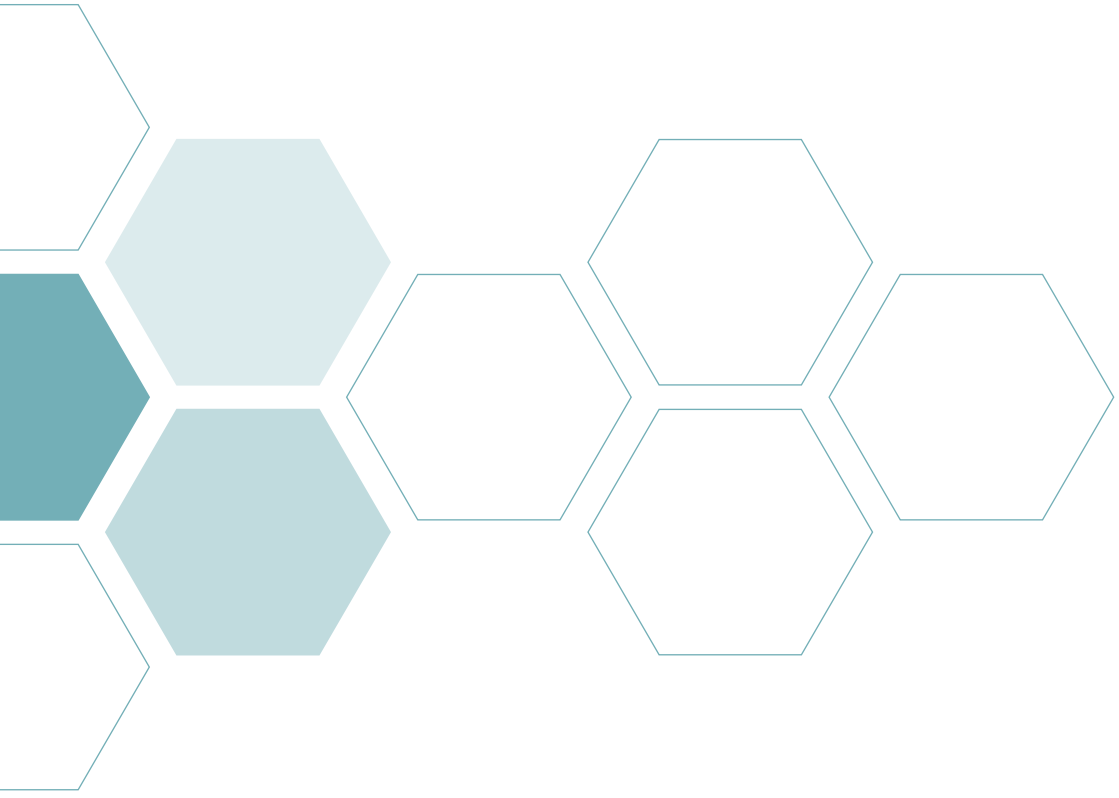
Roadmap for Navigating the Provider Side of Cell and Gene Therapy (CGT) Patient Access in U.S. Managed Care



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Alliance for Regenerative Medicine

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Cell and Gene Therapy Navigation Roadmap 2020

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Roadmap for Navigating the Provider Side of Cell and Gene Therapy (CGT) Patient Access in U.S. Managed Care

Eric Faulkner, MPH; Michael Werner J.D.; R. Falb

I. Summary

An initial group of cell and gene therapies (CGTs) have launched within the past two to three years, opening the door for what are arguably transformative health outcomes in oncology and rare disease. Much has been written about the payer-side considerations associated with CGT uptake, but the provider-side is just as critical to patient access to novel CGTs. Considerations such as provider knowledge and willingness to adopt, provider expertise, administrative infrastructure, adoption incentives, reimbursement uncertainty, and other factors can all influence acceptance and uptake.

This study evaluates the provider side of U.S. managed care, from the U.S. hospital and health system perspective. The provider-side is an aspect of the CGT delivery infrastructure that is arguably not as well understood nor discussed in the same detail as payer acceptance. However, navigation of the provider-side of CGT is equally essential to appropriate patient access to these transformative therapies.

The results are intended to help health stakeholders identify and understand where provider-side challenges and opportunities associated with offering CGTs exist. They can also help the next wave of CGT developers prepare for a provider environment that is more complex than that traditionally associated with traditional small molecule and biological therapies.

II. Introduction

Novel health technologies such as, medical devices, precision medicines, immunotherapies and CGTs entering the U.S. managed care environment face many navigational challenges *en route* to patient access. While the greatest emphasis from an access perspective is often on health technology assessors and payers that leverage coverage, coding, and payment tools to manage beneficiary reimbursement processes, the provider-side of acceptance and uptake is also critical to consider.

It has been well-documented that CGTs, which have the potential to transform or cure disease, were not anticipated by global reimbursement or payment systems.[1,2,3] Factors such as single-administration (that can offer years or a lifetime of health benefits), complex handling and administration, lack of payment models built for transformative therapies and their associated costs have been shown to influence uptake on the payer-side of the CGT acceptance equation.[4]

However, unlike most small molecule and biological therapies, the provider side of CGTs is particularly complex, critical to patient access, and arguably less well understood. Disincentives for acceptance and uptake can include factors such as appropriate facilities and training to administer CGTs, manufacturing turn around and supply chain considerations, lack of single-administration therapy fit into hospital purchasing and payment systems, uncertainty around reimbursement, hospital affordability and profitability considerations, requirements for handling/storage/preparation and other factors.[5,6,7,8,9]

This paper will consider the state of the union and issues necessary for successfully navigating CGTs (also referred to as regenerative and advanced therapies) through the provider-side of a U.S. health system that is not fully built to receive them. It is meant to be a companion document to the ARM NAMCP Reimbursement Roadmap Published in 2019.[10] This publication is also intended to highlight key considerations necessary for optimizing the

ability of providers to offer CGT as standard-of-care as these therapies expand in the U.S. marketplace.

III. Methods

The Genomics, Biotech, Emerging Medical Technology Institute (GBEMTI) was established in 2011 as an institute of the National Association of Managed Care Physicians (NAMCP). The NAMCP has over 20,000 members and represents medical directors from payer, purchaser (employers), and provider systems such as independent practice associations (IPAs), accountable care organizations (ACOs), physician-hospital organization (PHOs) and medical groups. The goal of GBEMTI is to support and characterize the value of genomics, biotechnology, CGT medicines and medical technologies as these new modalities enter and impact the healthcare system. The GBEMTI seeks to support collaborative stakeholder engagement around emerging health technologies to consider their potential to improve patient outcomes, impact on managed care management practices and value to the health care marketplace. The Institute is guided by an Executive Leadership Council (ELC) comprising approximately 100 payer and manufacturer members. The GBEMTI is unique in that it is a multi-stakeholder group centered around bringing medical director decision makers and manufacturers together to address key trends and topics, that are transforming U.S. health care, and explore means to improve managed care decision making and patient access to emerging health technologies.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory and reimbursement initiatives to advance this innovative and transformative sector, which includes cell, gene, and tissue-based therapies. Early products to market have demonstrated profound, durable, and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. Hundreds of additional product candidates contribute to a robust pipeline of potentially life-changing regenerative medicines and advanced therapies. In its 11-year history, ARM has become the voice of the sector, representing the interests of more than 350 members worldwide, including small and large companies, academic research institutions, major medical centers, and patient groups.

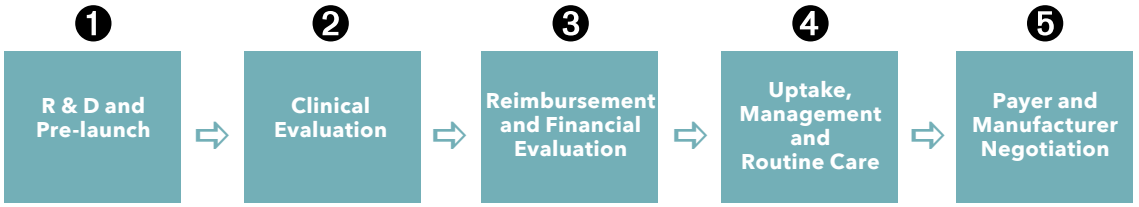
This study, conducted between October 2019 and March 2020, involves both a survey of medical director members of NAMCP and a face-to-face workshop between payers representing a range of U.S. health plan types and ARM CGT medicine company representation. The survey questions addressed key payer perspectives on CGT medicine and highlights key issues relevant to payers, providers, and manufacturers. The survey was randomly disseminated to medical director members of NAMCP and 42 total responses were obtained. Of the total respondents, approximately 70 percent identified themselves as medical directors at health system and provider organizations and 30 percent identified themselves as commercial managed care organizations (MCOs) that service health system and provider organizations. Of the provider sample, approximately 30 percent were from community or regional hospitals, 15 percent were from academic medical centers, and 20 percent were from independent or private practices. Additional feedback was obtained through a workshop involving regional and academic hospital system executives (though executive and treating physician decision drives may differ or conflict) and commercial payers from both national and smaller regional plans, to add context, clarify responses and explore solutions that would help characterize provider considerations and clarify manufacturer challenges associated with ensuring patient access to CGTs.

IV. Findings and Implications

As a framework for identifying critical success factors for navigating CGTs through the provider-side of the U.S. health system, the following core domains (Figure 1) were covered to explore the process involved in each domain from a U.S. provider perspective. Participants also discussed how CGTs can be integrated into the existing system, identified gaps, and captured perspectives on solutions for uptake challenges associated with available CGTs. Differences related to the following variables were also considered: provider type, disease prevalence and severity, adult versus pediatric treatment, and setting of care to help identify special considerations important for manufacturers and other stakeholders to consider.

The following describes key findings from the survey and in-person workshop around each domain associated with adoption drivers, demonstration of benefits and risks of CGTs. This flow is intended to isolate key steps in the provider decision flow, stakeholder involvement and perspectives, and special considerations for CGT use via U.S. healthcare systems and provider organizations. While additional details beyond the scope of this paper will apply, this road-mapping approach is intended as a guide for navigation of the core steps required to achieve successful patient access

Figure 1: Understanding Provider-side Decision Flow, Process Considerations, and Stakeholder Drivers: Core Domains Covered in this Analysis



As we discussed this journey, the following considerations were also discussed:

- **Provider type:** Community or regional hospitals, academic medical centers, indepenent or private practices.
- **Disease prevalence/severity:** e,g., Orphan versus Oncology versus other disease areas
- **Adult versus Pediatric** considerations
- **Setting of Care:** Inpatient versus Outpatient

in the U.S. managed care provider and hospital environment for transformative, or curative CGTs.

A. Provider Engagement During Development and Prelaunch

Clinical trials and other studies represent the front-line for provider engagement in development and launch of CGTs. Initial clinical development is a crucial time (and opportunity) to identify and streamline acceptance drivers involved in providing a new CGT to patients. While not all of these factors are specific to CGTs, and some may have more in common with the factors one must consider in developing new innovative medical devices, the culmination of factors does make planning for provider acceptance of CGTs a different consideration from conventional drug planning. This section evaluates key factors for CGT during the pre-launch period and the benefits of early engagement between CGT manufacturers and providers.

Degree of Early Manufacturer Provider Engagement

Just over 40 percent of survey respondents indicated that early engagement between providers and manufacturers or payers occurred during CGT development (Figure 2). Perhaps not surprisingly, the greatest degree of engagement was found to presently occur at academic or integrated health systems. This is consistent with the niche or rare focus of many of the vanguard of transformative CGTs in development.

Because of the provider distribution, (i.e., a blend of provider types in the respondent pool as described in the methods), this finding does not necessarily indicate inefficiencies in the engagement model. However, it is safe to conclude that additional attention to provider engagement and education will be required to prepare the broader provider community and network that will be required to support patient access to novel CGTs.

Scope and Nature of Provider Early Engagement Around CGTs

Payer experience with CGTs has been shown to be highly variable in past ARM NAMCP research. Similarly, provider experience is also variable, which is perhaps not surprising given the limited number of CGTs launched to date and their generally niche focus. Figure 3 highlights provider survey results on the degree of experience with CGT clinical trials, registries, risk sharing agreements and offering of available therapies.

Approximately half of the providers who responded to the survey had direct experience conducting clinical trials of CGTs versus 70 percent that had experience administering in-line and/or available therapies. Over half (52%) of these respondents were from either academic medical centers or regional medical centers associated with integrated health systems, suggesting the initial vanguard of therapies are offered in centers with sophisticated facilities and emergency resources needed to address all aspects of this complex treatment paradigm. Perhaps not surprisingly, approximately 50 percent of the surveyed providers also had experience participating in registries required by FDA for CGTs. In addition to clinical trials, most CGTs will require a registry as per FDA requirements (particularly if they follow the Regenerative Medicine and Advanced Therapies

Figure 2: Provider Engagement with Payers and Manufacturers

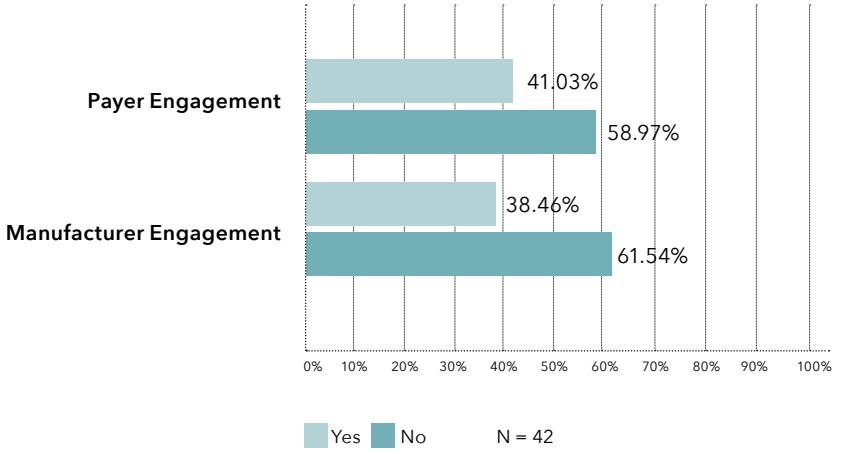
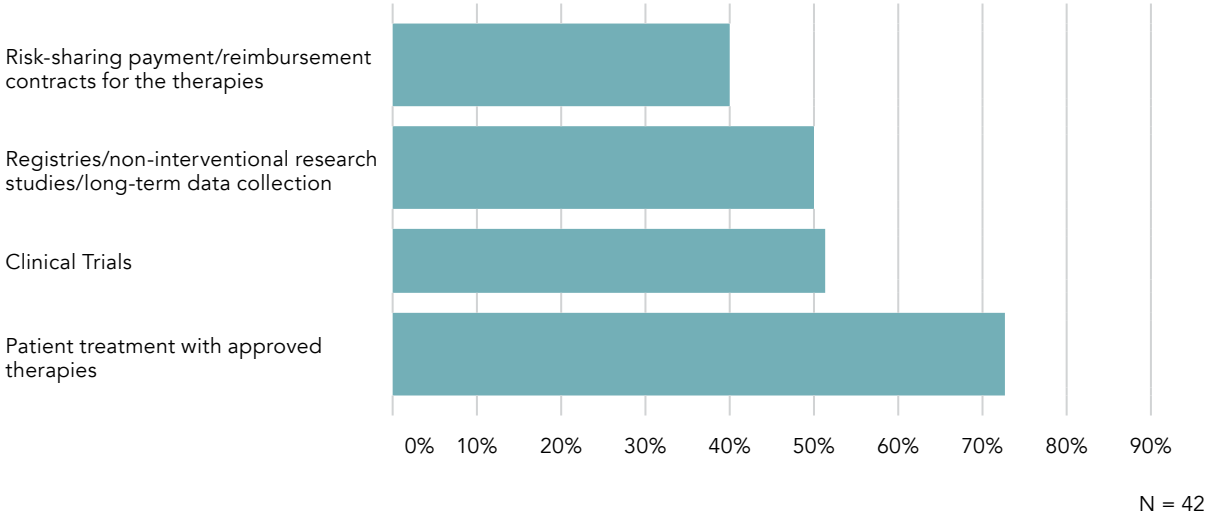


Figure 3: Provider Engagement with Cell and Gene Value and Access Activities



[RMAT] pathway) and some manufacturers may also consider risk sharing programs as an option for reducing payer acceptance hurdles. For those providers with registry experience, workshop participants noted that provider burden for longer-term data collection and challenges of long-term patient tracking remain key challenges in establishing long-term duration of effect. As data collection methods continue to virtualize and methods to link or tokenize patient data between sources improves, these challenges are thought to become easier over time.

A smaller proportion of provider respondents (40%) have been contacted by manufacturers or payers around risk sharing agreements. However, this number is not indicative of the percentage of provider respondents that have been involved in successfully executing a risk-sharing agreement, negotiated as part of CGT patient access. Both providers and payers participating in the workshop indicated that (a) risk-sharing agreements in the U.S. remain the exception versus the rule and (b) are less likely to be applied to niche or rare disease areas, even for those in the current price range of marketed transformative CGTs (noted as > $400,000 to $2,000,000).

Table 1: Key Considerations that Can Influence Provider Willingness to Accept and Use CGTs

- Complexity of the cell or gene therapy platform – e.g., cell-based versus gene-based, involvement of gene-editing, if cell-based (autologous versus allogeneic, type of cell), if gene-based (type of virus, potential for viral shedding, potential for immune response, natural versus altered or synthetic promoter), manufacturing turn-around requirements, safety and follow-up requirements to protect against adverse events (AEs).
- Complexity of the administrative process – e.g., degree of provider handling/manipulation (e.g., constitution of a therapeutic dose), type of administration – injection, infusion, level of anesthesia, involvement of complex medical devices – standard catheter, guided, mapping catheter), requirements for image-guided administration, level of provider training or specialization requirements.
- Complexity of the episode of care – e.g., process for extracting cells or other material required for the therapy (e.g., bone marrow aspiration, cell mobilization, cell collection), process for purifying the cells (e.g., apheresis, extraction column or process, gene-editing or cell manipulation [often done as part of manufacturing process]), process for storing and handling the product, complexity of administration and staff requirements, opportunities to identify efficiencies in treatment flow.
- Setting of care – e.g., inpatient versus outpatient
- Facility preparedness and requirements for scaling the therapy – e.g., logistics and supply chain, storage (e.g., refrigerated, deep cold storage) and reconstitution, facility services required to administer the procedure (e.g., lab, bone marrow transplant facilities, special devices) staff training and capacity, proximity to emergency or intensive care in the event of an AE, requirements for "held" bed space in case of AEs, need for equipment/technology to support longer-term outcomes measurements to support outcomes-based agreements.
- Facility operational considerations – e.g., time requirements for staff versus other treatment options, potential for the therapy to be disruptive to other services (including those that may be provider financial drivers), staff and training requirements, provider types involved and treatment decision chain, who prescribes versus actually administers the therapy, patient flow and triage, documentation and patient monitoring requirements versus other therapies.
- Patient considerations that may have access connotations – e.g., patient characteristics that may influence reimbursement and access, underlying or subpopulation considerations that could be contra-indications, patient concerns on therapy acceptance, anticipated coverage steps (e.g., prior authorization, step therapy, other administrative requirements), requirements for Medicaid or other beneficiaries to travel out of state for treatment under smaller Center of Excellence (COE) models and misalignment with access drivers.
- Potential fit into existing coding and reimbursement mechanisms – e.g., uncertainties around payment, potential for hospital financial loss versus existing therapies, risk of being considered an investigational or experimental therapy by payers.
- Challenges in handling purchasing and payment – e.g., requirements to buy-and-bill versus rapid supply, financially floating the CGT purchase while waiting for reimbursement to "catch up".
- Requirements to follow-patients long-term – e.g., up to 15 years to meet regulatory requirements and provider preparedness to perform this follow-up (at least in circumstances where the patient is cared for during this time by a single provider), ability to track patients across multiple health plans over this timeframe, patient willingness and compliance to be tracked.

As CGT trials continue to expand and the underlying technologies evolve, workshop participants anticipated that provider experience would expand, beyond that noted in Figure 3, and outside of academic centers and integrated care facilities into community settings. This was dependent of course on a range of factors, and it was noted that some applications may always require specialty center expertise to ensure safe delivery and care (e.g., if they involve complex or invasive device delivery). However, more generally, expanded provider experience was thought to happen as (a) allogeneic therapies evolve, (b) there is greater shift from inpatient to outpatient delivery models for CGTs, and (c) development and administration processes simplify over time (where possible).

Provider CGT Acceptance Drivers to Consider in Early Development

There are a range of factors that can drive or inhibit provider willingness to use any technology, but the number and nature of them is more complex in the CGT development space. Key drivers of provider willingness to accept and use CGTs, identified by workshop participants, are included in Table 1, with results being augmented by feedback from

manufacturers with in-line CGTs in subsequent discussions. Table 1 characterizes these key factors.

Workshop participants and additional manufacturer experts with direct CGT commercial experience, who were consulted, noted that requirements to consider and address the implications of such drivers go beyond traditional drug development. As such, these considerations have the potential to be missed by both providers, and manufacturers, who approach development through the lens of conventional drug development.

Timing and Content of Early Provider Engagement

When asked about the ideal time for CGT manufacturers to engage with providers, workshop participants indicated that early engagement and partnership, including the pre-clinical stage, were recommended. Participants suggested that addressing CGT development in a transactional manner has significant potential to miss key opportunities to build the CGT value story and care pathway and process.

Aside from the more routine aspects of engaging providers early for clinical development, this research suggests that it would significantly benefit manufacturers to think about the range of acceptance drivers necessary to support acceptance and uptake. This was noted by workshop participants as particularly true in scenarios where new reimbursement codes and/or payment mechanisms will be required. Manufacturers in the CGT space will ideally look beyond the clinical and economic aspects needed to populate value dossiers and models to the practical and operational aspects of offering CGTs that transcend the requirements of conventional drug development.

Importance of Building a Robust Provider Network

A key takeaway from Figure 2 is that manufacturers developing novel CGTs should not assume that providers are familiar with all the different aspects required to support a commercially launched therapy. Close alignment with provider partners around acceptance drivers necessary for facility or health systems to support and to optimize patient access, can help shorten any gaps necessary to migrate CGTs towards standard of care.

Workshop participants indicated that the early clinical development stages represent a key opportunity to build the provider network that will be necessary to (initially) support the launch of a novel cell or gene therapy. The value of this network building was noted as something not to be underestimated and something beyond the requirements of small molecule and biological development. If the therapy is overly complex or rare, this is particularly relevant where access may be limited to a Center or Excellence model (e.g., like organ transplantation infrastructure). This network is critical for building experience with the novel therapy and understanding uptake drivers from a provider perspective. It also represents an opportunity for knowledge transfer of best practices and lessons learned, that can improve the care delivery process or patient experience.

Further, where the therapy is sufficiently novel, and may require a new reimbursement code or mechanism, leading key opinion leaders (KOLs) from this provider network can also be helpful in supporting the need for appropriate reimbursement. As the ARM NAMCP Reimbursement Roadmap companion publication published in 2019 indicated, provider support in conveying the evidence and rationale is critical in developing a new case rate for procedures involving CGTs.[11] Workshop participants also highlighted that the strength of such partnerships may be important where access extension studies may be necessary to bridge to the full, financial viable reimbursement models for CGTs. From the research on early provider engagement, Table 2 describes key lessons for both manufacturers and payers.

B. Clinical Experience and Use of CGTs

Although currently in the earliest stages, provider experiences with CGT are beginning to grow as new products continue to launch. A little over two years ago, the first transformative CGTs with curative potential were made available to patients. This section covers current provider experiences with CGTs.

Focus of Provider Relationships with CGT Manufacturers

Beyond early engagement activities, providers were found to engage with manufacturers on a range of topics and issues related to CGT value demonstration and use (see Figure 4). The most frequent topics discussed were network establishment to support these therapies (35%) and clinical trial development (23%). A smaller percentage of respondents engaged on patient access support planning (17%), reimbursement planning (11%), supply-chain (6%), and need for structure of risk-sharing arrangements (6%). No respondents (0%) noted that providers and manufacturers engaged around administrative challenges of offering CGTs or on longer-term patient follow-up requirements. Note that in Figure 2 stakeholders are engaging on the *need* for longer-term follow-up and in Figure 4 the survey asked about registry implementation. It is unclear whether those results represent a misunderstanding of respondents,

Table 2: Early Engagement Lessons for Manufacturers and Providers

Lessons for Manufacturers	Lessons for Providers
• Understand the roles and responsibilities of the treatment center in support of the patient journey. There are multiple dimensions that must be considered in ensuring that the provider model is prepared to deliver the CGT compared to conventional drugs and biologicals; organize around the most important to systematically ensure they can be addressed at the provider-level. • Not all providers or provider-types will have experience with CGT; site selection/data collection approach and engagement model should take into account this variability, including in termsof the anticipated provider type and network "footprint" needed at launch. • Engagement during clinical development is also a means by which to work with provider partners to assess and address all dimensions required to provide the therapy post-launch. • Early engagement with providers is important for building a network that will ultimately drive uptake for patient use. • Provider relationships may be important to support patient access in areas where complex or novel reimbursement approaches are necessary, or in disease, or treatment scenarios where CGTs have not yet entered the treatment environment; manufacturer network build can be critical to success. • Full provider acceptance may also depend on access to feasible reimbursement models and patient monitoring requirements.	• Early engagement during CGT development represents a significant opportunity to understand and build the infrastructure needed to operationally offer CGTs. • The vast majority of CGT developers are in the biotech sector (versus large pharma, though acquisitions are accelerating), and as such may have a limited bandwidth or experience in building the provider network that will be necessary to optimize CGT uptake. • Based on results, a significant number of providers did not indicate experience with CGT registries that will be required for these therapies; providers should be aware of and prepare for more integrated data collection models. • While all product developers understand that factors like perception of benefit, "fit" into provider flow, and reimbursement must be considered, the focus on other aspects such as complex logistics, complex handling and degree of financial risk under buy-and-bill models in the CGT space. • Where reimbursement is uncertain, manufacturers would require provider champion to establish a new case-rate or code to cover the therapy cost.

or simply denote that long-term follow-up (e.g., longer-term clinical trials) is being discussed, but that a significant proportion of providers are not yet involved in CGT registries.

Despite the importance of these activities highlighted in Figure 4 for CGT value demonstration and access, manufacturer-to-provider engagement on these topics was limited. This is perhaps not surprising given the limited number of marketed therapies, but is a key consideration given the literally hundreds of clinical trials underway in this area, suggesting that developers (a) may be treating development of these therapies more like a conventional drug or biological and (b) may not be taking sufficient steps to address the provider side of the CGT *"equation"*. These results would indicate that significant educational and network-building opportunities for developers of CGTs remains to help ensure appropriate patient access.

Provider Experience with Available CGTs

We also discussed provider experiences with available CGTs (see Figure 5). Based on survey responses, 37 to 41 percent of provider respondents had experience offering the two available CAR T therapies (i.e., Kymriah® and Yescarta®) and under 20 percent had experience offering another cancer therapy, Imlygic® (< 20%). Given the comparative rarity, greater patient concentration around academic or specialty centers, and variability across provider-types, respondent experience with rare CGTs was lower (i.e., < 10% to 18%).

Figure 4: Nature of Provider Relationships around CGTs with Manufacturers

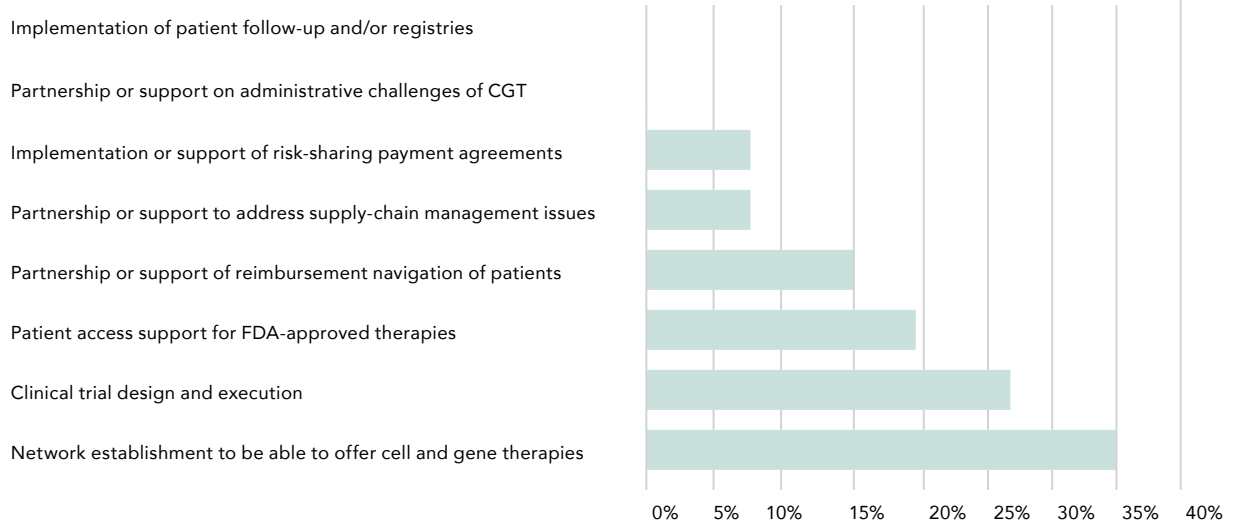
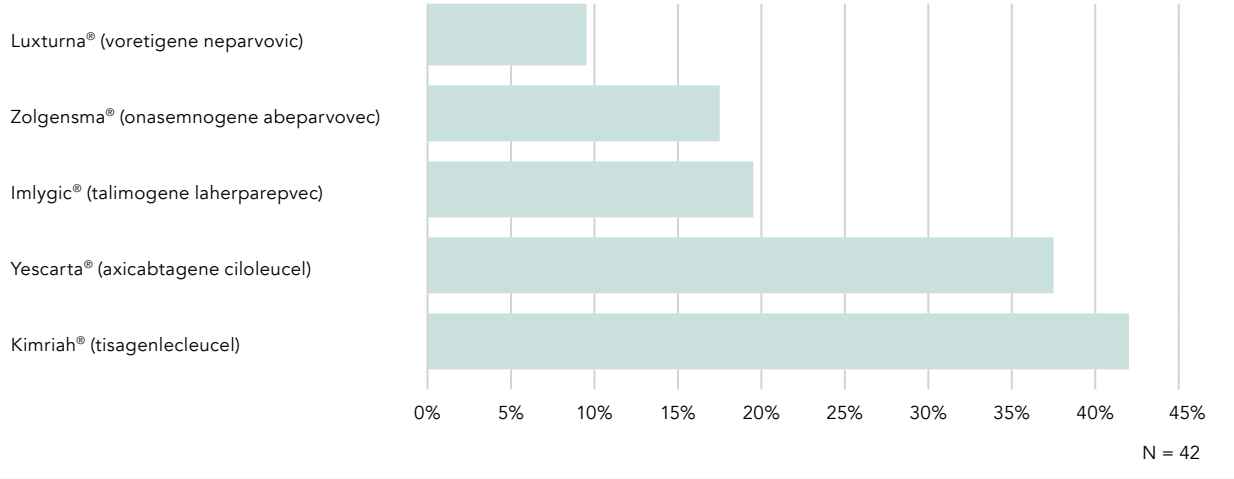


Figure 5: Provider Experience with available CGTs



The variability in provider type respondents may also have influenced these results given that this vanguard of initial therapies are currently offered via specialty centers or Center of Excellence-type delivery models and not all providers may have had the full range of facilities and services that may be necessary to handle administration of CGTs. Despite this consideration (and similar to the ARM NAMCP Reimbursement Roadmap survey results on payer responses published in late 2019) stakeholder experience with existing CGTs is significantly different than what is often seen in conventional drug or biologic uptake models.[12] This also supports the notion that significant emphasis on provider education and exposure, perhaps beyond that given to conventional therapies, is necessary to optimize novel CGT uptake. This may be particularly true when just over 70 percent of providers in the survey had some experience with CGTs, but a much smaller percentage were actively engaged in determining how to navigate the supply chain, operational, reimbursement and payment considerations that differ from conventional drugs.

Table 3: Key Patient Journey Key Considerations to Support Provider Acceptance

Consideration	Implications
Diagnosis and patient workup	• How the patient diagnosis and workup occur is key to characterizing or documenting whether patients may be indicated for the new cell and/or gene therapy. • Aside from antibody tests which may be commonly used prior to gene therapy administration, consider whether other molecular or biomarker tests may be used to identify a candidate, or potential responder, for the cell and/or gene therapy. • What other molecular tests may indicate the patient as a candidate for a precision medicine or immuno-oncology (IO) therapy; if a patient is a candidate for both, how would treatment selection be handled and/or reconciled? • How factors like referral networks, disease progression, patient identification, and triage factor into patient assessment and access.
Providers involved in the journey	• Treatment of high unmet-need patients with transformative CGTs can complex. It is critical to understand which provider types are involved in patient workup and treatment decisions. • Input and involvement of different provider types and patient management practices may vary markedly by disease; understanding provider role and decision flow can be critical to CGT acceptance and use. • Shared decision making between providers and patients can play a stronger role with complex therapies like CGT.
Decision nodes and inflection points	• Every patient journey involves key decision or inflection points (e.g., diagnosis, treatment choice, prior authorization and selection); key to identify core decision nodes in terms of CGT patient access. • Understanding who the key decision players are at the point of treatment selection and what factors or criteria drive the treatment selection choice for a cell and/or gene therapy can be critical to ensure appropriate patient access.
Key decision maker for cell and gene therapy	• It is critical to determine which physician type would be the key prescriber for CGT Does this differ from the key prescriber for alternative therapies? • Is the key prescriber type in a position to influence acceptance and uptake of the therapy for patient use?
Patient and physician education and perceptions	• Given the novelty and uncertainty that may be associated with CGT, understanding patient or provider limitations to use of CGT versus other therapies can be a unique and important part of the patient journey.
Approval processes required	• Clearly characterizing the approval processes involved for use of CGTs, including in contrast to alternative therapies, can be important to identifying decision drivers and factors. • Technical details of the approval process may involve clinical pathways, financial considerations, understanding whether the therapy would hit the medical or pharmacy benefit, quality measures or accountable care measures, prior authorization processes or other factors.

(continued)

(continued)

Consideration	Implications
Administrative complexity and time and resource requirements	• Administrative complexity of the procedure may also influence provider willingness to accept and use a novel CGT (though balanced versus degree of transformative effect). • Does the provision of CGT require special staff or training? Does it require specialty providers to do the administration? Does it require special facilities or services, including patient handling in the event of safety considerations?
Product handling and supply chain	• CGTs can have more complex handling and supply chain issues. How and to what extent do these fit into and/or challenge conventional aspects of treatment provisions? Are there new handling and supply chain issues that must be considered to support the therapy? • There may be significant limitations to buy-and-bill acquisition approaches for providers given the cost point of transformative cell and gene therapies; some providers may not financially be able to take the risk of therapy acquisition in scenarios where reimbursement is uncertain versus acquisition and risk costs associated with conventional biologicals.
Clinical pathways and use incentives	• To what extent do cell and gene therapies represent a transformative or curative option versus alternatives? How much do provider champions view the therapy as a "must have" versus "nice to have" therapy? How much are they willing to push for the cell and gene therapy versus alternatives? • How and to what extent does the new cell and gene therapy "fit" into existing clinical pathways? Where should it optimally fit? • What would be required to ensure appropriate fit into clinical pathways? • Are there therapy selection and use incentives or disincentives that would influence cell and gene therapy selection versus alternative therapies?
Setting of care considerations	• Setting of care (e.g., inpatient versus outpatient) may significantly influence cell and gene therapy acceptance. In the inpatient setting, where the cost of the therapy is bundled into the episode of care costs, pricing of the cell and gene therapy can significantly influence acceptance and uptake. In the outpatient setting, where cell and gene therapy pricing may be separately payable versus the procedural costs, cell and gene therapies can often have broader pricing latitude. • While separate or appropriate pricing may be easier to address in the outpatient setting, evaluation of the patient journey should consider how and to what extent the therapy represents a financial loss to the institution in the setting of care in which the therapy will be administered. • Even if the therapy is able to be sufficiently paid, a loss to the provider institution may represent a key limit to therapy acceptance; this is readily seen in scenarios like bone marrow transplant where novel therapies that fall outside of the payment rate may be rejected, in part, based on financial feasibility to the provider institution.

(continued)

Fit of the new therapy into operational flows	• Do cell and gene therapies represent a risk versus more established procedures that represent key profit centers for a provider or hospital? Are alternative therapies viewed as "reasonably effective" and a lower operational or financial hurdle versus cell and gene therapies? • Are there elements of operational provision of cell and gene therapies that represent and high or perceptually undue burden versus alternatives that fit more readily in existing operational paradigms? • Are there administrative attributes of the therapy that are underpaid (e.g., number of injections for cell therapies for critical limb ischemia) that may represent a risk or financial loss to providers? • Does administration require complex medical devices (e.g., novel catheters and administration requirements for cardiac cell therapy, neurological or optical procedures) that may also represent reimbursement and profitability uncertainties that do not exist with other therapy choices?
Fit of the therapy into financial flows	• If the therapy represents a key financial risk for providers, it is possible that they may opt for lower cost cell/gene therapy alternatives. To what extent is reimbursement for the cell and gene therapy uncertain (including the provider and/or administrative components of the therapy)? • To what extent are providers willing to take a loss on the therapy to establish differentiation versus the financial acceptance drivers that may exist when cell and gene therapies are at scale? • How and to what extent does the novel CGT fit into financial flows (e.g., purchasing and buy-and-bill financial risks, reimbursement and payment). • Requirements for outcomes tracking and patient monitoring
Disruptive implications of the new therapy	• Overall, what degree of disruption does the new CGT represent? Are there key risks for provider financial loss that may limit or preclude uptake? What are these risks and drivers? • Does the novel cell/gene therapy disrupt existing financial or treatment flows for the hospital?

While Focusing on the Destination, Do Not Forget the Journey

A cornerstone of understanding provider acceptance of CGT is to understand the key elements and decision drivers of cell and gene therapy use accurately and realistically along the patient journey. This flow of decisions more than many others is, according to workshop participants and other external experts, one of the easiest to underestimate for cell and gene therapies given that the factors involved often go well beyond that applicable to conventional drug or biological therapies.[13] The following table is meant to be illustrative of the most critical considerations for cell and gene therapies along the patient journey raised by workshop participants and strongly supports careful mapping of this process as a strategic assessment for all novel CGTs.

Further, given that we are at the earliest stages of cell and gene therapy launch and acceptance, acceptance and use drivers may be more highly subject to change as additional advanced therapies become available versus conventional therapies. The complexity of acceptance drivers along the patient journey is also further complicated by emergence and expansion of other emerging technologies, including precision medicine, oligonucleotide therapies, immunotherapies, nanotechnology-based therapies, and others that all have different differentiation characteristics.

Registries and Risk Sharing Agreements

For CGTs that follow the Regenerative Medicine and Advanced Therapy (RMAT) regulatory pathway under the U.S. Food and Drug Administration (FDA),[14] or are otherwise noted as an advanced therapy, each one will have to have a registry. Although it depends on the disease, it is not uncommon that these registries will run up to 15 years. This expands the scope and nature of data collection and patient management for CGTs beyond that applicable to most conventional drug or device therapies.

While workshop participants indicated that in the academic medical setting, or with experienced clinical trial sites, providers often have experience with registry data collection, they indicated that this was an important consideration for CGTs. Some providers were noted as having less experience or that variability in data capture and medical record systems may represent a learning curve issue that is important to consider early in development. Registry requirements at the site level were also noted as challenging under some circumstances where an individual site may only see or collect data on a very small number of patients (versus academic centers that may have specialty offerings in rare disease). The ability to follow patients for sometimes up to 15 years was also noted as a challenge by those providers with direct experience in CGT clinical development. However, this was predominantly related to difficulties in tracking patients for regulatory purposes as they have reason to receive care by other providers or payers over time.

Given what may be viewed as a higher price point (currently in the range of $400,000 to $2,000,000) associated with transformative CGTs, and the fact that value capture most frequently happens around a single administration, CGT developers have considered risk- sharing agreements with payers. While much has been published around such agreements, for CGTs payment may occur in chunks over a number of months or years, with some payments contingent upon certain patient outcomes, like continued duration of effect.[15,16] From the provider side, this largely represents a requirement for additional data collection for patients receiving CGTs that are required by the FDA to be tracked in registries for long-term safety and efficacy follow-up. Payers are also cognizant of potential for, and degree of, hospital mark-up with therapies in this price range.

Some providers in the workshop indicated that their organizations had been approached by manufacturers, including CGT developers, to discuss the risk-sharing agreements that involve additional data collection or novel payment models that they would like to negotiate with payers. Like payer discussions in prior ARM NAMCP engagements, providers in the workshop indicated that such agreements are not the norm and may rarely be accepted in practice. Payer participants in the workshop indicated that such agreements also tend to be very legally complicated and often intentionally steer away from them. Both payer and provider stakeholders suggested that the administrative burden for risk sharing in niche treatment areas, even taking into consideration the price points of CGTs, also largely precluded such agreements for rare disease treatments.

This significantly draws into question some aspects of how proposed value-based purchasing or payment models (VBP) may be realized from both a payer and provider perspective. The 2020 Proposed Rule for the Medicare In-Patient Prospective Payment System includes integration of VBP options in the Medicaid program.[17] To the extent that this is realized, research findings suggest that it will be critical to consider (a) a model that focuses on administrative simplicity, (b) selection of metrics that represent limited provider/payer/manufacturer data collection burden or legal risk, and (c) degree of data collection burden that is both reasonable and feasible where outcome-based agreements are possible. Other factors such as patient portability, anti-kickback rules, and other factors were also noted as key areas to consider.

Table 4 highlights key lessons for manufacturers and providers for optimizing engagement during the early CGT development period. This period, as discussed, represents a key opportunity to develop the provider network and explore provider drivers and inhibitors required to ensure routine patient access. Current limits on provider uptake of the vanguard of CGTs underscores the importance of addressing all aspects of the provider acceptance, uptake and use model.

C. Patient Access, Reimbursement and Financial Impact

Beyond development of evidence that supports the use of CGTs, these therapies enter reimbursement systems that were not built with transformative or curative therapies in mind. From the provider side, this has many implications, including *"fit"* into coding systems, patient access approval processes, procedural profitability to the provider facility and acceptance drivers, use incentives versus alternative therapies, and provider *"buy-in"* to transformative therapy benefits, among others. This section considers key drivers of patient access, reimbursement, and financial impact perceptions of CGTs.

Table 4: Clinical Development and Use Lessons for Manufacturers and Providers

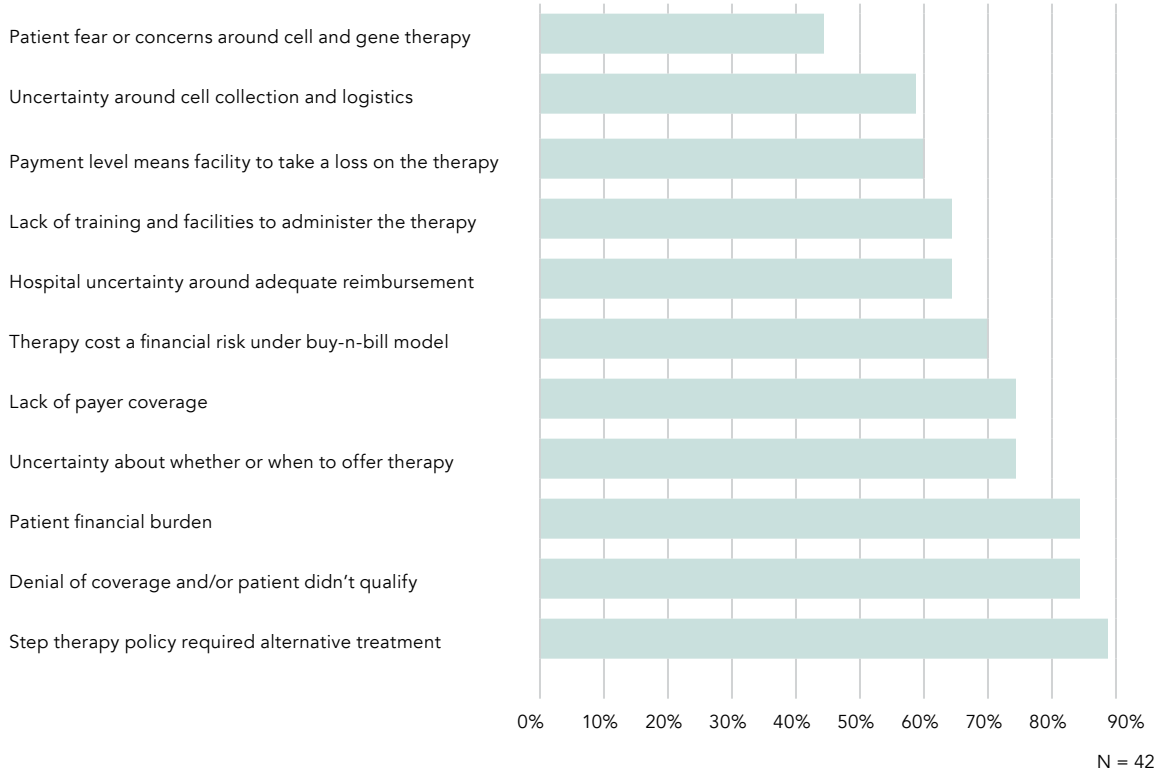
Lessons for Manufacturers	Lessons for Providers
• Perhaps not surprisingly, at present the bulk of provider experiences with CGTs center on conduction of clinical trials and preparation for broader future use and network set up. • While a significant proportion of provider respondents may have experience with patient treatment with CGTs, this experience is presently diffuse (and in most institutions) far from standard of care practice. ◦ Much of it is currently concentrated in academic or integrated health systems/networks ◦ The greatest proportion of treatment experience with commercial products is currently in oncology and certain rare disease specialty/academic centers; new use case scenarios will require significant education to address and optimize uptake. • Only a narrow percentage of providers may have significant experience navigating supply chain and administration solutions or reimbursement-related aspects of CGTs. • Many providers may not be prepared for the need to address longer-term data collection and registry-bridging needed for CGT value demonstration, aside from other loss-to-follow-up challenges. • Carefully mapping the patient journey to characterize acceptance drivers and limits is more highly warranted for cell and gene therapies versus conventional therapies given the additional complexity involved. • Consideration of novel support items (e.g., travel support) given the uniqueness of some CGT patient journeys.	• Many CGTs are currently launched in small and rare patient populations, where the standard-of-care patient population may not be well characterized, requiring natural history studies. • CGTs may involve more complex supply chain handling, treatment administration and patient monitoring versus conventional treatments; preparation for this can be accomplished during clinical development to ensure optimal ability to address patient treatment post-launch. • Most existing reimbursement codes were not built with CGTs in mind; evidence development and provider support of the therapies can be important to characterize the level of effort needed to ensure that reimbursement appropriately covers all aspects of the episode of care. • Given the transformative nature of many CGTs, they have the potential to influence or alter existing clinical pathways. • Most CGTs will require long-term follow-up of up to 15 years depending on the disease.

Factors that Influence CGT Acceptance and Uptake

Our survey and workshop discussion explored a range of factors related to patient access, reimbursement and financial impact on providers offering CGTs. Survey results identified several factors that have prevented providers from using existing CGTs. Virtually all the factors tested were identified as a barrier to adoption by > 50 percent of the respondents (Figure 6). This suggests that there are many factors that must be anticipated addressed to optimize patient access to CGTs by both manufacturers and providers. Of those factors that were identified as barriers, in 70 percent or more of the survey responses, the majority were reimbursement-related, including lack of available coverage policies, patient coverage denials, patient financial burden flowing from cost shifting and overall cost of the therapies, and requirements to fail on other less expensive or established therapies prior to CGT access. This feedback is consistent with the ARM NAMCP Reimbursement Roadmap payer survey results published in 2019 showing that coverage has lagged for this therapy type compared to more conventional therapies. This is perhaps not a surprise given that health system payment mechanisms were not built with reimbursement of CGTs in mind.

The other two areas at this high level included uncertainty around when to offer the therapy and provider concerns about financial risk for offering

Figure 6: Factors that have Prevented Provider and Hospital Use of CGT



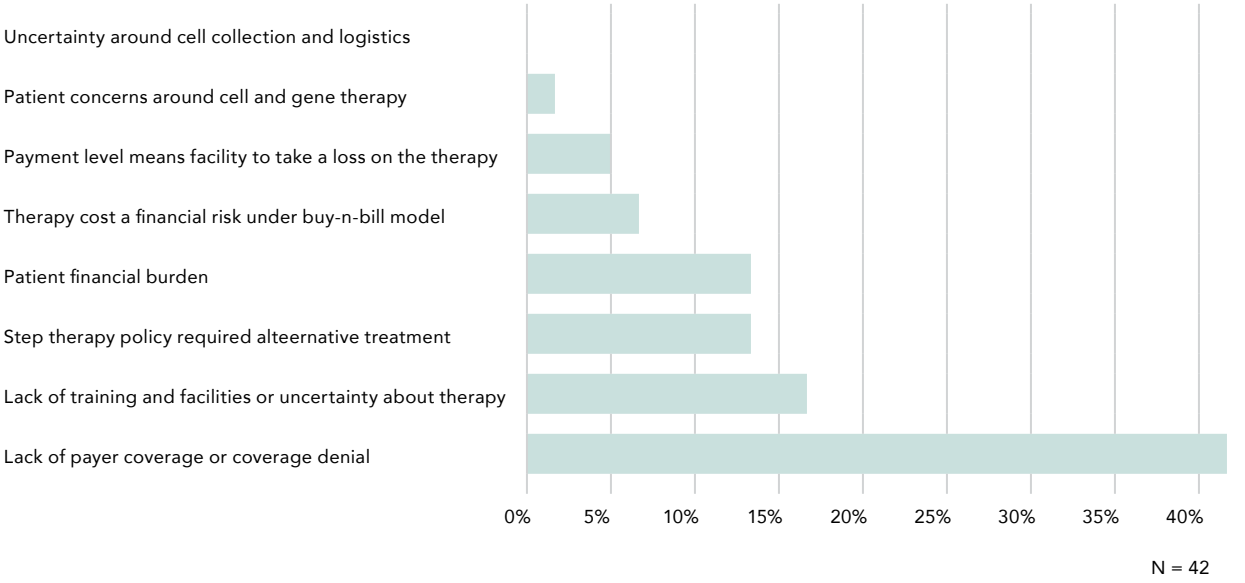
CGTs under a *"buy-and-bill"* model. Workshop participants indicated that both the patient financial burden and the provider financial risk under *"buy-and-bill"* reflected the comparatively higher cost of CGTs versus many conventional drugs and biologicals.

Of all the factors that represent a hurdle to patient access to CGT from the provider perspective (Figure 7), the most frequent answer noted as the top challenge by survey respondents was payer coverage (almost 40%) being almost three-fold higher than any other factor. Other challenges such as, payer requirements for patients to step through alternative therapies, and patient financial burden were mentioned by a small percentage (15% or less) of the sample. However, aside from coverage and reimbursement factors, provider perspectives on top challenges to patient access to CGTs were broad ranging.

These results suggest that of all factors that influence uptake and must be addressed to ensure appropriate patient access to CGTs, reimbursement elements of coding, coverage and payment remain fundamental hurdles. Other factors such as, how the product is framed to address market fit can also influence uptake.[18]

Provider-side impacts of mis-aligned reimbursement models and payment rates for the same, with initial CGT, have been noted for CAR T therapies, where payment rates may not cover the full administrative costs of the therapy.[19,20] Under such circumstances, workshop participants and press releases have noted that provider losses on individual procedures may range as high as more than $100,000 to $1,000,000. These stakeholders noted that while possible to absorb now, at higher volume this would represent a severe limiting factor to provider use. CMS did recently finalize a new DRG for CAR T therapies, that will help close off the gaps in payment when all factors such as outliers are tabulated.[21] Focus on identification and execution of sustainable reimbursement solutions, including rethinking or developing new approaches, will be needed for CGT to mature as a standard-of-care. While commercial payers in the workshop indicated that they have the latitude to develop new case rates for CGT or other procedures, they cautioned that this was an exception rather than standard way of

Figure 7: Top Provider Challenges to Offering CGT



operating and often a long and arduous process.

Financial Impact and Affordability

We explored with workshop participants the current financial impact of CGTs on provider willingness to adopt them routinely. As might be suspected, given that we are at the earliest stages of CGT launch, providers indicated that the overall financial impact of CGTs is currently limited because the number of use cases is comparatively limited. Our discussions included consideration of circumstances around use and rejection of therapies that represented a financial loss to provider organizations. Workshop participants indicated that physicians try to do the *"best thing"* for patient care, but that it is becoming increasingly complicated to support use of therapies that may not be covered under health insurance. That being said, the majority of providers generally indicated that if a therapy is viewed as transformative, they can often *"find a way"* to offer the therapy to select patients in special scenarios where there are no alternatives, even where there is risk of a financial loss.

Workshop participants did note that decisions to take a loss on CGT provision, however, represented an entirely different level and magnitude of organizational risk for products priced in the $500,000 to $2,000,000 range. In the absence of reimbursement, it was noted by workshop participants and manufacturers of in-line CGT, that many provider organizations would not be allowed to take on that kind of financial risk (directly confirmed in Figure 6). This also applied to uncertainty of reimbursement in *"buy-and-bill"* scenarios, suggesting that *"just in time"* models were preferred to *"buy-and-bill"* from a risk perspective, including allogeneic cell therapies or gene therapies, that may be able to be stocked like more conventional treatments. Some participants suggested that the differences in CGT under the current system configuration may require rethinking many aspects of supply chain, handling, and reimbursement approaches.

Providers indicated that they may have more latitude to address financial limitations on aspects of administration that may be considered routine care for CGTs. However, several noted that while this may be acceptable in the early days of CGT, it may preclude use of CGT at scale if reimbursement rates do not adequately reflect costs of the episode. Current CAR T payment rates were again advanced as the exemplar, where some providers were noted to take a significant financial loss on elements of the administration. When they represent the exception, financial losses on some therapies may be absorbed by the health system, but in the long-term, this was not viewed as sustainable. It was also noted that this could be an underlying driver of the more limited levels of uptake of CGTs. Providers also suggested that even if the novel CGT were curative, they may be forced to ultimately select *"good enough"* therapies for some diseases (where available) in scenarios where the financial loss is viewed as severe.

Both payer and provider workshop participants noted that getting to greater predictability of reimbursement and access for CGT is important. They also suggested that advancement of more standard models, such as bone marrow transplant or dialysis, may be required to help achieve broader and more uniform patient access. Manufacturer and payer lessons associated with patient access, reimbursement, and financial impact of CGTs are described in Table 5.

D. Payer and Manufacturer Negotiations with Providers

While many engagements between providers and payers occur when a prior authorization request or medical claim is filed, providers do engage early for therapies viewed as being valuable and/or worthy of early engagement. Workshop participants indicated that the relationship building that can come with early development, and (KOL) physician involvement, in clinical trials could be important to support later reimbursement. While payers involved in the workshop tended to dislike the potential conflict of interest, represented by KOLs, that would champion new treatments, they did listen to them and also seek local or regional network physician perspectives when they must address claims for novel therapies or are making coverage determinations. If physicians in the community are very verbal about need to ensure patient access, payers will take those perspectives into consideration. In contrast, payers also indicated that when physicians were quiet or blasé about a new therapy, it also signals to the payer the importance and impact of a new therapy. If multiple physicians were requesting a therapy, or for a reimbursement determination, payers also would engage to gain a better understanding of the issues and rationale supporting the novel product, as there is intense competition among health plans for beneficiaries.

Specific Considerations Around Reimbursement Negotiations

Workshop participants indicated that there is typically more latitude or flexibility on evidence supporting reimbursement of a new technology if it is targeted to pediatric populations or rare populations with a clear unmet need. Providers in the workshop indicated that they would consider a range of factors when deciding to champion reimbursement for novel areas, including:

- Degree of unmet need and availability of alternatives.
- Degree of clinical benefit to the patient versus alternatives. For CGTs, they confirmed that magnitude of effect, duration of effect, and patient and/or caregiver benefits were core considerations.
- Degree of difficulty in achieving reimbursement.
- Impact of the new therapy on treatment and/or operational flows (i.e., whether the therapy disrupts or replaces another type of therapy that may be of financial importance to the hospital.

Providers did not express an explicit perspective on whether patients fell under commercial, Medicaid or Medicare, with the exception that under CMS,

Table 5: Patient Access, Reimbursement and Financial Impact Lessons for CGTs

Lessons for Manufacturers	Lessons for Providers
• The single greatest risk to CGT acceptance and uptake is reimbursement. CGT therapy manufacturers should start planning for how to address reimbursement in the very earliest stages of development. • In scenarios where new coding and payment is required, the process for addressing this can take several years. • If the therapy is inpatient the risks, options and timelines for achieving reimbursement are more complex than in the outpatient setting. • Carefully consider how the supply chain and purchasing flow will work for the provider. Buy-and-bill models may be precluded based on the cost of the therapy. • The ability of providers to take a loss on novel therapies is narrowing. Because CGT reimbursement often involves a full episode of care, data collection around this (e.g., via time-in-motion or related methodologies) may be warranted to ensure adequate coverage of provider costs. • If reimbursement issues are not addressed more universally, providers cautioned that reimbursement would be a key limitation to future use of CGT as standard of care.	• Be prepared for how the hospital will handle patient questions or concerns about CGT, including resources that may support Q&A to cover more common questions. • Understand purchasing and financial implications of the purchasing model as impact potential may be more significant than with conventional drug models. • The reimbursement environment for CGTs is still evolving as U.S. coding and payment systems were not built with CGTs in mind. For CGTs that the hospital or health system truly believes in, having voice in scenarios where reimbursement is uncertain may help both patient access and development of appropriate reimbursement models.

VA or other government-driven payer segments, that different decision rules were applied and access more complex. They also indicated that justification of particularly costly therapies under Medicaid was in general more challenging than under other payer types.

Payers in a later ARM NAMCP web-based discussion on the implications of COVID-19 also underscored that achieving reimbursement therapies given employer and Medicaid state budget impacts in the near-term, post COVID would be a particular challenge for therapies in the $500,000 to $1,000,000 range.

When Novel CGTs do not "Fit" into Existing Reimbursement Mechanisms

Under circumstances where a new CGT needs to make a case for a novel commercial case rate that covers cost of the procedure and cell and/or gene component, workshop participants indicated that manufacturers will need and require the support of providers. They indicated that the provider and not the manufacturer must submit and support a case for such a request. This underscores the value of provider network development and careful consideration of the evidence package that would need to be developed to support a new case rate.

The evidence package, which would flow from typical manufacturer development activities would make a clinical case for the new therapy, as well as an economic case. To the benefit of both payers and providers, having detailed information on resource requirements for administering the procedure can be critical to ensuring that both the manufacturer and provider organization administering the therapy are financially covered (this could be in the form of a time-in-motion or similar study).

Given the complexity of CGTs, not supporting this case properly was noted as having the potential to (a) result in substantial hospital losses and (b) ultimately serve as a significant disincentive to adopt CGTs. This also supports the notion that policy makers should be acutely aware of the patient and facility impacts that can flow from slow or even antiquated coding processes that were not built for novel therapies, in particular potentially transformative CGTs.[22]

Provider Clinical Pathway Development

The research team also considered the degree to which providers were involved in clinical pathway development for novel CGTs. In general, provider experience in this area was relatively low, ranging from < 15 percent to just under 40 percent (Figure 8). Further, the lower prevalence of disease (e.g., biallelic RPE65mutation-associated retinal dystrophy that is targeted by Luxturna® being the smallest target population), the more limited provider experience was found to be, as would be expected, based on differences in patient volume (even under Center of Excellence model scenarios).

Manufacturer and payer lessons associated with payment and contract negotiation are described in Table 6. These results suggest that greater engagement and education of the provider side of CGT may help additionally streamline acceptance and uptake beyond the vanguard of CGTs. Further, as the use of CGTs expands outside of very niche areas into increasingly crowded areas that have other arguably transformative therapies (e.g., immune oncology therapies, enzyme replacement therapies), the need to focus on how these technologies will be fitted and supported in evolving clinical pathways becomes increasingly critical.

Figure 8: Provider Experience Developing Clinical Pathways for CGTs

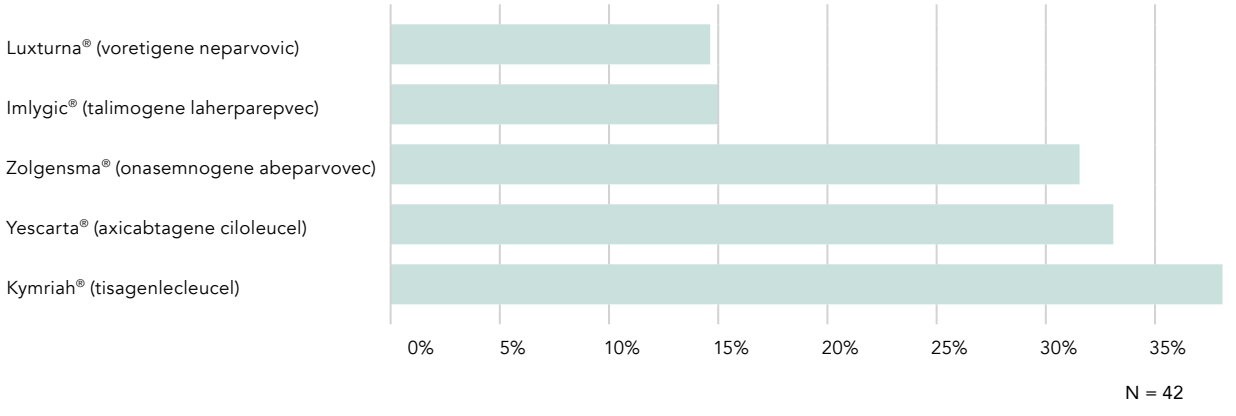


Table 6: Contract Negotiation Lessons for Manufacturers and Providers

Lessons for Manufacturers	Lessons for Providers
• Engage early with the payers and providers. The 21st Century Cures Act opens the door for pre-approval information sharing (unbranded and without promotional claims) that can help surface access issues early and prepare stakeholders for novel CGTs en route to market. • In scenarios where new reimbursement codes/models/ mechanisms are required to support appropriate reimbursement, providers are a key component in interfacing with payer decision makers. • Manufacturers can help arm providers with the materials needed to clinically and economically argue for novel reimbursement, where required.	• Many manufacturers developing CGTs may have a frame of reference around traditional drug development models. As such, experience in collecting evidence around full episodes of care may not always be considered to the extent thst it is in medical device development. Engage early with manufacturers to ensure that the type of data needed to make a case for the full episode of care is accounted for to help ensure that payment levels are aligned with representative cost/resource use flows.

E. CGT Uptake, Management and Routine Care

Beyond the dimensions of current provider experiences with CGTs, our research explored future factors, and other issues relevant to broader CGT uptake, and drivers or inhibitors of expansion to routine use. The following section overviews key takeaways from the survey and workshop discussions.

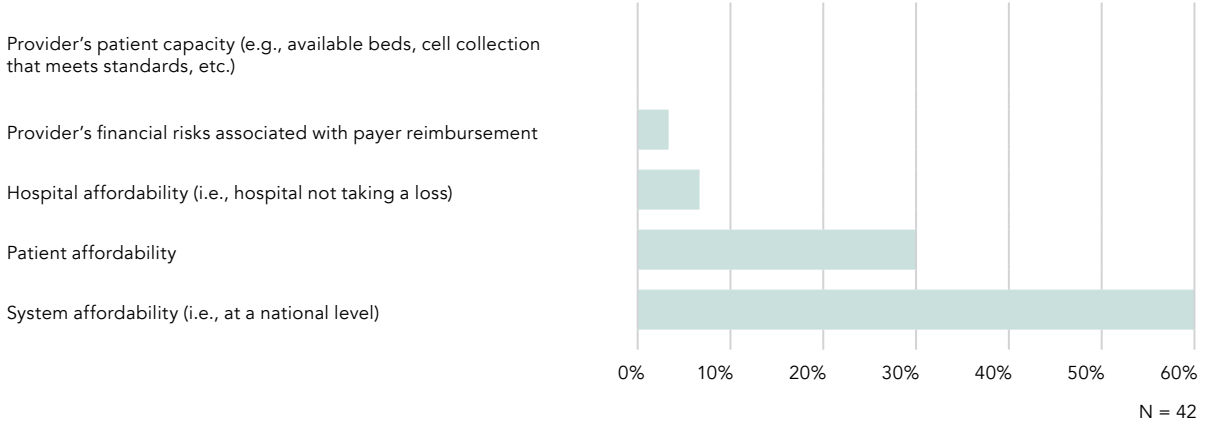
Future Challenges to Offering CGT

Of all factors tested regarding future CGT challenges, the most important identified in survey responses was system affordability, noted by 60 percent of respondents (Figure 9). This was followed by patient affordability (30%), where some providers felt that cost sharing and patient financial burden could inhibit access to CGTs. However, in-line product experts suggest that patient affordability can be mitigated with high premium and/or low deductible plans and that patients with such plan access are more likely to remain with their current employer. This suggests that the other issues such as provider capacity/facilities/experience, financial risks, and hospital affordability were viewed as more readily *"solvable"* by survey respondents and consistent with our ability to overcome hurdles to patient access for any new therapy.

Workshop participants discussed affordability in significant detail. Like feedback during development of the payer reimbursement roadmap, provider and payer participants expressed concern about the cost range of CGTs in the $400,000 to $2,000,000 range. Some participants specifically noted the price shock of recent entrants approaching the $2,000,000 range and concerns about financial impacts as the number of CGTs increases over time. Despite these concerns, uptake of therapies in the upper cost bracket appear to be healthy (for a rare disease), outpacing market expectations.[23,24] This does not however guarantee similar uptake of CGTs in other disease areas, depending on the nature of available alternatives.

We also discussed a range of other topics related to future acceptance and uptake of CGTs. These included the consideration of health system impacts beyond those that are the typical focus of health

Figure 9: Top Future Provider Challenge to Offering CGT



technology assessment which expand our lens for how value and impact of cell and gene therapies may be defined.

The following key lessons for manufacturers and providers flowing from this discussion of uptake and management considerations have been identified in Table 8. Insights from these management considerations may be helpful in terms of considering special uptake drivers commonly considered or relevant to CGTs.

V. Study Limitations

Limitations of this analysis may include respondent bias, as it was not possible to determine whether

Table 7: Additional Provider and Payer Considerations for Ensuring Future Acceptance and Uptake of CGTs

Consideration	Overview and Implications
Consideration of health system impacts beyond the those typically included in HTA	Currently, our conventional HTA processes in the U.S. focus on the evidence supporting a new therapy with consideration of comparative benefit. Most of this assessment, and rightly so, is patient-focused and considerate of the cost impacts of adoption. However, with transformative or curative CGTs, the value and health system impacts have the potential to extend beyond this current lens of focus. Benefits may include elimination of the need for lifelong costly treatment alternatives, patient and caregiver impacts that improve ability to optimize quality of life and pursue activities of daily living, indirect cost impacts to employers and other stakeholders as a result of reduced burden, and improved efficiencies in patient flows and potential for cost reductions at the provider level. Workshop participants noted the value of these improvements but acknowledged that they currently sit outside conventional value assessment processes. They stated that current incentive structures do not typically take these broader system impacts into perspective and indicated that CGTs may warrant consideration of impacts beyond those in typical HTA processes. However, acceptance of such a process would require rethinking and reshaping our perceptions of value and how we measure and reward innovations that do have potential for broad and transformative impacts at the system level.
Value: devil is in the definition	Discussion with both payer and provider workshop participants suggested that beyond the "sticker shock" associated with CGT, both stakeholder groups do not always fully consider the cost offset potential offered by CGTs. Most of the perception is centered on shorter-term perceptions of value, possibly grounded in our conventional expectations for drug and biologic value and cost scenarios before the advent of transformative therapies. Workshop discussions did indicate that there was a more intuitive understanding of the ability to truly realize cost offsets potential in areas where costly multi-year or lifetime therapies exist (e.g., rare diseases where enzyme replacement therapy is standard of care, hemophilia). In these scenarios, participants noted that it was "easy math" to understand cost offsets if SOC therapies were no longer required. In examples discussed, it was also noted that it was more complex to justify price points in the current range where (a) no therapies or costly therapies exist as a clear reference point or (b) in rare diseases where outcomes are more challenging to measure and unfold over many years. This suggests that developers of CGTs must pay particular attention to economic justification of these therapies and aligning value stories so that this element is clear and readily understandable. This difference in perception represents a significant educational opportunity for rare disease patients and advocates to providers and payers regarding the variability of rare disease and potential value of framing archetypalcconsiderations that could inform greater consistency in value assessment. Workshop findings also suggest that stakeholders may be focused more on short-term cost and outcome considerations than on longer-term system impacts. It also indicates that reopening a dialogue on how we assess and recognize value may be warranted in future health reform efforts.[26]

(continued)

(continued)

Table 7: Additional Provider and Payer Considerations for Ensuring Future Acceptance and Uptake of CGTs

Consideration	Overview and Implications
Need to quickly and flexibly evolve coding and payment to keep up with CGTs that does not inhibit patient access	The need to ensure timely and flexible coding and payment was also discussed. Provider participants in the workshop reiterated that (a) reimbursement is the top current challenge in access to CGTs and (b) that most existing coding scenarios, whether inpatient or outpatient were not designed with cell or gene therapies in mind. This has been noted by the National Academy of Medicine as one of several key translational success considerations for CGT.27 As these therapies continue to emerge, some of which may also include complex delivery devices in the episode of care, modernization of our approach to coding and payment development will also be important to ensure consistent patient access. How payment models adapt for single administration therapy scenarios that may or may not involve value-based payment mechanisms is also key to future success. Some companies at the vanguard of CGT development are currently trying to help with this transition or bring creative approaches to health stakeholders, which participants noted was reasonable to consider, but harder to execute without significant changes to provider and payer processes and operations, sometimes involving major legal and policy changes. It was clear from discussions that stakeholders would benefit from alignment to develop such new models.
Alternate study designs and requirements for collection and use of real-world evidence (RWE)	Workshop participants indicated that value assessment is more challenging with some of the novel types of study designs (e.g., single-arm studies, adaptive or basket studies) that are increasingly common with CGT or precision medicine studies. Changes in standards for trial design and use of RWE are evolving, in part driven by technology advancement and increased focus on rare disease.28,29 Further, many cell and gene therapies may involve single-arm trials when they focus on niche populations or are fast-tracked, creating additional need for RWE comparative data to address payer questions.30 These often must be accompanied by RWE studies that help inform comparative effectiveness assessment during health technology assessment processes in the U.S. and other markets.31 Participants indicated that they are just beginning to learn about the methodological considerations associated with RWE versus typical randomized controlled trials (RCTs). As study designs continue to alter, close communication with physicians and payers to address rationale for study designs, methodological considerations and value demonstration decisions can help evolve our acceptance of new evidence approaches.

respondents held a particular interest in CGTs and/or are early adopters. Based on the limited number of respondents, survey findings may not be fully representative of U.S. provider, hospital, and health-system perspectives, but do point to trends in payer and provider views on CGTs.

VI. Conclusions

This evaluation helps all stakeholders understand the complexity and current state of the provider-side of cell and gene therapy; an area that despite being an essential component of transformative therapy acceptance and uptake has received comparatively limited attention. A sound and sustainable foundation of providers and health system partners is a cornerstone of patient access to transformative medicine. Despite some initial *"goodness of fit"* considerations, our analysis suggests that providers are a willing and engaged stakeholders in cell and gene therapies. However, ensuring their long-term ability to support these therapies is also contingent on an environment that enables profitable and practical operations, as appropriate.

The following provides some overarching conclusions based on this body of research, including survey and deep contextually rich discussions from the in-person workshop.

- **Reducing reimbursement and payment barriers is the single most important factor in building a sustainable provider environment for cell and gene therapies.** Of all factors impacting provider acceptance and use of cell and gene therapies, reimbursement was the dominant disincentive to patient access. Limits of existing coding and payment systems, lack of models for single-administration transformative or curative therapies, and legal and practical limits of multi-year value-based payback models were some of the most formidable hurdles to ensuring that providers can be *"made whole"* for administering these innovative therapies. Provider acceptance in the

Table 8: Uptake and Management Lessons for Providers and Manufacturers

Lessons for Manufacturers	Lessons for Providers
• Optimization of reimbursement, acceptance and uptake of CGTs would benefit from a uniform voice and rationale from the industry. While one-off novel approaches to reimbursement or payment may be necessary, they are unlikely to drive a groundswell or call to action to ensure appropriate patient access to novel CGTs. The changes needed to optimize HTA, reimbursement and payment in this emerging technology space are multi-faceted, complex and beyond the ability to address of many manufacturers. • Do not disregard the potential for articulating broader health system impacts of a novel cell and gene therapy to augment to core value package. • Do not assume that providers or payers have a detailed understanding of alternative study designs (e.g., single-arm studies), RWE methods, or the rationale behind them. Ensure that rationale linking the value demonstration plan is clear and that explanation of some of the underlying methodological considerations may be necessary to clearly articulate a case for novel CGTs.	• Developers of CGTs face a complex development landscape that can involve novel single-arm or adaptive designs, potential need to collect RWE to address comparative effectiveness of the therapy, and requirements for long-term patient follow-up to document safety and duration of therapeutic effect. • As novel CGT influence efficiencies at the hospital- and health-system level it will be important to (a) work with CGT developers to document the procedure-related and broader effects to help ensure adequate payment for the therapy and (b) consider whether there may be health system effects beyond the norm that could help make a case for the benefits of transformative or curative therapies (e.g., freeing up time for other procedures, hitting facility quality and performance metrics, improving facility reputation).

short term may readily revert to non-acceptance as increasing numbers of cell and gene therapies enter the treatment environment in the coming years. It will take close working collaboration of providers, payers, manufacturers, and policy makers to address such reimbursement hurdles in a timely and patient-centric manner.

- **Early engagement with providers is a foundational element of developing and supporting use of novel cell and gene therapies**.
  Development and patient use of cell and gene therapies is substantially more complex than what is typically associated with conventional drugs and biologicals. Early engagement models that look beyond clinical trials towards solving for real, operational reimbursement and other hurdles are a critical success factor for advancement of transformative therapies. Limits on the uptake of existing cell and gene therapies, in part, reflect the difficulty of the transformative therapy learning curve. In many ways, providers, and manufacturers, in these early days of cell and gene therapy, are pioneering a new way of thinking about and administering care. There are also many opportunities for sharing lessons learned as our conventional health delivery models flex, are reshaped to support transformative therapies that involve different patient and operational flows, which may ultimately enable broader health system efficiencies.
- **Providers partnerships with manufacturers and other stakeholders should ensure appropriate data collection around cell and gene therapy.**
  A key *"miss"* associated with some early CGT is ensuring that data collection adequately accounts and makes a case for covering the cost of administration of cell and gene therapies. Close partnership with developers and focus on data collection of the resource use involved in the provision of CGT can help ensure that provider costs are appropriately considered and procedures are financially viable and sustainable. Further, as CGTs help reframe our expectations for long-term duration of effect, they are at the same time helping reinforce another fundamental shift in evidence-based medicine, where evidence collection is a *"journey and not a destination"*. As value-assessment models shift towards a continuum, driven by novel study designs and RWE and rapid data analytical capabilities, the provider is *"in it for the long haul"* as a partner in the process for managing treatment, follow-up and monitoring of CGT patients including outcomes-based agreements.
- **Addressing the affordability "frontier" will require rethinking and updating various elements of health delivery.**
  While affordability was noted as the key concern for future acceptance and use of CGT, and potentially further limited based on economic restraints in the wake of COVID-19, it was clear from the workshop that we have not yet fully engaged in envisioning a new model where transformative therapies may be a norm. Assuming these therapies reach their promise, or even a part of it, we have the opportunity to re-envision, arguably

outmoded elements and ways of working in health care, help realize efficiencies in a flexible manner that enables us to interactively apply system learnings. Reconsidering how novel evidence collection is linked to patient access and reimbursement models, building more flexible coding systems that accommodate rapid technological and data advancement, enabling use of rapid e-learning and decision support systems, rewarding technologies that may offer system impacts and efficiencies beyond that seen with conventional therapies, and developing incentive structures and payment mechanisms suitable for transformative or curative therapies are a few examples. As with reimbursement systems, harnessing the benefits of CGT in a manner that addresses affordability concerns is a responsibility involving all health stakeholders navigating an era of rapid health reform.

We are just beginning to understand the challenges and opportunities flowing from novel CGTs. This analysis suggests that we have more work ahead to ensure a fluid and long-term sustainable provider-side model for CGT. As more therapies approach real-world patient use, we will have additional opportunities to continue to improve our ability to offer these therapies in a streamlined manner with patient-benefit as a driving factor.

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