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MAY 17, 2019

Gene Therapies Force Payment Innovation

Milestone-based contracts, other strategies may avert losses on million-dollar treatments

By Gina Shaw

San Diego—Of the 48 gene therapies in phase 3 trials, several may hit the market this year or next, and some have the potential to transform care, according to experts presenting at AMCP's Managed Care & Specialty Pharmacy 2019 Annual Meeting.

But as effective as the treatments may be, high setup costs, variable clinical responses, and

issues with reimbursement and coding have resulted in significant losses for some manufacturers and providers.

“The one-time administration for these therapies introduces a mismatch with benefits,” said Jane F. Barlow, MD, MPH, MBA, a senior advisor for the MIT Center for Biomedical Innovation, in Scottsdale, Ariz. “The cost is front-loaded, but benefits accrue over time, creating a challenge as patients move in and out of plans. This is very different than what we see with chronic medications.”

Still, the effort to work out these financial kinks is well worth it, given the huge clinical upside of gene therapy. In hemophilia, for example, gene therapy offers a possible “cure” for the disease, said Edmund Pezalla, MD, MPH, the CEO of Connecticut-based Enlightenment Bioconsult, adding a caveat: “Let’s keep that in quotes. Patients may still need factor replacement under certain conditions, but we may be able to move them from severe disease to moderate disease, or even mild.”

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In the trial of BioMarin's hemophilia A gene therapy (the farthest along in the pipeline of at least six gene therapies for hemophilia A in active clinical trials), the annual bleed rate among 15 patients (all with severe disease) fell from 16.3 episodes to 0.5 per year, with the number of factor VIII infusions decreasing from 136.7 to 8.5 per year, according to data presented by the company at the International Society on Thrombosis and Haemostasis 2017 Congress.

Gene therapy for hemophilia B is farther back in the pipeline but also is showing great promise. In the phase 1/2 proof-of-concept trial for uniQure's hemophilia B gene therapy (*N Engl J Med* 2014;371[21]:1994-2004), the 10 adult patients achieved an overall 84% reduction in spontaneous annual bleed rate, and eight of the 10 have discontinued prophylaxis, Dr. Pezalla noted.

In phase 1 of the START trial of onasemnogene abeparvovec/AVXS-101 (Zolgensma, Novartis), involving 15 children with the progressive, usually fatal neurodegenerative disease spinal muscular atrophy (SMA) type 1, 100% of patients were alive and free of mechanical ventilation at 20 months of age, compared with 8% of historical controls (*N Engl J Med* 2017;377[18]:1713-1722).

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Susan Trieu, PharmD

"When they looked at motor end points, 75% of patients in the trial were able to roll over and sit unassisted for 30 seconds, and about 13% of them were walking," said Susan Trieu, PharmD, the director of enterprise specialty clinical solutions at MedImpact Healthcare Systems, in Southlake, Texas. "None of the historical controls could achieve any of those motor end points. It's awe-inspiring, but it will come at a cost," she noted. (For more coverage of SMA type 1, see article, page 6.)

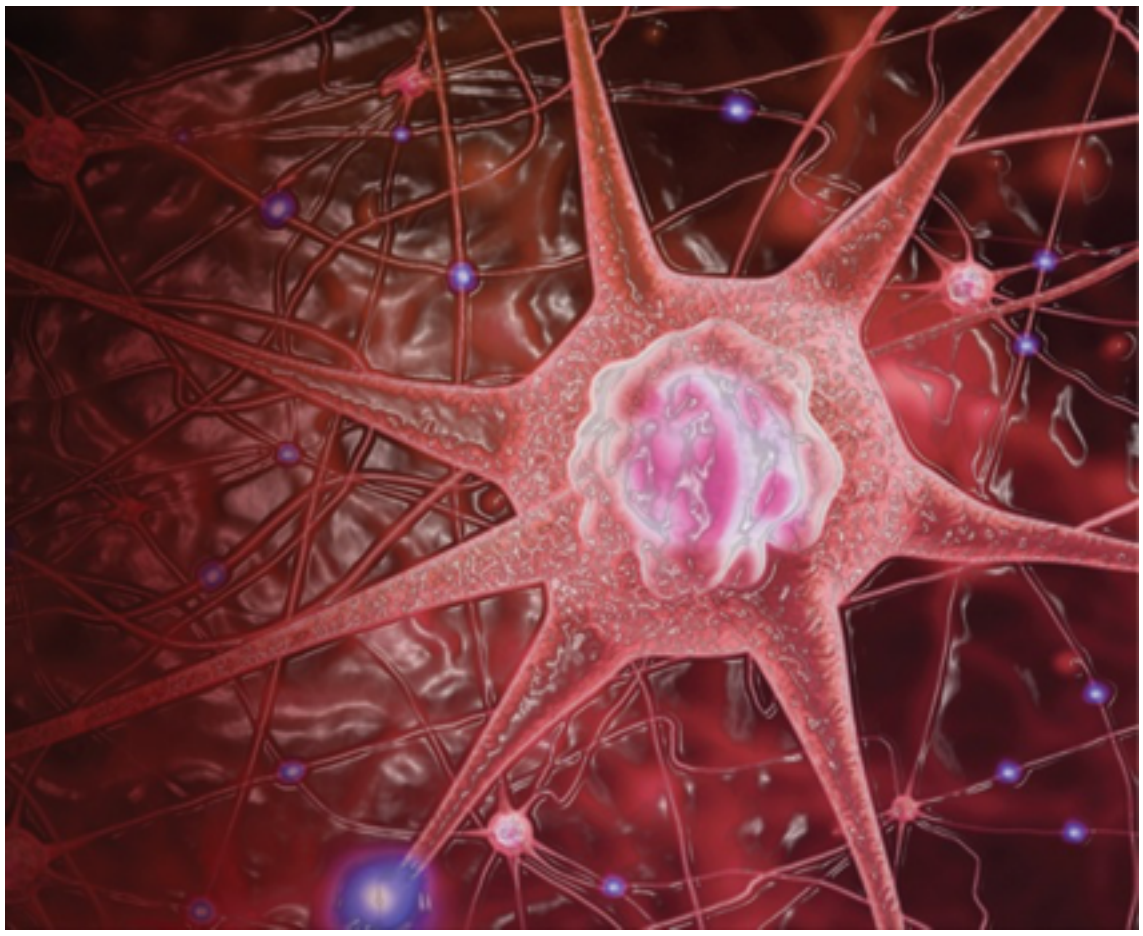
Of the four products most likely to hit the market soon (see box below), onasemnogene abeparvovec has an expected FDA decision date of May 2019; the other three therapies (for hemophilia A, beta thalassemia and aromatic l-amino acid decarboxylase [AADC] deficiency) are expected to file with the FDA by the end of this year. These products would join the three gene therapies on the market: 2 chimeric antigen receptor (CAR) therapies—tisagenlecleucel (Kymriah, Novartis), for relapsed/refractory B-cell precursor acute lymphocytic leukemia and

relapsed/refractory large B-cell lymphoma, and axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead), for relapsed/refractory large B-cell lymphoma—and voretigene neparvovec (Luxturna, Novartis), for biallelic *RPE65* mutation–associated retinal dystrophy.

High Cost of a Cure

These previously approved gene therapies already are breaking price records, with costs ranging from $373,000 to $850,000 for a one-time dose.

Although Novartis hasn't set a price for onasemnogene abeparvovec, the company has argued that it would offer good clinical value at a price between $4 million and $5 million. (The Institute for Clinical and Economic Review puts the cost-effectiveness threshold for the drug at $900,000). Analysts have projected that the hemophilia gene therapies could cost between $1.5 million and $2 million.



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The costs associated with gene therapies may prove challenging to sustain for manufacturers and providers alike.

"We now have a full year's worth of data on Kymriah and Yescarta from a sales perspective, and they haven't done as well as we thought they would do," Dr. Trieu said. "For example, sales of Kymriah only reached $76 million at 90 authorized treatment centers in 2018, with Yescarta reaching $263 million at 74 authorized centers. Several institutions may even be losing money

doing these CAR-T gene therapies, because of inability to recoup their costs."

The financial loss is partly a function of becoming an authorized treatment center, which requires an enormous investment in data management, staff training and patient education. At a panel held during the 2019 National Comprehensive Cancer Network (NCCN) Annual Conference in March, cancer center officials cited another problem: Medicare's hospital billing codes, which are not designed for the care involved in CAR-T therapy. Panelists at the NCCN meeting estimated that the real cost to an institution of providing one patient with CAR-T therapy is between $800,000 and $1 million. "The process of paying for it doesn't allow Medicare to reimburse enough for hospitals to pay for the therapy," said Frederick Locke, MD, the co-leader of the immunology program at Moffitt Cancer Center in Tampa, Fla. "How is that going to work? We can only do this for so long where we're not getting fully paid."

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At the AMCP meeting, Dr. Trieu pointed to the cautionary tale of the world's first gene therapy, alipogene tiparvovec (Glybera, uniQure). Approved in Europe in 2012, for the treatment of hereditary lipoprotein lipase deficiency, it was withdrawn from the market in October 2017. Even

with a $1.2 million price tag, the cost of manufacturing each dose meant the company lost money on the drug. “Based on the combination of a lack of sufficient market demand and requirements for additional studies and surveillance of patients, uniQure deemed it too expensive to continue,” she said.

Playing With Risk

The high price tags and front-loaded cost burden of these novel gene therapies are leading payors to experiment with innovative approaches to manage their financial risk, presenters at the AMCP session said.

“Nothing has disrupted how we code and pay and reimburse as much as gene therapy has,” said moderator Clifford Goodman, PhD, the senior vice president and director of the Center for Comparative Effectiveness Research at The Lewin Group. “Many groups are looking at new payment models.”

The MIT Center’s Dr. Barlow said payors already are working on several solutions. For example, in MIT’s FoCUS (Financing and Reimbursement of Cures in the US) payor survey conducted in the fall of 2018 (unpublished), payors reported they plan to use multiple mechanisms to manage the financial risk and impact of these therapies:

- 74% said they would restrict use to centers of excellence;
- 50% said they would rely on short-term, milestone-based contracts;
- 44% would use population risk pooling;
- 36% would employ long-term, milestone-based contracts; and
- 33% would spread payments over multiple years and tie each payment to achievement of performance measures.

Dr. Barlow categorized these mechanisms into three primary “precision financial solutions”:

Milestone-based contracts. These typically are less than two years in duration and involve specified payment end points tied to early outcomes. “This doesn’t take away the high single-year cost or the issues around timing, but it addresses performance risk,” Dr. Barlow said.

Performance-based annuities. These are defined as contracts longer than two years—most likely three to five years—with payments spread out across a contract period and tied to performance over time. “This type of contract may get at some of the actuarial risk because you’re spreading out your payments, timing and performance risk,” she said. For example, payments for a high-value gene therapy, such as onasemnogene abeparvovec, might be made at 20% over four years:

20% on therapy initiation and 20% each year after, assuming agreed-upon milestones are met.

Risk pooling. This involves a carve-out of underwriting for novel breakthroughs. “That’s very attractive to a lot of payors. Everyone wants to carve that out to the federal government, but it may or may not be a viable solution in this case,” Dr. Barlow said.

MIT’s FoCUS program is planning pilots of some of these models, including performance-based annuities with commercial payors and milestone-based contracts with public payors, Dr. Barlow said. “The solutions you need to manage this new, disruptive therapy might differ by treatment characteristics and the financial challenge the payors might experience,” she explained. “There’s no ‘one size fits all.’”

‘A Paradigm Shift’

“This is a paradigm shift,” agreed Sophie Schmitz, the managing partner at Partners4Access, a global consultancy specializing in access to orphan drugs, based in Amsterdam. “Gene therapy does have the potential to revolutionize medicine, but if that is to be the case, then we need to be thinking in a revolutionary way about how we evaluate and pay for gene therapy.”

Staged-payment contracts, not tied to milestones or performance, could soften the initial impact of new high-cost gene therapies on the health care budget. “In these arrangements, the manufacturer is almost acting as a bank,” Ms. Schmitz said. “But with so many gene therapies being developed by small [biotech companies], it can be challenging for them to get sufficient returns on a short-term basis.” She noted that the initial payment must be sufficient not only to cover the manufacturer’s costs but also the provider’s cost of delivering treatment.

In addition, although payors can spread their cost over a certain amount of time, staged payments don’t necessarily address the uncertainty over long-term benefits. “Just because you’re paying over four years doesn’t mean you get four years’ worth of benefits,” Ms. Schmitz said.

The type of financial solution deployed, she said, is likely to depend on the conditions that a particular gene therapy will treat (see box on MIT’s Project Cure). Outcomes-based payments, whether short-term and milestone-based or longer-term and performance-based, solve that problem to the extent that they are conditioned on performance. “If the therapy is less effective than what was originally anticipated, then the next payments will not be made,” Ms. Schmitz said.

“Of course, from a manufacturer or industry perspective, it’s a nerve-wracking system because you need to have total confidence that your therapy is going to do what you say it will do. How can you design a clinical trial that will give you that confidence?” Furthermore, are the end points that worked in a clinical trial feasible for widespread replication in outcomes-based contracts?

that worked in a clinical trial feasible for widespread replication in outcomes-based contracts? For example, the primary end point of the clinical trial that led to the approval of voretigene neparvovec was patient performance on the multi-luminance mobility test, in which a patient navigates a maze at varying light levels, stepping over and around obstacles to reach a door at the end. “That’s difficult to use in a larger outcomes-based payment system.”

Dr. Trieu reported that her spouse is employed by AstraZeneca. Dr. Barlow reported financial relationships with Pictet, Real Endpoints and Therapeutics MD. Dr. Pezalla reported a financial relationship with BioMarin. Drs. Goodman and Schmitz reported no relevant financial relationships.

MIT’s FoCUS Project Cure Archetypes

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The type of financial solution deployed for gene therapy in real-world outcomes-based payment systems is likely to depend on the conditions that a particular therapy will treat, suggested Sophie Schmitz, managing partner with Partners4Access. She agreed that the four “archetypes” described by MIT’s FoCUS project offer a good framework for projecting financial impact:

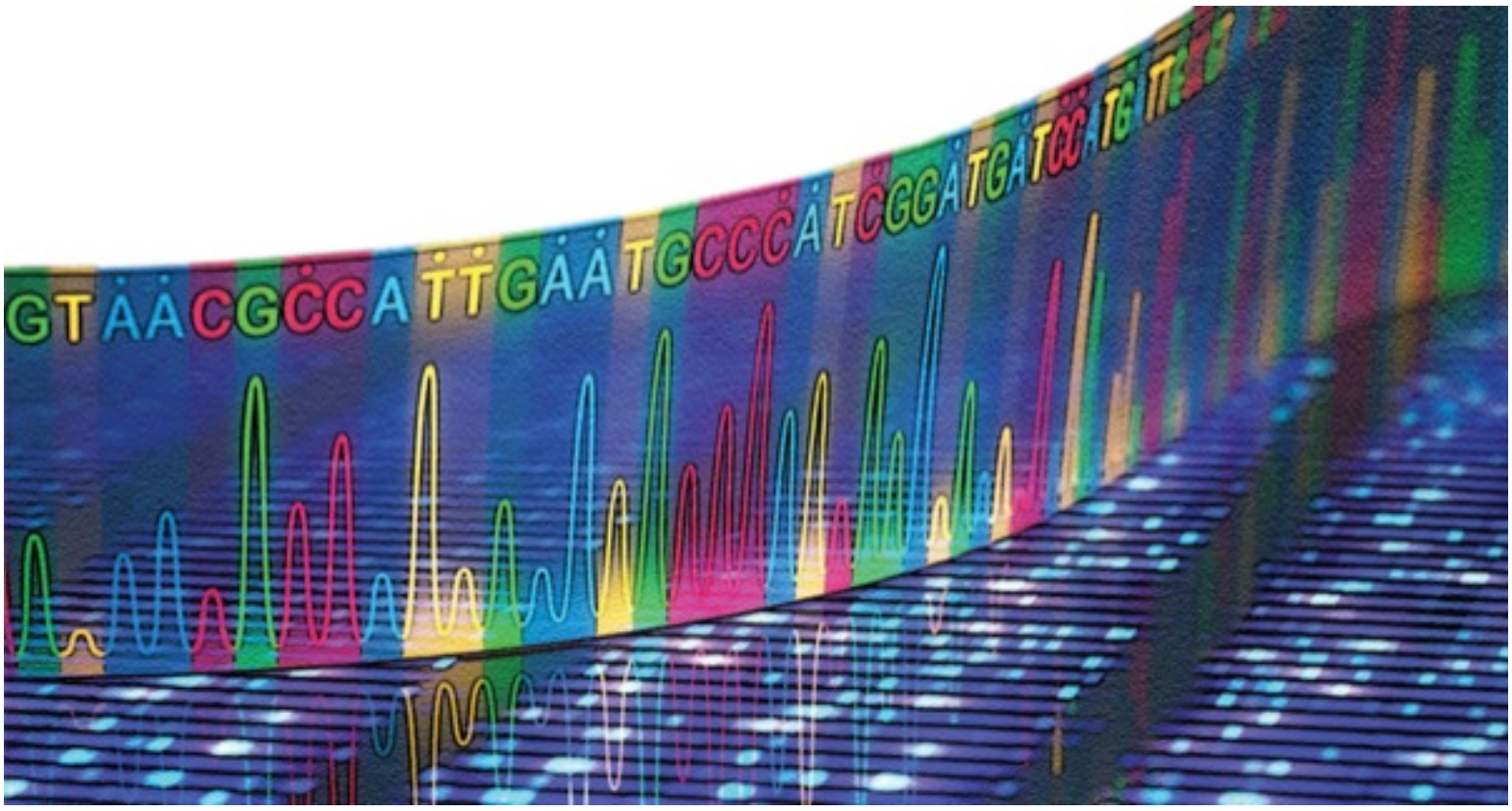
- **Novel breakthroughs:** treatments for ultra-orphan diseases with a high unmet need and no alternative therapies. “While the price for these therapies would be very high, the budget impact could be manageable, because you haven’t got that many patients,” Ms. Schmitz said. “But if there is uncertainty about the long-term effects—perhaps you only have three years’ worth of data—outcomes-based staged payments would work quite nicely.”
- **Orphan disruptors:** new treatments for orphan diseases with a preexisting, established clinical pathway, such as spinal muscular atrophy type 1. “The budget impact here could be manageable if you think about using those therapies in only newly diagnosed patients,” she said. “But if you use it in the treated population, the short-term, one-off high budget impact is likely to require staged payments. The complication here is all around current standard of care and what’s going to happen to it.”
- **Oncology products:** treatments such as CAR-T therapies for oncology indications with high incidence and low prevalence, where the durability of the novel treatment is defined by a range of about 12 to 18 months. “Therapies like CAR-T have a smaller period of benefit and

their durability is not as great as some of these other gene therapies," Ms. Schmitz said. "The way outcomes-based staged payment would work here is if a treatment's efficacy is really uncertain, but over a much smaller time period, not year by year."

- **Quantum leap:** treatments with large incident and prevalent populations representing a significant burden—areas such as cardiology, metabolic disorders, neurology and rheumatology. "That's where the budget impact would be enormously high and a major issue, but we are not likely to see those very soon."

—G.S.

Gene Therapies Nearing FDA Approval



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The following gene therapies (or gene-modified cell therapies) are among the candidates for approval within the next 24 months:

- **Onasemnogene abeparvovec/AVXS-101** (Zolgensma, Novartis), a treatment for the progressive, usually fatal neurodegenerative disease spinal muscular atrophy (SMA) type 1. SMA is believed to affect as many as 10,000 to 25,000 children and adults in the United States, making it one of the most common rare diseases.
- **Valoctocogene roxaparvovec/BMN-270** (BioMarin), for the treatment of hemophilia A. According to the National Hemophilia Foundation, about 16,000 people are living with hemophilia A in the United States.
- **Lentiglobin** (bluebird bio), for the treatment of beta thalassemia. An inherited blood disorder characterized by reduced levels of functional hemoglobin, beta thalassemia is relatively uncommon in the United States but is one of the most common autosomal recessive disorders worldwide. More than 60,000 infants are born with the disease every year.
- **GT-AADC** (PTC Therapeutics), for the treatment of AADC deficiency. There are no approved treatments for this rare inherited disorder, which usually appears in the first year of life and involves impaired production of an enzyme responsible for synthesis of the neurotransmitters dopamine and serotonin. Patients with severe forms of the disorder usually die before 7 years of age.

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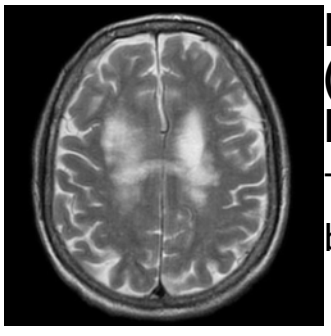

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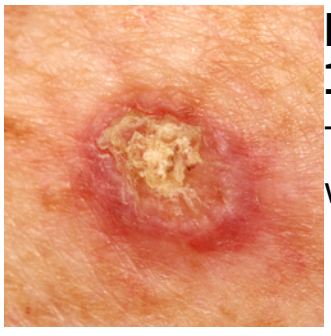

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