a $450 million settlement with the U.S. Justice Department on claims it overcharged the government.

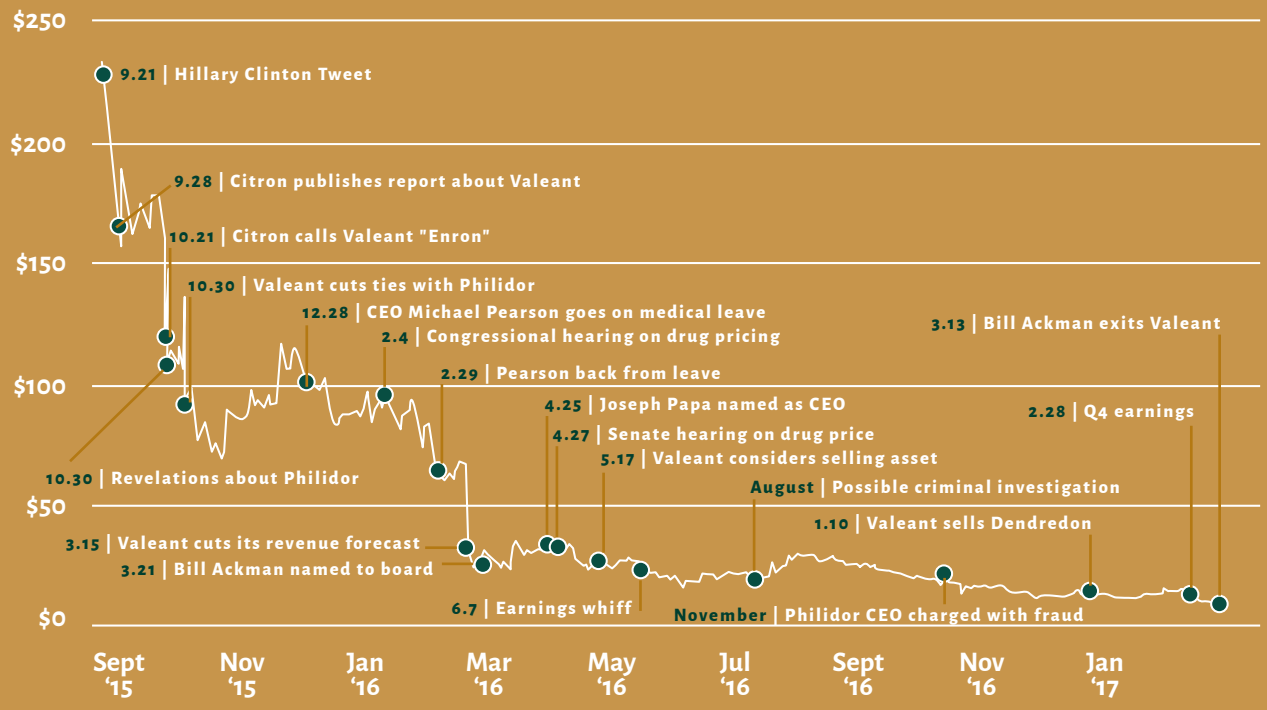
DEAL-DRIVEN **GROWTH**

SOME DRUG MAKERS ARE CUTTING DOWN ON R&D INVESTMENT, BETTING ON DEBT-FUELED ACQUISITIONS TO ACHIEVE SALES GROWTH



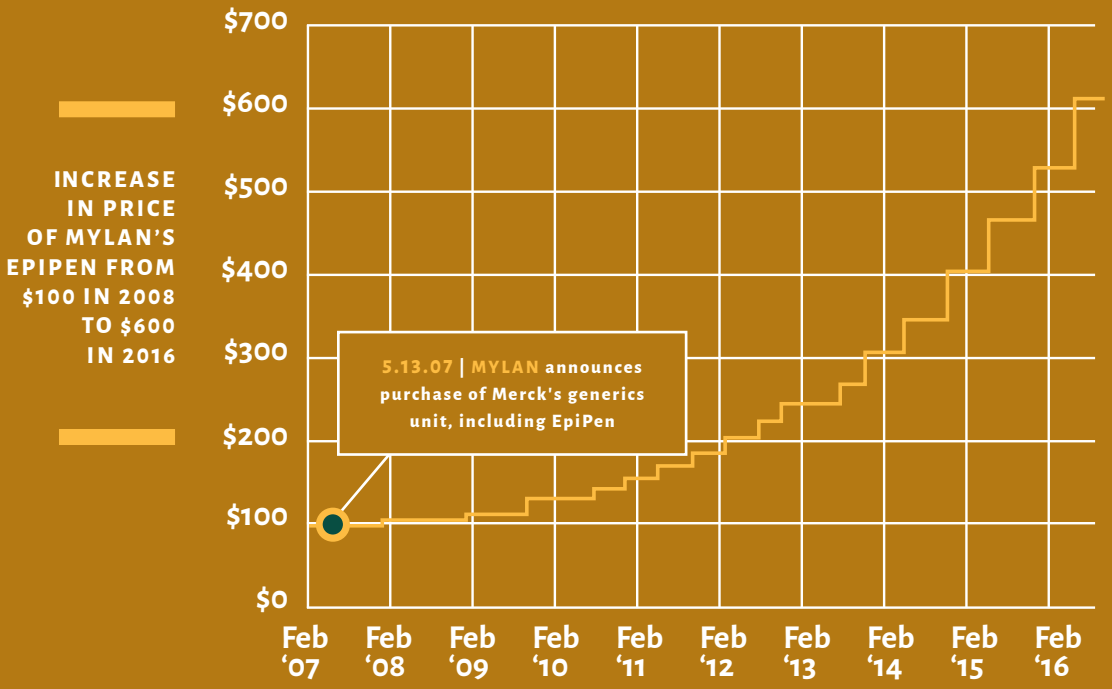
Source
Bloomberg

VALEANT'S **STRUGGLES**



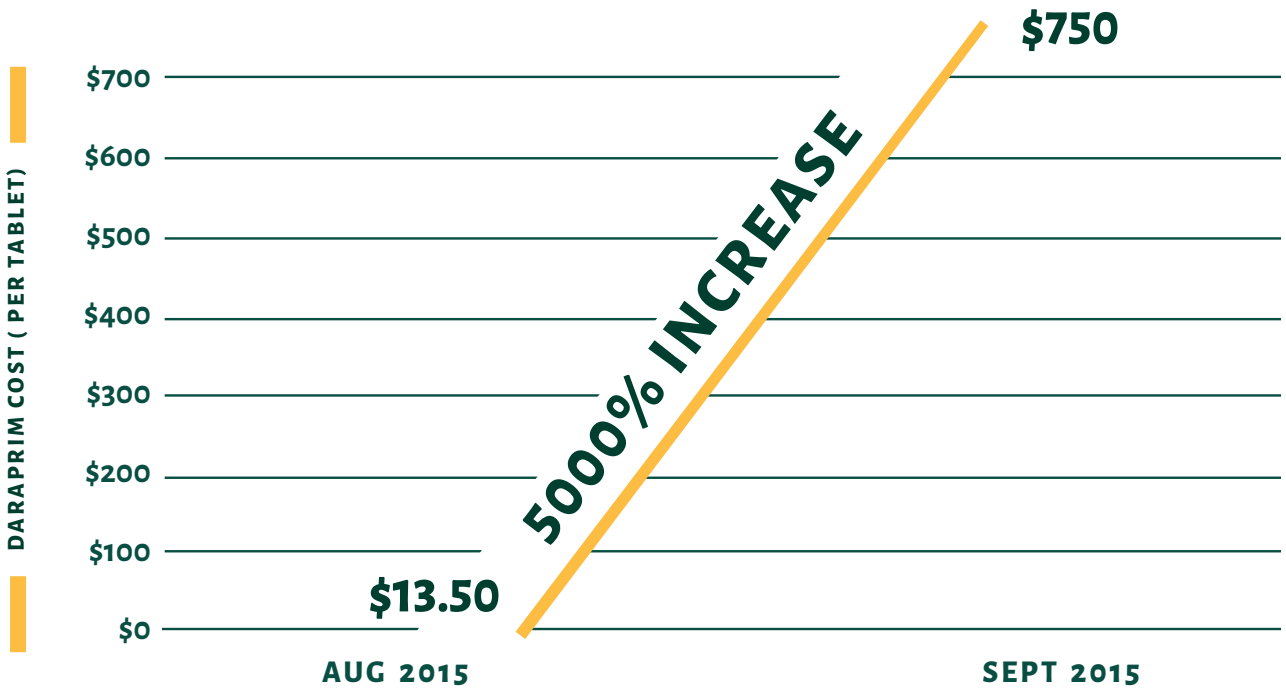
Source Bloomberg | Business Insider

EPIPEN PRICE **UNDER MYLAN**



Source Truman Health Analytics | Business Insider

DARAPRIM **COSTS**



Source The New York Times

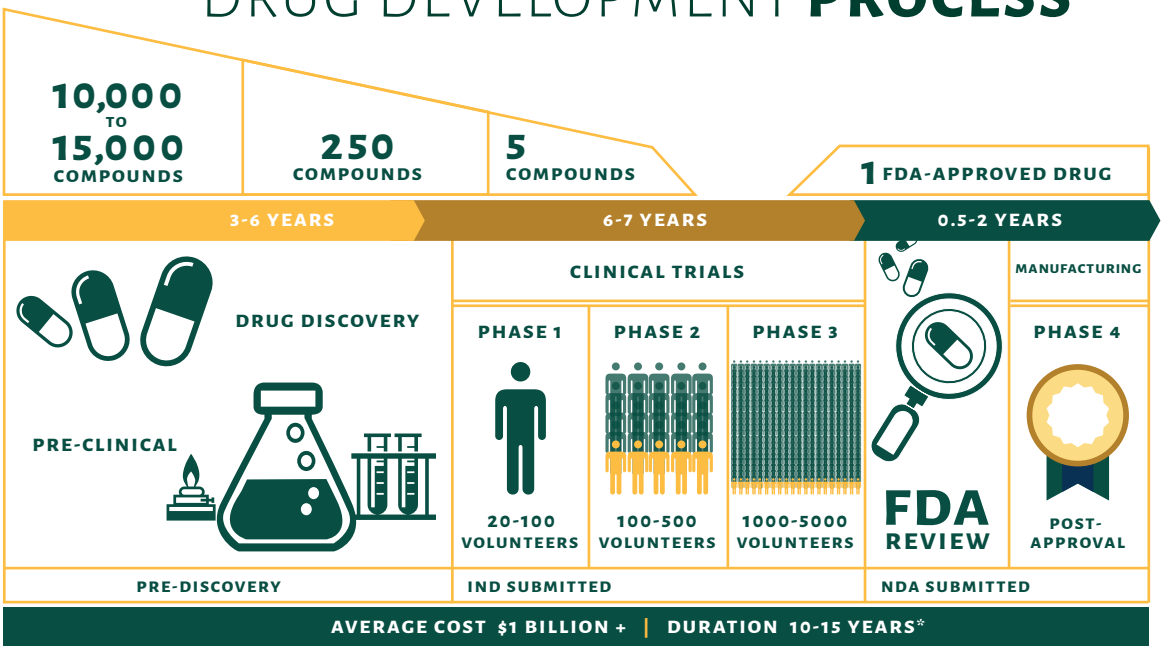
The most notable bad actor to emerge from the national conversation on the exploitation of biopharmaceutical prices and predatory practices was Martin Shkreli, former CEO of Turing Pharmaceuticals. As CEO of Turing Pharmaceuticals, Shkreli acquired an anti-parasite medication, Daraprim, and arbitrarily and abruptly raised its price from $13.50 to $750, decreasing the level of access to people in need of the medicine. Daraprim treats toxoplasmosis, which is fatal to people with weakened immune systems who may be dealing with chemotherapy or suffering from AIDS. Although Shkreli used the standard biopharmaceutical defense of increasing drug prices to subsidize research, it is hard to ignore that Turing Pharmaceuticals exploited its monopolistic position to provide Daraprim to the detriment of the few thousand patients that needed it each year.

The argument that high drug prices support innovation not only for the U.S. but for the rest of the world is common, but it is too simple and unsatisfactory as a crutch in a world demanding increased transparency and rationale for price increases. Although the United States has been the most productive biotech innovation engine in the world,[2] this innovation has occurred within the context of an implicit social contract. That contract has allowed for substantially subsidized R&D by the U.S. government while waiving the ability to negotiate directly with manufacturers on drug prices. In return, the biopharmaceutical industry was allowed to recoup its R&D investment during a limited post-approval period under the parameters of the Hatch-Waxman Act, with the expectation that drug prices would be set at a level to help ensure reasonable access to the general population.

NOTE: 2 Scientific American 7th Annual Worldview Scorecard

Source Getty Images

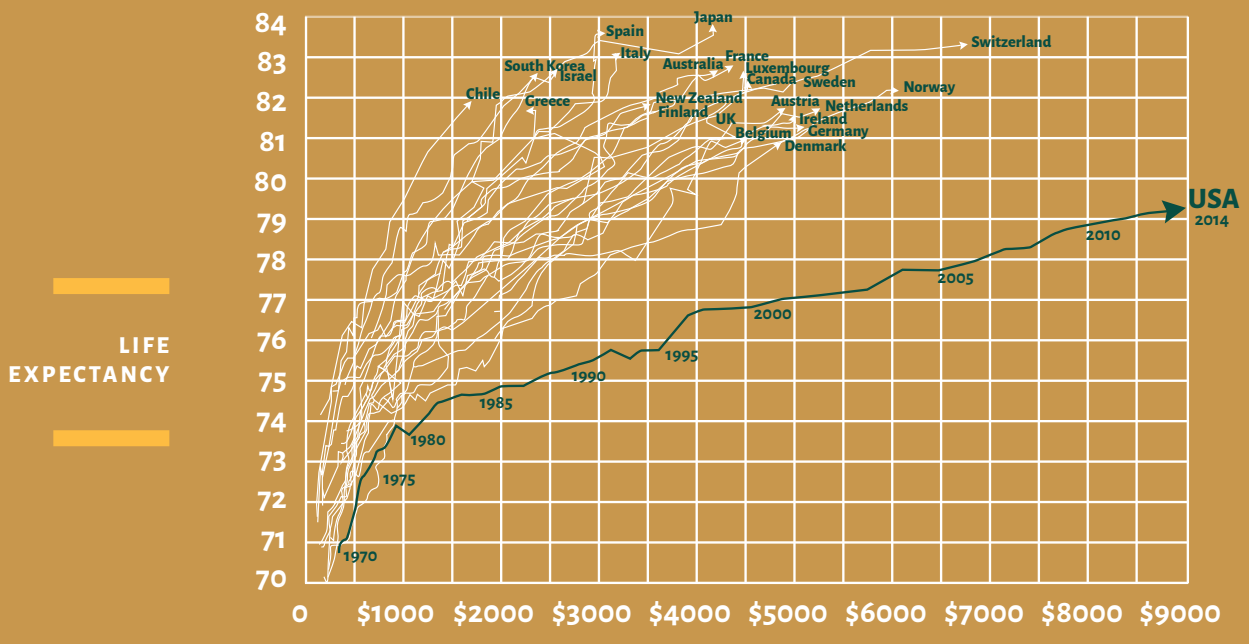
DRUG DEVELOPMENT **PROCESS**



*ACRO
Source PPD.COM

In the United States, per- capita spending on prescription drugs grew to $9,253 in 2014 and is expected to grow by 6.3% annually through 2024, outpacing inflation and total health care expenditures nationally.[3] Analyzing the rapid escalation of per-capita spending on prescription drugs in the last decade reveals a difficult justification and may reflect the lack of price transparency, complex industry structure and inability for the end user to negotiate. The complex web of rebating structures and other gross-to-net adjustments in standard pricing mechanisms obscures the effective net price of the drug. These rebating schemes can inappropriately affect physician prescribing patterns and possibly hinder competition and innovation. Above all, the time and effort in people and processes to maintain the current complex system is most likely wasteful. We believe there needs to be a new way forward in drug pricing solutions that are contingent on linking outcomes and defining value to patients, payers and society at large.

HEALTH EXPENDITURE **TO LIFE EXPECTANCY**



PER-CAPITA SPENDING ON PRESCRIPTION DRUGS

NOTE: 3 https://www.cms.gov/research-statistics-data-and-systems/statistic

VALUE-BASED CARE PARADIGM

Value-based drug pricing is a paradigm that prices therapies in accordance with clinical and economic benefits. All things being equal, a drug that provides an additional year of survival to a cancer patient would be priced above one that delivers only half of that benefit. A cholesterol-lowering drug for a broad patient population should be reimbursed in accordance to its ability to deliver reductions in mortality, hospitalizations and other cardiovascular-related complications above and beyond previous standard of care. While seemingly simple, the economic framework for measuring benefits and costs of drug therapy is not new and has been studied and applied extensively by academic researchers and industry decision-makers alike.

Rewarding drug innovation on the basis of its net clinical and economic benefits is part of a large trend toward value-based care, which we discussed in a previous white paper, "***The Future of Healthcare.***" The continued rise in medical costs, a generally favorable healthcare policy backdrop and enthusiasm toward the use of healthcare data analytics have all driven a migration away from fee-for-service medicine toward alternative payment models emphasizing outcomes over volumes. While drug costs typically constitute only 10-15% of total healthcare costs, drug utilization is being increasingly viewed within the context of total cost of care, with the promise that some drugs may deliver actual long-term healthcare savings in addition to powerful clinical benefits. Some have even argued that this holistic view has been an important driver of vertical integration between payers and pharmacy benefit managers. Given the trend toward value-based care, we believe drug pricing will follow an inevitable trend toward a value-based paradigm. Rather than fight this trend, early supporters of this value-based paradigm in biopharmaceutical will likely be the leaders. In our view, these companies tend to already have either significant R&D efforts, are first-movers in re-aligning R&D to this new reality or have competitive advantages in their commercial organization that are not entirely apparent to the market.

Value-based pricing, in our opinion, is not a net negative for the drug industry from an investment perspective. Collective industry adoption of value-based principles, which increase rigor in the assessment of new technologies, could enhance drug pricing transparency and improve the reputation of the entire industry as pricing is based on a firmer analytical basis. Access to new medicines may also improve as novel reimbursement mechanisms materialize. In effect, the industry would be on a more sustainable revenue path.

Despite our optimism on this secular movement, we acknowledge several barriers could stymie the adoption of value-based pricing. In spite of the broad usage of electronic medical records, more technological infrastructure needs to be in place to adequately measure healthcare quality and costs to enable outcomes-based reimbursement. Incentives are not necessarily aligned either, as many payers may not feel that long-term cost reduction of some breakthrough therapies is worth the money given high turnover of their commercial book of business. In addition, legislation may be required to overcome legal and regulatory impediments.

GENE **THERAPY**

Value-based pricing in the context of curative therapies like the Hepatitis C drugs is challenging. How do you price for a cure? This question is increasingly becoming important. Gene therapies have the potential to cure genetic diseases with a one-time treatment. With the advancement of technologies like this, we may see a wave of curative therapies in the future. Luxturna, developed by Spark Therapeutics, was the first in vivo gene therapy to be approved in the U.S. Luxturna is designed to fix a specific mutation in a gene, called RPE65, which causes blindness. The price of Luxturna is $425,000 per eye, which may seem shockingly high, but the therapy creates significant value for an extended period of time. More therapies like Luxturna are in biopharmaceutical companies' development pipelines. While these therapies are still early in development, payers are increasingly concerned about the financing of a high-priced cure. Some suggest charging an annuity payment for each year the patient remains cured as a way to lessen the upfront cost burden and provide some downside protection in case the curative effects fade. Formalizing value-based pricing is especially important as we begin to see cures for larger disease markets, such as hemophilia A. Value-based pricing for curative therapies remains a challenge but in the near term it appears to be more aligned with long term stakeholders, which include government programs and patients.

HOW DO YOU **PRICE FOR A CURE?**

In addition to the evolution of the healthcare sector toward value-based care, ignoring value-based drug pricing is no longer an option for investors or for biopharmaceutical players from an innovation standpoint. We believe a revolution in gene-based and cell-based therapeutics is underway. The FDA has recently approved a number of medical breakthroughs in cancer and rare genetic diseases that can provide durable benefits. Drugs coming from these classes of drugs, called gene therapies and CAR-T therapies, feed the hope for a "one and done" cure, providing substantial clinical benefit over several years, not to mention life-altering and psychological improvements to the patient. The business model of near curative therapies is not clear to some investors given uncertainties of a consistent revenue stream. The traditional payment paradigm tends to favor chronic drug therapies. As one Goldman Sachs report mentioned in April 2018, "Is curing patients a sustainable business model?"[4] We believe that if drug pricing does not reward innovators in line with value-based pricing principles, the risks of producing these durable therapies, which are motivated in part by exciting science, will be too great for the biopharmaceutical industry. As innovation is often its life blood, the biopharmaceutical industry has every incentive to shape value-based pricing to maximize its return on R&D.

As a case in point, Gilead's development of a Hepatitis-C cure through their drugs Sovaldi and Harvoni, undeservedly received criticism for initially pricing their Hepatitis-C treatment at $84,000. It is worth highlighting that these drugs were not therapies but a cure that had an astonishing success rate of up to 95%. Considering prior treatments and costs, one could easily argue that the price Gilead set was not egregious. Given that Sovaldi and Harvoni are cures to Hepatitis-C, the patient prevalence pool declined after the first two years of receiving treatment. The pool is expected to decline further, leading to market concerns on the sustainability of future cash flows. Gilead and other companies providing cures should be allowed to price cures effectively and should be lauded for their innovation. Unfortunately, the U.S. healthcare system is not equipped and structured to deal with expensive and quick cures for a significant patient population unless new payment structures are devised.

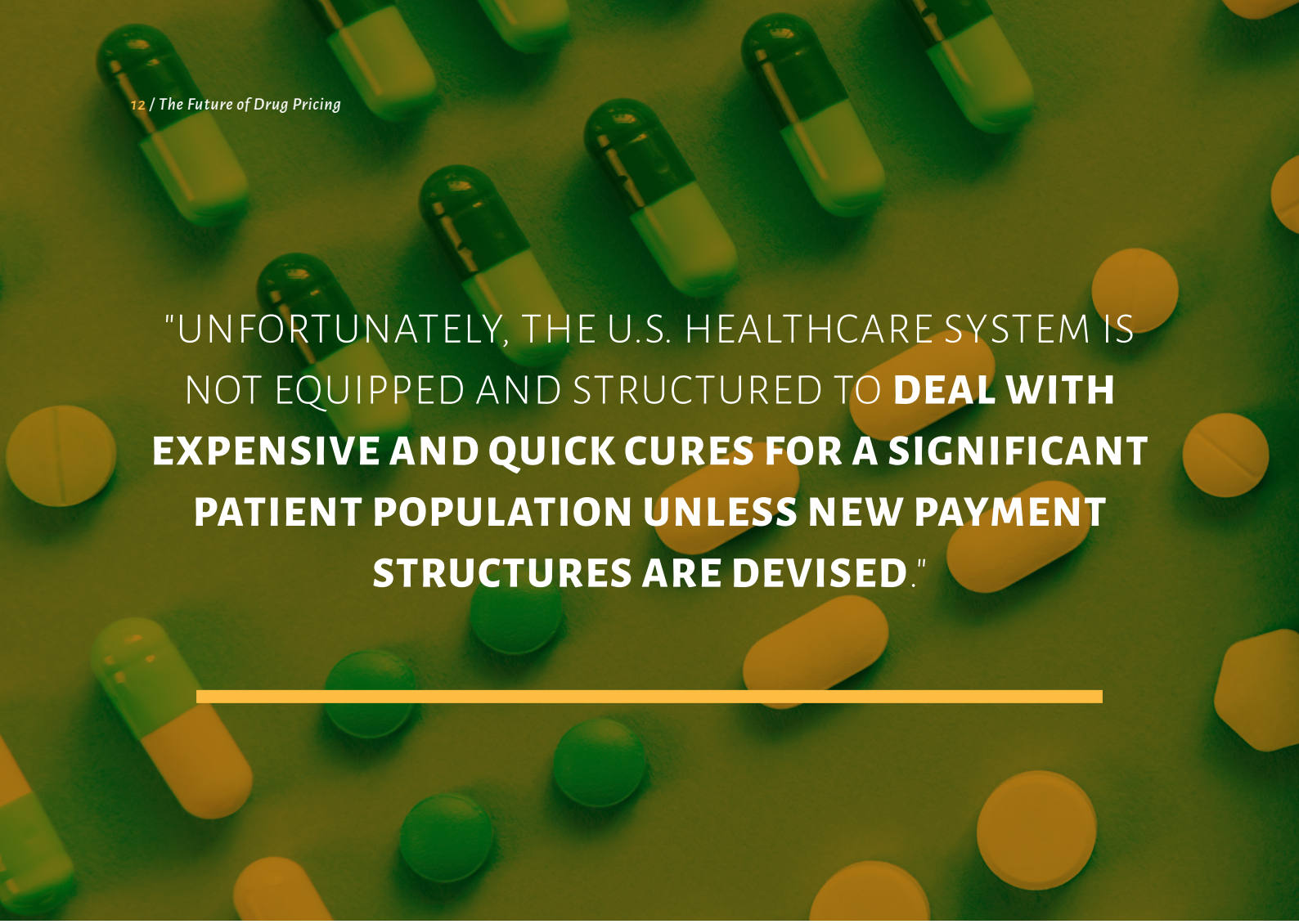
TALLYING THE COST OF **HEPATITIS C**

IT COSTS **$84,000** FOR TREATMENT OF HEPATITIS C ON GILEAD'S SOVALDI, BUT THE ALTERNATIVE – ALLOWING THE DISEASE TO PROGRESS – COSTS MUCH MORE.

A LIVER TRANSPLANT MAY COST ABOUT $200,000, PLUS THE PATIENT WILL NEED ANTI-REJECTION MEDICATION, WHICH CAN COST **$40,000** A YEAR, FOR THE REST OF THEIR LIVES.

Source Dr. Douglas Dieterich, Mt. Sinai Hospital | CNBC

NOTE: 4 Goldman Sachs Equity Research (April 2018), Profiles in Innovation Series, "The Genome Revolution: Sizing the genome medicine opportunity."



"UNFORTUNATELY, THE U.S. HEALTHCARE SYSTEM IS NOT EQUIPPED AND STRUCTURED TO **DEAL WITH EXPENSIVE AND QUICK CURES FOR A SIGNIFICANT PATIENT POPULATION UNLESS NEW PAYMENT STRUCTURES ARE DEVISED**."

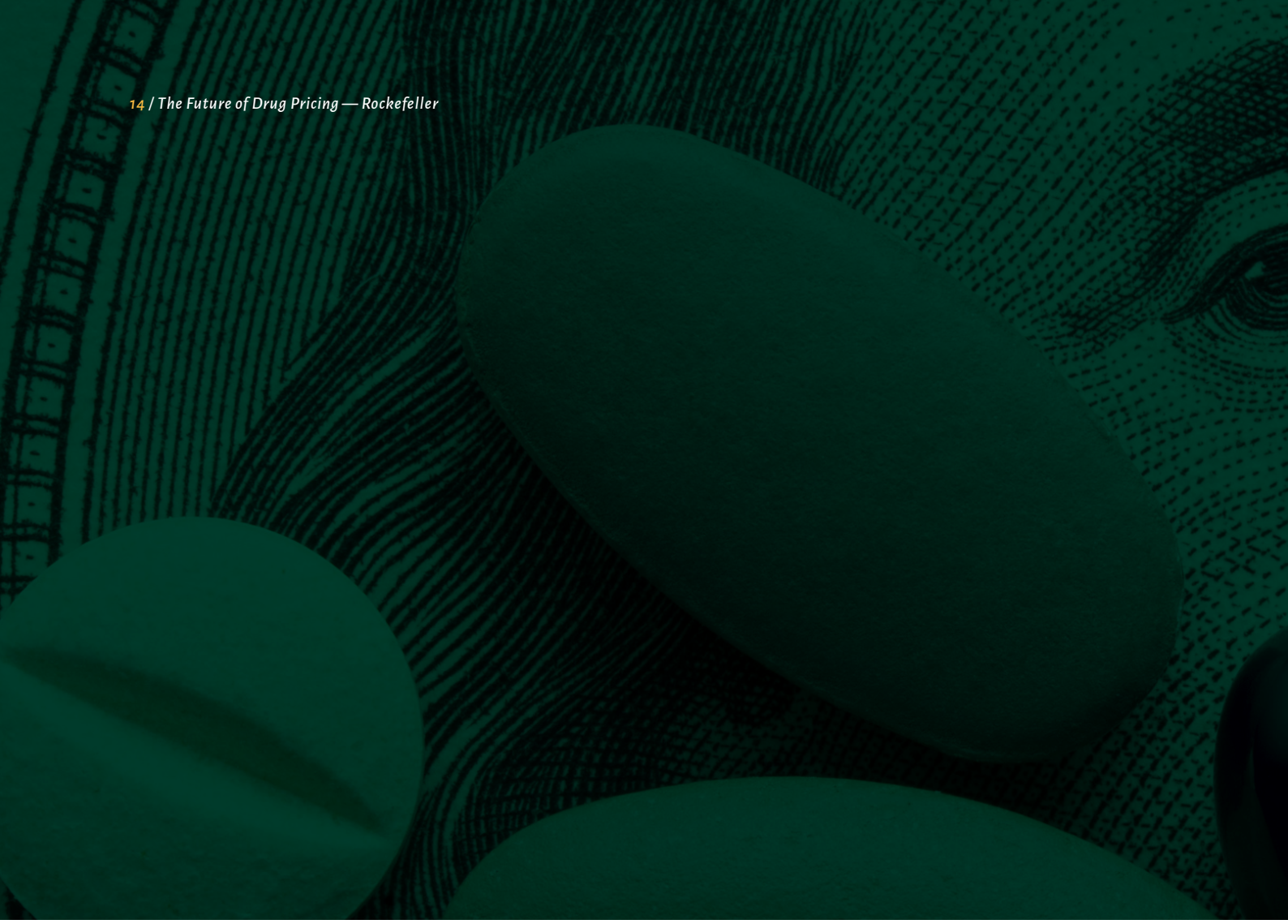
ALTERNATIVE PAYMENT STRUCTURES

Biopharmaceutical companies and payers are considering several types of alternative payment models. With respect to durable therapies for small "orphan" indications, payers and biopharmaceutical companies have been exploring annuity-style payments that stop if the therapy fails to yield further benefit. For larger indications in line with classical disease prevention, so-called at-risk models under discussion reward innovators for improving actual outcomes or lowering total costs over a large patient population. More provocative payment models, which we do not think will occur anytime soon (yet have been discussed in policy and academic circles), involve governments rewarding scientists or innovators a lottery-sized financial prize for breakthrough therapies up front and setting drug pricing at marginal cost.

INDUSTRY **SELF-REGULATION**

The Institute for Clinical and Economic Review (ICER) is a non-profit that is privately financed and largely funded by the Laura and John Arnold Foundation, an independent organization that weighs the benefits of medical technologies against their prices. The organization has historically had a strained relationship with the biopharmaceutical industry due to criticism over the high cost of drugs. We believe ICER's influence is increasing within the biopharmaceutical industry as it is the first independent organization to publicly share comprehensive medical technology assessments.

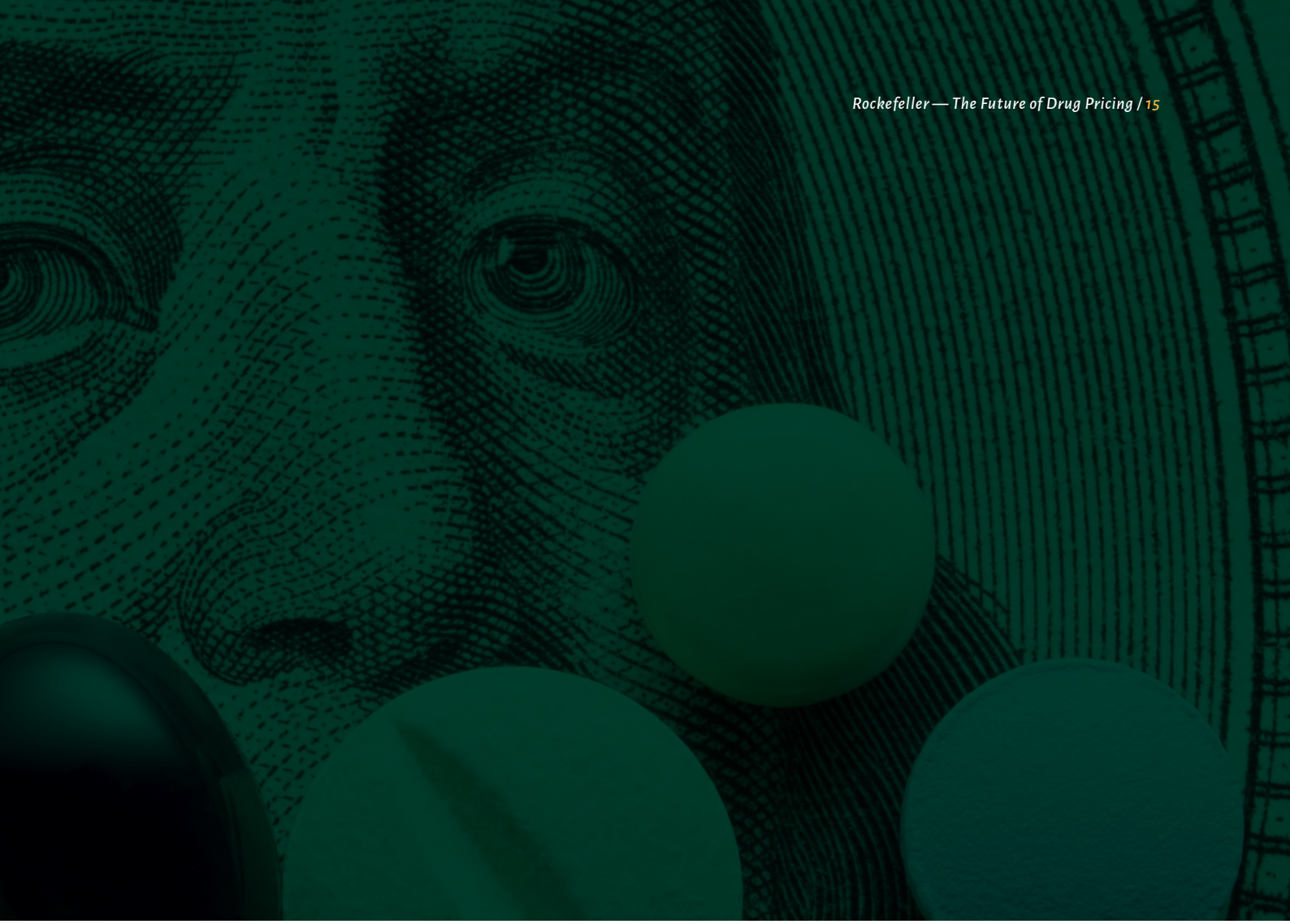
We believe CVS Caremark's announcement that they will be leveraging ICER analysis to limit the drug pricing power of biopharmaceuticals and place pressure on manufacturers to reduce launch prices to reasonable levels begins to elevate and formalize ICER's role in pricing decisions. Although biopharmaceutical companies may not endorse ICER's methods initially, we believe the industry will need to align itself to incorporated ICER assessments if it seeks to avoid political backlash and oppressive regulations. Independent evaluations have the potential to advance pricing schemes more closely to the added clinical benefits that drugs provide. According to ICER, "the ideal result of any health benefit design is for patients to have access to all high-value treatments, and for pharmaceutical innovation to be fairly rewarded." As drug pricing continues to command attention in the U.S., we believe independent organizations such as ICER may be critical for biopharmaceutical companies to construct a framework for self-regulation.



THE ICER **INFLUENCE**

Regeneron Pharmaceuticals and Sanofi are biopharmaceutical companies that have partnered for over a decade on a number of therapies for a range of disorders, including inflammatory conditions, cancer and heart disease. While the use of health economic frameworks is commonplace in the industry, Regeneron and Sanofi, on two separate occasions, have worked with the Institute for Clinical and Economic Review (ICER) and have priced their drugs consistent with ICER's analysis on the reported clinical utility of their drugs in clinical trials. We believe the collaboration with ICER and these companies could lead to more examples in the industry and therefore move pricing closer to clinical value. While general efforts to align price and value through cost-effective analysis and/or alternative payment models could depress industry pricing, we believe greater patient access and pricing based on rigorous, economic and transparent frameworks will lead to more sustainable industry revenues.

Specifically for Regeneron and Sanofi, Dupixent is an injectable antibody-based treatment that is approved for moderate-to-severe atopic dermatitis, a chronic inflammatory condition marked by itching that can be debilitating for patients. Although Dupixent's list price could have been set at list prices of $50,000/year, consistent with comparable drug treatments for psoriasis, the companies instead charge $37,000. According to an ICER report in May 2017, Dupixent, at a typical discounted price off the list price, met ICER's cost-effective criteria. More recently in March 2018, Regeneron and Sanofi announced they would lower the price of their cholesterol-lowering drug, Praluent, at levels consistent with the economic value as assessed by ICER. Down the road, these companies could go even further by creating contractual relationships with payers that reward them for conducting future clinical trials and collecting real-world evidence to optimize identification of patients best suited for this treatment.



INVESTMENT **IMPLICATIONS**

As long-term investors, we believe the incorporation of fundamental research that includes Environmental, Social and Governance (ESG) attributes allows for deeper engagement with biopharmaceutical companies — engagement that provides insight into varied drug pricing transparency and methodologies. We believe drug pricing discussions could not only enhance our ability to evaluate a company's fundamentals, but also provide company management important feedback about its overall long-term strategy. Although the drug pricing issue may be contentious at times, there is clear recognition of the value of the discussion from a long-term strategic perspective. It is increasingly clear that value-based concepts are the way forward, but there is still lack of clarity around the structures and frameworks to make the model truly effective. Drug pricing, as we have highlighted, can have severe financial and reputational risks for biopharmaceutical companies if the rationale for a price increase is not clear and communicated effectively. Instead, we believe companies must realize a balance that takes into account patient outcomes and societal impact while not hindering the research and development capital needed to advance innovation. The biopharmaceutical companies that are attempting to get ahead of this issue may mitigate risk but also benefit from the long-term results of incorporating value-based pricing attributes. The biopharmaceutical pricing models of the future will be pioneered through innovative healthcare delivery models that stem from multi-stakeholder collaboration that builds trust and greater transparency. Long-term investment performance in biopharmaceutical relies upon healthcare systems that appropriately reward breakthrough innovations that take several years of R&D, as opposed to quick shortcuts to earnings growth. We intend to continue our engagement efforts, to ask the tough questions and suggest best practices that we believe will have a positive impact on the company's bottom line as well as their customers.

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