



ADDRESSING THE VALUE OF GENE THERAPY: ENHANCING PATIENT ACCESS TO TRANSFORMATIVE TREATMENTS

AN AMERICAN SOCIETY OF GENE & CELL THERAPY WHITE PAPER



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TABLE OF CONTENTS

Executive Summary	3
The Importance of Addressing the Value of Gene Therapy	3
• Value—What Is It and Why Does It Matter?	
• Sidebar: A Primer on Genes	
The Human and Financial Impact of Genetic Diseases	5
• Patient Experience: Pushing Through the Pain: One Woman Braves Sickle Cell Disease and Looks to Gene Therapy to Improve Her Life	
• The Unique Benefits of Gene Therapy	
• Defining Clinical Success	
• Sidebar: Limitations of QALY Measures for Gene Therapies	
Enhancing Patient Access to Gene Therapies.....	8
• Patient Experience: CAR T-Cell Therapy Returns a Teacher to Her Students	
• Patient Experience: First Ever Gene Therapy for an Inherited Genetic Disease Restores a Young Woman’s Independence	
• The Fundamental Questions About Paying for New Therapies	
• What Payers Value: Benefit, Duration, Safety, and Cost	
• Barriers to New Payment Models	
• Reimbursement Issues	
• Payer Opinions on Payment Models	
• New Payment Models Are Already Here	
Coming to Consensus and Next Steps	12
• Moving Toward Consensus	
• ASGCT Position and Recommendations	
• Conclusion: Patient Access Is Essential for Actualizing Value of New Treatments	
References.....	14

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EXECUTIVE SUMMARY

Gene therapy is a radical shift in our approach to disease treatment. By modifying the expression of a patient's genes or repairing abnormal genes, gene therapy often addresses the root cause of diseases. While several new gene and cell therapies have received FDA approvals over the past 20 years, the field has recently experienced a turning point. Three gene therapies were approved for human medical use in the U.S. in 2017,¹⁻³ including the first in the country for an inherited condition, and many more are likely on the way.⁴

The newly approved gene therapies offer substantial benefits to patients who otherwise have little to no hope of cure or even meaningful improvement. They treat two forms of non-Hodgkin lymphoma, an acute form of leukemia, and a hereditary genetic defect that nearly always leads to blindness. Each is a potentially one-time treatment—just a single infusion—that may provide long-term, durable efficacy.

These new treatments have escalated important discussions about how to place a value on gene therapies and how our health care system will pay the upfront costs for these often one-time treatments. In essence, payers are being tasked with paying a larger price today versus paying repeatedly for treatments that may be taken at regular intervals for months, years, decades, or even a lifetime. But assigning value to gene therapies and comparing them to potentially lifelong illness is not an easy or straightforward task. Despite the complexity, this paper identifies unique and relevant aspects that should be considered when assessing the value of gene therapy.

While high upfront costs for the high value of gene therapy has resulted in concerns about sufficient reimbursement to allow patient access to these therapies, the significant benefits of gene therapies will not be realized unless patients have access to them. Stakeholders are discussing these issues, and the payment models being developed for the newly approved gene therapies provide an early indication of the flexibility that will be needed from treatment manufacturers, payers, and policy makers to optimize patient access.

Maximizing patient access to effective gene therapies is an integral part of the overall mission of the American Society of Gene and Cell Therapy.

"I believe gene therapy will eventually become a mainstay in treating, and maybe curing, many of our most devastating and intractable illnesses." -- Scott Gottlieb, MD, FDA commissioner³

THE IMPORTANCE OF ADDRESSING THE VALUE OF GENE THERAPY

The gene therapy field reached a turning point in 2017 when the FDA approved three breakthrough gene therapies.¹⁻³ Many more approvals are expected in the near future; MIT's New Drug Development Paradigms program estimates FDA approval of three dozen new gene therapies by 2022.⁴

Gene therapy offers new and unique approaches to treating previously intractable diseases. Rather than treating disease symptoms, gene therapy can address the root causes of genetic diseases by modifying expression of a patient's genes or by repairing or replacing abnormal genes. Many experts believe that gene therapies are "shifting medicine away from a chronic disease management approach toward disease interception and prevention."⁵

Successful gene therapies have the potential to prevent years or even decades of morbidity with perhaps just one treatment. In exchange, gene therapies would potentially entail a one-time cost, which may seem high until it is compared against many years of expensive, ongoing care. This shift in the timing of health care costs, along with anticipated new gene therapy approvals, has increased the urgency of discussions about how to determine the "value" of gene therapy. It is important to note that while they are typically intended as one-time treatments, the durability of response to gene therapies will only be established with time.

The term "**gene therapy**," as used in this paper, refers to a set of strategies that modify the expression of an individual's genes or repair abnormal genes. Specific types of treatments include vector-delivered gene therapy, gene-modified cell therapy, and gene editing.

The newly approved gene therapies illustrate the substantial and unique benefits these therapies can deliver to patients with serious illnesses and conditions who otherwise have little to no hope of meaningful improvement. Each of the new gene therapy treatments is intended to be administered just once—a single injection or infusion that can dramatically improve a patient's life. And while more study is needed, early results regarding the durability of response to these treatments is positive. Ensuring patient access to these benefits is crucial.

- *Tisagenlecleucel (Kymriah) treats patients up to 25 years old with B-cell precursor acute lymphoblastic leukemia that is resistant to other treatments or is in second or later relapse.¹ Long-term survival of these patients is about 5 percent with standard chemotherapy and stem cell transplantation treatment.⁶ In the Kymriah clinical trial, the overall remission rate was 81 percent at 3 months (no detectable leukemia).⁷ The rates of event-free survival (survival free of certain complications, symptoms, or return of cancer) and overall survival were 73 percent and 90 percent at six months and 50 percent and 76 percent at one year, respectively. Its price is \$475,000 (see: "Second Indication Approved for Kymriah").*
- *Axicabtagene ciloleucel (Yescarta) treats aggressive forms of non-Hodgkin lymphoma in adult patients with large B-cell lymphoma that has relapsed or is resistant after two or more lines of systemic therapy.² The median overall survival time for the previous standard of care treatment is just six months.^{9,10} In a Yescarta clinical trial, 72 percent of treated patients had an overall response (tumor shrinkage or elimination) and 51 percent had no detectable cancer (complete remission) six months following treatment.¹¹ Its price is \$373,000.*
- *Voretigene neparvovec-rzyl (Luxturna) is the first gene therapy for patients with a hereditary disease³--vision loss due to mutations on both copies of a particular gene (RPE65) that nearly always progresses to complete blindness. Before approval of Luxturna, patients had no treatment options. In a Luxturna clinical trial, treated patients were able to complete vision-related mobility tests at two levels of light lower than before treatment while those not treated saw no change in their ability to complete this vision-related test.¹² Three-year follow-up data from the Phase III trial provide evidence of sustained results, as well as safety.^{13,14} Its price is \$850,000, total, for an injection in each eye.*

Value: What Is It and Why Does It Matter?

An independent, non-partisan research organization that calculates the value of medical treatments includes both short-term affordability and long-term value for money in its formula.¹⁵ Long-term value includes comparative clinical effectiveness, estimated incremental cost effectiveness, contextual considerations (e.g., severity of the condition, availability or anticipated availability of other treatments, ethical priorities), and additional benefits or disadvantages, including measures beyond efficacy that matter tremendously to patients, such as ability to return to work and reduction of family and caregiver burden.

While all of these elements may be relevant for defining the value of medical treatments in general, some are difficult to quantify, such as the ability to return to work. Others, such as comparative effectiveness and incremental cost effectiveness, cannot be determined for first and only treatments for a condition, which may be a relevant issue for gene therapies.

Another challenge to defining the value of gene therapies is the non-centralized nature of the U.S. health care system. In-depth cost effectiveness analyses are commonly used in Canada and Europe to make decisions about the value of treatments within their centralized health systems, but these analyses have historically been discussed less in the U.S. where critics see such analyses as excessive government involvement in health care.¹⁶

When the term "value" is used in this paper, it refers broadly to the worth, benefits, and importance of gene therapy in human lives, since providing a precise definition of the value of gene therapy is not as essential as addressing its significance.

The most crucial issues to address are identifying and considering the unique value of gene therapy and its potential for transformative and durable improvements in human lives, and the importance of maximizing the ability of patients to access that value. A treatment that is unavailable to patients who need it has no value at all.

Patient access to gene therapy may be hampered by payer challenges to covering the upfront costs of gene therapies. In addition, some current reimbursement policies and processes are affecting patient access to these life-altering therapies.

Second Indication Approved for Kymriah

Kymriah received FDA approval for a second indication as this report was going to press.⁸ On May 1, 2018, the FDA approved Kymriah for the treatment of adult patients with certain types of relapsed or refractory (r/r) large B-cell lymphomas. Before approval of Yescarta, which also treats relapsed or refractory large B-cell lymphomas, these patients had no treatment options and a median life expectancy of approximately 6 months.^{9,10} In the Kymriah trial for the new indication, the overall response rate in treated patients was 50 percent and 32 percent had a complete response. The Kymriah price for treatment of r/r large B-cell lymphomas is \$373,000.⁸

Maximizing patient access to effective gene therapies is an integral part of the overall mission of ASGCT.

A PRIMER ON GENES

Genes hold DNA, the basic building blocks that make us who we are. Nearly every cell in the human body holds our entire set of approximately 24,000 genes. The job of most genes is to produce one or more unique proteins. A mutation in a gene's normal DNA sequence can prevent it from doing its job. A mutated gene may produce too much or too little protein, damaged protein, or none at all.

These protein abnormalities can lead to hereditary diseases, such as sickle cell disease, a severe form of anemia caused by an inherited defect in a gene that produces hemoglobin. They can also complicate disease treatment, for example when the HER2 gene produces excess protein, which makes certain breast cancers more aggressive. These are just two examples of thousands of diseases for which gene therapy could offer safe, effective treatment and provide long-term benefit.

The payment challenges will increase as more gene therapies come to market and as the indications for the recently approved therapies will likely expand to include more patients. In their assessment of CAR T-cell therapy for B-cell cancers, ICER (Institute for Clinical and Economic Review) wrote, "We expect the candidate populations for CAR T therapies to expand beyond the relapsed and/or refractory subsets currently under consideration by the FDA,"¹⁷ and in a separate article, Dr. Jae Park of Memorial Sloan Kettering Cancer Center in New York City said, "We're in the process of pursuing the use of CAR T-cell therapy in earlier lines of therapy. In my opinion, the earlier, the better."¹⁸

THE HUMAN AND FINANCIAL IMPACT OF GENETIC DISEASES

Perhaps the easiest financial and human burden to visualize is in children born with severe hereditary diseases, such as Tay-Sachs disease, cystic fibrosis, sickle cell disease, hemophilia, and others. Care of children who cannot walk, or even breathe or swallow on their own, is taxing, both physically and emotionally. Tragically, many of these children die young or become severely disabled by adolescence. For diseases with longer life expectancy, such as sickle cell disease and hemophilia, patients face a lifetime of intensive and expensive medical care.

"Severe rare diseases affecting children have immediate spillover effects on loved ones and may, for some diseases, span three to five decades." – Anupam Jena, MD, PhD and Darius N. Lakdawalla, PhD¹⁹

Chronic diseases that begin in childhood create not only a lifetime financial burden on families, but a physical and emotional one as well, as they often need to provide extensive direct care.^{20,21} It is not difficult to imagine how much might be saved, both in direct and indirect costs, if effective interventions were available early in the lives of children with hereditary diseases²¹ (see: "Pushing Through the Pain: One Woman Braves Sickle Cell Disease and Looks to Gene Therapy to Improve Her Life", p. 6).

A Closer Look at the Human and Financial Costs of Two Lifelong Inherited Diseases

Sickle cell disease and hemophilia are rare, inherited, chronic genetic diseases that require lifelong treatment resulting in high personal and financial burdens on individuals and their families, as well as healthcare systems and society in general.^{22,23} The yearly and lifetime cost of hemophilia treatment is such that ICER determined emicizumab (Hemlibra) is cost saving even with its annual price exceeding \$400,000. Hemlibra, which is not a gene therapy, was approved by the FDA in November 2017 as a once-weekly injection for patients with hemophilia A who have developed inhibitors, or resistance, to other treatments.²⁴

Estimating the annual and lifetime costs of such conditions is challenging due to variable disease presentations, type and frequency of treatments required, access to follow-up care, and payer source (e.g., private vs. public insurance).^{22,23} These estimates of both financial and human burden were derived by independent investigators' reviews of relevant literature about hemophilia and sickle cell disease and costs^{22,23} prior to the approval of Hemlibra for a subpopulation of patients with hemophilia A:

Pushing Through the Pain: One Woman Braves Sickle Cell Disease and Looks to Gene Therapy to Improve Her Life

Keziah is a 25-year old college graduate who can still recall the shock of having her first sickle cell crisis when she was just 8 years old. She lay in her hospital bed in severe pain and unable to walk as sickle-shaped red blood cells blocked blood flow to her organs, muscles, bones, and other tissues.

Sickle cell disease gets worse over time. "I have some amount of pain every day," says Keziah. "I can manage my mild pain crises, which come about every 1 to 2 weeks, primarily with a TENS unit that stimulates my nerves; lying down helps, but I can't do that at work." More severe crises that cannot be managed with prescription pain medication land her in the emergency room every few months. She also has monthly transfusions to replace her own sickled red blood cells.

It took 6 years, but Keziah earned her BS in legal studies. She had to take two semesters off because of her disease; one was because she had a TIA, or "mini stroke." She works at the University of Pittsburgh and plans to go to law school or graduate school for public and international affairs. "But first," Keziah says, "I'm going to have gene therapy."

Keziah is enrolled in a clinical trial. She has traveled to Atlanta for consultation and blood work and soon investigators there will harvest her own red blood cells, which will be modified and transplanted after she undergoes chemotherapy to wipe out her diseased bone marrow.

"If this gene therapy works, I won't have to take off work every month for blood transfusions or deal with the daily pain," she says. "It would improve my life in ways that are hard to even imagine right now."

Sickle Cell Disease²²

- The total health care cost for an average patient with sickle cell disease who reaches age 45 was estimated at \$953,640 in US\$2009.
- The cost of care for people with sickle cell disease (SCD) increases with age from \$892 per month for those aged 9 years and younger, to more than \$2,500 per month for those aged 50 to 64 years. (US\$2009)

Direct costs of SCD care include inpatient hospitalizations, which account for the largest proportion of costs; emergency department and physician visits; prescription drugs; home health; and skilled nursing facility care.

Hemophilia²³

- The average annual health care expenditure for a U.S. patient with hemophilia was \$155,136 from 2002 to 2008.
- People with severe hemophilia are diagnosed at a median age of 1 month and those with mild hemophilia at 36 months.²⁵ Since males with hemophilia can expect to live about 10 fewer years than males without hemophilia,²⁶ this equates to an average of nearly 67 years of treatments, which totals nearly \$12 million (not accounting for inflation).

Direct costs are attributed to: antihemophilic medication, which accounts for more than 80 percent of health care costs; clinician visits; hospitalizations; medical and surgical procedures; and laboratory tests. Chen and colleagues recognized that people with hemophilia also experience **indirect costs** including reduced productivity and increased absenteeism (e.g., resulting from complications such as recurrent bleeding), disability, and premature death, as well as **intangible costs** including decreased quality of life, emotional and psychological effects, pain, and suffering.²³

- 80 percent of patients with hemophilia and 63 percent of parents of children with hemophilia report negative impact of hemophilia on their employment.
- The estimated annual cost to the U.S. economy of underemployment due to hemophilia is \$4 million.
- 89 percent of patients with hemophilia report that pain interfered with their daily life in the past 4 weeks and 50 percent report constant pain.

The Unique Benefits of Gene Therapy

The potential benefits of gene therapies are numerous.^{17,19,20,27,28} Gene therapies can increase survival and decrease morbidity. In some cases, gene therapy can halt disease progression entirely by addressing and correcting its underlying genetic cause. For example, in a recent Phase II clinical trial of patients with the genetic blood disorder transfusion-dependent β-thalassemia, treatment with the patients' own genetically-modified stem cells reduced or eliminated the need for long-term transfusions in all 22 treated patients.²⁹

Like all medical treatments, gene therapies undergo rigorous clinical trials to assess their safety before they are approved for routine use. In addition, staff in facilities authorized to administer these treatments must undergo training with respect to safety and rescue, should life-threatening toxicities occur.³⁰

Even if the direct cost of a gene therapy were estimated as equal to the lifetime direct costs related to medical treatments for the same disease, the additional benefits of a potentially one-time treatment with a durable response need to be considered.²¹ Gene therapy can offer quality of life improvements such as improved function, reduced or eliminated pain and suffering, and a psychological sense of well-being.²¹ The anticipated durability of gene therapies is atypical among disease treatments, but time and additional study are needed to quantify it.

With reduced strains on their time and resources for caregiving, families may be able to increase their functional capacity and work productivity, which is beneficial not just for them, but for society.²⁰ Reduced absenteeism and less presenteeism—which the Harvard Business Review defines as being on the job, but not fully functioning because of illness—can reduce costs to employers.³¹

It will be important that scientists, regulators, and payers consider the benefits of gene therapies as they develop outcomes for clinical trials, review data for product approvals, and consider reimbursement decisions. The FDA has acknowledged that a new framework is necessary to encourage the development of novel gene and cell therapies.³² Because gene therapy clinical trials are often in rare disease settings, the FDA is looking at alternative statistical assessment methods beyond those used in clinical trials of more common diseases to address the challenges posed by trials for small patient populations.³³

The FDA is also making efforts to use novel endpoints and obtain patient-centered outcomes to make regulatory decisions, which highlight the relevant benefits of gene therapies for payers. For example, the FDA provided input to clinical trial designers to establish a novel endpoint to assess efficacy of Luxturna.³⁴ The patient-focused endpoint in the trial was designed to approximate real-world situations rather than simply measuring a patient's ability to see light. Payers should therefore consider gene therapy clinical trial endpoints as clinically relevant, even if they are not the typical measures of efficacy used to determine reimbursement for other types of treatments, because they may better represent the functional benefits conferred by gene therapies.

Defining Clinical Success

Some of the outcomes of gene therapy are clear and easily quantified. Tina, a teacher diagnosed with lymphoma, was facing a rapidly progressing, refractory non-Hodgkin lymphoma (see: "CAR T-Cell Therapy Returns a Teacher to Her Students," p. 8), for which median overall survival is roughly six months with standard of care treatment.⁹ Just two months after CAR T-cell therapy, Tina was cancer free, back in the classroom, and, at the time of this report, preparing for her one-year follow up.

Other outcomes are less easily defined. In the Phase III trial of Luxturna, efficacy was measured as improved "functional vision," or the ability to perform normal daily activities that are vision dependent.¹² Patients like Katelyn may not achieve perfect vision after treatment (see: "First Ever Gene Therapy for a Genetic Disease Restores a Young Woman's Independence," p. 9), but Katelyn no longer lives in fear of blindness, enjoys near-normal freedom of movement, and has a vastly improved quality of life.

Quality-adjusted life years (QALY)* is a common measure used to quantify the added benefit, or value, of new therapies compared with existing treatments.³⁵ QALYs attempt to capture both quality and quantity of life, but as one expert pointed out, "This is not simple math, and it never will be."³⁶ In addition, QALY measures may be of even more limited value in assessing gene therapies (see: "Limitations of QALY Measures for Gene Therapies").

LIMITATIONS OF QALY MEASURES FOR GENE THERAPIES

One of the challenges inherent in the use of QALY for novel gene therapies is that long-term studies have not yet been completed. Studies supporting gene therapy approvals often include only small numbers of patients, making it difficult to generalize their results using typical methods like QALY.³⁸ Moreover, it is not straightforward to compare a year of full health to, for example, a year living with vision loss of varying degrees across individual patients. The lack of long-term and large-scale experience and the subjective nature of some assessments limit the utility of QALY as an assessment tool for accurately determining the value of gene therapies.

These challenges are not unique to the U.S health care system. A bill was recently proposed in Ireland to exempt orphan drugs from use of conventional measurement tools, such as incremental cost-effectiveness ratio thresholds and QALY.³⁷ According to the spokesperson for the bill, these standard measures “disadvantage orphan medicinal products due to the often low availability of quantitative data as, by definition, a rare disease affects only a small number of patients.” Because of small patient populations and high individual costs, the bill lists a number of new criteria for considering orphan drugs, including “budget impact, level of unmet need and severity of the disease, and the availability of the drug in other European countries.”

* The core concept of a QALY is to measure both the quality and quantity of life lived.³⁵ A level of health that is more desirable is considered more valuable. The QALY scale is 0 to 1 where zero equals death and one equals perfect health for one year.

ENHANCING PATIENT ACCESS TO GENE THERAPIES

Enhancing patient access to life-changing, novel gene therapies will require flexible thinking about assessing their value and determining how to pay for the upfront costs of potentially single-administration treatments. Equitable access for all patients is crucial to actualizing the enormous potential value of these therapies. Stakeholders need to continue to consider creative approaches to pricing and reimbursement now and as more of these novel therapeutics enter the health care marketplace.

Mark Trusheim, who directs the New Drug Development Paradigms program at the Massachusetts Institute of Technology, has an interesting perspective on how payers might view the “sticker shock” of the price of these new therapies when they do consider payment. Gene therapies, he says, are moving medicine from a model of ‘renting’ treatments to one of ‘buying’ long-term health improvements.³⁸ Indeed, if long-term follow-up of already treated patients continues to show durable efficacy and safety, we will move further into a new era, one in which gene therapies mean devastating inherited diseases and even advanced malignancies do not inevitably result in chronic illness, disability, and death.

Pricing determinations for future approved gene therapy products is a topic worthy of further discussion. An important factor to consider in such conversations is that ICER has deemed CAR T-cell therapies to be cost-effective.¹⁷ In addition, ICER has indicated that if a societal perspective is used, for a younger population, Luxturna is also likely to be cost-effective compared to standard of care.³⁹ For this reason, and because FDA-approved gene therapies are already in use, initial priorities include reimbursement policies and novel payment models that encourage patient access to these treatments.

CAR T-Cell Therapy Returns a Teacher to Her Students

As Tina lay in her hospital bed, she expected to hear that she would need surgery, perhaps a hysterectomy, for the abdominal pain that had been plaguing her for many weeks. Instead, her doctor told her she had non-Hodgkin lymphoma. “Wait,” she thought, as she struggled to absorb the diagnosis. “I think that’s cancer.”

The diagnosis was followed by months of hospitalizations while she was undergoing three different types of chemotherapy. Each time the result was the same—temporary improvement and then the disease would come roaring back. Luckily, the 50-something, previously healthy fifth-grade teacher was eligible for a Phase III trial of CAR T-cell therapy. “I was the last person enrolled in that trial” she remembers.

Much of the period immediately after the CAR T cells were infused is lost to her; she has little memory of being in intensive care to manage its neurologic adverse effects. But those problems subsided and in a little more than a month, Tina was home recovering. Two months later Tina was back in her classroom, reassuring her young students that she was okay.

A year later, Tina is still well, though she still has neuropathy in her feet from the chemotherapy. She was excited to find out that the CAR-T therapy [Yescarta] she had been given in the trial was approved and would now be available to more patients. “But I worry,” she said, “about how people will pay for it. Will patients find themselves in debt for the rest of their lives? We all worry about that. A lot,” she said.

First Ever Gene Therapy for an Inherited Genetic Disease Restores a Young Woman's Independence

Katelyn's vision was never good, especially in low light conditions. A pediatric ophthalmologist diagnosed Katelyn with Leber congenital amaurosis, a rare inherited retinal disease, when she was only 9 months old, and Katelyn was told at age 14 that she would eventually be completely blind.

As a youngster, Katelyn had access to appropriate schools and adaptive equipment, but her disability made it challenging to make friends. To fill her time, she studied hard, took violin lessons, and ran track. Using various adaptive devices and accommodations, Katelyn was able to start college, but her deteriorating vision made it increasingly difficult to keep up with her studies. "I wanted to finish my education. I wanted to be independent and for that, I needed to be employed," Katelyn said.

Her parents were always on the lookout for any treatment that might help Katelyn. "I even got a passport so I would be ready to go anywhere in the world to enroll in a clinical trial," she said. After years of looking for a study that might help Katelyn, a Phase III trial of the novel gene therapy voretigene neparvovec opened in the United States and Katelyn enrolled.

Katelyn underwent treatment during a school break--a one-time injection into the eye with nine days between the procedures on each eye. "An air bubble holds the retina in place," Katelyn explained. "Within a couple of days, as the air bubble diminished, it became apparent that I could already see better in the first eye they treated!"

Today, Katelyn has a master's degree in epidemiology and a full-time job. Her vision is not perfect. She still uses some adaptive devices to enhance her vision, but she no longer fears blindness and has the independence she always wanted. "My life is very different from what it would have been without this miracle treatment."

The Fundamental Questions About Paying for New Therapies

Philosophically, the question of a durable, potentially curative treatment versus a lifetime of chronic disease or of a life cut short is easy to answer. But practically speaking, those involved with bringing these innovations to market, as well as those who are entrusted and burdened with paying for them, must consider fundamental questions, such as:

- What payment models have been proposed or are in use to pay for the value that patients receive, and can they ease the burden of higher upfront costs?
- What are the policy, legislative, and other barriers to adoption of novel payment and reimbursement structures, and can they be overcome or changed?
- How can current models be expanded or modified to accommodate new treatments that are delivered only once (or infrequently) but provide extraordinary benefit?

What Payers Value: Benefit, Duration, Safety, and Cost

In a recent survey sponsored by the Alliance for Regenerative Medicine (ARM) and the National Association of Managed Care Physicians (NAMCP),⁴⁰ managed care executives and decision makers said the most important aspects of value that would drive their decisions about covering gene therapies are the magnitude of effect on key treatment endpoints (i.e., efficacy/benefit), duration of the effect, safety, and cost. Payers are also interested in seeing improvements in productivity and reduced care burden.²⁸

In assessing relative value, payers also consider conditions and diseases for which "good enough" therapies are already available. Payers have indicated that value will be easier to establish for treatments that address diseases and patients with high unmet needs, such as cystic fibrosis, hemophilia, or sickle cell disease.⁴⁰

Despite concern for the bottom line and the challenge to remain financially solvent, particularly among smaller private payers, payers appear willing to pay for treatments that work. More than 90 percent of respondents in the ARM/NAMCP survey viewed the magnitude and duration of treatment effect as the most important factors influencing acceptance of new therapies.⁴⁰ In other words, outstanding efficacy that lasts is the No. 1 factor leading to a positive coverage decision.

Barriers to New Payment Models

In addition to the challenge of harmonizing disparate visions of what constitutes value, there are structural barriers to development and acceptance of payment and reimbursement strategies for transformative but costly novel gene therapies.

In the competitive U.S. marketplace, a “one size fits all” reimbursement solution is not feasible. Payers will design and offer their own unique contracts, manufacturers will offer or accept varying pricing models, and legislators will have differing views on what constitutes fair and equitable patient access.

The Value-Based Payment Consortium, organized by the Duke-Margolis Center for Health Policy brings together stakeholders from a variety of sectors, including manufacturers, payers, regulators, and providers to hear their views.⁴¹⁻⁴³ “Manufacturers would prefer to have buy-in from payers, so there is a strong interest in building cooperative partnerships”, according to Marianne Hamilton Lopez, PhD, research director at Duke-Margolis. “Nevertheless,” she says, “we all have to work within the constraints of a competitive system.”

Within the current U.S. health insurance environment, “beneficiary churn,” in which members move from one insurer to another, is a complicating factor in efforts to negotiate payments spread out over time, which is a favored option among payers.⁴⁴ If the effectiveness is durable and payments take place over a period of years, will the original payer be responsible for all the installments if the patient has left the plan, or will payers be able to negotiate who is responsible for paying remaining installments?

Value-based payment agreements may also be complicated and even prevented by “aspects of the current U.S. statutory and regulatory landscape.”⁴⁵ For example, Medicaid Best Price[†] regulations require that Medicaid receive the lowest price the manufacturer offers to any purchaser. Prices are tracked through monthly and quarterly reporting by the manufacturer.⁴⁷ If a manufacturer accepts an installment payment that is lower than the price it gave a Medicaid program, a new best price could be established at just a fraction of the actual price set by the manufacturer.

Reimbursement Issues

Issues related to reimbursement have also become apparent with newly-approved gene therapies. As with other new treatments, lack of reporting and billing codes for hospital services that are specific to new therapies may lead to delays or risk of denial in reimbursement under current miscellaneous codes until new codes are assigned. Any delay is significant because diffuse large B-cell lymphoma, for example, is a fast growing and aggressive lymphoma. Hospitals may not wish to cover costs for CAR T-cell therapy without assurance that they will be reimbursed adequately.

Limitations specific to current Medicare and Medicaid reimbursement policies have also become apparent. Medicaid is the single largest health insurer of U.S. children, especially those with special health needs,⁴⁸ which is relevant for both Kymriah and Luxturna patient populations, and approximately 56 percent of new cases of non-Hodgkin lymphoma are in patients of Medicare age (65+).⁴⁹

The American Society for Blood and Marrow Transplantation (ASBMT) has indicated that for CAR T-cell therapies, the high cost of acquiring the personalized CART product is additive to the cost of the hospital services required to administer the therapy in the inpatient setting, where the procedures are typically performed.^{50,51} The likely bundled Medicare payment (diagnosis related group) that would be assigned through existing claims submission and reimbursement processes would leave hospitals facing vast financial losses for direct expenses, even after factoring in the possibility that CAR T-cell therapy may qualify for additional outlier payment—supplemental payments to hospitals designed to protect hospitals from significant financial losses resulting from patient-care cases that are costly.⁵²

The Centers for Medicare & Medicaid Services (CMS) recently proposed grouping CAR T-cell therapy with the higher-weighted diagnosis related group (DRG) for autologous bone marrow transplant. CMS is also considering additional options, including establishing a new DRG for CAR T-cell therapy in 2019, and approving company applications for New Technology Add-on Payments (NTAP), which can provide additional payment for breakthrough technologies for Medicare patients. Under current regulations, Medicare can pay a marginal cost factor of 50 percent on the costs of the new technology in excess of the DRG payment. CMS has requested comments on these options,⁵³ and is expected to publish a final rule in August 2018.

[†]The Medicaid Best Price program requires drug manufacturers to give Medicaid the best price given to any other purchaser by providing it with a mandatory rebate of 23.1 percent of the average manufacturers’ price or, if another purchaser is offered a greater rebate, that greater rebate amount.⁴⁶

Medicaid program determinations for reimbursement are made at the state level. The New York State Medicaid fee-for-service (FFS) program provides an example of how to sufficiently reimburse for the three new gene therapies, by reimbursing facilities for the drug in addition to the bundled payment for services.⁵⁴⁻⁵⁶

Medicaid Best Price reporting may limit the ability for pharmaceutical companies to charge for new gene therapies in installments, a payment model proposed by Spark Therapeutics⁵⁷ (see: "New Payment Models Are Already Here"). Because best price rebates are averaged across all prices, installment payments would be averaged as if they were "full prices" and would reduce the gene therapy price dramatically.

One way to potentially address this problem posed by Medicaid Best Price requirements is offered by Spark Therapeutics' proposal to enter into an agreement with commercial payers under which the payer's specialty pharmacy, rather than the treatment center, purchases Luxturna. The specialty pharmacy then could arrange to receive payment in installments on its own.⁵⁸

Medicaid Best Price requirements may also impede value-based pricing that offers rebates based on outcomes, for example, if a company were to offer a 70-percent discount if efficacy were not attained for a single patient, even if he or she were privately insured, then it would need to extend that level of rebate to all Medicaid patients regardless of their outcomes.

Payer Opinions on Payment Models

Many payment models have been proposed to enable patient access while addressing payer ability to cover high upfront costs and supporting continued innovation.^{20,21} All stakeholders need to work collaboratively on a suitable approach. Because a workable solution depends upon payer input, and because payer surveys and workshops have provided insights into their thinking, ASGCT is prioritizing the assessment of payer-preferred solutions. Another priority is to evaluate solutions that are already being attempted or implemented, or being proposed for implementation, for approved therapies.

Payer preferred solutions include outcome-based contracts that share risk, in which the payer's exposure is reduced or eliminated if a patient does not respond to treatment; contracts that offer installment payments spread out over time; and risk pools, to provide insurers with a resource to which they all contribute and that serves to support them all when a patient's medicine costs exceed a certain threshold.²⁰

At a workshop attended by private payers, the high-risk pool model emerged as a favored long-term option.⁴⁰ In risk pooling (with carve-out), private payers, budget holders, employers and/or state governments would put a certain percent of their premiums or health care budget into a dedicated fund for specified high value medicines. If a patient's medicine costs exceed a certain predetermined threshold, monies would be paid out from this fund.²⁰ Similar findings were noted in another survey of payer perspectives, which reported that "payers favor performance-based milestone contracts and risk pool strategies."⁴⁴

Payers favor models that include installment payments over time, particularly if they include an outcome-based stop payment clause.⁴⁴ This model requires diagnostic monitoring: "if the patient stops responding, the payer organization stops reimbursing the therapy."⁴⁰ The requirement of additional reporting, however, may add a logistical and financial strain on health care providers that could limit the frequency of outcomes reporting.

Likewise, the manufacturers, payers, and regulators brought together at the Duke-Margolis Health Policy Value Payment Consortium appeared to favor three approaches that modify or augment current financial systems, according to Dr. Hamilton Lopez:

- Upfront payment for therapy, with rebates based on outcomes
- Installment payments linked to outcomes
- Contracts developed with input across three major stakeholders: health care providers, payers, and pharmaceutical companies

New Payment Models Are Already Here

New payment models are already being offered for recently approved gene therapies. Spark Therapeutics is offering agreements that include rebates to payers at 30 to 90 days and 30 months if Luxturna falls short of established efficacy goals, which compare full-field light sensitivity threshold scores against baseline measurements before treatment.^{36,58,59} Michael Sherman, chief medical officer of Harvard Pilgrim Health Care, a Massachusetts-based insurer, called the outcome-based rebate arrangement “truly innovative, as it ties payment for the therapeutic not only to a short-term goal, but also to a longer-term, 30-month assessment of efficacy.”⁵⁹

Spark has also proposed a plan that would enable the company to offer payers the option to pay by installments over several years and to provide greater outcomes-based rebates than current pricing regulations allow.^{36,58} In addition, Spark is proposing to contract directly with commercial payers or their specialty pharmacies, rather than with treatment centers. Doing so would reduce the financial risk for those facilities of costs associated with administering the therapy.⁶⁰

Likewise, Novartis has offered an outcome-based pricing strategy for its CAR T-cell therapy, Kymriah, for its leukemia application. The company has developed agreements with hospitals not to invoice for Kymriah until the 30-day outcome test is completed, and invoice only for patients who have responded successfully to treatment.⁶¹ This plan “allows for full payment only when patients respond to Kymriah by the end of the first month after treatment.”

In addition to outcome-based pricing and other strategies, while payers are developing their coverage policies, companies offer patient access and support programs to help navigate payment challenges and logistics.^{52,62} The makers of all three recently approved gene therapies have established patient support programs to assist with insurance, travel, and accommodations before, during, and after treatment.^{58,63,64}

These early pricing and payment models may pave the way for other manufacturers, providers, and payers to find ways to facilitate patient access while encouraging continued pharmaceutical innovation. Still, it is important to note that these payment models are for treatments approved for small patient treatment pools, which limits payer exposure and may give them more flexibility than they will have in the future when gene therapy treatments are approved for larger numbers of patients.

COMING TO CONSENSUS AND NEXT STEPS

Pharmaceutical companies, payers, and policy makers need to work together to ensure payment models allow patients access to the next generation of transformative medicines. Health care professionals, scientific researchers, professional societies, and patient advocacy groups should actively provide their unique and valuable insights to help in this endeavor.

Two areas in which scientific organizations and their professional members may be able to offer expertise are in setting or evaluating standards and in monitoring real-world evidence regarding gene therapy safety and efficacy. Societies, such as ASGCT, may also participate in research, support, and advocacy for feasible payment models for gene therapies with the dual goals of ensuring patient access to effective treatment and encouraging further scientific innovation.

Ongoing discussion and knowledge sharing among stakeholders, including recognizing the need to consider new and future gene therapies in any cost and payment discussion, is essential. For instance, at the end of 2017, the Center for Medicare and Medicaid Innovation (CMMI) requested input on plans to test models in 8 focus areas, including new pricing and payment model designs for prescription drugs.⁶⁵

In response, ASGCT recommended that CMMI consider testing existing and new payment methodologies for gene and cell therapies “to ensure access to care to these durable and potentially curative treatments.” Additionally, ASGCT recommended that if outcomes-based testing models for gene and cell therapies are created, “CMMI establishes a process to obtain input from experts in the field to contribute to identifying the criteria that will define successful outcomes, as well as the anticipated time frame for such criteria to be attained.”⁶⁵

ASGCT looks forward to continuing its contributions as it fulfills its mission to bridge the interests of researchers, patients, developers, and society.⁶⁵

Moving Toward Consensus

Several groups have organized live meetings to facilitate conversations among stakeholders. In addition, to obtain input from broader samples of decision makers, surveys have been developed to identify barriers to coverage of treatment costs and payer preferences. These efforts must continue and intensify, as stakeholders attempt to identify workable solutions.

To that end, ASGCT is planning a value summit to gather stakeholder representatives, including public and private payers, pharmaceutical manufacturers, patient advocates, provider representatives, health policy analysts, and representatives from key organizations for a day of presentations and discussion. The primary goals are to discuss current proposals for improving patient access to gene therapy, and to identify shared priorities across stakeholder groups and opportunities for next steps. Participants will have a chance to interact with each other on key issues, especially exploration of alternative reimbursement and financing models.

ASGCT Position and Recommendations

As the leading society representing gene and cell therapy research, ASGCT supports efforts to advance scientific knowledge and bring new and transformative therapies to patients with unmet needs. Maximizing patient access will likely require a combination of solutions created through the efforts of multiple stakeholders in the field. ASGCT calls on every stakeholder examining proposed value-based models for transformational gene therapies to support the broadest possible patient access without limiting scientific innovation.

ASGCT is committed to engaging in the following actions on priority solutions that could enhance patient access to currently approved gene therapies:

- Support the creation of new reporting and billing codes for provider services that are specific to new therapies, to prevent potential delays or risk of denial in reimbursement under current miscellaneous codes.
- Encourage solutions that would increase Medicare reimbursement levels, to improve coverage of hospital costs for both the gene therapy and the hospital services to administer it.
- Promote the adoption of payment policies by state Medicaid programs that sufficiently cover the costs of both the gene therapy and the cost of services to administer the therapy.
- Facilitate the creation of national registries to collect post-approval data on gene therapy consistent with FDA requirements for the collection of long-term data (15 years). Researchers and manufacturers must be urged to report all ongoing findings and to analyze post-marketing data, whenever possible, to provide updated, mature results that confirm (or modify) initial reported outcomes. Such data could be utilized to determine revised outcome measures for use with value-based payment models.
- Recommend further exploration of the following in terms of feasibility of implementation, enhanced patient access, and risk reduction for a variety of stakeholders:
 - Direct billing of payers, or their specialty pharmacies, by pharmaceutical companies to reduce risks to hospitals.
 - A high-risk pool to limit exposure by any one payer or budget holder.
 - Value-based payment models, including their ability to produce cost savings for gene therapies.
 - Payment over time, with payments spread out over a defined number of years.
 - Decreasing barriers to solutions such as value-based payment and payment over time that are posed by Medicaid Best Price requirements.

American Society of Gene & Cell Therapy

The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. ASGCT's strategic vision is to be a catalyst for bringing together scientists, physicians, patient advocates, and other stakeholders to transform the practice of medicine by incorporating the use of genetic and cellular therapies to control and cure human disease.

Conclusion: Patient Access Is Essential for Actualizing Value of New Treatments

The challenges to development of gene therapy treatments were monumental, and yet, researchers worked tirelessly for years to bring us new transformative therapies, with more on the way. These therapies have the potential to transform our entire approach to disease treatment, but only if they can be accessed by the patients who will benefit from them.

The pathway to payment for these remarkable new therapies is also filled with potential challenges including policy limitations, differing perspectives on their value, and the interests of various stakeholders. Nevertheless, now that the first approved products are here, it is the responsibility of all stakeholders to take on the challenge, maximizing patient access to medicines that can transform lives while encouraging continued scientific innovation of these treatments.

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