The Price *Isn't* Right

Breakthrough drugs for rare neurologic diseases are staggeringly expensive. We explain why and how to effect change.

BY GINA SHAW

In November 2015, 23-month-old Camille Callais didn't have time to spare. The Louisiana toddler was slowly losing motor function due to spinal muscular atrophy (SMA) type 2, a progressive disease that affects the motor neurons in the spinal cord. Camille's parents, Brandon and Casie, had heard about a clinical trial of nusinersen (Spinraza), a promising new drug for SMA, but Camille was just shy of 2 years old, the cutoff age to participate.

So for the next year, as encouraging reports from the trial made headlines, Brandon and Casie watched their daughter decline. In early 2016, they took Camille to Nemours Children's Hospital in Orlando, FL, where Richard Finkel, MD, chief of neurology, was the head researcher on a branch of the nusinersen trial. Although he became Camille's doctor, it was still too late to enroll her in the trial.

"We did everything we could for her while waiting," recalls Brandon. "But she got weaker and weaker. She's very tall for her age, and with every growth spurt she'd have a big drop in strength, and it would take her a few months to rebound."

In December 2016, shortly after Camille's third birthday, nusinersen was approved by the US Food and Drug Administration (FDA). The manufacturer, Biogen, launched it with the shocking price tag of $750,000 for the first year and $375,000 every year after that—indefinitely.

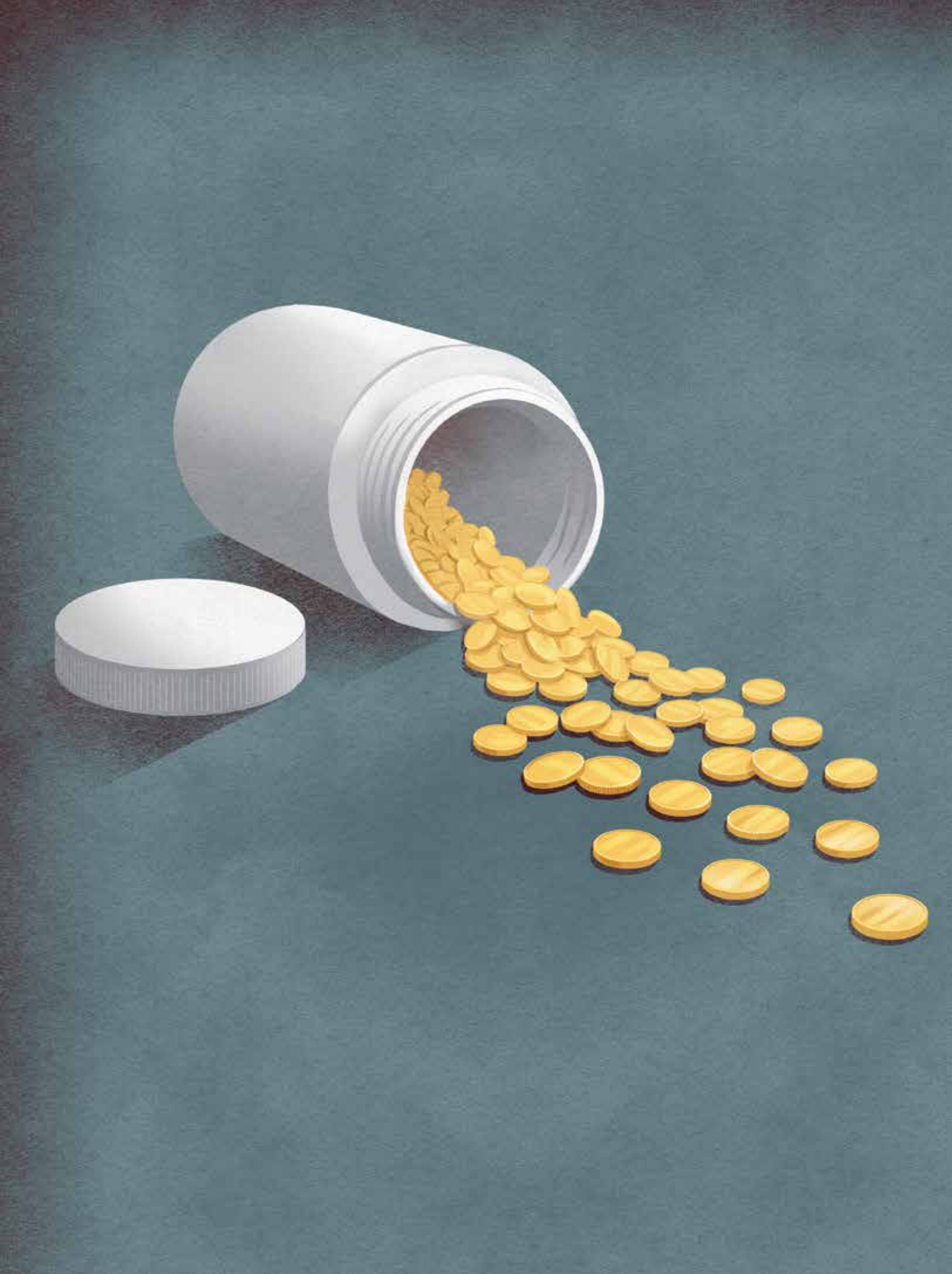
The Callais family waited anxiously for their insurance company, Blue Cross and Blue Shield of Louisiana, to authorize coverage for the drug. In March 2017, Camille developed pneumonia and was admitted with a collapsed lung to the pediatric intensive care unit in a hospital near their home in New Orleans. "Our nurse case manager at Blue Cross thought that because Camille was so sick, her claim would be approved more quickly," says Casie. "So Dr. Finkel's team in Orlando had Camille scheduled for her first dose. But after we had everything ready to go, we received word that she had been denied coverage."

5 BLOCKBUSTER DRUGS WITH BIG PRICE TAGS

Drug	Condition	Annual Cost
Nusinersen (Spinraza)	Spinal muscular atrophy	**$750,000** first year, then $375,000/year
Cerliponase alfa (Brineura)	Batten disease	**$702,000**
Alglucosidase alfa (Lumizyme)	Pompe disease	**$626,400**
Eteplirsen (Exondys 51)	Duchenne muscular dystrophy	**$300,000** (dose based on weight)
Edaravone (Radicava)	Amyotrophic lateral sclerosis	**$146,000**

Note: The "sticker price" isn't what insurance companies actually pay for the drug. That price, known as the WAC (wholesale acquisition cost), is an estimate of the manufacturer's list price to wholesalers or other direct purchasers—but that doesn't account for discounts or rebates that are almost always given to third-party payers like private insurance companies, Medicare, and Medicaid. As for the real cost to your insurance company of a drug like edaravone or nusinersen, the manufacturer and the insurance company might know, but the public doesn't.

ILLUSTRATIONS BY MARCO MELGRATI



> "If only 1,000 people are eligible to take the drug instead of 100,000, **it's harder** to recoup the investment without setting a high price."
>
> —ANUP PATEL, MD, FAAN

PROMISING DRUGS

Although they are not cures, drugs like nusinersen, eteplirsen (Exondys 51) for Duchenne muscular dystrophy, and edaravone (Radicava) for amyotrophic lateral sclerosis (ALS) offer symptomatic relief for neurologic diseases once considered untreatable. "It's exciting to be entering into an age of meaningful treatment for these devastating conditions," says Nicholas Johnson, MD, FAAN, assistant professor of neurology, pediatrics, and pathology (with a focus on inherited neuromuscular disorders) at the University of Utah, who chairs the American Academy of Neurology's Government Relations Committee.

But these new treatments come with annual costs that dwarf the prices of even the most expensive drugs already on the market, leading some insurance companies to do what the Callais' insurer did—deny coverage. Even *with* coverage, many families wonder how they will manage the high costs of what may be a lifetime of therapy.

7 REASONS FOR SKY-HIGH PRICES

1. SUPPLY AND DEMAND. Five of the most expensive drugs to come on the market recently (see "5 Blockbuster Drugs with Big Price Tags," on page 40) have two things in common: they all have novel mechanisms of action, and they have been designated by the FDA to treat orphan diseases, which are rare or ultra-rare conditions, a designation that confers certain advantages in the approval process and tax benefits.

"Drug prices are based on multiple factors," explains Anup Patel, MD, FAAN, section chief of neurology at Nationwide Children's Hospital and assistant professor of clinical pediatrics and neurology at The Ohio State University College of Medicine. "One of those factors is how much the company invested and how much risk it took in developing the product."

Industry groups say it can take about 10 years and well over $1 billion to get a new drug to market. "Cost is also affected by the severity or rarity of the disease being treated," says Dr. Patel. "The rarer and more severe a condition, the more the drug will likely cost. If only 1,000 people are eligible to take the drug, instead of 100,000, it's harder to recoup the investment without setting a higher price."

2. UNIQUE MECHANISMS OF ACTION. The type of drug is another factor, says child neurologist Thomas Crawford, MD, co-director of the Muscular Dystrophy Association Clinic and neurologist for the Ataxia Center at Johns Hopkins University in Baltimore. "Many of these new drugs employ novel ways to treat diseases," he says. Nusinersen, for example, uses synthetic strings of nucleic acid to bind to RNA and change the way a gene expresses itself, he explains. And if these drugs have no competitors, manufacturers have no limits to what they can charge.

3. CERTAIN UNKNOWNS. Uncertainties about particular drugs—how effective they are, how long they will remain effective, at what age they will be most effective, or how long patients will need to take them, for instance—make calculating their costs and benefits even more challenging.

4. RESISTANCE TO COMPETITION. Some prices for neurologic drugs remain high decades after they were introduced, long after the manufacturer presumably recouped its investment. Multiple sclerosis (MS) is a classic example, says Dennis Bourdette, MD, FAAN, chair of the department of neurology and director of the Multiple Sclerosis Center at Oregon Health and Science University in Portland. "The three original drugs for MS—interferon beta-1a (Avonex), interferon beta-1b (Betaseron), and glatiramer acetate (Copaxone)—all have annual prices over $80,000, even though they have been on the market since the mid-1990s. And when a new drug enters the market, the prices of these drugs don't go down to compete with the new medication; instead, they've often gone up."

In fact, the average annual cost of MS therapy rose from $16,000 in 2004 to $78,000 in 2016, according to the National Multiple Sclerosis Society. A letter to seven manufacturers of MS drugs from House Democrats in August 2017 accusing them of "shadow pricing"—hiking prices to meet the price of newer entrants in the drug market—and requesting answers about the price hikes. No further action has been taken at this time.

5. PATENT WORKAROUNDS. Even when generics come to market, manufacturers can find ways to thwart price competition. In June 2015, Glatopa, the first generic equivalent of Copaxone, was approved by the FDA. But in 2014, with its patent about to expire, Copaxone manufacturer Teva introduced a new patented 40 mg version that reduced the frequency of injections from daily to three times per week, and many patients were switched to the more convenient new formulation.

6. INABILITY TO NEGOTIATE. By law, Medicare cannot negotiate with drug manufacturers. The Medicare Modernization Act of 2003 (MMA), which established Medicare Part D, the Medicare entity that pays for most prescription drugs, included a ban on such negotiations. Medicaid and the Department of Veterans Affairs (VA), on the oth-

er hand, are allowed to negotiate. The VA is estimated to pay drug prices that are about half those paid at retail pharmacies, and Medicaid pays about one-third less than Medicare Part D, according to a 2016 report from the Commonwealth Fund, citing the Congressional Budget Office.

7. PRICE GOUGING. In other instances, manufacturers may engage in excessive profit-making tactics. One such example is the marketing of adrenocorticotropic hormone (Acthar), which was developed in the 1950s from pig pituitary glands. For years, it was used off-label to treat infantile spasms, at a cost of about $40 per vial. In 2001, a company called Questcor bought the rights to the drug; six years later, the price was $23,000 per vial. Questcor has since been purchased by Mallinckrodt, and a lawsuit filed in October by plaintiffs representing Medicare Advantage organizations notes that the companies have raised prices for the drug by 85,000 percent since 2001. "These companies have not invested in developing the drug, but they are now trying to increase the price because of high demand and low supply, which is wrong," says Dr. Patel.

INSURANCE OBSTACLES

As drug prices climb, insurance companies are re-categorizing drugs or establishing more rigorous processes for determining coverage. For example, many insurance companies have categorized ocrelizumab, a new MS drug, as a third-tier medication

> "We need to find ways **to lower the cost** of these ultra-high-priced drugs while still encouraging research and innovation."
>
> —NICHOLAS JOHNSON, MD, FAAN

for relapsing-remitting MS, says Dr. Bourdette. (A typical insurance drug benefit has tiers that determine the patient's portion of the drug cost; costs vary per plan but the third tier typically requires copays of $38 to $42. Some plans have a fourth tier for nonpreferred drugs and a fifth tier for specialty drugs. These two tiers usually include most ultra-high-cost drugs and require patients to pay a percentage of the drug cost, known as coinsurance, rather than a flat copay amount. For fourth tier drugs, it's typically 45 to 50 percent of the drug cost. For fifth tier drugs, it's typically 25 to 35 percent.)

In the case of eteplirsen, some insurers will cover it only under certain circumstances. "The drug was approved under an accelerated approval process that says the efficacy is unknown, which gives insurance companies justification for denying coverage," says Pat Furlong, president of Parent Project Muscular Dystrophy, a nonprofit organization in Hackensack, NJ. "Several insurers require a six-minute walk test [which uses walking ability as a measure of disease progression]."

Those requirements have plagued Alison Willis Hoke's ability to get coverage for her twin sons, Jack and Nolan, who were two of the original 12 boys in the pivotal trial of eteplirsen. "They were the only ones who lost ambulation during the trial, but at 9 years old they were also two of the three oldest boys," she says. "Now they're 16, and their pulmonary and cardiac function are much better than expected given the natural history of the disease. Once they had to skip a dose, and they really felt it: they were sluggish and lethargic. They had hand cramps, arm pain, and contractures, which they very rarely have. I cringe to think what would happen if they couldn't get the drug."

But that's a looming worry for Hoke. Her Blue Cross and Blue Shield plan in New York denied the boys coverage after they finished the extension part of the drug trial, which ended in August 2017. Their medication is currently funded by an independent nonprofit foundation called The Assistance Fund while Hoke appeals the insurance denial.

A Call to Action

The American Academy of Neurology (AAN) and other leading medical organizations have called for major changes in how drug prices are determined in the United States. In early 2017, the AAN issued a position statement focused on three major areas of action that would lower drug costs:

- **NEGOTIATE PRICE. Grant authority to federal agencies to negotiate prices with drug manufacturers under Medicare. This would allow the government to use its purchasing power to obtain prescription drugs at a lower price. (And where Medicare goes, private insurers typically follow.)**
- **BE TRANSPARENT. Require manufacturers to disclose pricing information, including how drugs are priced and the prices paid by insurers and consumers, and limit direct-to-consumer advertising, which creates demand for unnecessary or inappropriate medications and contributes to marketing costs.**
- **ALLOW IMPORTATION. Allow the importation of the same high-quality prescription drugs from Canada when prices for those prescriptions are less expensive than in the United States. Many specialty drugs are priced much higher in the United States than in other countries.**

HOPEFUL REVERSALS

In November 2017, Anthem Blue Cross Blue Shield reversed its decision from 2016 not to cover eteplirsen, clearing the drug as medically necessary—although it does require patients to be able to walk, a fact that may complicate Hoke's appeal.

And after working closely with their nurse case manager at their own Blue Cross plan, the Callais family gained approval for nusinersen. Camille had her first dose in April 2017. "Very quickly, we noticed she was hungrier and eating better. Her voice was louder and she seemed to have more energy," says Casie. "At first we thought we were just seeing her through our parent goggles, but she kept improving. She can raise her arms higher and take off her socks and put them on by herself. Her balance and head and trunk control are better, and she's able to walk short distances with a walker."

It's not just her parents' observations: during the first six months on the drug, Camille gained four points on the Hammersmith Functional Motor Scale; by comparison, many of the children in the original trial didn't show a four-point improvement until they'd been on the drug for 12 months.

PUSHING FOR CHANGE

Many people still have to fight for coverage of nusinersen, and not all are getting approved, says Casie. "We have a private Facebook group with other SMA families, and some people have

been approved for the first loading dose only to have their insurance companies change their policies or require a certain amount of improvement on the Hammersmith Scale before they will cover any more doses," she says.

Patient advocacy groups continue to push for more comprehensive coverage for these costly new drugs. For example, Anthem's decision to cover eteplirsen came after months of letters, meetings, and data from Parent Project Muscular Dystrophy. Furlong notes that her organization has also helped other families successfully appeal denials of coverage by private insurers.

Kenneth Hobby, president of Cure SMA, agrees that advocacy groups are making headway. "At the start, some insurers were putting restrictions around the extremes of the disease, even though the FDA approved the drug for all types of SMA. Over time, the restrictions have loosened as additional data have come out from the trials to back up the FDA's labeling."

Still, the process is far from perfect, a reality the American Academy of Neurology (AAN) is facing head-on. "The AAN has formed a drug pricing task force to study the environment of drugs for neurologic disease and how we can help address this issue," says Dr. Johnson. "We need to find ways to lower the cost of these ultra-high–priced drugs while still encouraging research and innovation." NN

WEB EXTRA: For more about this topic, visit **bit.ly/NN-Congress**, **bit.ly/NN-HelpforHighCosts**, and **bit.ly/NN-BecomeAnAdvocate.**