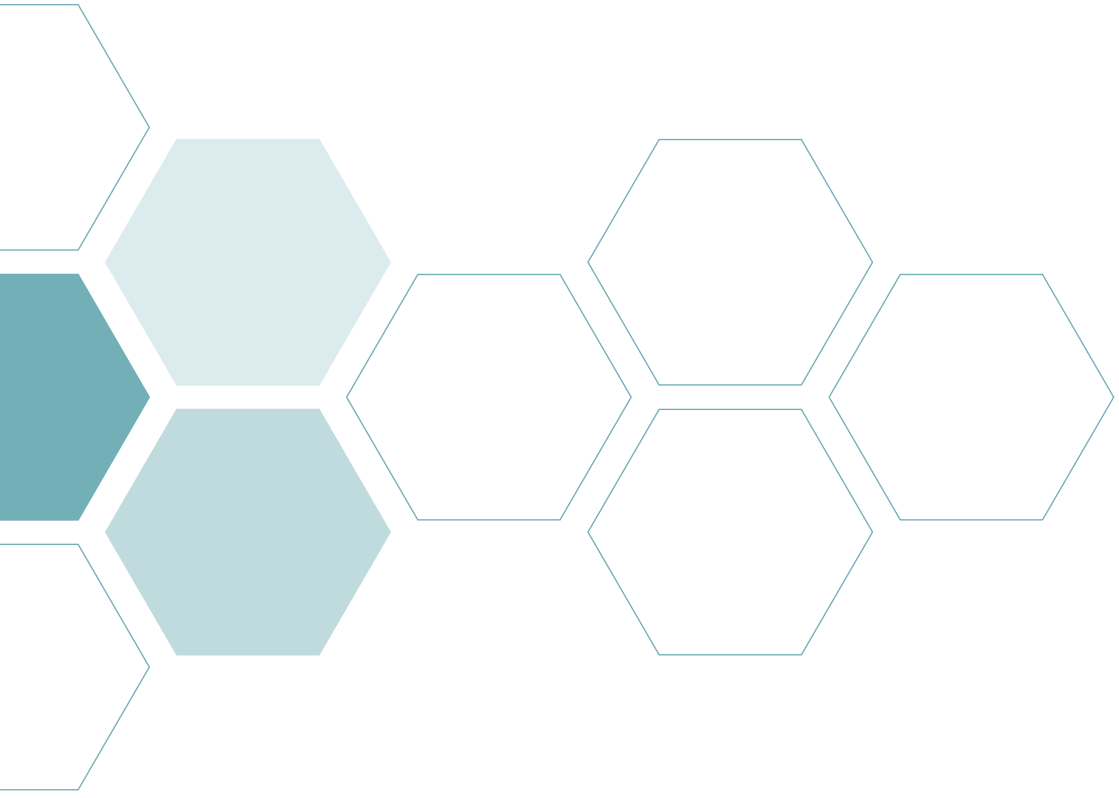
Roadmap for Navigating Cell and Gene Therapy Value Demonstration and Reimbursement in U.S. Managed Care



NAMCP
WHERE MEDICAL DIRECTORS TRANSFORM KNOWLEDGE INTO IMPROVED OUTCOMES

Alliance for Regenerative Medicine

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Reimbursement Roadmap Monograph 2019

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Roadmap for Navigating Cell and Gene Therapy Value Demonstration and Reimbursement in U.S. Managed Care

Eric Faulkner; Michael Werner; Robert Falb

I. Summary

The vanguard of transformative and potentially curative cell and gene therapies have launched, bringing new era of therapeutic options to patients. Despite their potential value, there remains significant uncertainty around value assessment, reimbursement, and payment models for these therapies. Factors such as the greater magnitude of clinical and patient-centric effects, prolonged duration of therapeutic effect, and lack of ideal or developed payment models for value-based reimbursement of comparatively high-cost, single-administration therapies provide opportunities and challenges in a system that was not built with such therapeutics in mind. This step-by-step study evaluates U.S. managed care reimbursement process for cell and gene therapy (also referred to as regenerative and advanced therapies), from the perspectives of U.S. commercial payers and manufacturers. The results are intended to help both payers and manufacturers understand and navigate the challenges, special considerations, steps and system changes that are warranted for cell and gene therapies.

II. Introduction

We currently live in an age where rapid proliferation of novel health technologies significantly influences the U.S. health system, including medical devices, precision medicines, rare disease treatments, immunotherapies and other advancements. It is not uncommon that innovations develop faster than the evolution of value assessment, coding and payment systems, and delivery structures.[1,2,3] When novel innovations do not "fit" neatly into existing healthcare models, there can be disincentives for use and significant uncertainty around patient access, regardless of the realized benefit exhibited by a particular therapy.[4,5] Cell and gene therapies (also referred to as regenerative and advanced therapies) have uncertainties around all dimensions, value demonstration, coding and payment. Issues such as demonstration of transformative and curative effect and duration of therapeutic effect increase, lead to complexity in health technology assessment (HTA) by introducing issues that have not been routinely considered.[6,7] Likewise, coding and payment models for potentially curative therapies have not yet been broadly developed, though Centers for Medicare and Medicaid Services (CMS) has recently initiated a National Coverage Determination including coverage with evidence development for chimeric antigen receptor therapy (CAR T therapies).[8] While many have discussed novel time-based payment models and other options such as risk pooling models, there is not yet a definitive payment approach to address the implications of a one-time therapy that has potential to last years or a lifetime.[9,10,11,12,13] However, some manufacturers like Avexis, Spark Therapeutics, and bluebird bio are working to advance novel payment options for their therapies that go beyond conventional models.[14,15,16] This paper will examine the current state of play and issues necessary to consider to successfully navigate cell and gene therapies through a system not built to receive them developing upon our first organizational collaboration and publication.[17]

III. Methods

This study involves the participation of members and representatives from the Genomics, Biotech, Emerging Medical Technology Institute (GBEMTI) and Alliance for Regenerative Medicine (ARM). The GBEMTI was established in 2011 as an institute of the National Association of Managed Care Physicians (NAMCP). NAMCP has over 20,000 members and represents medical directors from payers, purchasers (employers), and provider systems such as independent practice associations (IPA), accountable care organizations (ACO), physician-hospital organizations (PHO), and medical groups. The goal of GBEMTI is to support and characterize the value of genomics, biotechnology, cell and gene 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 healthcare market place. The institute is guided by an Executive Leadership Council (ELC) comprising approximately 100 payer and manufacturer members. The GBEMTI 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. healthcare and explore means to improve managed care decision making and patient access to emerging health technologies.

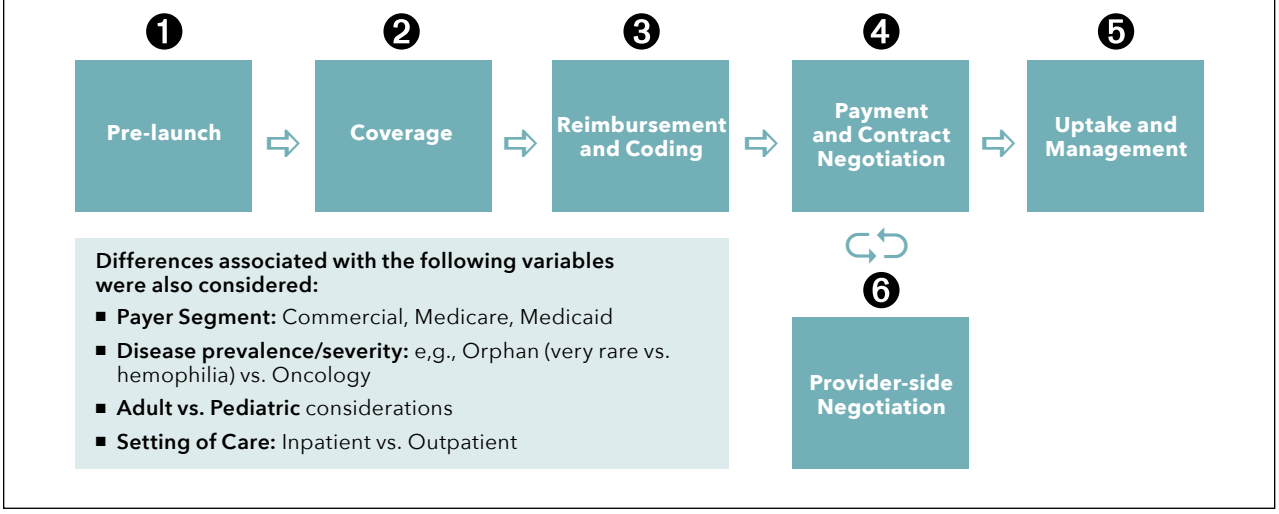
ARM is the pre-eminent global organization focusing on cell and gene therapies. It is also a multi-stakeholder organization that fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

To gain a better understanding of payer perceptions of gene and cell therapy and how the payer community is preparing for their expansion, NAMCP and ARM undertook a study, conducted between October 2018 and June 2019, involving a survey of medical director members of NAMCP, a face-to-face workshop between payers representing a range of U.S. health-plan types and ARM cell and gene medicine company representatives and a desktop landscape research of the topic. The survey questions addressed key payer perspectives on cell and gene medicine and highlighted key issues relevant to payers, providers, and manufacturers. The survey was randomly disseminated among medical director members of NAMCP and yielded 44 responses. Of the total respondents, approximately 75 percent identified themselves as medical directors at commercial managed care organizations (MCOs) and 25 percent identified themselves as medical directors of health system and provider organizations (e.g., academic medical centers, hospital and other health systems, and large physician practices). The sample also included payer decision makers from leading U.S. MCOs (i.e., Aetna, Cigna, WellPoint, United Healthcare), which collectively represent more than 115 million covered lives in the U.S. Additional payer and manufacturer feedback input was obtained through a workshop involving commercial payers from both national and smaller regional plans, add context, clarify responses and explore solutions that would help characterize payer expectations for manufacturers and resolve manufacturer challenges at key stages of the managed care process.

IV. Findings and Implications

As a framework for identifying critical success factors for navigating cell and gene therapies through the U.S. managed care environment, the following core domains (Figure 1) were covered to explore the process involved in each domain from the U.S. managed care perspective. Participants also discussed how cell and gene therapies can be integrated into the existing system, identified gaps, and captured perspectives on solutions. Differences related to the following variables were also considered: payer segment, disease prevalence/severity, adult versus pediatric treatment, and setting of care to help identify special considerations important for manufacturer and payer stakeholders.

Figure 1. Understanding Payer Decision Flow, Process Considerations, and Stakeholder Drivers: Core Domains Covered in this Analysis



Key findings from the survey and in-person workshop around each domain associated with evidence development and reimbursement of cell and gene therapies are described in the following section. Input from both sources are interspersed throughout, as appropriate to the topic. This flow is intended to isolate key steps in the decision flow, stakeholder involvement and perspectives, and special considerations for cell and gene therapies. 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 in the U.S. managed care environment for transformative or curative cell and gene therapies. This will be followed by a third collaboration exploring cell and gene therapy navigation of the provider-side of managed care.

A. Payer Early Engagement

As manufacturers develop any new therapy, it is increasingly important to understand not only the regulatory acceptance requirements, but also the payer and provider acceptance requirements.[18] This is true even in biotech development scenarios, where the core goal is optimizing asset value prior to sale or engagement of a large pharmaceutical partner to support commercial uptake.[19] As risks to successful product launch and commercialization continue to grow, integration of market access and commercial needs into the earliest stages of clinical development has become a "got to have."[20,21] Investors increasingly want to know that a new product developer has done sufficient diligence around acceptance and uptake drivers to adequately characterize asset value and avoid delays or failure at launch.

When asked about the ideal time for cell and gene therapy manufacturers to engage with payers for early advice (e.g., prior to initiation of Phase II), payers participating in the face-to-face workshop indicated that despite their interest in understanding new therapies, many commercial payers (including large plans) do not have the bandwidth to interface with manufacturers prior to launch. All the commercial payers participating, while not representing all U.S. commercial payers (but including several of the largest U.S. commercial health plans) indicated that they do not have a formal function to engage with manufacturers on pipeline products to inform study design or address acceptance considerations. This result runs contrary to the desire of most life sciences manufacturers who value early input on clinical, value demonstration and market access plans to reduce product development risks. It also poses a risk disadvantage for the developers since they will be "ready" for launch without the benefit of payer input. Further, the face-to-face input is from a small number of commercial payers and manufacturers indicate that actual payer willingness to meeting with early cell and gene therapy manufacturers, given the potential impact of these therapies on plan financials, is more open than noted.

Commercial payers in the workshop did, however, indicate that they do keep abreast of new technology development via news-feeds, literature, conferences, and continuing medical education. They also indicated that traditional market research via qualitative interviews or advisory boards organized by manufacturers are the ways in which they are most commonly engaged to provide feedback on pre-launch assets. Most commonly, the medical director or pharmacy director of the plan would participate in such activities, but other stakeholders (e.g., plan financial managers, and plan staff that deal with hospital interface) may also participate when reimbursement or payment topics are considered.

When asked about the kind information they would want to see at this early engagement stage, workshop participants noted the following:

- **Target patient population/subpopulation with rationale** for selection
- **Study design and preferably outcomes overview** (primary, secondary, and exploratory endpoints), including any early study data available; **target product profile** information
- **Intended use and fit/positioning in the care pathway**; information on the **way the new therapy will address unmet need**
- **Longer-term outcomes plan** (for cell and gene therapy to demonstrate duration of effect)
- Ideally, **information on the cost band anticipated for the therapy**

We also discussed the scenarios where payers are more likely or most motivated to engage. The main driver for engagement is the volume of patient population and/or cost of the therapy, where significant financial impacts are expected. Cell and gene therapies would fall into their area of interest, largely because of the high anticipated unit cost of the therapies and because payers are still

learning about these relatively novel technologies. Rare disease scenarios, even in terms of high unit cost products, were less likely to prompt early payer engagement due to payer perceptions of limited budget impact. While product novelty (e.g., a new platform or mechanism of action) could stimulate payer interest in meeting, this was the least likely variable noted as supporting early payer engagement meetings. At present, however, given the true novelty of this space, cell and gene therapy novelty may well support early engagement as payers explore issues and impacts of this new therapy area. This suggests that many cell and gene therapy development scenarios would not support in-person early engagement meetings. Rather, and conventional market research approaches are the affordable and approachable means to obtain broad feedback from a key sample of U.S. commercial payers to inform early development.

Fast-track and expedited regulatory approval programs such as rare disease or regenerative medicine advanced therapy (RMAT) regulatory designation that may apply to cell and gene therapies were also discussed. In those scenarios, obtaining early feedback is even more important to help de-risk development approaches.[22,23] Faulkner E. Navigating Acceptance, Uptake and affordability of advanced therapies across the lifecycle: what does good look like? Alliance for Regenerative Medicine Meeting on the Mesa. For a therapy type with value proposition that is both transformative and curative with anticipated long-term effect, there was thought to be tremendous risk of market entry challenges with an incomplete evidence package to support coverage. Under fast-track scenarios, workshop participants thought that obtaining payer feedback was even more critical to understand whether planned study outcomes would address payer and provider decision needs, particularly if they would be anticipated to launch in the $500,000 to >$1,000,000 price band that payers associated with cell and gene therapies. This was particularly true in situations where reasonable treatment alternatives are available. While fast-tracked therapies were noted as being accepted with, what is viewed as, an incomplete evidence package, particularly in rare disease or protected product class scenarios, payers did indicate that there would likely be much greater emphasis on how the product would be managed in terms of step therapies and other access restrictions. They also noted that there may also be delays associated with uncertainties in product assessment that have the potential to delay decisions by 6 to 12 months. How fast-track processes bridge to conditional coverage approaches, which enable development of evidence overtime, is another key area that remains uncertain.[24]

Core items that manufacturers most frequently miss in early development were also examined. The items listed in Table 1 were noted by payers as key areas of the cell and gene therapy value proposition that are most often overlooked during periods where

Table 1. Areas that Payer Participants Identified as Common "Misses" in Cell and Gene Therapy Value Story Development

- **Insufficient focus on linking surrogate markers to "harder" outcomes** (e.g., mortality, morbidity, health resource utilization) that payers care most about. This noted as one of the most common reasons for non-coverage, and was particularly relevant to high-cost cell and gene therapies where there is expected to be less flexibility in decision making (driven by cost considerations).
- **Unclear rationale for the target patient population and positioning** (e.g., based on epidemiology data, biomarker data and other rationale) and/or **insufficient information of core subpopulations**. Lack of ability to perform post-treatment subpopulation analysis was also cited as precluding any "back up option" for coverage of a more discrete population subset where outcomes may be improved versus standard of care (SoC).
- **Unclear burden of disease, natural history or SoC impact** (i.e., key gaps or uncertainties around SoC outcomes lay the foundation defining the transformative outcomes needed to support cell and gene therapies).
- **Basing the entire value proposition on minimalist or surrogate endpoints** for a cell and gene therapy that is anticipated to have transformative or curative effect.
- **Lack of sufficiently comprehensive value story to "cover the bases"** important to a well-rounded value story. While payers did note that in some rare disease scenarios a less robust value story may be acceptable; in the case of cell and gene therapies, they anticipate much greater scrutiny and lower willingness to accept evidence gaps than in other less costly treatment scenarios.
- **Lack of evidence considering the therapy in context of SoC/lack of comparative effectiveness.**

Table 2. Early Engagement Lessons for Manufacturers and Payers

- In the case of cell and gene therapies nothing should be taken for granted. It is even more important to "do your homework" in terms of clearly defining payer and provider information needs. While the same processes associated with other therapy assessment will apply, the scrutiny associated with these novel therapies will often be greater, introducing additional risk.
- Do not anticipate that direct payer engagement for testing development and pre-launch access plans will be readily available with all plans, though are likely to meet with all manufacturers.
- Plan for sufficient early work, leveraging primary research as the primary way to obtain feedback from payer stakeholders.
- Consider development of the most comprehensive a value proposition as possible, particularly in fast-track scenarios that challenges the core "value pillars" of cell and gene therapies (i.e., magnitude and duration of effect).
- Manufacturers in the cell and gene therapy space have a key need to characterize acceptable product value early in development. This need is not optimally aligned with payer business models based on current operational incentives and constraints. However, the benefits of early feedback accrue to all stakeholders in the form of improved alignment of development plans with value and acceptance expectations.
- Cell and gene therapies may have health system effects beyond what is typically included in payer and provider decision processes, flowing from the potential to significantly delay or avoid altogether significant disease impacts and/or costly chronic care or end-of-life outcomes for some diseases. These therapies may require key stakeholders to rethink current cost-offset and health efficiency assumptions.
- Addressing key evidentiary considerations associated with cell and gene therapies, including the difference to conventional drug/biologic treatment scenarios in magnitude of effect, expanded patient and caregiver effects, and duration of effect, along with linking payment around an often-single administration from conventional. For this vanguard wave of novel therapies, engagement will be fundamental to addressing new evidentiary, reimbursement, payment and delivery model implications, including beyond the remit of any individual commercial payer.

the greatest emphasis is on regulatory acceptance.

Payers in the workshop indicated cell and gene therapy developers would be well warranted to understand payer-decision requirements prior to engagement in pivotal Phase II trials and plan for development of as the most comprehensive value case in fast-track scenarios. The groundwork laid in early development was thought to be foundational to establishing clear and defensible product coverage and patient access.

Table 2 describes key early engagement lessons for both manufacturers and payers.

B. Establishing Coverage for Novel Cell and Gene Therapies

In the U.S., there are hundreds of health plans, both public and private. While there are similarities, each maintains their own individual process for establishing coverage decisions. Payers in the workshop indicated that many variables such as the number of coverage policies the plan maintains annually, number and nature of staff involved in the technology assessment process, where evidence is sourced, how evidence is assessed, and processes seeking external input influence how coverage decisions are made. This variability has been documented in other assessments.[25] Not every technology will have an individual coverage policy, and in other cases, plans will bundle multiple technologies under a single policy in disease areas where multiple treatment solutions exist. However, given payer perceptions of the cost of cell and gene therapies, workshop participants noted that it is highly likely that most cell and gene therapy access will be managed through development of coverage policies that address specific cell and gene therapies (i.e., that these therapies are unlikely to "fly under the radar" and/or avoid inclusion in specific coverage policies).

Who is involved in general coverage decision making?

Larger U.S. health plans depend on staff to assemble available evidence for coverage review. Once assembled, the evidence package is reviewed by the Medical Policy or Pharmacy Policy Committee of the plan. Whether the therapy falls under the medical or pharmacy benefit will influence not only how coverage is managed, but also the associated reimbursement and payment policies that apply. For cell and gene therapies, whether the medical or pharmacy committee reviews the product depends on a number of factors, including how the plan manages cell and gene or biologically-derived products, which plan cost center offers the best managed care controls, how imbedded into a procedure use of the advanced therapy component is, and how the therapy is handled (e.g., special handling requirements or steps, such as cell extraction, onsite processing steps, storage, and reconstitution, etc.) and administered. Coverage evaluation process can vary markedly depending on the size and resources available in the payer organization, or in some cases,

outsourced to a third-party. However, the evidence assessment virtually always involves a literature search, evaluation of clinical practice guidelines, consideration of existing coverage, consideration of product fit under existing infrastructure, and consultation with physicians with expertise in the disease area of interest. Most coverage decision processes occur one or more times throughout the year. Timing and requirements are highly variable by plan, but typically occur 3 to 12 months after launch according to the face-to-face workshop participants.

Physician experts in a particular area may be called upon by the payer to discuss their perceptions of the value and impact of a new therapy versus the existing SoC. This is particularly true in rare disease and other scenarios where the patient population may be poorly understood, as Medical and Pharmacy Directors cannot have fully comprehensive knowledge of all the multiple disease treatments and technology types flowing through plan decision processes. Payers in the face-to-face workshop stressed that they are skeptical of so-called "key opinion leader" physicians because of perceptions of their frequent use to inform novel product development. A first key consideration is whether the novel technology meets medical necessity requirements or falls under a special protected category of therapy (e.g., anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants).[26,27]
Medicare and Medicaid therapies were noted as following evidence assessment processes for coverage similar to that use in commercial populations. However, special "guardrails" associated with these patient populations (e.g., protected disease classes) may differentially apply under these payer types. As payers can maintain a large number of varying plan offerings (e.g., 20 – 40) for very large national payers, the HTA process feeding them is often the same and management is then governed downstream by individual plan rules and governmental requirements according to different patient type (i.e., commercial, Medicare, Medicaid). Payers in the face-to-face workshop viewed Medicaid to be the most challenging for cell and gene therapies because of (a) the high variability among state Medicaid management processes and budget constraints and (b) limited ability of a smaller state population pool to absorb costly therapies. Payers indicated that across Medicaid plans there may be more gaps in access for vulnerable populations, particularly for therapies in the $500,000 to $1,000,000 range of on-market advanced therapies.

What coverage management tools are often applied to cell and gene therapies?

It is important for cell and gene therapy manufacturers to understand that coverage is one of the primary access and cost management tools of the plan. Once the product is determined to be covered and recommendations are made about access restrictions, how the product is managed is governed by financial and operational mechanisms that vary widely by payer. Further, products covered under Medicare and Medicaid that may be managed by commercial insurers must also meet statutory requirements and processes that can differ or do not apply under commercial scenarios.

Further, it is also possible that coverage may be more restrictive than the FDA label, for example, if the payer perceives information associated with a key subpopulation is not sufficient to support coverage. One recent example of this is seen in initial coverage of Spinraza (nusinersen), a drug treatment for pediatric patients with spinal muscular atrophy (SMA). While not a cell or gene therapy, this rare disease therapy was particularly costly, with first year annual costs approaching $750,000 and within the band of initial advanced therapy pricing. In this scenario, several U.S. payers initially determined that there was insufficient patient data supporting access in some SMA disease subtypes, which has hence been addressed by additional clinical evidence to cover all three main subtypes.[28] Similarly, the first advanced therapy launched for SMA, Zolgensma® (onasemnogene abeparvovec-xioi), priced at over $2,000,000 has also faced more restrictive coverage upon launch.[29]

Commercial plans also have the discretion to deny a product as investigational or experimental even in scenarios where the Center for Medicare and Medicaid Services (CMS) decides for coverage. Payers in the workshop indicated that such decisions are typically made when project value is unclear evidence-driven, particularly in scenarios when product benefit is unclear or there are significant gaps in the value package. Costly therapies, which include cell and gene therapies, were also noted as being at greater risk for investigational/experimental decisions, particularly given that a key pillar of the value proposition is prolonged duration of therapeutic effect. In scenarios where it is difficult or impossible to render a product investigational (e.g., oncology/pediatrics), the payer may instead develop very comprehensive access restrictions that would only be removed if new evidence emerges to support a previously restricted use. A key lesson here for cell and gene therapies is to ensure a sufficiently

comprehensive evidence package that anticipates the decision requirements across different U.S. payer types. The types of scrutiny applied to cell and gene therapies, according to face-to-face participants is not dissimilar from other therapies but based on (a) novelty and (b) perceptions of high cost, these therapies will face more intense scrutiny than more conventional biopharmaceuticals. Determination that evidence is insufficient or uncertain can result denials or significant delays in offering novel cell and gene therapies to patients that in terms of the disease areas targeted for development often have high unmet need for transformative solutions.

According to the NAMCP member survey and face-to-face workshop participants, most commercial plans do not have special coverage or management processes for cell and gene therapies. Only a small fraction of respondents indicated that there is movement in this direction, largely because the number of on-market therapies remains small and has so far been focused in rare or niche patient populations that do not yet warrant proactive plan management steps. More generally, respondents indicated that there is a movement in some plans to manage very expensive therapies under the pharmacy benefit to enable greater access and pricing controls and better manage economic impact through benefit design more tightly than tools often available under the plan Medical Benefit. This was noted as including, but not to be limited to, cell and gene, rare disease, and oncology therapies.

What do payers look for in coverage determination?

Most, but not all, plans typically look at the clinical evidence separately from cost or economic evidence. This is particularly true for the largest U.S. commercial plans, as well as for Medicare and Medicaid—though respondents indicated that they all will indirectly think about volume and cost impacts of therapies as they assess value. Smaller health plans are more likely to consider clinical and economic impact simultaneously as they have less budget latitude to buffer unanticipated financial impacts vs. larger and more diversified payer organizations. For those plans that transition the HTA process to a third-party (e.g., Pharmacy Benefit Manager [PBM] organizations) for evaluation (often smaller plans or large employers), the ultimate coverage decision (and any amendments) is still retained by plan Medical or Pharmacy Directors and other administrative executives.

Table 3 below highlights the most common information missed to support or optimize coverage potential new therapies, including for cell and gene therapies.

The main feedback that payers in the workshop provided on existing advanced therapies that they have experience with (i.e., predominately CAR T therapies and the ocular therapy Luxturna™) are (a) their strong perspective that these therapies yield transformative benefits, particularly considering their perceptions that these therapies are high cost and (b) uncertainty around duration of benefit. For therapies that had a more uncertain or marginal benefit, payers in the workshop noted that short of statutory protections, these therapies would face the greatest risk for either non-coverage or very limited coverage (i.e., with many coverage hurdles to overcome to gain access).

Payers in the workshop also confirmed prior

Table 3. Areas Payer Participants Identified as Common "Misses" in Advanced Therapy Coverage Support

- Clear enough information about how patients would be identified (e.g., using biomarker or symptomatic data) as candidates for the new therapy.
- Comparative effectiveness data (though not a requirement, in the absence of direct evidence, commercial health plans will consider it indirectly); from the manufacturer's perspective, this can be a double-edged sword and must carefully be considered carefully be considered.
- Sufficiently robust indirect data in single-arm trial scenarios.
- Information on "hard" health outcomes (i.e., mortality, morbidity, quality of life) that go beyond surrogates; clear evidentiary link between surrogates and "hard outcomes" of interest.
- Sufficiently clear clinically-relevant interpretation of patient-centric outcomes (focused on functional status vs. socio-emotional factors).
- Clear enough information about what SoC treatment/services may be replaced/displaced.
- Sufficient evidence of duration of effect, most frequently defined as 2 to 3 years to be minimally acceptable.

findings of NAMCP research on duration of effect and noted that 2 to 3 years of duration data is viewed as minimally acceptable with 5 or more years viewed as ideal.[30,31] Payers acknowledged the challenge of needing to go to market in a reasonable timeframe, including pursuit of fast-track launch, balanced against the need to demonstrate long-term effect. While they understood the rationale behind a flexible process enabling initial coverage with risk sharing and follow-up, they acknowledged that (a) such risk sharing agreements are far from the norm and (b) when they do, often center on disease areas with the highest/volume and cost impacts (e.g., diabetes, congestive heart failure). For cell and gene therapies, most payers in the workshop felt "stuck" with the need to make coverage decisions at time of launch and cited limited mechanisms for consideration of follow-on or real-world evidence (RWE) development requirements as routine payer processes under current models. This suggests three key issues: (a) it is important for the manufacturer of a cell or gene therapy to collect data on every patient that the therapy is used on to make the longest duration case possible at launch (e.g., via early registry start), (b) U.S. payer understanding and acceptance of RWE is still evolving and rationale for/education around RWE approaches may be important to acceptance of more iterative evidence collection, and (c) manufacturers may need to look beyond payers to other third parties (e.g., PBMs, reinsurance companies) that have greater latitude to for flexible value demonstration and payback models and ability to pool risk beyond that held by any one commercial payer.

What additional tools do payers leverage to manage coverage and access for cell and gene therapies?

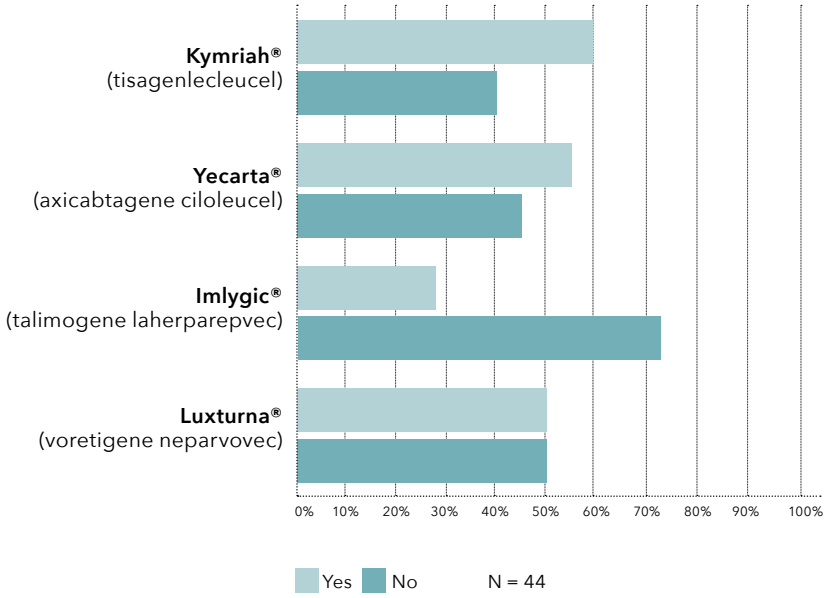
For cell and gene therapies, and true for virtually all therapies that may be considered high cost, payers in the workshop indicated that *prior authorization* is a requirement for all such therapies to ensure that the patient is eligible for coverage. Depending on the treatment scenario (e.g., common vs. rare disease, acute vs. chronic disease etiology, serious and costly symptoms or disease effects, availability of reasonable alternatives), *step therapies* may also apply. Step therapy access policies require patients to exhaust an established/lower cost prior therapy step before moving to a new/often more costly therapy step. Even when therapies demonstrate transformative effect, pricing of cell and gene therapies may place these therapies into a higher cost/management tier if successful and more affordable alternatives exist. This feedback suggests that manufacturers have strong, clear and comprehensive evidence of (a) where their therapy fits in the continuum of care and (b) what differentiates the new therapy from other therapies and (c) for which patient subgroups.

Other payer strategies beyond coverage include leveraging *tiering* to control access and costs and shift additional cost implications to patients. Based on the costs, workshop participants noted that cell and gene therapies would almost certainly, where managed through a pharmaceutical tiering process, be included in the highest tier, along with most other biological agents. It was unclear whether a new tier for therapies with curative intent could be instituted as an additional management strategy. Payers will commonly negotiate *discounts,* and in rarer cases, *risk-sharing agreements* where a manufacturer will guarantee a pre-negotiated outcome in exchange for access. Payers in the workshop almost universally indicated that they prefer discounting as it is more administratively straightforward. They further stated that risk-sharing agreements were infrequently negotiated and predominately reserved for high volume and cost treatment scenarios. Workshop participants noted that such arrangements would rarely be applied to rare diseases, even when cost is in the range of current cell and gene therapies (i.e., $500,000 to >$1,000,000) because U.S. commercial payers do not aggressively manage access to rare disease treatments, beyond establishing coverage policies with clear access restrictions. Alternatively, manufacturers noted that special risk sharing or payback provisions are the preferred tools to help ensure patient access by manufacturers for single-administration advanced therapies, predominately as a practical means to manage the uncertainty associated with demonstration of long-term effect.[32] Deductibles were also noted as a means to moderate access, though this tool would not have different application to cell and gene therapies vs. other technology types.

How are payers currently managing coverage and access for cell and gene therapies?

We also considered how U.S. commercial payers have addressed coverage for initial transformative advanced therapies launched in 2017–18. While other cell and gene therapies (e.g., chondrocyte therapies) have been launched in the past, this wave of therapies represents the vanguard in what many would consider transformative or curative therapies, with a bolus of >1,000 additional therapies in their wake. A recent study from MIT anticipates that

Figure 2. U.S. Payer Coverage Policies for Initial Transformative Therapies



another 30 to 60 therapies are likely to launch within the next decade.[33] Figure 2 illustrates survey results from the 44 payer respondents of the survey.

At the time of the survey, coverage for initial advanced therapies had not been established in 52 percent (with a range of 40% to 70% depending on the specific therapy) of plans surveyed. While some of this lack of coverage policy development reflects both time of launch for these therapies and timing of cycles within which payers establish coverage polices, this outcome is commercially challenging for therapies that may be considered to have transformative effect. Given the rarity of some conditions targeted by these oncology and rare disease therapies, it is also possible that coverage policy development has not yet been stimulated by claims requests for patient access from physicians. It is unclear from survey data the extent to which coverage may have been delayed, however it may reflect that we are still in a learning phase of cell and gene therapy acceptance where market education is critical. Further, current coverage restrictions noted for CAR T therapies under CMS policy limit access to non-community settings and hospital inpatient or outpatient settings only, may further delay or inhibit access as providers navigate access for the initial vanguard of patients.[34]

At the time of the workshop, payer participants only had experience with advanced therapies in oncology, but not with Luxturna™, a therapy for patients with a rare ocular condition. While payers in the workshop indicated that, to their knowledge, cases requiring treatment by Kymriah®/Yescarta®/Imlygic® were not subject to any specially negotiated terms like risk sharing, a minority of payers in the survey indicated that special arrangements for these therapies have been developed. Aside from any discounting/other arrangements, which could not be divulged, all workshop payers indicated that at present they are simply paying for the therapies upfront (though this was not viewed as an ideal solution). This suggests that payment approaches for cell and gene medicines in the U.S. remains highly heterogenous, making predictions of realistic commercial uptake and ROI less predictable than conventional therapies, which could be normal for truly breakthrough therapies with limited precedent.

These findings suggest the following for manufacturers: (a) commercial payers are not behaving any differently in establishing coverage for cell and gene medicines, despite the transformative nature of initial therapies, though in some cases, they may not be rushing to establish coverage decisions, (b) given the novelty and cost of these therapies, establishing access will take more time and field effort than that commonly associated with conventional therapies, and (c) there is significant variability in how plans are addressing these therapies, though the majority appear to be employing upfront payment. No stakeholders from the survey or workshop divulged whether arrangements to manage coverage and access were being maintained by other third-

party organizations (e.g., PBMs), and the extent to which this may be the case is unclear.

What other special considerations should be considered in establishing coverage?

Workshop participants also discussed other considerations for establishing coverage for regenerative and advanced therapies, including differences in adult vs. pediatric scenarios, Medicare or Medicaid considerations versus commercial coverage scenarios, and prevalence of disease. These special considerations are described as follows:

***Payer segment*:** Many U.S. commercial payers administer benefits for both Medicare and Medicaid patients, in addition to traditional commercial plan offerings. Payers in the workshop indicated that Medicare and Medicaid therapies generally follow similar processes for evidence assessment as commercial plans, although Centers for Medicare and Medicaid Services (CMS) requirements around medical necessity, protected disease classes/groups, and other factors can differ in terms of coverage. Because commercial payers often maintain a large number of plan offerings, e.g., <100 for very large national payers, the HTA process feeding them is the same and management is governed downstream by individual plan rules and requirements. The staff involved in HTA and coverage development may vary markedly by plan, with small plans having very limited resources to support this process and often engaging external parties like Hayes and ECRI to support HTA efforts. This variability speaks to the critical nature of having a well-defined evidence-based value proposition to optimize access to the most critical information supporting product value. Payers in the workshop viewed Medicaid to be the most challenging for establishing cell and gene therapy coverage because Medicaid plans tend to institute more restrictive access management policies for high cost therapies.

***Special considerations*:** Payers acknowledged that *pediatric situations* in chronic or life-threatening conditions do received special considerations vs. adult treatment scenarios. This may result in lower scrutiny or acceptance hurdles for pediatric treatments in high unmet need areas/diseases with severe or fatal outcomes. However, in scenarios where alternative treatments are available, payers have much greater latitude to limit access to or even reject new therapies. In the case of cell and gene therapies, payers in the workshop noted that there may be a potential for application of step therapy procedures, particularly if the novel therapy is deemed to have uncertainties or marginal outcomes. Similarly, in areas where there are so-called *"protected classes of therapies"* (e.g., oncology), payers may relax evidence standards or degree of scrutiny, including for commercial beneficiaries where this may not be mandated by statute, but represent high potential areas for public backlash and increasing competition for patients.

Workshop participants also discussed differences in consideration of *rare disease treatment scenarios*. Payers in the workshop indicated that they may consider rare disease coverage differently, including completeness of the evidence package supporting the treatment, if the therapy is severe and/or fatal and few or no alternative treatments exist. However, payers indicated that with the emphasis on rare disease treatment over the past decade that "running into a rare disease treatment scenario is no longer rare" with the perception that 1 in 10 patients potentially having something that met the definition of a rare disease and that aggregate financial impacts on the plan are a growing area of concern, particularly as unit prices of rare disease treatments were also noted to have increased.[35] As rare diseases receive greater emphasis in terms of new therapy development, payers in the workshop indicated that access hurdles are likely to increase vs. scenarios where no sufficient therapy exists. Despite this acknowledgment of the growing financial impact of rare disease treatments, the majority of U.S. commercial payers in the workshop indicated that their plans have not categorically tried to manage the cost of rare disease treatments outside of establishing coverage policies and associated access restrictions, unlike other countries.[36]

Payers also noted concern that many rare disease trials have small numbers, and in the case of cell and gene therapies, increased uncertainty regarding magnitude and duration of effect. They stressed the importance of making a clear and comprehensive outcomes case, including plans for addressing duration of effect past the point of initial coverage (e.g., registry data collection is mandated by regulators for cell and gene therapies pursuing RMAT designation).[37] Payers in the workshop cited recent rare disease launches in Duchenne's muscular dystrophy as an example where uncertainty around evidence and outcomes resulted in initial rejections or implementation of heavy restrictions in rare disease coverage.[38] They also cited recent SMA treatment as an example where lack of having an insufficient number of patients outside of those with Type I disease resulted in restriction of access to only Type I patients. Payer participants noted that such limitations are currently uncommon in U.S.

managed care but are likely to become increasingly applied to rare disease scenarios due to expanding aggregate volume and cost of therapies addressing these patient populations.[39]

Payers noted that they would consider cell and gene therapies for rare disease differently if (a) there are not alternatives or (b) there is clear evidence that they can replace symptomatic or "band-aid" therapies or scenarios where costly chronic or lifelong therapies (e.g., enzyme replacement therapies, IVIG) are required. Replacement of enzyme replacement lifetime treatment models was cited as an example where they could see transformative and particularly curative cell and gene therapies as having advantages for the system and the patient. Under such scenarios, if the cell or gene therapy is truly transformative, it may have greater potential to jump to first-line therapy vs. higher volume disease areas. Payers also noted that it may be challenging in some rare diseases to measure outcomes in scenarios where disease effects unfold slowly over many years. In these situations, payers cited the importance of (a) developing a comprehensive evidence strategy and (b) carefully considering what is possible to measure in the short-term and link to long-term, more severe effects.

What can cell and gene therapy manufacturers do to best support coverage?

A product value dossier was noted by payers as helpful in the coverage evaluation process as it synthesizes the specific evidence that the manufacturer deems critical to characterizing dimensions of product value. Value dossiers also provide an opportunity for the manufacturer to articulate their evidence-based value story supporting the product in the context of unmet need and SoC. While the AMCP format dossier was noted as enabling a summary of evidence, dossier frameworks that are structured around the value story (i.e., more similar to value message-driven global value dossier formats), where each story theme is supported by supporting evidence, workshop participants preferred value story driven formats. The preferred document would also have a succinct executive summary with a clear and concise narrative and ideally a companion evidence-based slide deck to accompany the dossier.

In the absence of a value communication tool such as a dossier, the health plan process may miss some of the key value dimensions posited by the manufacturer. In general, payer respondents indicated that at the time of the coverage review, the committee may have 5 to 20 minutes to absorb and discuss the value proposition for a new therapy under typical commercial coverage review scenarios. This feedback strongly supports development of organized and succinct value communications materials.

Manufacturer and payer lessons associated with coverage and access to cell and gene therapies are described below. While coverage and access processes applied to these therapies are similar to conventional therapies, the perception of cell and gene therapies as high cost also influences the level of scrutiny and degree to which payers view it necessary to develop robust management approaches. Careful diligence and testing of therapeutic product profiles (TPPs) grounded in a detailed evidence development plan in early asset development and early stakeholder engagement is a key strategy to ensuring that the evidence package is sufficient to address payer need ad anticipate specific coverage and access considerations.

C. Coding, Reimbursement and Payment Considerations

The following section highlights key coding, reimbursement and payment considerations for cell and gene therapies in U.S. managed care.

Addressing Coding Challenges for Cell and Gene Therapies (and Linkage to Payment)

In the U.S., health services are paid for by codes that describe a particular procedure or service. If a code does not adequately describe a new procedure or service, this can mean that it will not be eligible for (sufficient) reimbursement, which is often a significant barrier to patient access. Even if a new procedure or service could potentially fit an existing code description, this does not mean that the payment rate associated with a specific code is sufficient to cover the cost of the technology, putting both the manufacturer and provider of the procedure or service at risk for financial loss and serving as a significant adoption barrier. The setting of care (i.e., inpatient or outpatient) can also substantially impact both coding fit and payment latitude. Lack of having a proper code can lead to significant delays in cell and gene therapy access, as therapies enter systems where the reimbursement route is uncertain, or at worst preclude patient access.[40]

It is currently common that cell and gene therapies enter an environment where they do not fit easily into an existing coding system that did not anticipate potentially curative technologies. Irrespective of the potential impact of a therapy, if it does not fit into existing coding and payment systems, this can represent a substantial acceptance and uptake hurdle for manufacturers, providers and patients. An example is highlighted in a recent editorial considering access challenges for breakthrough

Table 4. Coverage and Access Lessons for Manufacturers and Payers

Lessons for Manufacturers	Lessons for Payers
■ Manufacturers should understand coverage submission deadlines and review time frames for their top target plans to avoid coverage delays. Manufacturers should also anticipate that coverage decisions for cell and gene therapies may take longer. Ensuring a sufficiently robust payer engagement strategy can help minimize delays due more limited familiarity and special administration or market channel scenarios that may apply to these therapies.	■ Although the number of large biopharmaceutical companies entering the cell and gene therapy space is growing, the majority of cell and gene therapy developers remain innovator biotechs. These smaller organizations may not have the capacity or same familiarity with coverage processes as their larger counterparts and such organizations will seek early engagement to manage investment and development risks for cell and gene therapies.
■ Cell and gene therapy manufacturers should consider how prior therapies have been covered, even if proxy therapies are not in the specific target disease area. Benchmarking on common factors such as population size of the disease, availability of alternatives, and what types of evidence strategies are successful or not can lend significant clues to evidence that is acceptable to payers, level of granularity, and scope/nature of scrutiny applied in coverage policy rationale. This is particularly important in development scenarios where disease outcomes are non-obvious, difficult to measure, not well-established (e.g., link of surrogate markers to hard outcomes), or where disease unfolds over very long periods of time.	■ Coverage of early cell and gene therapies seem to lag behind conventional small-molecule and biological models that are better understood or accepted, even in scenarios where such therapies have demonstrated transformative or arguably curative benefit. Lack of coverage or significant coverage lags may be construed by manufacturers and other investors as an uncertain market signal, even if these therapies enable outcomes not possible by conventional therapies.
■ Discussion of TPP attributes in early development with payers can also help to identify specific elements of the value story and determine which can be covered in pivotal studies vs. other health economics and outcomes research or RWE efforts.	■ Many of the disease areas targeted for development of cell and gene therapies are currently not as well established in terms of alternative SoC therapies. In such cases, coverage precedent and anticipated acceptable evidence packages are less clear for manufacturers to navigate. Early payer engagement can clarify trial and evidence package design to address the issues most important to payers, giving the payer both early insight into novel therapies and the ability to inform asset development (versus a mode where they are reactive to what may be at higher risk for becoming a suboptimal evidence package).
■ In scenarios where successful therapeutic alternatives are available, payers will consider the value of novel cell and gene therapies in the context of SoC. In such scenarios, novel transformative therapies are much more likely to be subject to step therapies and other coverage limits. Developing clear rationale and differentiating evidence is particularly important under these circumstances.	■ Risk-sharing agreements are a key manufacturer consideration for cell and gene therapies, both in broad and rare disease scenarios. There would be particular benefit in articulating payer acceptance criteria for such agreements so that manufacturers can pursue such approaches with realistic expectations.
■ Delay in coverage is a key payer approach when there are key uncertainties about the benefits of novel therapies. In such scenarios, payers are more likely to apply investigational or experimental rationale to deny coverage and seek additional evidence of value to address perceived gaps in the evidence package.	
■ U.S. payers are more likely than ever to deny access to subpopulations not included in clinical trials. Payers are much less likely to take "leaps of faith" in extending coverage given perceived cost impacts.	
■ Prior authorization will virtually always be applied to cell and gene therapies due to novelty and cost.	
■ Manufacturers should clearly understand whether a specific asset is subject to special disease area or "protected class" considerations and evaluate implications for their particular scenario, including market precedent.	
■ While public (i.e., Medicare and Medicaid) and commercial rules may differ, similar processes for evidence review underly all commercial payer coverage processes. Ensuring that value communication materials highlight information specific to each payer segment (e.g., impacts in patients >65yrs of age in Medicare populations) can help avoid some coverage denials and restrictions.	
■ Manufacturers should develop strong and comprehensive evidence-based dossiers and economic justification that address payer decision drivers. Beginning this process can start early in development, at least in basic ways. In the absence of doing this, the manufacturer will be more subject to payer interpretation of value and strength of supporting evidence. Do not take for granted the importance of telling a clear and well-supported value story.	

CAR T therapies.[41] This scenario highlights challenges of entry into a coverage, coding and payment environment that was not designed with cell and gene therapies in mind. Absence of coding, noted as a challenge for novel CAR T therapies and requirements for using a non-specific code, can also result in underpayment and risk to providers and manufacturers alike. Under such conditions, hospitals take a significant risk in providing these therapies where (a) reimbursement is uncertain and (b) not all aspects of procedural expense may be sufficiently paid, even if the product is reimbursed. Further, Medicaid Best Price rules and other legal/statutory issues also severely limit discounting potential and implementation of alternative financial strategies for cell and gene therapies.[42] Although coverage has now been established, it remains to be seen whether the payment levels established under this policy, which some may view as insufficient to cover costs of the therapy and administration will support patient access and uptake.[43]

Payers viewed absence of a payment structure to make the provider financially whole in providing cell and gene therapy to be as significant a hurdle to acceptance/uptake as addressing reimbursement fit in the health system. Payers cited scenarios where bone marrow transplant facilities have viewed $30,000 to $40,000 financial risks or cord blood reimbursement under buy-and-bill to be untenable, suggesting that is even more unlikely that provider organizations can/will sustainably take a $500,000 to $1,000,000 risk to offer patients cell and gene therapy (particularly when therapies begin to enter in volume). Provider acceptance hurdles were noted as even more likely in circumstances where alternative or "good enough" treatments are available.

In the *inpatient setting*, diagnosis-related group (DRG) codes are used to define specific medical procedures and all procedural steps, resource requirements, and any drugs or devices used in the procedure are bundled under a single payment. Transformative cell and gene therapies in inpatient settings face significant risks of not fitting into the DRG from a payment perspective because the bundle may undervalue or not account for the additional complexity, effort, time, or resources required to administer this novel therapy type.[44] Another key inpatient challenge under Medicare and Medicaid is that creation of a novel DRG by CMS is an exceedingly rare event. While commercial payers do not create new DRGs, payers in the workshop did cell and gene therapies to be sufficiently novel to justify creation of a new DRG for inpatient cell and gene therapies and were hopeful that CMS would also acknowledge this need, given the number of therapies in development. While DRG payments do not enable separate drug payment, there are alternatives. A manufacturer, for instance, can apply for a new technology add-on payment (NTAP) under the CMS hospital inpatient prospective payment system (IPPS), if the following criteria are met for the treatment:

- Must be considered new
- Must have a high cost that exceeds the level of the MS-DRG payment amount
- Must represent substantial clinical improvement in the diagnosis or treatment of Medicare patients

However, the likelihood of achieving success with new NTAP applications is historically low, in the 35 percent range, though many applications fail because they to do not provide adequate support of the three core criteria. Further, even if a technology is successful in achieving and NTAP payment, this is no guarantee that the payment will be sufficient. In the outpatient setting, drugs and biologics have greater latitude for separate pricing from the procedure, which help disentangle incentives, provided that the resources required for the procedural component are anticipated in the procedural code.

In the absence of having a specific code for a novel cell and gene therapy, one of the options would be to pursue a novel DRG or unique Ambulatory Payment Classification (APC) code. In the inpatient setting, obtaining a new DRG has historically been particularly challenging, and the CMS NTAP process noted above is not a guarantee of establishing a code or sufficient payment.[45] In the outpatient setting, unique APC codes provide more relief in terms of covering drug costs, but associated procedure costs spanning the episode of care must also be carefully considered if special technology or steps are required for cell extraction, administration (e.g., a guided mapping catheter, multiple injections beyond SoC, image guided administration) and monitoring.

Payers in the workshop noted that add-on payment models, as they currently exist, are unlikely to be sufficient to cover additional costs of cell and gene therapies. We also briefly discussed the new NTOP payment being considered as one option under current CMS rules by the Duke Margolis Institute.[46] NTOP payment would be an additional payment for certain eligible curative therapies that qualify for an NTAP payment. Payers in the workshop acknowledged that while the possibility of advancing and NTOP payment is framed under the constraints of the existing system, this type of alternative is (a) not sufficiently predictable for advanced therapy developers (i.e., very high risk)

Table 5: What Involves Establishing a New Commercial Payer Case Rate?	
Case Rate Consideration	**Detail**
Basic Criteria for Advancement	■ Procedure must be viewed as medically necessary.
	■ Procedure description/inclusive aspects are not anticipated by existing payment structure.
	■ Procedure must be unique and not fit into existing payment scheme; cell and gene therapies were thought to have higher potential to justify new case rate development.
	■ Procedure must be something that physicians or physician associations are pushing for because there is a significant patient access barrier and they believe in the potential of the therapy.
	■ Procedure must be viewed as having substantial or even transformative impact and address a serious unmet medical need. Payers would not consider a new case rate necessary where the medical intervention fits reasonably well into the existing coding system. Just being more expensive was not viewed as an adequate justification for establishment of a new case rate. There must be differences versus established procedures that is not anticipated by existing coding and payment structures.
Breadth	Covers the entire episode of care associated with the procedure, including preparation (e.g., bone marrow aspiration), administration (e.g., prepping the cells, special device or procedural requirements for administration) and monitoring prior to patient release. Note that often the process for cell development (e.g., expansion, manipulation) and gene modification is included in the cost of the cell and gene therapy product) that can be included in the overall costing of the case rate.
Ease of Establishment	Similar to DRGs, but with greater flexibility, commercial payers do not lightly develop new case rates and carefully condider whether a new technology should be absorbed under existing payment structures. Payers in the workshop did acknowledge that cell and gene therapies are a sufficiently novel scenario that warrants consideration of new case rates because current payment systems did not anticipate them. New case rate establishment requires substantial coordination by the manufacturer, and significant effort of one or more provider champions (i.e., a bottoms-up approach). In contrast, a new DRG or APC code of add-on payment, while also challenging, is a top-down approach because commercial payers routinely use these codes in their own systems, ensuring broader uptake potential without the level of coordination required to drive development of case rates across multiple commercial payers in the U.S.
Who drives establishment of a new case rate?	Case rates cannot be driven by the manufacturer. They must be driven by the provider, requiring a provider "champion" to see the need for a new therapy and push for establishment of a new case rate and associated payment. However, a manufacturer can support collection all clinical and financial/economic data to support a new case rate and provide it in the form of a dossier or focused slide deck to the provider champion who believes in the therapy and could leverage to make a case for the new case rate. This also requires substantial coordination by the manufacturer, and significant effort of one or more provider champions (i.e., a bottoms-up approach). In contrast, a new DRG or APC code of add-on payment, while also challenging, is a top-down approach because commercial payers routinely use these codes in their own systems, ensuring broader uptake potential without the level of coordination required to drive development of case rates across multiple commercial payers in the U.S.
Who makes the determination to establish a new case rate?	While Medical Directors that are involved in the HTA and coverage determination processes would be involved in evidence evaluation for a new case rate, in most plans the determination to accept/adopt a new case rate is driven to the highest executive levels of the plan and often require actuarial and other impact analysis and sign off by CFO and/or CEO.
Timing and process detail	A provider or provider organization submits a request with supporting information to the payer. The plan reviews the submission with a Medical Director(s) and other staff. Then there is an iterative process of requesting additional information that may take anywhere from 6 to 24 months. The plan executive officers decide whether the new case rate should/should not be pursued. If accepted, the new case rate policy is developed and implemented. In some plans or circumstances, this process can take 36 or more months depending on the timing of the inquiry in regards, alignment with payer processes for updating coverage and payment policies, and the level of information available to support the request.

and (b) is a stop-gap step en route broader value-based payment reform required to fully address reimbursement and payment challenges that cell and gene therapies face.

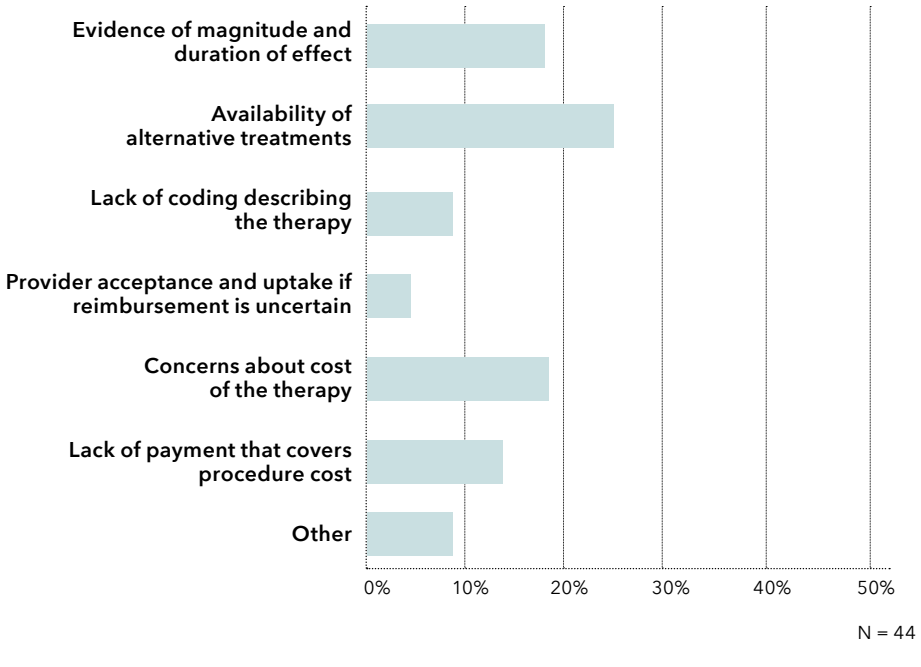
Aside from traditional coding routes, commercial payers also have the latitude to establish new case rates outside of the traditional CMS-affiliated coding systems. However, some states Medicaid may also pay via case rates or per diems in the in the hospital outpatient department (HOPD), which will also impact access for cell and gene therapy. Manufacturers note that some plans may engage in case-by-case payment decision, suggesting that it is important to have a clear and substantiated evidence package to support reasonable payment. Table 5 provides basic insights into the scope of case rates, process for establishing them, and tradeoffs vs. more common practices or developing a new code. While the greatest downside associated with establishing a case rate is the level of effort and coordination involved, the upside is that this can be one channel for building sufficient data to make a solid case for a novel code via more conventional channels. Further, in the inpatient setting, this could have a disadvantage to future cell and gene therapy agents if they would be priced considerably higher than the first therapy to establish a case rate. Either way, the process for establishing a new code or case rate is incredibly time and resource consuming (e.g., taking 18 to 36 months, plus preparation time) and is frequently under-anticipated by product manufacturers.

Other Reimbursement Considerations for Cell and Gene Therapies

A broader range of reimbursement challenges were considered in the survey and discussed further in the in-person workshop (Figure 3). When asked about the top reimbursement considerations for cell and gene therapies, survey respondent feedback was mixed. However, evidence of magnitude and duration of effect, availability of alternative payments, and concerns over payment affordability were the most frequently noted challenges. Provider acceptance was noted as the least important, though in-person discussions suggest that vocal providers from the payer's network can have significant influence on reimbursement decisions. This suggests that payers take a broad view of issues that would result from decisions to reimburse new therapies.

Payer management approaches applied to currently launched cell and gene therapies (i.e., Kymriah®, Yescarta®, Imlygic®, and Luxturna™) were also included in the survey and discussed at the in-person workshop. For these initial therapies, 100 percent of the surveyed payers required prior authorization before coverage is allowed and approximately 75 percent require some form of

Figure 3. Top Payer Reimbursement Decision Challenges for Cell and Gene Therapies



step therapy provision, where the patient must fail prior therapies before accessing cell and gene therapy (Figure 4). However, it is uncertain whether therapies with a truly curative effect would be less subject to step therapy provisions, particularly in rare disease scenarios where few or no treatments would be available. Payers will also look for easy-to-apply strategies such as biomarker testing to inform and/or limit access to cell and gene therapies, suggesting that precision medicine management practices (i.e., a priori responder identification) would be applied to manage access if available.

Just under 70 percent of the survey respondents indicated that they are applying some form of requirement for additional evidence development after coverage, even though a majority (> 60%) are not negotiating risk-sharing agreements with manufacturers. It is unclear from the survey how this requirement is administered in practice, and it may simply be that payers anticipate aggressive re-review and may alter initial coverage policies as the evidence of long-term duration of effect matures. This is consistent with other work on risk-sharing in U.S. commercial setting.[47,48] At present, it appears that most payers (i.e., 60% to 70%) are not applying stop-payment clauses, volume caps, or discounting contracts as a means to manage on-market cell and gene therapies. These findings are aligned with the coverage findings discussed above and suggest that U.S. commercial payers are early in their journey toward developing more refined and predictable approaches to address coverage and reimbursement for cell and gene therapies.

Payer perspectives for addressing reimbursement or transformative therapies that do not fit with existing reimbursement structures were also considered. Similar to payer perspectives on coverage, findings in Figure 5 were also variable, though balanced between denying the therapy as investigational (assuming insufficient evidence is available), carving out the therapy from main payment structures, transferring the therapy to reinsurance or development of a new case rate or code to accommodate reimbursement for new cell and gene therapies. In regards to denial of therapies as investigational, workshop participants indicated that this step is a key lever that may be used on cell and gene therapies with marginal or incomplete evidence packages. Such a step is easier to control versus utilization management, including any limits that may be built into a coverage policy.

Figure 4. Payer Management Approaches Applied to Initial Transformative Therapies

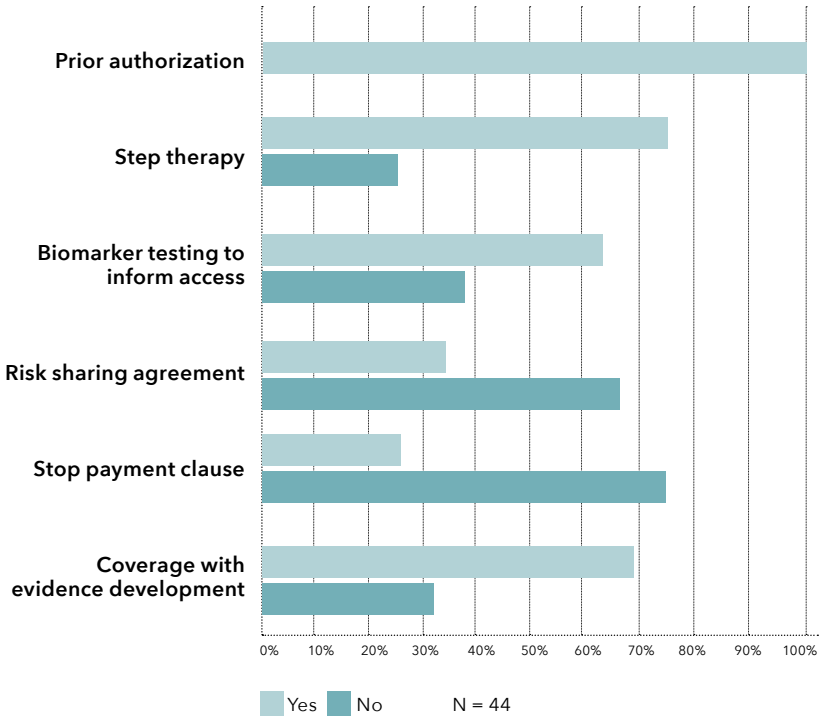
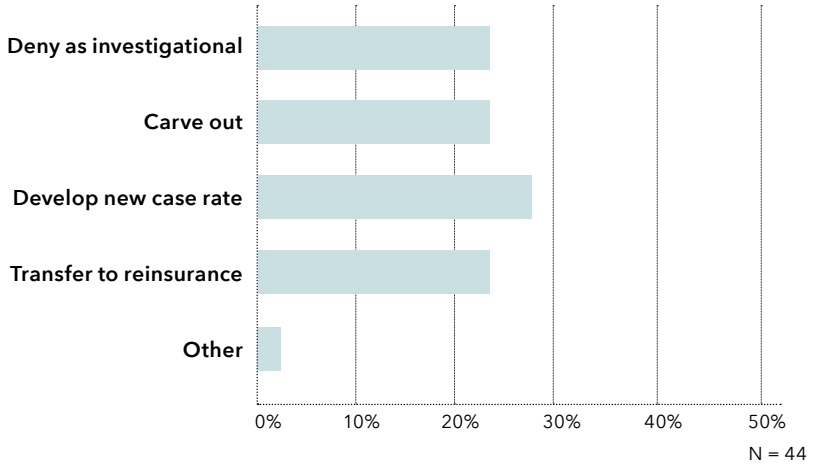


Figure 5. Payer Perspectives on Addressing Reimbursement for Transformative Therapies that do not "Fit" Existing Reimbursement Structures



Carve outs were also discussed as an option, but not viewed as a sustainable solution. Similarly, in the short-term, transferring the financial risk to reinsurance agencies is a short-term option. However, several of the payers in the face-to-face workshop noted that there is significant risk associated with this option for commercial plans. Under a scenario where a payer with relative frequency would transfer the financial risk to a reinsurer for $500,000 to >$1,000,000 costs for cell and gene therapies, payers indicated that the fear is that the reinsurer would in turn deny services to the entire health plan or adjust the rate structure in a manner that mitigated the value of such an approach.

Manufacturer and payer lessons associated with coding and reimbursement cell and gene therapies are described Table 6.

Table 6. Coding and Reimbursement Lessons for Cell and Gene Therapies

Lessons for Manufacturers	Lessons for Payers
■ Coding is a challenge for virtually all cell and gene therapies that are zentering a coding and reimbursement system that did not anticipate them. ■ While there are options for obtaining payment in coding scenarios where the therapy does not "fit", it is likely that payment levels will be suboptimal from a manufacturer and provider perspective. When providers are at risk of non-payment or limited payment, this can serve as a significant barrier to acceptance. ■ Manufacturers may want to consider both top down (i.e., pursue a novel code) or bottoms up (pursue a new case rate with individual commercial payers) approach in assessing viability of their uptake and commercial strategy. ■ U.S. commercial payers acknowledge that existing coding, reimbursement and payment systems are inadequate for cell and gene therapies and would look to CMS and other stakeholders to help advance more broadly applicable solutions outside of the latitude of individual health plans. ■ Payer reimbursement management processes are currently highly variable.	■ In the absence of broadly applicable coding solutions, there will be significant patient access barriers to cell and gene therapy use, driven largely by inability of providers to obtain adequate payment for services. This includes both the cell and gene therapy component and the procedural component. ■ Variability in perspectives on reimbursement approaches is also resulting in patient access barriers to the initial vanguard of arguably transformative and potentially curative therapies. ■ Existing reimbursement tools such as carve-outs and reinsurance are not viewed by payers participating in this study as long-term solutions when cell and gene therapies emerge in number. New reimbursement mechanisms and associated tools for managing financial risk will need to be developed to support sustainable patient access as this area grows. Cross-cutting solutions that set above the individual payer may be required to support equitable risk sharing and access.

D. Payer Payment and Contract Negotiation

One issue that is particularly unique to cell and gene medicine versus most drug or biologic treatment scenarios is single-administration delivery, (i.e., that the therapy is only delivered once through injection, infusion, or other administration versus conventional regimens that require multiple doses over time). On the clinical side, this is because the therapy is likely to have long-lasting or permanent effects on patient health. On the safety side, for some cell and gene therapies, there is also the risk that the body develops antibodies to the therapy or in the worst-case patients experience adverse events (AE) associated with a therapy that may not be able to be "turned off." For this section of the analysis, however, our focus is on how single-administration scenarios impact contracting and payment models.

Due to the single administration, product value capture and payment centers around this single event, versus the more familiar model of paying for each incremental dose of a drug or biological today. The challenge for cell and gene therapies associated with single-administration models is that early examples of these therapies have ranged in the $500,000 to >$1,000,000 price range. In a scenario where there is a single, upfront[49] payment associated with these treatments, the impact on payer cashflows can be significant (in multiple markets, including those with societally-focused systems) versus models where payment is spread over multiple payment events. In some cases, such as with initial hepatitis C therapies, difficult to predict and significant financial impacts have resulted in insolvency of several small- to mid-sized U.S. commercial plans. This has been explored in our prior ARM NAMCP paper in greater detail.

In our survey, we asked payer respondents if they are currently simply making a one-time upfront payment for the initially marketed U.S. cell and gene therapies (i.e., Kymriah®, Yescarta®, Imlygic®, Luxturna™) or pursuing another type of payment model. Just over 50 percent of payer survey respondents indicated that they were making one-time, upfront payments, with the remaining 48 percent contracting for something other than a one-time payment (Figure 6). However, payers in the workshop did not view one-time payment as a long-term sustainable option.

This result suggests that, at least at this early stage of the evolution of cell and gene therapies, around half of U.S. commercial payers are not yet considering options other than one-time, upfront payments. Workshop participants indicated that this result likely has two drivers: (a) transformative and curative therapies are sufficiently early in their life-cycle that many payers have not developed special provisions for handling them[50] and (b) the cash flow and/or budget impact of upfront payment models has not yet prompted some plans to consider alternative payment models.

Additionally, when asked whether they had negotiated special payment arrangements for this initial wave of cell and gene therapies, 70 percent of payer respondents indicated that they had negotiated special payment arrangements for one or more of

Figure 6. Percentage of Payer Respondents that are Paying for Cell and Gene Therapies Upfront

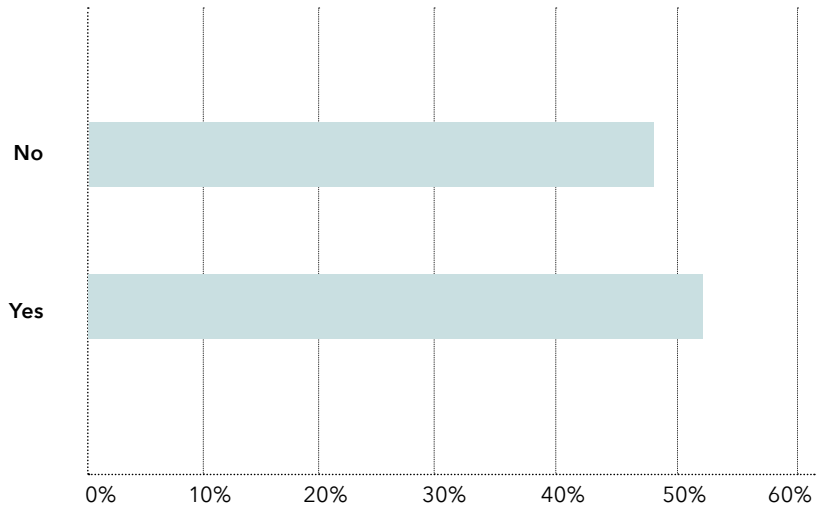
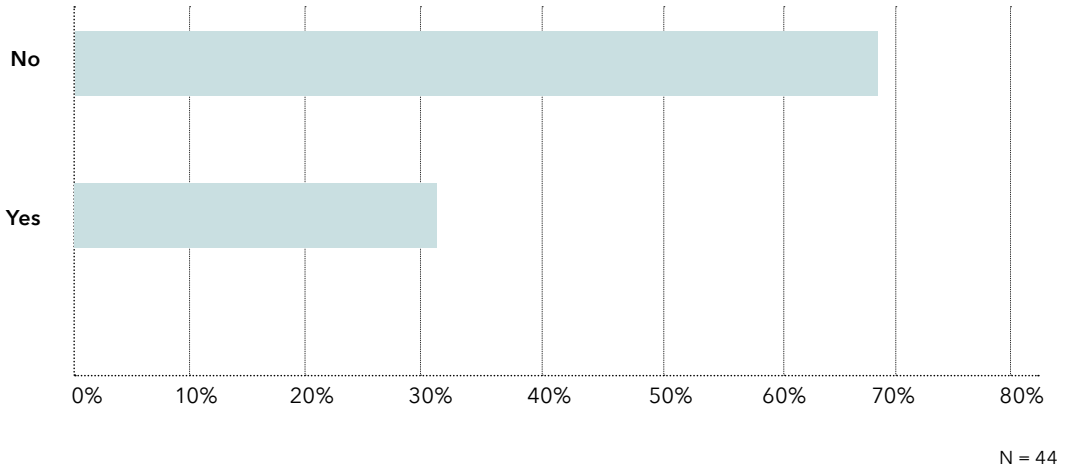


Figure 7. Percentage of Payer Respondents that have Negotiated Special Payment Arrangements



the initially launched therapies (Figure 7). Of those that were able to divulge information on the type of agreement, 86 percent indicated that the arrangement centered on outcomes-based risk sharing tied to one or both of the following: (a) stop payment clause and (b) deep discounting or non-payment/clawback provisions in cases where the negotiated response was not achieved. The remaining 14 percent of this group negotiated some form of bundled payment, the details of which were not disclosed.

Payers from the workshop noted that simple discounting approaches are more administratively attractive, but acknowledged that the single-administration scenario and the cost of initial transformative therapies are likely to prompt some payers to consider risk-sharing agreements (which remain relatively rare in U.S. managed care). The first-year payback model negotiated for the SMA treatment Spinraza®, where the $750,000 was spread into three payments throughout the year, was discussed by payers in the workshop. This approach as a model for cell and gene therapy payment was viewed as a reasonable and actionable means to help spread the cost impact of very costly procedures. Long-term/amortized models beyond 24 to 36 months were ruled out by workshop payers at this time as they would (a) be difficult to administer under existing commercial plan rules and (b) create difficulties in managing payment models when patients transfer to other plans (i.e., it remains unclear who would be responsible for downstream payments). However, some upcoming cell and gene therapy developers are proposing multi-year, outcomes-driven payback schemes, though the commercial acceptance of them is still to be determined.[51,52]

Workshop participants also discussed the following key issues associated with payment and contracting for cell and gene therapies as highlighted in Table 7.

Table 7: Additional Payer Payment and Contracting Considerations

Additional Payment and Contracting Considerations	Payer Perspectives
Establishing a new payment model	Workshop participants also discussed the requirements to institute a new payment model in scenarios where one-time cell and gene therapy payment presents financial challenges to a commercial plan. Payers indicated that under such circumstances a new payment model may be negotiated between the payer and manufacturer. **What may be considered?** Aside from simple discount or volume-based discount models, the plan must consider whether the model being proposed (a) violates the health plan, state and national rules (b) conforms to Medicare and Medicaid requirements outlined in CMS guidance and statute. While the workshop participants indicated that payment over time is typically not done, payers anticipated that spreading payments over a brief period would work under most existing requirements. Other provisions must be considered on a case-by-case basis.

Table 7: Additional Payer Payment and Contracting Considerations	
Additional Payment and Contracting Considerations	**Payer Perspectives**
Establishing a new payment model	*(continued)* **Who is involved in decision making?** The decision to institute a new payment contract is often managed by the CEO, CFO and other members of the plan executive team. Medical and Pharmacy Directors involved in benefit management would also be consulted (including about the evidentiary underpinning the therapy), as would actuarial experts and others involved in assessing the financial impact of a new payment model or contract. Steps and requirements of this process vary by plan and are influenced by geographic and nature of beneficiary coverage of the plan. **Are there payer mix considerations?** Payer participants anticipated that it would be easiest to implement new payment models for commercial plan beneficiaries. They anticipated greater complexity for Medicare and particularly Medicaid scenarios because regulatory requirements offer less flexibility for innovative approaches. **Are there site of care considerations?** Payer participants anticipated that it would be more challenging to implement novel payment models in the inpatient setting versus the outpatient setting because there is less flexibility around payment models and it is more difficult to isolate individual therapies due to bundling effects.
Addressing patient portability in payment	Currently, majority to treatments and health services do not have a need to explicitly address patient portability. In the case of cell and gene therapies where a single administration occurs but the value of the treatment may accrue for years or a lifetime, patient portability in U.S. health plans is a key issue. Workshop participants indicated that sinse beneficiaries change plans every 12 to 24 months, a key payer concern based on what is viewed as the high cost of cell and gene therapies is how to handle multiple payment scenarios that may be negotiated with a particular payer when the recipient beneficiary changes plans. In such a case, it is unclear which payer organization would then bear the responsibility for any downstream milestone payments after the plan switch. Further, in a scenario where a patient is truly cured, this was viewed by workshop participants as a benefit to the plan actuarial pool versus a patient with a lifetime of costly interventions for serious chronic diseases. Payer management of payback provisions beyond 24 to 36 months was cited as one of the most significant disincentives for entering into long-term risk-sharing models. Payers were willing to consider this approach if there were a third party administering the payback (e.g., a PBM or specialty pharmacy), where all participating plans had similar incentives, though this does not solve for non-participating plans not supported under such a third-party mechanism. Portability challenges were also thought by workshop participants to be solvable via institution of a national high risk pool or fund supported by participating plans and/or government agencies. This latter approach is perhaps more complicated to engineer (beyond the scope of any single entity) and patient access criteria would need to be carefully considered.[53]
Linking long-term value demonstration to payment	When we discussed current approaches to linking demonstration of long-term outcomes to reimbursement provisions, workshop participants indicated that U.S. payers indicated the lack of well-developed processes rewarding long-term outcomes in the current system. While payers do re-assess coverage policies and leverage tools like payment tiering to manage access and costs, most commercial payers do not routinely enter into long-term outcomes-based risk sharing agreements.In unique cases where such contracts are developed, they are viewed as rare and focusing on areas of tremendous financial impact to the plan (e.g., heart disease, diabetes, respiratory). Payer participants in the workshop did acknowledge the benefits of monitoring continued treatment effect with diagnostic tests or other patient metrics. They indicated that this is ideally tied into value-based access and payment models, but acknowledged that in the commercial plan environment concepts like "coverage with evidence development" are rarely considered and may even be avoided due to perceptions of risk to the plan. Payers in the workshop also acknowledged limited knowledge about methodological considerations for long-term follow-up using RWE methods like registries. Payers in the workshop did understand the need for long-term value demonstration for transformative or potentially curative therapies. However, they also have not formally integrated long-term value demonstration into therapy management processes involving re-evaluation of coverage or continued value demonstration. As risk-sharing or other payment agreements continue to evolve in this area, expectations were anticipated to become clearer and more heterogeneous. The extent to which ongoing requirements for continued evidence development may be integrated into a third-party managed model facilitated by a PBM was unclear. This more limited understanding of novel study design and RWE approaches, this also extends to understanding of scenarios where RWE is used to fill in gaps at pre-launch phases, e.g., single-arm studies. New study designs and use of RWE to fill or address evidentiary uncertainties is currently being defined by the FDA under the 21st Century Cures Act and other activities.[54] Ultimately, greater flexibility in design, driven in part by expansion of biomarkers and evolution of AI/machine learning tools to better leverage retrospective data, will become more of a norm and disrupt thinking and acceptance of evidence conventional hierarchy models.[55] This suggests that payer engagement around alternative value demonstration approaches (e.g., non-randomized-controlled trial [RCT] approaches), where they are applicable at all stages of asset development, will be critical in the short-term to cell and gene therapy or other asset acceptance.

Manufacturer and payer lessons associated with payment and contract negotiation are described below in Table 8. These areas are rapidly evolving, and the environment is currently open to consideration of novel payment approaches, though some are more likely to gain immediate acceptance and others will take some time to evolve.

E. Provider-side Negotiation and Considerations

The workshop participants also discussed that for a novel cell and gene therapy, payers typically work with providers to establish a novel reimbursement model. Payer respondents indicated that they most frequently addressed the need for novel coverage or reimbursement as initial provider claims hit the health plan. This typically involves one or more provider organizations raising a reimbursement challenge/concern or contesting a reimbursement denial. Payers then seek to characterize the nature of the services, map this information to plan coverage policies, medical necessity requirements, and make an assessment around "goodness of fit" with existing reimbursement mechanisms, including available coding and payment model options.

At the time that such a request from providers occurs, payers often look for a data package of information to substantiate (a) why an existing coding/payment option does not fit the scenario and (b) the evidentiary or other justification and the new procedure suggests a new solution. This information is almost exclusively submitted by a provider organization(s) seeking coverage and reimbursement for what is perceived as a new health service. According to workshop participants, it is virtually never initiated according to workshop participants, by product manufacturer organizations. However, the underlying information required is similar to the type of information developed by manufacturers as product value dossiers. Further, the act of initiating such a request does not guarantee (a) acceptance of the service or procedure in question as new/valuable or (b) that associated payment levels will be within

Table 8. Contract Negotiation Lessons for Manufacturers and Payers

Lessons for Manufacturers	Lessons for Payers
■ While many payers are reluctant to negotiate outcomes-based risk-sharing agreements, almost half of U.S. commercial payers responding our survey are considering them for novel cell and gene therapies. This suggests that manufacturers should consider such options to optimize acceptance and uptake, but also ground expectations in the reality to not all payers' organizations will engage in such agreements. ■ Of those agreements that have been developed, a majority focus on outcomes-based risk sharing, often where key outcomes are assessed within the first 6 to 12 months and tied to either stop-payment and/or claw-backs. ■ As of the time that this study was conducted, no more complex amortized payment model has been observed by survey or face-to-face workshop participants. ■ Payers indicated they could implement short-term payment plans unfolding over the first 1 to 3 years under current plan structures, but long-term payment models are currently challenging or impossible to implement for some plans, including models with portability concerns. ■ Results suggest that manufacturers, including as a community, consider third party models to help manage budget impact and spend on transformative or curative therapies. It is also possible that such a third party could operate outside some of the barriers faced at the individual plan level.	■ Clinical trial models, particularly in oncology and rare disease, are beginning to evolve, including single-arm, adaptive, basket or bucket trials where RWE is often used to address evidence gaps or developed indirect comparator arms. This will be further driven by greater acceptance of RWE at FDA-level. ■ This means that the evidence package associated with many emerging therapies is likely to be different (in some cases) versus the traditional RCT model. It will be important for payers to rethink evidentiary requirements in tandem with these value demonstration shifts. ■ Cell and gene therapies and other emerging technologies are encouraging a shift from evaluation at the time of coverage toward a more iterative process. It will be important to consider how coverage, re-evaluation processes, and access management processes will shift in the near term.

the range desired by submitting providers.

Payers in the face-to-face workshop indicated that they are often leery of new reimbursement scenarios by so-called "key opinion leaders" that may be brought in, as they often view them as consultants for industry and/or potentially biased. Instead, when such coverage and reimbursement requests for new products or services come from providers or health systems, they often reach out to and include trusted individual providers with the necessary expertise to inform assessment and development of a new reimbursement code/payment for novel services.

While core incremental steps involved in provider-side negotiation were not discussed due to time constraints, several other aspects were discussed, including the following highlighted in Table 9.

Table 9. Additional Provider-side Acceptance and Uptake Considerations

Additional Provider Considerations	Payer Perspectives
Center of Excellence (COE) requirements	Payer workshop participants indicated that under some circumstances, coverage of novel cell and gene therapies may require treatment in designated COE facilities (as compared to broader provision by specialists). The following scenarios were advanced as key scenarios when such requirements are demanded by commercial health plans: (a) when a therapy is truly novel and complex (e.g., involving multiple steps in collecting , processing and administering the therapy), (b) when a truly novel therapy is first introduced/early in the lifecycle, (c) when there is significant potential for AEs that require immediate access to emergency or specialty care, (d) when administration requires special expertise (e.g., using a guided/mapping catheter to inject cells), and (e) when treatment requires very special expertise (i.e., some rare diseases). Note that while initial launch may occur in a COE environment, as providers become more familiar with procedural requirements, the treatment or procedure may migrate outside of the COE environment. In general, whether in a COE environment or not, payers also anticipated that a very costly cell and gene therapies would require be channeled through a specialty physician versus a general practitioner. This was thought to apply to all payer segments, including commercial, Medicare and Medicaid beneficiaries, except for any scenarios that are statutorily precluded.
Willingness of providers to "go at risk" for reimbursement	The willingness of providers to "go at risk" (i.e., offer the therapy to patients prior to gaining reimbursement approval) in offering cell and gene therapies was also discussed. At the time of discussion, workshop participants did not have any direct examples of where this may have occurred. In some scenarios, even if the therapy is viewed as transformative or curative, if the cost impact to providers in the absence of reimbursement is significant, providers may not have the financial ability to absorb losses not reimbursed by payers. However, two alternative examples were raised and discussed by payers in the workshop: **Defitelio for veno-occlusive disease:** Initially offered under a compassionate use program, where the costs of care were borne by the manufacturer during the companionate use period, this therapy was viewed as a substantial improvement in care by providers. However, after the compassionate use program elapsed, utilization of the therapy was noted to drop because a reimbursement model to support this novel therapy, which did not fit into conventional coding/payment structures, was not in place. This same risk to patient access was noted as a significant possibility for cell and gene therapies that did not take proper steps to secure appropriate reimbursement. **Cell therapies adjunct to conventional hematopoetic stem cell transplant (HSCT):** AEsthat often accompany conventional HSCT can include severe or fatal transplant rejection, graft-versus-host disease, infection and other adverse outcomes when patients are not ideally immunologically matched. The example of cord blood therapies was offered as an illustrative example of provider willingness to go-at-risk for novel therapies. Cord blood therapies are a key alternative to sibling-matched or haploidentical allogeneic cell therapies. They range in cost from $25,000 to $50,000, depending on whether a single or double cord blood transplant is required, based on patient body weight. Since the margins for HSCT procedures are very proscribed, when payers do not approve reimbursement, many bone marrow transplant (BMT) centers are unable to absorb the financial risk of providing these life-saving therapies. By extension, payers in the workshop believed that most provider organizations would not accept the risk associated with providing cell and gene therapies in the cost range associated with conventional cell and gene therapies (i.e., $500,000 to $1,000,000). Payers likewise noted that buy-and-bill of cell and gene therapies is unlikely due to significant cost and risk to the provider organization, suggesting that alternative supply chain and/or reimbursement models will be necessary to support widespread, predictable acceptance and uptake by providers. Some payers in the workshop noted that an adaptation of the PBM-type model is a possible solution due to PBM's ability to (a) spread risk and (b) deploy decision and management apparatus across multiple payer organizations. *(continued next page)*

(continued)

Implications of direct to payer negotiations on provider acceptance	Payers in the workshop did note that they were aware that some models were being advanced by manufacturers that would limit (or place a ceiling on) provider mark-up of specific cell and gene therapies and/or require purchasing via a specialty pharmacy. One example of this is seen in the SparkPath model being promoted by the advanced therapy developer Spark Therapeutics, as a means of multi-stakeholder risk sharing in the early days of novel cell and gene therapy development. This innovative pilot program includes several dimensions, comprising of outcomes-based risk sharing tied to discounting, controlling provider mark-up via specialty pharmacy channel management, and consideration of a multi-year payment model with CMS.[56] While noting additional complexity compared to existing simple discount models, payers noted that if implemented properly, such a model would be advantageous to payers. Workshop participants were uncertain about provider-level incentives associated with such new models. Some participants noted that provider-limiting arrangements may also be perceived as a disincentive where alternative treatments with higher or more certain margins were available to provider organizations. This may suggest that additional steps tying such models to accountable care or similar quality/cost programs may be helpful to support broader and more uniform adoption of such solutions. While mixed, this feedback suggests that the current payer and provider environment is more open to innovative models that address payer stakeholder incentive structures and operational realities. Further, as operational models in payer and provider systems continue to evolve, additional opportunities for more tightly linking these novel approaches to evolving value-based care models may emerge.

The following Table 10 highlights the lessons associated with provider-side incentives for acceptance and uptake of cell and gene therapies for manufacturers and payers. Limitations on workshop discussion time and absence of provider representatives precluded a more robust discussion of provider-side decision factors. However, future work in this area is warranted as provider-side dynamics have even greater potential to influence and inform value assessment and patient access models for novel cell and gene therapies, but that was beyond the scope of this assessment. The next ARM NAMCP collaborative effort will explore the provider-side acceptance dynamics further.

Table 10. Cross-stakeholder Negotiation Considerations for Manufacturers and Payers

Lessons for Manufacturers	Lessons for Payers
■ Advancement of novel case rate development is often driven by providers versus manufacturers. If reimbursement or a new payment rate needs to be established, support of provider champions for the new therapy is key.	■ Payers should carefully consider payer-provider model interfaces in the context of cell and gene therapies that may have long-term transformative or curative effect and offer novel health system efficiencies versus SoC.
■ Manufacturers are best served by supporting the development of a comprehensive evidence base to support provider reimbursement requests for novel therapies that do not "fit" into conventional payment models.	■ Increasingly, novel cell and gene therapy reimbursement or payment models may cross stakeholder boundaries to address multiple incentive streams. Through this lens, payers may have greater latitude to test innovative risk-sharing models and align them to changing pressures on operational models.
■ Providers are highly unlikely to go-at-risk for novel cell and gene therapies where payment is uncertain. Steps to ensure or support appropriate payment are as equally important to optimal patient uptake as development of clinical and economic value evidence.	■ As the vanguard of these new models is developed, information sharing among stakeholders can help expedite clarification and diffusion of best practices.
■ Manufacturers should not underestimate the value of developing strong provider network models for cell and gene therapies to help navigate patient access for these novel therapies across all reimbursement dimensions (i.e., coding, coverage, and payment).	■ As evidence development approaches become more interconnected and value assessment model shift to more of a "journey than a destination", novel assessment and reward models involving multiple stakeholders may need to evolve in tandem.

F. Cell and Gene Therapy Uptake and Management Considerations

A range of other uptake and management topics were discussed with payers in the workshop, including engagement in pilot programs, use of RWE, influence of cell and gene therapies on future reimbursement and payment models, and affordability considerations. Payer perspectives from these discussions are described as follows:

PILOT AND PARTNERSHIP PROGRAMS:

Given the novelty of many cell and gene therapies, and concerns about "fit" into reimbursement systems not explicitly built for these therapies, many manufacturers in this sector are considering risk-sharing or pilots as a means of reducing delays in or resistance to reimbursement. Payer interest in and willingness to execute pilot and partnership programs to explore new models for value demonstration and reimbursement of cell and gene therapies was discussed. In general, U.S. commercial payers in the workshop indicated that there are few incentives at present for novel pilots around cell and gene therapies, noting that payer incentive structures typically prompt them to be more reactive than proactive. This is particularly true in the case of the nascent field of cell and gene therapies, where only a handful of potentially transformative therapies have entered the marketplace (i.e., not of sufficient budget impact versus other cost drivers to be a core area of focus). This also includes truly out-of-the box risk-sharing agreements that are increasingly being discussed by a range of health stakeholders and across a variety of global markets.

Payers in the workshop did acknowledge that they are aware that a substantial number of advanced therapies are in development, and that their aggregate costs are anticipated to have significant budget impact in the mid- to long-term, but they are not generally resourced to adopt potentially high-risk pilots. Payers did note that in the few instances where U.S. pilots have been implemented, they have focused on the highest cost driver disease areas for the plan (e.g., heart disease, diabetes, hypertension). Workshop participants clarified that it would be unlikely for a commercial payer to enter into a partnership agreement around rare diseases because the financial impact is not viewed as sufficiently impactful versus other competing budget management pressures.

Most plans, despite having potential interest in pilots and new initiatives, were thought to be poorly set up to execute complex pilots or risk-sharing arrangements. In instances where a pilot would be considered, payer workshop participants indicated that the pilot must be (a) simple and (b) address a key financial area that is a management priority to the plan. They also expressed concern about risk-sharing agreements in scenarios where interpretation of the risk-sharing component is unclear and becomes a significant administrative burden for the plan that could quickly outweigh the value of implementing such an agreement. Many payers noted that simple discounting strategies are the easiest to address under current operational models, though they acknowledged that these could be more challenging under single administration scenarios.

Despite reservations about ability to implement pilot and risk-sharing agreements, payers in the workshop acknowledged that where they do occur and are published, if the result is clearly implementable, they would consider integrating practices tested in pilot partnerships, where the benefit to the plan is obvious.

USE OF RWE:

Use of RWE was discussed with workshop participants. While U.S. commercial payers do consider and use RWE in coverage and access management decision making, they (a) have a strong preference for RCT data, particularly in terms of establishing coverage and (b) indicated limited understanding of RWE methodologies and the evidentiary trade offs associated with different study design approaches.

We also discussed the implications of increasing integration of RWE into product value demonstration packages, largely driven in the U.S. by the requirements of the 21st Century Cures Act. This Act opens the door to use of RWE to help characterize current SoC and burden of disease, including in scenarios where single-arm launches may be common (e.g., oncology and rare disease) or fast-track programs are in play (e.g., RMAT), as well as in indication expansion and long-term data collection (e.g., registry models) scenarios.

The U.S. payer workshop participants were not intimately knowledgeable of details and emerging requirements for use of RWE in regulatory decision making. However, they did communicate that some of the changes in study designs where RWE can help fill gaps (e.g., synthetic control arms, better matched historical controls) introduce uncertainty around reliability of evidence versus RCT approaches. Payers also had general perceptions that RWE studies were a lower quality design and subject to greater bias and confounding than more traditional controlled approaches. This suggests that significant education and rationale around study design may need to accompany value package submissions with a strong RWE component. Payers also suggested that just because information is suitable for the FDA, does not mean that it will be acceptable by U.S. commercial payers during the HTA process. Because of this potential disconnect, manufacturers may be well warranted to vet RWE-heavy designs upfront to ensure that key uncertainties, bias, and confounding effects can be managed to the greatest extent possible at the study design stage.

(continued next page)

USE OF RWE: *(continued)*

Payers were clear that registries and/or other long-term follow-up approaches are critical to understanding broader duration of therapeutic effect and long-term value of cell and gene therapies. Ideally, from a payer perspective, such registries would be disease registries that would enable direct comparison to other alternative treatments, where available. However, payers did acknowledge that there may be commercial drivers for stand-alone registries focused on tracking a single asset because the design and use of that registry data is more within the realm of the sponsor manufacturer's control, though more costly to build and maintain versus shared registry models. Advanced therapy manufacturers in the workshop indicated that while the industry is exploring pros and cons of disease registry approaches, most registries to date are asset-specific.

Further, both payers and manufacturers acknowledged that registries for potentially curative therapies should include not only safety requirements mandated by regulators, but also incorporate measures of effectiveness to further characterize the value of cell and gene therapies. Having such evidence was thought to be a significant advantage in access negotiations as an asset moves through steps in the launch sequence, including in other markets where evidence is transportable, and in defending access as target disease areas become more crowded over time.

FUTURE MANAGED CARE MODELS:

Workshop participants spent some time discussing the implications of reimbursement models on cell and gene therapies. Payers acknowledged that increasing emphasis on long-term value demonstration that may be driven by transformative or curative cell and gene therapies would influence evolution of more iterative technology assessment and payment models. They indicated that the advent of curative therapies will place additional pressure on conventional agents in terms of "what good looks like," altering acceptability and use case scenarios.

From a payment standpoint, payers anticipated the need to develop a broader cost-distribution model to enable wider patient access to transformative or curative therapies. This was anticipated as a model administered by a third party outside of the individual health plan which provided coverage or supplemental payment relief, that would (a) reduce the likelihood that unanticipated, high cost, single-administration therapies create significant financial flow challenges for commercial plans and (b) reduce the single plan impact of such therapies on the actuarial pool and plan costs. Another alternative would be enablement of longer-term amortized payment models that can address patient transferability (i.e., patient switching of insurance plans every 12 to 24 months) issues that are presently challenging for long-acting therapies.

Payers viewed that with more transformative and curative therapies entering the market, that prices would go down over time based on marketplace competition. They also anticipate that if cell and gene therapies are truly long-term transformative or curative that prior SoC therapies would be displaced, resulting in shifting of treatment approaches/practices and guidelines. Workshop participants also discussed that they imagine precision medicine and cell and gene therapies will, in some cases, converge as the field develops and companion or co-diagnostic tests would increasingly be used to identify subpopulations of responders, further targeting their use.

Payers in the workshop also anticipated that in scenarios where therapies are curative or have long-term effect (in years), such outcomes would also have potential to change SoC and clinical practice, yielding potential guideline and system changes that do not often flow from conventional therapies. Such system changes may ultimately be built into accountable care or other incentive models at the intersection of the payer, provider and manufacturer relationship.

AFFORDABILITY CONSIDERATIONS

Similar to past discussions with NAMCP payer members, and confirmed by other research in the space[57], affordability of cell and gene therapies was again cited as a key mid- to longer-term concern. While payers acknowledged that these therapies have the potential to transform or cure the disease, the price points of market entry for the initial vanguard therapies (noted as $500,000 to $1,000,000) were viewed as a significant challenge to system sustainability. Workshop participants noted the financial impacts of hepatitis C curative-intent therapies, as well as the growing cost and impact of rare disease treatments as examples of challenges to system affordability.

While payer participants did not advance specific long-term solutions, near-term solutions included creation of a fund to support and spread the financial risk for curative therapies, variants of high-risk pool models, and leveraging reinsurance and/or other third parties (e.g., PBMs) to administer a broader risk sharing model that goes beyond the individual plan level. U.S. commercial payer participants also looked to CMS to evaluate and advance solutions relevant to Medicare and Medicaid beneficiaries that may be leverageable in other beneficiary segments. In the absence of such longer-term solutions, payers indicated that very costly products, whether transformative and curative or not, are anticipated to face greater scrutiny and may be more subject to denials as investigational/experimental if they are submitted with incomplete evidence packages.

The following key lessons for manufacturers and payers flowing from this discussion of uptake and management considerations have been identified in Table 11. Insights from these management considerations may be helpful in terms of considering special uptake drivers commonly considered or relevant to cell and gene therapies.

Table 11: Uptake and Management Lessons for Payers and Manufacturers

Lessons for Manufacturers	Lessons for Payers
■ While most cell and gene therapy manufacturers will routinely consider risk-sharing or even pilots to support market entry, a significant subset of payer organizations may not engage in novel arrangements. Targeting plans that are more amenable to novel approaches may help, including leveraging outcomes to support broader acceptance. ■ Strategies that have strong RWE component will require attention to methodological justification and rationale to support the broadest payer acceptance. On a broader level, engagement in policy dialog around use of RWE through channels such as FDA and other HHS agency request for comments can also help support increased flexibility in value demonstration approaches and acceptance of novel study design alternatives. ■ Long-term follow-up via registries is a key tool for value demonstration that needs to look beyond safety-only requirements. When properly planned, registries can be leveraged as a long-term differentiation approach, including for building a case of indication expansion and addressing changing medical affairs requirements. ■ Although early in the evolutionary cycle, cell and gene therapy executives should be exploring novel payment solutions with a mind toward addressing what may be a growing emphasis on affordability and redefining value thresholds.	■ There will be an increasing focus on novel single arm, adaptive, basket and other study designs that will leverage RWE, which will result in a shift over in the type of evidence package that commercial managed care will routinely see. ■ Development of evidence of benefit is beginning to shift toward an iterative model, where additional evidence and gap-fill occurs after launch. This may also precipitate shifts in how HTA, coverage, and patient reimbursement/access models are facilitated. ■ For those cell and gene therapies that do result in curative effect, current system incentive structures may make it difficult to realize the efficiencies brought by such therapies.

V. Study Limitations

Limitations of this analysis may include respondent bias, as it was not possible to determine whether respondents held a particular interest in cell and gene therapies and/or are early adopters. Based on the limited number of respondents, survey findings may not be fully representative of U.S. medical director perspectives but it does point to trends in payer and provider views on cell and gene therapies.

VI. Conclusions

This evaluation, approximately two years after the first truly transformative cell and gene therapies entered the marketplace, provides a broad perspective on how U.S. payer executives in managed care are experiencing this first generation of therapies. The report is intended as an initial, high-level roadmap for manufacturers and payers alike to identify opportunities and challenges in making transformative and potentially curative therapies more broadly available to patients. The following provides some overarching conclusions based on this body of research, including survey and deep, contextually rich discussions from the face-to-face workshop.

- **Reducing barriers to coverage will be critical for equitable patient access to cell and gene therapies.**
  With only about half the broader survey of 44 payer executives having established coverage policies on the vanguard of transformative therapies over a 12 to 24-month period since their launch, uncertainty associated with how to address coverage and management of

single-administration therapies appears to be a significant patient-access barrier. Some of the lack of coverage may arguably fall within typical decision windows for health plan coverage updates, but this phenomenon points to a key area of concern that warrants further consideration. Additionally, given the heterogeneity of coverage, there are also likely to be broader challenges in equitable access to transformative and potentially life-saving therapies. Without a clear and timely route to coverage for cell and gene therapies, manufacturers and investors may be prompted to reconsider investment in this nascent and promising area that has not only potential to transform patient care, but also, ultimately, systems of care.

- **Improving stakeholder alignment on evidence requirements and a value framework for cell and gene therapies is key to support more rapid coverage and access decisions.** Cell and gene therapies, largely due to their enhanced magnitude and duration of effect, are also changing our expectations for evidence-based medicine. Along with efforts of the FDA to better integrate RWE into decision making, clinical trial approaches are changing in tandem. So far, each of the vanguard of cell and gene therapies was launched with single-arm trials that are heavily reliant on RWE to characterize outcomes associated with SoC. Similarly, there has been much discussion in the U.S. and the EU about requirements for disease- and asset-level registries that help characterize duration of effect. Currently, as evidence standards are shifting, there is little consensus and tremendous uncertainty about what "the new good" looks like, both for manufacturers developing new cell and gene products and payers who are faced with changing evidence packages driven by broadening availability of retrospective data and evolution of RWE and analytical methods. As we move into this new era of evidence-based medicine, it will be important for regulators, HTA agencies, payers, and manufacturers to align with this more iterative and continuous evidence-development environment and clarify their requirements.

- **Lack of appropriate fit into existing coding and payment systems creates significant risks for provider adoption and patient access.**
  As cell and gene therapies continue to enter the marketplace, it will be critical to develop replicable coding and payment models that (a) do not place providers at risk of financial loss, b) are predictable and avoid cash flow impacts of high cost, single-payment scenarios, and (c) are affordable to the system. From a coding standpoint, this begins with an acknowledgment that cell and gene therapies were not anticipated by the current system and categorically warrant new coding (that also fully accounts for provider-side resourcing, administration, and monitoring requirements). While several public-private efforts like ICER, the Duke Margolis Institute, and MIT NewDIGS are evaluating aspects of value assessment and payment models and some manufacturers are advancing new payment models (e.g., multi-year payback periods), the reality is that the next wave of therapies may enter in greater numbers into a system that has not developed payment models to handle them in volume. Based on the evidence of early uptake of the initial vanguard of therapies, more work is warranted to move away from one-off solutions to more predictable and broadly applicable payment approaches.

- **Cell and gene therapy manufacturers must think comprehensively and not take anything for granted in developing a value demonstration strategy.**
  Developers of new cell and gene therapies must plan carefully in structuring development plans that show the transformative nature of these therapies and think about strategies to ensure that more acute, patient-centric, or surrogate endpoints are clearly tied to the longer-term or "hard" endpoints (i.e., mortality, significant morbidity, and resource requirements) that payers focus the most attention on. It is clear that the payer environment is focusing greater scrutiny on access for costly therapies and taking little for granted themselves in terms of access, with more granular restrictions being more routinely applied, even in rare disease scenarios. This also means clearly defining the patient subpopulations in a way that payers can construct coverage around.

- **It is critical for commercial payers to actively engage in solutions for making truly transformative therapies available to patients in an affordable manner.**
  Payers in the workshop indicated that few incentives exist to "get ahead" of evidence, access and payment issues relevant to broader acceptance

of cell and gene therapies. In a scenario where commercial payers do wait to engage in this dialogue, solutions will advance that may not take into account payer needs for when cell and gene therapies become available in volume.

Following from the first collaborative effort of ARM and NAMCP, as would be expected with truly disruptive technology scenarios, many of the same challenges and opportunities exist. As we look to approximately 20 therapies poised to launch in the next two years, it is a critical time in the evolution of cell and gene medicine.[58] The initial vanguard of cell and gene medicine has so far delivered on the goal of yielding transformative effects for patients with severe or fatal conditions. It will take a truly collective and concerted effort among payers, providers, policymakers and manufacturers to address the many reimbursement barriers faced by these disruptive technologies and ensure appropriate patient access. Accomplishing this goal will also take vision and willingness to look beyond business as usual, considering the potential for this new treatment approach to also yield benefits at the health system level and redefine our practices and expectations for care delivery.

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Notes