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CELL AND GENE THERAPIES: Looking Ahead to 2022

INTRODUCTION

Cell and gene therapies are a new category of medicines transforming how we treat and potentially cure disease. Both cell and gene therapies seek to modify genetic material to fight disease. Cell therapies involve cultivating or modifying cells outside the body before injecting them into a patient. Gene therapies use genetic material to manipulate the expression of a gene or alter the properties of an individual's cells. In the US, the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) regulates cell and gene therapy products.

Today, seven cell and gene therapies are approved for marketing in the US and fewer than 10 are approved in Europe. Dozens of new cell and gene therapies are expected to become available in the US in the coming years. According to research by the MIT NEWDIGS FoCUS project, more than 1,000 cell and gene therapies are currently in development. By 2030, MIT NEWDIGS expects 50–75 therapies to be approved in the US.

In response to this growing pipeline and the hope these therapies offer, FasterCures has convened numerous roundtables and discussions to bring to light the unique regulatory and access considerations posed by cell and gene therapies. On November 3, 2021, we again brought together our stakeholder community, along with Peter Marks, director of CBER at FDA, in a virtual roundtable. The goals of the roundtable included taking stock of the current status of cell and gene therapies given the disruptions caused by the COVID-19 pandemic and identifying opportunities for collective engagement in 2022.

CELL AND GENE THERAPY LANDSCAPE AND OUTLOOK IN THE US

In the US, the FDA has approved seven cell and gene therapies for marketing (see Table 1). Five of the approved therapies are CAR-T cell therapies to treat certain hematological cancers. Two are gene therapies to treat two rare diseases: spinal muscular atrophy and inherited retinal diseases such as Leber congenital amaurosis or retinitis pigmentosa.

TABLE 1: APPROVED CELL AND GENE THERAPIES IN THE US

THERAPY NAME	MANUFACTURER	DRUG CLASS	INDICATION (YEAR APPROVED)
Abecma (idecabtagene vicleucel)	BMS, bluebird bio	CAR-T cell therapy	Relapsed or refractory multiple myeloma (2021)
Breyanzi (lisocabtagene maraleucel)	BMS	CAR-T cell therapy	Relapsed or refractory large B-cell lymphoma (2021)
Kymriah (tisagenlecleucel)	Novartis	CAR-T cell therapy	Relapsed or refractory B-cell acute lymphoblastic leukemia (2017) Relapsed or refractory large B-cell lymphoma (2018)
Luxturna (voretigene neparvovec-rzyl)	Spark Therapeutics	Gene therapy	Inherited retinal diseases, such as Leber congenital amaurosis or retinitis pigmentosa (2017)
Tecartus (brexucabtagene autoleucel)	Kite Pharma	CAR-T cell therapy	Relapsed or refractory mantle cell lymphoma (2020) Relapsed or refractory B-cell acute lymphoblastic leukemia (2021)
Yescarta (axicabtagene ciloleucel)	Kite Pharma	CAR-T cell therapy	Relapsed or refractory large B-cell lymphoma (2017) Relapsed or refractory follicular lymphoma (2021)
Zolgensma (onasemnogene abeparvovec-xioi)	Novartis	Gene therapy	Spinal muscular atrophy type 1 (2019)

Source: Paying for Cures Toolkit: For Patients, MIT NEWDIGS FoCUS (2021) and company reports (2021).

In 2022, six therapies with breakthrough designations are projected to be approved by FDA, including two gene therapies for the treatment of hemophilia (Table 2). The year 2023 may herald gene therapies to treat a variety of conditions, including sickle cell disease and diabetic peripheral neuropathy.

TABLE 2: PROJECTED APPROVALS OF THERAPIES WITH BREAKTHROUGH DESIGNATIONS IN 2022

THERAPY NAME	MANUFACTURER	DRUG CLASS	INDICATION
ciltacabtagene autoleucel	Janssen Pharmaceuticals	CAR-T cell therapy, ex vivo	Relapsed or refractory multiple myeloma in adults
Instiladrin (nadofaragene firadenovec)	FKD Therapies/Ferring Pharmaceuticals	Gene therapy, in vivo	High-grade, non-muscle invasive, bacillus Calmette-Guérin (BCG)-refractory bladder cancer in adults
LentiD (elivaldogene autotemcel)	bluebird bio	Gene therapy, ex vivo	Cerebral adrenoleukodystrophy in males aged less than 18 years
Zynteglo (betibeglogene autotemcel)	bluebird bio	Gene therapy, ex vivo	Beta-thalassemia major in transfusion-dependent patients aged 12+ years; transfusion-dependent beta-thalassemia in patients aged 12+ years with a beta-0/beta-0 genotype
etranacogene dezaparvovec	uniQure	Gene therapy, in vivo	Hemophilia B in adults
Roctavian (valoctocogene roxaparvovec)	BioMarin Pharmaceutical	Gene therapy, in vivo	Severe hemophilia A in adults

Source: Gene Therapy Pipeline Report, CVS Health (August 2021) and company reports (2021)

KEY DISCUSSION TOPICS

Launch of the Bespoke Gene Therapy Consortium

In late October 2021, FDA and the National Institutes of Health (NIH) announced a partnership with 15 biopharmaceutical companies and nonprofit organizations to develop the Bespoke Gene Therapy Consortium (BGTC). The collaboration is dedicated to accelerating the development of gene therapies for people with "bespoke" genetic diseases and disorders (i.e., those affecting populations too small to be commercially viable).

The BGTC will focus on a single gene delivery technology: adeno-associated virus (AAV) vectors, which are the most commonly used viruses to deliver gene therapies to different cells. Although AAV vectors are widely used in gene therapy clinical trials, recent events have called their safety into question.

The main goals of the BGTC include the following:

- better understand the basic biology of AAV technology itself (not from a disease-specific perspective but rather to help the entire field);
- accelerate preclinical and product testing by generating information that can be shared with the community;
- facilitate scientific and regulatory advances (e.g., by delineating for product sponsors the information that needs to be submitted to regulators and how complete that information needs to be); and
- bring therapies to people who need them sooner, including by investigating more efficient ways to do clinical trials.

One expected output of the consortium is an operational playbook that includes streamlined templates, master regulatory files, and uniform production processes.

The BGTC plans to fund four to six clinical trials, each focused on a rare disease. It will follow a disease-agnostic approach and seek input from the patient community, industry, and academia to select diseases for the program.

To engage in the consortium's work, the broader cell and gene therapy community can respond to two requests for applications (RFAs) to solicit research on AAV biology and a request for information (RFI) to help inform the selection of rare diseases and disorders.

The BGTC is rooted in Platform Vector Gene Therapy (PaVe-GT), a pilot project led by the National Center for Advancing Translational Sciences (NCATS) and launched in 2020. The goal of the PaVe-GT pilot is to test whether the efficiency of a gene therapy trial startup can be significantly increased through the use of a standardized process, with the same capsid and manufacturing

methods, for four different rare diseases. The work of PaVe-GT will continue, even as the BGTC gets underway. All results, documents, and learnings from the PaVe-GT project will be made publicly available to benefit future AAV gene therapy efforts.

What to Expect from CBER

In 2021, growth in investigational new drug applications (INDs) for cell and gene therapies resumed its pre-COVID-19 trajectory, according to CBER Director Peter Marks. FDA is staffing up, not only in the Office of Tissue and Advanced Therapies (which focuses on cell and gene therapies) but also in all the support functions. Marks expects staffing increases in various programs in the next two to three years and up to 50 percent in certain areas, in part facilitated by the upcoming reauthorization of the Prescription Drug User Fee Act (PDUFA VII). Now with a full year of functioning virtually because of COVID-19, FDA is considering hiring individuals outside of the Washington, DC, area as one way to maintain FDA's competitiveness in recruiting talent and retaining staff who are close to retirement.

According to Marks, CBER is contemplating ways to provide product sponsors with better defined expectations "on the first try" to limit the back-and-forth that can inevitably cause delays. At the same time, Marks expressed that a key learning from the COVID-19 vaccine experience is that iterative interactions between CBER and sponsors that enable resolution of issues in near real-time, rather than single meetings, are critical to accelerating development timelines.

Data Collection Journeys

For the seven cell and gene therapies approved for marketing in the US, FDA requires post-approval data collection for up to 15 years. Long-term follow-up data are needed to address the many unanswered questions about the long-term safety and effects of these therapies, but as discussed in prior FasterCures reports (July 2020 and November 2020), the data collection infrastructure needed to support such activities on a broad scale is not yet in place.

In parallel with the growth of the cell and gene therapy pipeline, multiple models to collect data have emerged that can offer best practices. According to Marks, CBER does not prefer any one approach. He envisions a role for registries to satisfy long-term follow-up requirements but encourages product sponsors to consult with FDA prior to a product's approval. Marks also encourages entities that are developing databases to design for interoperability with databases for other diseases—to enable future analyses across different diseases (for example, to examine the performance of a vector).

During the roundtable, representatives from Cure SMA, Center for International Blood and Marrow Transplant Research's (CIBMTR) Cellular Therapy Registry, and the World Federation of Hemophilia's Gene Therapy Registry presented on their organizations' data collection activities. Cross-cutting lessons from these activities include the following:

- Build a data collection system that can serve multiple purposes. When designing a database, it is important to understand the ways that the information needs of regulators, payers, industry, providers, and patients may differ and consider whether and how those needs should be addressed in data collection.
- Collect patient-reported outcomes to understand the patient perspective that a clinical measure might not capture.
- Formalize a feedback loop to patients and providers to build long-term commitment and engagement. Sharing findings through site-specific reports, meetings, and publications can incentivize further data collection by returning the insights to providers and patients who can then use that information to make decisions about care.

CURE SMA: A PATIENT ORGANIZATION-LED MODEL

Cure SMA is dedicated to supporting patients and families affected by spinal muscular atrophy (SMA). It funds and directs research that drive breakthroughs in treatment and care.

Since 2016, Cure SMA has invested in four major data collection efforts to provide information critical to improving quality of care, ensuring access, and developing new treatments.

- The membership database collects family-reported data and outcomes to better understand the natural history of SMA from the patient perspective and to measure the changing SMA phenotype as both current and anticipated future treatments become available. The data are used to recruit for clinical trials and focus groups as well as to inform discussions with regulators, payers, industry partners, and health-care providers.
- The SMA community survey is conducted annually to understand the burden of illness, treatment patterns, and quality of life.
- The clinical data registry collects data from electronic health records to inform evidence-based care, understand access to new treatments and the changing disease phenotype, and eliminate duplication of care documentation. As incentives for participating centers, Cure SMA offers grants and provides site-specific data back to the center. The registry is also used for clinical trial site development, trial recruitment, and new drug development.
- The newborn screening survey collects parent-entered data relating to positive newborn screen time to diagnosis and time to treatment in order to understand the impact of newborn screening on SMA.

CIBMTR'S CELLULAR THERAPY REGISTRY: ADAPTING AN EXISTING INFRASTRUCTURE FOR LONG-TERM FOLLOW-UP

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. CIBMTR maintains one of the world's largest observational databases of clinical information on hematopoietic cell transplantation (HCT).

Since 2016, CIBMTR has operated the Cellular Therapy Registry (CT Registry), which collects data on cellular immunotherapies for cancer. The CT Registry collects data on the baseline characteristics of patients, along with pre- and post-infusion data, infusion details, disease response, and outcomes. Similar to CIBMTR's HCT database, the CT Registry captures long-term outcomes of recipients of CAR-T cell therapies.

After the US approval of Kymriah (Novartis) and Yescarta (Kite) in 2017, CIBMTR developed post-approval safety studies, which are structured as prospective observational studies. The studies use the CT Registry as the infrastructure for the long-term follow-up of recipients of these therapies. Today, the CT Registry collects data on all five commercially approved CAR T-cell therapies in the US. Although mandatory for the CAR-T cell therapy manufacturers, data collection by the treatment center is voluntary. A key to the CT Registry's success is its reliance on an existing infrastructure, which enabled early adoption and seamless integration by treatment centers. Also key to success is the standardization of data collection across all CAR-T products.

Today, more than 5,000 CAR-T cell recipients are included in the CT Registry. Future plans include expanding the CT Registry to include newer indications in hematologic cancers and solid tumors, incorporating patient-reported outcomes, and enabling data collection for gene therapies.

WORLD FEDERATION OF HEMOPHILIA GENE THERAPY REGISTRY: PREPARING FOR THE ARRIVAL OF GENE THERAPIES

The World Federation of Hemophilia (WFH) is an international not-for-profit organization dedicated to ensuring that individuals affected by hemophilia and related inherited bleeding disorders have access to high-quality medical care and services.

WFH is leading the development of a global Gene Therapy Registry (GTR). The GTR is a prospective observational registry that aims to collect data on all people with hemophilia worldwide who receive gene therapy via clinical trials and at post-market approval (including previous trial participants).

A foundational step in the development of the WFH GTR was the publication in 2018 of a core outcome set for clinical trials of gene therapy in hemophilia. The outcomes—which were developed and agreed upon by a multi-stakeholder group—are considered essential to measure, demonstrate, and differentiate the effectiveness and value of a hemophilia gene therapy. The GTR protocol was developed with input from a multi-stakeholder steering committee that included regulators, international professional societies, and patient organizations. Using this same process, WFH developed a core data set that includes data on, among other things, demographics, safety, efficacy, quality of life, and mortality.

The data in the registry will be captured through data transfer from existing national hemophilia registries or directly from participating hemophilia treatment centers. A patient app will be used to capture patient-reported outcomes data. Notably, patient consent will be obtained for clinical and patient-reported data collection and use for clinical and other research purposes, including for economic analyses and precision financing schemes.

WFH is positioning the GTR to support multiple purposes including post-market safety surveillance, performance-based arrangements and other precision financing schemes, and health technology assessments and ICER (Institute for Clinical and Economic Review) reviews. GTR data collection is expected to begin in the second quarter of 2022.

How to Ensure That Cell and Gene Therapies Benefit All and Not Just a Few

The novelty of cell and gene therapies introduces different and more complex access challenges than do traditional medicines. Many patients may not become aware of the availability of these emerging treatment options, especially those living in areas with limited access to health care. Patient organizations, which serve as a vital source and conduit of information, may not possess the same level of experiential knowledge on new cell and gene therapies as they do with other types of therapies to share with their communities, especially in the initial months of a product's approval. The understanding of providers, too, will take time to develop.

The lack of diversity in the individuals seeking treatments such as CAR-T therapies and participating in clinical trial networks, offers troubling signs that not all patients who could benefit from cell and gene therapies can access them, according to roundtable participants. When individuals cannot access needed care in a timely and efficient manner, the cost to the health-care system is much greater than estimates of direct medical costs would suggest. According to EveryLife Foundation's Burden of Rare Disease Study, the economic burden of rare diseases in the US was nearly $1 trillion in 2019. The majority of this burden stems from indirect costs (e.g., productivity loss) and non-medical or uncovered costs (e.g., transportation or home/auto modifications). These findings were reinforced in a recently published study led by NCATS, which found that health-care costs for people with a rare disease are three to five times greater than those for people without a rare disease.

Much work remains to be done to understand the scope of logistical, informational, financial, and emotional challenges to accessing cell and gene therapies. With this goal in mind, FasterCures created a journey map that delineates some of the fundamental questions that patients and caregivers may have on their care journey. The journey map aims to help identify areas where that experience might be improved. However, systemic barriers in our health-care system mean that this journey will look very different depending on the individual. These systemic barriers include inadequacy or lack of insurance coverage, lack of geographic availability and accessibility of treatments, structural racism that causes inequalities in health-care access, and lack of culturally competent care.

As cell and gene therapies become viable treatment options for more diseases, health disparities will worsen unless meaningful actions ensure that all individuals can access these transformative therapies. Greater efforts to hear from diverse patient communities will be essential to developing educational and outreach tools that have resonance and impact.

CONCLUSION

The year 2022 offers great promise in the cell and gene therapy field. The pipeline is robust, and the community is committed to working together to ensure that these therapies reach the market. The work of the Bespoke Gene Therapy Consortium and additional resources at CBER will do much to advance the goal to deliver transformative therapies to patients faster. However, the road will not be smooth. Despite the benefits of data collection to enhance our understanding of cell and gene therapies and improve quality of care, developing a data infrastructure that is collaborative, interoperable, and does not place an undue burden on patients and providers will be challenging. Agreement on the data and evidence that can support care decision-making, regulatory decisions, and coverage and reimbursement will also be needed. Finally, the cell and gene therapy field could further health inequities in the US health-care system if we do not take a thoughtful and proactive approach to ensuring equitable access to these groundbreaking therapies.

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