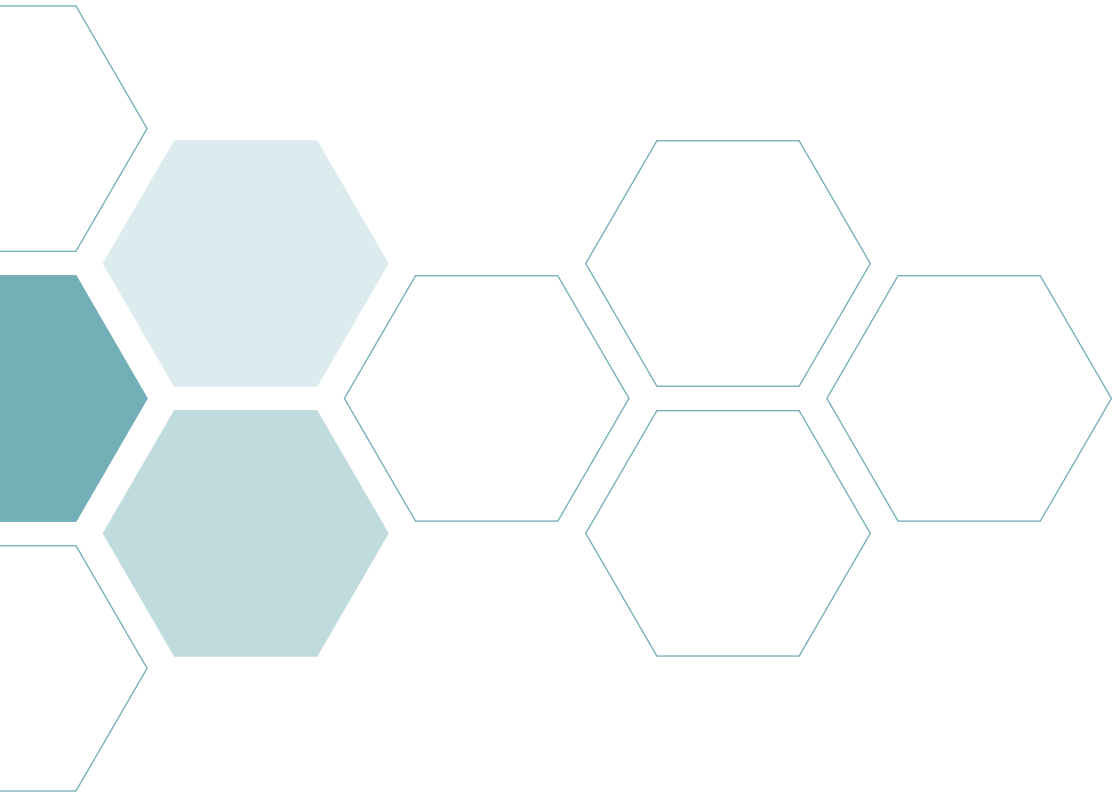
Ensuring Patient Access to Regenerative and Advanced Therapies in Managed Care: How Do We Get There?



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Ensuring Patient Access to Regenerative and Advanced Therapies in Managed Care: How Do We Get There?

Eric Faulkner; Michael J. Werner; Ted Slocomb; Donald Han

I. Summary

There are now more than 930 clinical trials of regenerative and advanced therapies currently underway, with approximately 630 in Phase II to III and nearing market entry. Unlike other therapies currently on the market, cell and gene therapies have the potential to transform current disease treatment. These products are poised to enter markets that did not anticipate the unique value characterization and reimbursement challenges associated with these truly novel technologies. How do we measure and determine whether a therapy is transformative or curative? How do we address the single administration models associated with these therapies where value capture must accrue around one event? What novel reimbursement and payment models will be needed to ensure patient access to those therapies that have a transformative impact on patients' lives or ameliorate certain diseases? This study explores managed care medical director perspectives on value demonstration and reimbursement for regenerative and advanced therapies and explores solutions to ensure appropriate integration of these therapies into our treatment armamentarium, as well as innovative financing models to ensure patient access to these transformational therapies is sustainable.

II. Introduction

As previously described in the Journal of Managed Care Medicine[1], the term "regenerative and advanced therapy" includes technologies comprising cell therapies (including cell therapy vaccines), gene therapies, and other biological materials (e.g., tissue engineered materials, biological matrices, cell-derived regenerative components) that aim to restore functionality to damaged tissue.[1] Likewise, there are many variants of gene therapy in pipeline development today and gene editing and related emerging approaches have enabled evolution of current technologies with potential to correct for genetic variations that are the source of some diseases. Administration of regenerative therapies can occur in many ways, though most commonly involve either infusion, simple injection (e.g., treatment site is intramuscular), or complex administration (e.g., use of novel catheter delivery systems or surgical implantation of biocompatible matrices that hold cells in place). As noted, this is a complex area with a range of rapidly evolving platforms and approaches. We use the term "regenerative and advanced therapies" in this paper to refer to all these technologies unless otherwise noted.

III. Methods

The Genomics, Biotech, Emerging Medical Technology Institute (GBEMTI) was established in 2011 as an institute of the National Association of Managed Care Physicians (NAMCP). The NAMCP has more than 20,000 members and represents medical directors from payer, purchaser (employers), and provider systems such as independent practice associations (IPAs), accountable care organizations (ACOs), physician-hospital organizations (PHOs), and medical groups. The goal of the GBEMTI is to support and characterize the value of genomics, biotechnology, regenerative and advanced therapies, and medical technologies as these new modalities enter and impact the health care system. The GBEMTI seeks to support collaborative stakeholder engagement around emerging health technologies to consider their potential to improve patient outcomes, impact on managed care management practices, and value to the health care marketplace. The Institute is guided by an Executive Leadership Council (ELC), comprising approximately 100 payer and manufacturer members. The GBEMTI is unique in that it is a

multi-stakeholder group centered on bringing medical director decision makers and manufacturers together to address key trends and topics that are transforming United States (U.S.) health care and explore means to improve managed care decision making and patient access to emerging health technologies.

The **Alliance for Regenerative Medicine** (ARM) is the pre-eminent global advocate for regenerative and advanced therapies. ARM is a multi-stakeholder organization that fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

This study, conducted between March and June 2017, involves both a survey of medical director members of the NAMCP and a face-to-face workshop between payers representing a range of U.S. health plan types and ARM regenerative and advanced therapy member company representatives. The survey questions addressed key payer perspectives on regenerative and advanced therapies and highlighted key issues relevant to payers, providers, and manufacturers. The survey was randomly disseminated to medical director members of the NAMCP and 36 total responses were obtained. Of the total respondents, approximately 70 percent identified themselves as medical directors at commercial managed care organizations (MCOs) and 30 percent identified themselves as medical directors of health system and provider organizations (e.g., academic medical centers, hospitals and other health systems, 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 feedback was obtained through a workshop involving commercial payers from both national and smaller regional plans, to add context, clarify responses, and explore solutions that would enable appropriate patient access to potentially transformative regenerative and advanced therapies. Consequently, while some issues may also be relevant to public insurance such as Medicare and Medicaid, this paper does not specifically address issues and solutions for those programs.

IV. Findings and Implications

A. Payer Understanding of and Preparation for Regenerative and Advanced Therapies

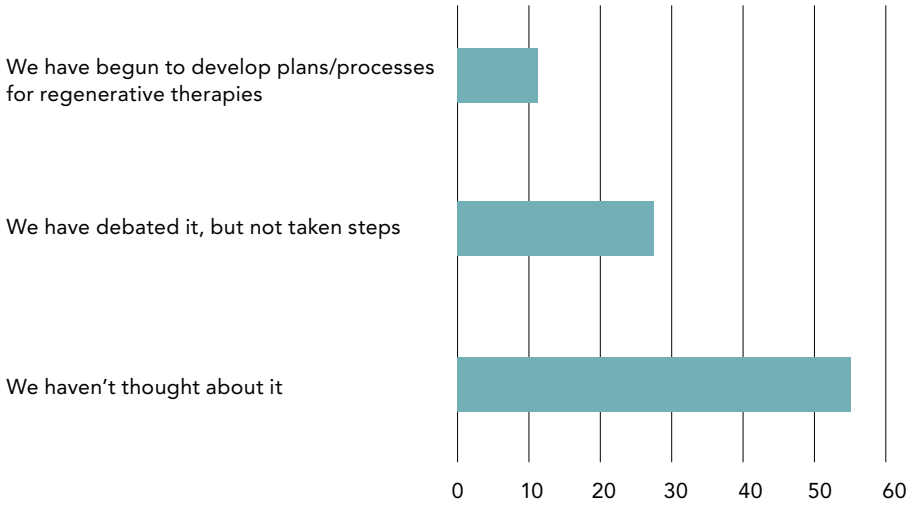
Managed care awareness and education around regenerative and advanced therapies are in the very early stages.[2] The survey component indicated that only around one-third of the payer respondents were aware that more than 930 regenerative and advanced therapies are in development. The majority, around 55 percent, of payer respondents, has not yet considered the implications of regenerative and advanced therapies for their plans. Only a small minority, just over 10 percent, has begun to consider coverage or operational issues associated with these therapies. Despite interest in the topic and excitement about the potential for transformative outcomes, payers also confirmed limited knowledge of the range and nature of products comprising regenerative and advanced therapies, including gene, cell, gene-modified cell, and other regenerative and advanced therapies, with or without special delivery systems.

Figure 1 provides an overview of "payer readiness" for regenerative and advanced therapy. Payers speculated that most plans have not seen a sufficient number of market entrants in the space to determine how and to what extent unique value assessment, reimbursement, or payment approaches are warranted. More broadly, results suggest that significant educational effort will be required to prepare the overall U.S. marketplace regarding the unique aspects of regenerative and advanced therapies, such as differences among technology and platforms, transformative or curative potential, and considerations for reimbursement of single administration therapies. Payers were open to dialogue to consider how regenerative and advanced therapies may influence care paradigms or require changes to existing reimbursement frameworks or operational processes if therapies do yield transformational results.

B. Characterizing the Benefits of Regenerative and Advanced Therapies

Prior GBEMTI publications on regenerative and advanced therapy have highlighted the unique aspects of these products, including substantially improved magnitude and duration of effect, that therapies can involve complex processing and administrative issues spanning entire episodes of care not anticipated by current global reimbursement systems, and payment challenges presented by single administration therapies.[3] First and foremost among the value drivers of regenerative and advanced therapies is (a) the potential for profoundly improved outcomes and (b), ability to deliver longer-term therapeutic effect. Such outcomes are foundational to the value proposition for these therapies. In general, payer respondents anticipated that "these new technologies will be more expensive than conventional therapies" but noted that if that is the case, then they will be required to deliver improved benefit commensurate with the cost. This raises considerations around the timeline for treatment and the potential for lifetime benefits from regenerative and advanced therapies versus conventional models that require repeat or

Figure 1: U.S. Payer Readiness for Regenerative and Advanced Therapies



N = 36; X axis = percentage of responses

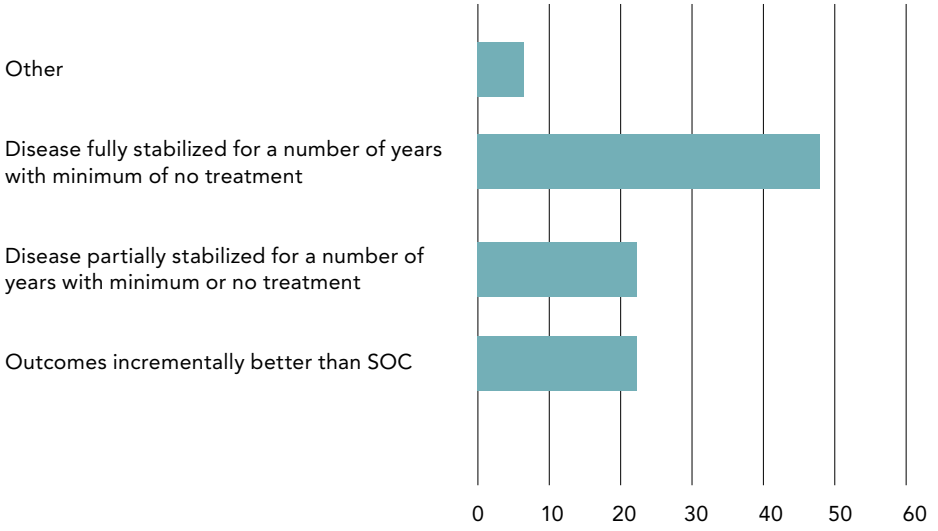
continuous treatment over time.

However, it is (a) currently unclear how managed care companies will determine whether a novel therapy has truly transformative potential and (b) whether such results would suggest that regenerative and advanced therapy reimbursement should be handled differently from existing therapies. Payers suggested that it would be unusual to develop special reimbursement or payment approaches based solely on the technology type (i.e., drug, biological, device, diagnostic). For example, advancements such as drug-eluting stents or monoclonal antibody therapies did not warrant development of special reimbursement or payment mechanisms. Instead, broader characterization (e.g., of therapies that are truly transformative or curative) was suggested as more likely because they could be designed to be more inclusive and not limited to a particular therapy or procedure type. It is unclear whether the terms "regenerative medicine" or "advanced therapies" would be sufficiently broad to be accepted as a basis for key changes to our existing reimbursement and payment systems under managed care.

To better understand what degree of improvement would be meaningful to payers, we explored the conditions under which payers would define a new therapy as transformative or curative. Clarity around such definitions, while still emerging, could become more important under scenarios where novel reimbursement or payment approaches need to be linked to regenerative and advanced therapies, particularly in a health care system that is more accustomed to marginal or incremental improvements, typically using chronic treatment.

Survey results in Figure 2 suggest that payer definitions of transformative therapy are highly variable, depending on a range of factors. Almost 50 percent of respondents viewed a *transformative* therapy as resulting in minimal or **no** signs or symptoms of disease for some number of years (degree of benefit was anticipated to vary by disease). If one expands this to include partial disease stabilization, another 25 percent of the sample viewed this degree of effect could also be viewed as transformative. Discussion during the payer workshop confirmed that factors such as disease severity, level of unmet need, and availability of reasonable standard of care alternatives/competitors, and effectiveness (e.g., magnitude/treatment effect size and duration of effect vs. standard of care) and safety vs. these alternatives can influence whether a particular health product is viewed as transformative. In the case of regenerative and advanced therapies, including perceptions that these therapies would be more costly than conventional therapies, payers generally felt that the treatment must **minimize or ameliorate symptoms (i.e., be disease modifying)** for a period of time significantly beyond what existing treatments are able to offer. Recent hepatitis C treatments were noted as examples of transformative therapies that exhibited

Figure 2: Payer Definition of Transformative Therapy



N = 36; X axis = percentage of responses

potential to cure disease.[4] Payers said that regenerative and advanced therapies with marginal benefits vs. available alternatives would face significant acceptance challenges if coupled with high pricing, particularly where they would be available to high-volume treatment populations.

This view on what constitutes a transformative therapy could have significant implications, both in terms of the need for systems to accommodate a vanguard of therapies that demonstrate transformative value, as well as in terms of the need to evolve reimbursement mechanisms in systems to address such therapies longer term. In the former, it is a matter of how best to ensure patient access to innovator regenerative and advanced therapies in systems not built to handle payment for single administration scenarios. In the latter, it is a matter of ensuring that appropriate reimbursement mechanisms exist to address a more mature state of entry of these technologies into global health systems.

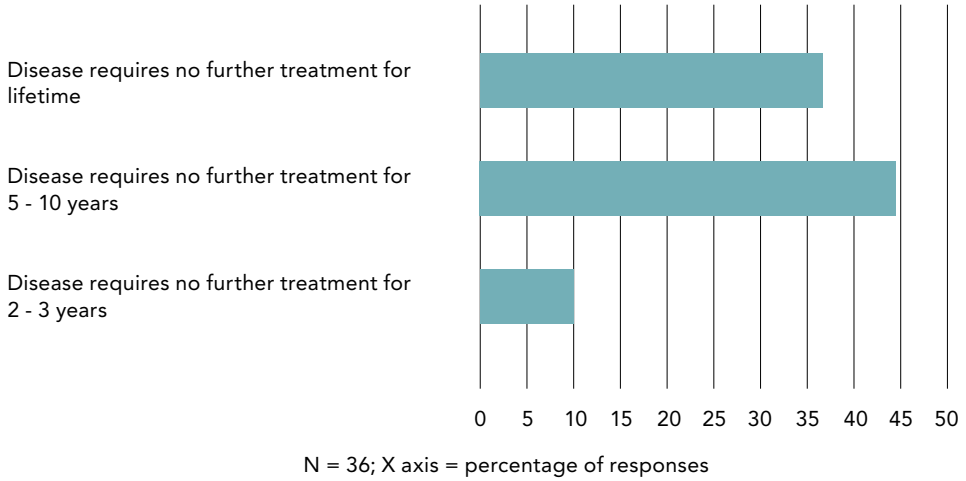
Transformative Versus Curative

Many regenerative and advanced therapies may provide a transformative clinical benefit – however defined. Some of these therapies, however, may also be classified as "curative."

While not all regenerative and advanced therapies are anticipated to be curative, and only a minority may earn such a moniker, it is important to note that our existing reimbursement system was not designed to recognize curative therapies. For regenerative and advanced therapies, a key distinction that separates many of them from virtually all predecessor biopharmaceutical treatments is the potential to cure disease through a single treatment, including the ability to leverage regenerative or advanced therapy platforms to address a number of diseases with few or no other (successful) interventional options. Single administration can have advantages for the health care system, such as avoiding downsides of long-term treatment, including compliance. However, the core challenge is that the full cost would then be incurred at the time of this single administration. Where transformative "ends" and curative "begins" is also a key consideration for regenerative and advanced therapies and may be scenario-dependent.[5]

Figure 3 confirms what health care stakeholders would expect, that the shorter the duration of symptom amelioration, the less likely a therapy is to be viewed as curative by managed care. Compared to defining "transformative," payers were more closely aligned around how they might define "curative." A minority of payers, around 10 percent, would view 2 to 3 years without treatment for a disease as curative. Whereas, around 45 percent of payers would define curative as a scenario that requires no treatment for 5 to 10 years, with approximately 40 percent expecting that the patient will be disease-free for a lifetime. This suggests that to fully stand apart

Figure 3: Payer Definition of Curative



N = 36; X axis = percentage of responses

from existing therapies, with the potential exception of serious diseases for which no treatment currently exists, regenerative and advanced therapies should not only be prepared to measure magnitude, but also duration of therapeutic effect.

Payers in the face-to-face workshop also raised several warnings about payer perspectives of both transformative and curative therapies, including:

• **Cure of one disease does not mean that the patient would not have other costly diseases –** cell and gene therapies in multi-factorial diseases may only address a *portion* of the problem, potentially reducing the value proposition.

• **Re-treatment** and stakeholder financial responsibility under single administration scenarios. For example, it can be contraindicated to re-administer some gene therapies because of potential for severe immune response or anaphylaxis in patients who may develop antibodies following initial treatment, while this may not be a concern with cell-based models. In addition, a key value argument for regenerative and advanced therapies is prolonged duration of effect; here re-treatment costs may be a concern if the initial price reflects that assumption.

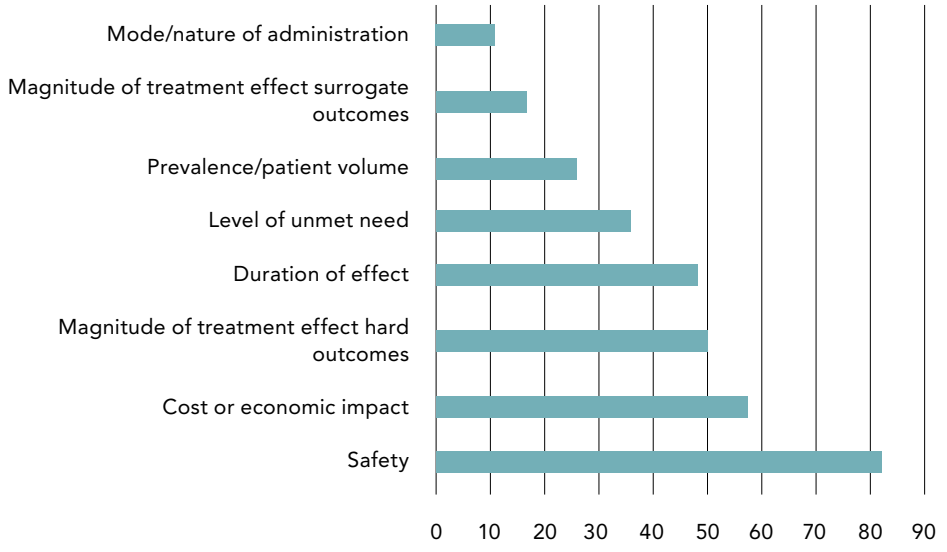
• **Uncertainties about whether the treatment would truly transform treatment of disease** but might result in other unanticipated problems, such as concerns about cell therapies resulting in downstream malignancies or altering key biochemical cascades. Payers specifically mentioned improvements of 2 to 3 months of life seen with some oncology agents as an example of what would not be viewed as transformative. The degree of improvement that would be viewed as transformative appears to be disease-context specific and would be influenced by unmet need, availability, and effectiveness of standard of care treatments, and other factors.

Payers were also quick to note that just because a technology is transformative or curative, it does not guarantee reimbursement. Factors such as medical necessity criteria, availability and benefits of alternatives, and affordability would also be taken into consideration. Ethical and other acceptance issues ranging from inability to "turn off" a single administration therapy to perceptions about genetic modification in general (e.g., fears of altering germline [inheritable] DNA, concerns about GMO products that may bleed over into regenerative and advanced therapy) were also raised in the context of managed care's remit to ensure that therapies do not pose unnecessary risks to patients. This underscores the strong need to educate the market as the field unfolds to demystify the area and address stakeholder concerns.

While the technology assessment process for regenerative and advanced therapies was viewed as similar to current therapies, some potential unique considerations were discussed. For example, how transformative and curative technologies are integrated into tiered/preferred status paradigms and where the funding for them comes from may differ from that of therapies not viewed as transformative or curative. A particular descriptor, like transformative, that characterizes those therapies that stand apart from standard of care, but are not fully curative, may also be important for policy development.

In the absence of an appropriate set of descriptors to characterize the differential impact of these

Figure 4: Most Important Aspects of Value Demonstration for Regenerative and Advanced Therapies



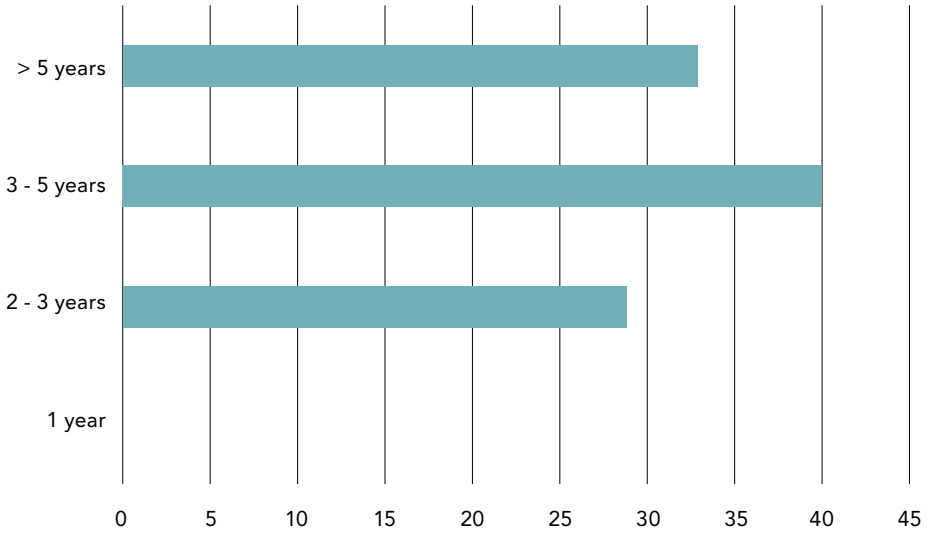
N = 36 Shown from least to most important based on payer responses; X axis = percentage of responses

therapies, regenerative and advanced therapies may face integration challenges in health systems that did not anticipate their unique attributes. If special mechanisms were created to accommodate regenerative and advanced therapies, but technology-level definitions could not be applied, another descriptor would be required. For example, in a recent evaluation completed for the National Institute for Health and Clinical Excellence (NICE), a leading Health Technology Assessment (HTA) body in the UK, assessment of CAR T-cell therapies adopted a new categorization-"therapies with curative intent"-to recognize a difference in how regenerative and advanced therapies may impact clinical and economic outcomes.[6] However, during the workshop, payers were reluctant to define "transformative" given variability in disease states/severity, performance of SOC treatments, and degree of unmet need, suggesting that the case-by-case nature makes applying a single definition difficult in practice and additional dialogue on "what defines transformative" may be warranted in the U.S. managed care arena.

During the discussion, we also broadly explored how managed care plans would assess the value of regenerative and advanced therapies, including the information demonstrated during health technology assessments. While survey responses (Figure 4) around the most important aspects of value demonstration for regenerative and advanced therapies were mixed, in-person discussions suggested that (a) the magnitude of effect on key treatment endpoints, (b)the duration of effect, (c) safety, and (d) cost were the four most important dimensions in value estimation. Payers counseled regenerative and advanced therapy manufacturers to focus first on establishing benefit, because without a standout value proposition, acceptance at higher price points would be difficult. This held especially true when prices fell into the range of higher-cost rare disease treatments (e.g., $200,000 and up). Payers in the workshop had heard from the media and other sources discussion of regenerative and advanced therapies that may exceed $1 million and noted that irrespective of value, treatments at such a price point emerging on the market in numbers would be a significant challenge for commercial plans to absorb. This suggests that manufacturers must carefully consider what outcomes and benefit profile will be viewed as transformative to patients, providers, and payers and yield broader health system and societal benefits. It also indicates that comprehensive planning around value demonstration for these therapies is warranted to help overcome acceptance hurdles and cost concerns.

Similar heterogeneity of opinion was noted in terms of duration of therapeutic effect for regenerative and advanced therapies (Figure 5). The greatest number of responses (~40%) suggested a time horizon of 3 to 5 years as ideal, though 30 percent of respondents considered 2 to 3 years to be minimally

Figure 5: Anticipated Duration of Therapeutic Effect for Regenerative and Advanced Therapies



N = 36; X axis = percentage of responses

sufficient. Payers did note that transformational duration of effect could vary by disease area, particularly for acute terminal scenarios, but they noted that conventional time horizons of under a year would not be viewed as significant for therapies that would claim a transformative therapeutic effect. This confirms earlier findings of GBEMTI's previously cited study of managed care perspectives on duration of therapeutic effect. Therapies with <1 to 2 years of benefit were generally thought of as being comparable to modern biopharmaceuticals, and likely would not warrant differentiated consideration.

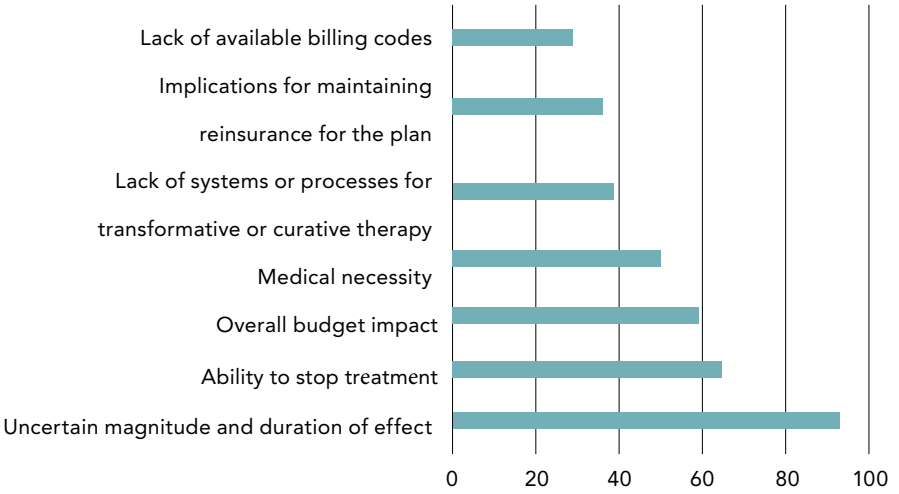
C. Acceptance, Uptake and Reimbursement of Regenerative and Advanced Therapies

Payers in the survey were asked to identify from a list whether certain factors were more or less important to driving acceptance of regenerative therapies. Of those factors influencing acceptance, > 90 percent viewed magnitude and duration of effect as the most important factor. The second most common responses were ability to arrest/turn off the treatment (62%) if a significant safety issue emerged and cost weighed in as the third most important factor (58%). Payers in the workshop noted that cost of regenerative and advanced therapies could have significant impact on willingness to accept regenerative and advanced therapies from an affordability standpoint, irrespective of other factors. Around 38 percent to 45 percent of those surveyed noted that uncertainties around medical necessity and the ability to maintain reinsurance could be impacted by these therapies, and the fact that lack of systems and processes for accommodating these therapies could also impact patient access and ability to realize any broader societal gains that may result. Lack of available billing codes was not noted as a significant acceptance barrier, with respondents indicating that plans could apply some flexibility there so long as evidence around costs of the care episode appropriately supported the payment amount.

Payers in the workshop also noted that there is a significant incentive disconnect for covering some regenerative and advanced therapies under *current* reimbursement models not readily configured to receive transformative therapies with high associated costs. In other words, the absence of appropriate reimbursement mechanisms is viewed as a key uptake barrier. The following were the key reimbursement considerations that managed care must grapple with in terms of enabling patient access to regenerative and advanced therapies:

• **Fiduciary responsibility to beneficiaries and medical necessity** was raised by multiple attending managed care representatives. Payers indicated that if costs of regenerative and advanced therapies were substantial that they would have to think about coverage tradeoffs that the plan could make. The example of paying approximately $1 million for an ultra-orphan therapy vs. vaccinating a large

Figure 6: Factors Influencing Acceptance and Uptake of Regenerative and Advanced Therapy



N=36; (percentage answering 9-10 of 10 where 1 = lowest level of challenge and 10 = the greatest level of challenge); X axis = percentage of responses

population was advanced as a managed care decision dilemma. Payers noted that as emphasis on rare disease treatments has increased dramatically, financial allocation decisions are becoming more complex. A few payers indicated that under such scenarios they may be forced to reject such therapies, irrespective of value, or risk bankrupting their plan. Risk of bankruptcy was raised as a real issue for small to mid-sized plans characterized as "barely holding on" under current models. Payers noted that some plans are "a few more costly rare disease payments away from bankruptcy."

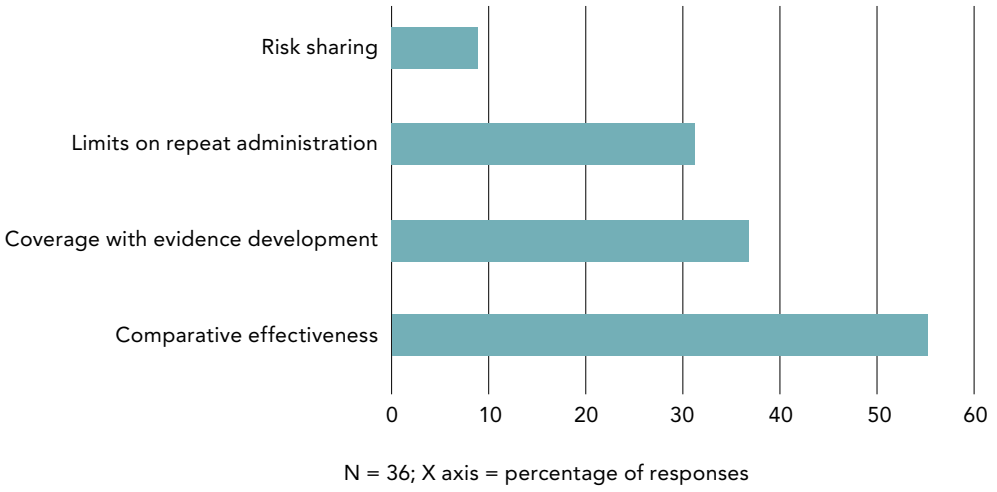
• **Beneficiary churn** was also noted as a substantial barrier. Payers noted that, given the typical member turnover rate in commercial plans, the health plan paying for a regenerative and advanced therapy may no longer have the member after 18 to 24 months. This issue would complicate any negotiated payment models that would range beyond 2 to 3 years.

• **Risk to ability of the health plan to maintain reinsurance** was noted as a potential challenge. If regenerative and advanced therapies enter the marketplace in number, and several claims require excessive reliance on reinsurance, reinsurers may prevent plans from renewing their reinsurance contracts because of more frequent or profound impact of high-cost events hitting the actuarial pool. The workshop participants also believed that the scenario around these therapies could result in an overhaul of how reinsurance plans operate in general in the U.S. While ~35 percent of surveyed payers viewed reinsurance as a payment route, payers participating in the face-to-face meeting did not believe that this was a long-term solution.

• **Acceptance of "good enough" therapies in lieu of transformative therapies.** The number and degree of benefit offered by available treatments was noted as having significant influence on acceptance potential. Payers in the workshop indicated that even if therapies were covered, access may be severely limited if "arguably imperfect, but good enough" therapies were available. Payers in the workshop indicated that high unmet need areas like cystic fibrosis, hemophilia, or sickle cell disease may be easier to develop a value story around than for other conditions with less apparent need for health solutions. It was clearly noted that regenerative and advanced therapies not viewed as transformative, but entering disease areas where effective alternatives exist, could experience coverage limits (e.g., step therapies, requirements for therapeutic monitoring to ensure the treatment is still working). This suggests that (a) non-inferior evidence development approaches may place regenerative and advanced therapies at significant risk for acceptance and (b) focus on transformative impact would be necessary for acceptance of therapies in higher price brackets.

• **Applying investigational or experimental language.** Respondents indicated that managed care may be much more aggressive with applying investigational or experimental labels to very costly products in this space (which may vary based on a

Figure 7: Payer Perspectives on Reimbursement and Access Concepts that may be Applied to Regenerative and Advanced Therapy



N = 36; X axis = percentage of responses

range of factors, including whether the disease area is in a protected class like oncology), particularly given cost concerns around the potential high cost of these therapies. Payers in the workshop did note that pediatric diseases would be considered differently vs. adult diseases in terms of the severity of coverage restrictions that may be applied. Discussion of the potential for non-coverage also compared and contrasted regenerative therapies like Glybera® (not available in the U.S.), which had an uncertain therapeutic effect and cost of >$1 million and, conventional biological therapies like Exondys 51®, a recent treatment for Duchenne muscular dystrophy that was denied coverage by some U.S. plans based on claims of insufficient evidence, versus hepatitis C drugs, which emerged with initial pricing around $90,000 but clear curative benefit[7]. In general, if regenerative and advanced therapy benefits are unclear and pricing is very high, therapies will face rejection, even if targeting high-unmet-need, rare disease indications.

• **Lack of coding to characterize regenerative and advanced therapies.** Coding was also noted, but more from a timeline perspective vs. ability to obtain codes that characterize regenerative and advanced therapies. Obtaining new coding was predicated on the assumption that existing codes did not adequately describe the procedure and evidence of value to support novel coding. Payers in the workshop did recognized that many of these therapies are truly novel, that the health system did not anticipate the reimbursement scenarios associated with them, and that new coding to accommodate proven applications would be warranted in many cases as the field evolves.

The survey also considered commonly discussed market access concepts that may be applied to regenerative and advanced therapies. These included risk sharing, limits on repeat administration, coverage with evidence development and comparative effectiveness (Figure 7).

As might be expected, approximately 55 percent of payers indicated that they would look for information on the comparative effectiveness of therapies versus available standard of care. While payers prefer direct head-to-head data, they also noted acceptance of indirect evidence published from peer-reviewed literature, databases or direct chart or prospective longitudinal data that characterizes the standard of care "baseline" clinical and cost-effectiveness. Around one-third of payers surveyed indicated that regenerative and advanced therapies would include policy caveats limiting or precluding repeat administration (if possible to re-treat based on the treatment platform). Payers were less interested in coverage with evidence development and risk sharing for these therapies, with only 37 percent and <10 percent of respondents indicating these as key options. Payers in the workshop did note that having clear stop payment clauses if the treatment ceased being effective could be acceptable. Under this scenario, payment may be spread over a 2 to 3 year period and would make regenerative therapies easier to absorb by the health care system. Overall, payers were concerned that the payer framework is confined to the system in place today and that it may

be necessary to evolve alternative financing models to optimally support access to regenerative and advanced therapies.

Two examples of where payers have introduced more novel management strategies in rare disease were also discussed. One was Spinraza® for spinal muscular atrophy, a non-regenerative and advanced therapy with a year one price of approximately $750,000 spread over three payments in year one, with a $350,000 maintenance regimen each year for the remainder of the patient's life. The caveat is that this therapy also requires diagnostic monitoring where, if the patient stops responding, the payer organization stops reimbursing the therapy. This is one example of how a therapy's particularly high costs can be absorbed by the system, avoiding the impact of absorbing the $750,000 in a single payment with some guarantees of continued effectiveness in the stop payment coverage clause. The other example is the Duchenne muscular dystrophy drug Exondys 51®, which under some plans also requires evidence of ongoing effectiveness as a condition of continued administration. In terms of regenerative and advanced therapy, payers noted that a stop payment clause may be considered over a narrow window of 2 to 3 years or potentially clawback clauses attached to measures of effectiveness. Such models require both payers and manufacturers to share risk and balance payment and performance.

Payers in the workshop and across other discussions of regenerative and advanced therapies within the GBEMTI ELC, also anticipated application of stringent reimbursement limits that may be narrower than the FDA-approved label. This is evident in Spinraza® coverage policies, where some plans have limited access to only certain patient genotypes deemed to have sufficient evidence. Payers also noted that the higher the price of any treatment, the more aggressive they may be in erecting coverage limits or rejecting therapies as investigational. Payers cautioned regenerative and advanced therapy developers to carefully consider the patient populations for which they would seek to obtain reimbursement. This also suggests that manufacturers should carefully consider how reimbursement restrictions may be applied in developing the evidence base of regenerative and advanced therapies (beyond that minimally required for regulatory approval).

D. Addressing Payment for Single Administration Regenerative and Advanced Therapies

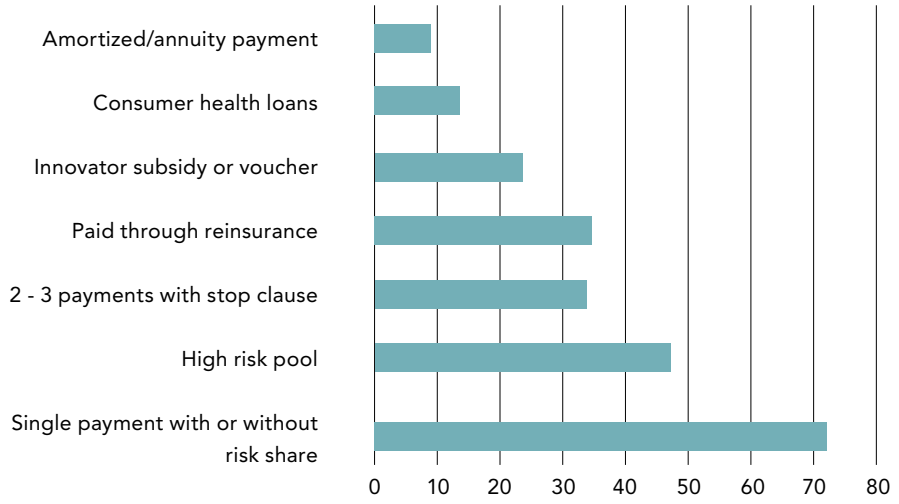
Of all the factors discussed in the payer workshop, price, affordability, and payment model were the most concerning aspects of regenerative and advanced therapies to U.S. commercial payers, and has been discussed in other quarters.[8,9] Concerns about the potential cost of regenerative and advanced therapies were noted within a broader set of concerns about the rising cost of biopharmaceuticals overall. Payers also noted that if pricing for transformative or curative regenerative and advanced therapies were at or beyond the upper bound of higher priced rare disease treatments, that payment models must be, in their words, "equally disruptive" to ensure broad patient access to successful treatments.

In general, payers in the workshop initially anticipated that regenerative and advanced therapies would be significantly more costly than existing therapies. Some payers also noted that it would be possible to price regenerative and advanced therapies out of the marketplace such that the therapies would not be covered. Others noted that under some pricing scenarios, coverage of even curative therapies may not be feasible under current financial models. Subsequent discussion clarified the broad range of regenerative and advanced therapies, many of which may not be priced at the upper end of biopharmaceutical pricing paradigms. This suggests the need for significant education on the scope and nature of regenerative and advanced therapies, including case scenarios addressing different core technology applications and a careful eye toward coverage considerations.

Several different payment models were tested via survey and in the workshop. Figure 8 shows the results of the payer survey, which were consistent with results of the workshop discussion. The following summarizes key findings.

- More than 70 percent of survey respondents anticipated that a **one-time payment** would be the most likely option available, given that U.S. health system infrastructure is not set up to accommodate amortized payment schemes. However, this option was viewed as the most difficult for plans to absorb.
- While survey responses indicated that a minority of payers anticipated the use of **2- to 3- year payment models**, payers in the workshop argued that such an option may help increase acceptance potential based on ability to spread costs over time. As previously noted, beneficiary churn in plans was noted as a chief concern for any payment models greater than one year, with the key issue being responsibility for payment of the balance of costs if the patient switches plans before a negotiated payment scheme elapses. Managed care also indicated that the current reimbursement system is focused on a 12-month financial cycle and is not structured to recognize health interventions whose value accrues over years or decades. They suggested that financing structures that better recognize the unique aspects

Figure 8: Payment Models that Managed Care May Consider for Regenerative and Advanced Therapy



N = 36; X axis = percentage of responses

of regenerative and advanced therapies could help address such hurdles and streamline access.

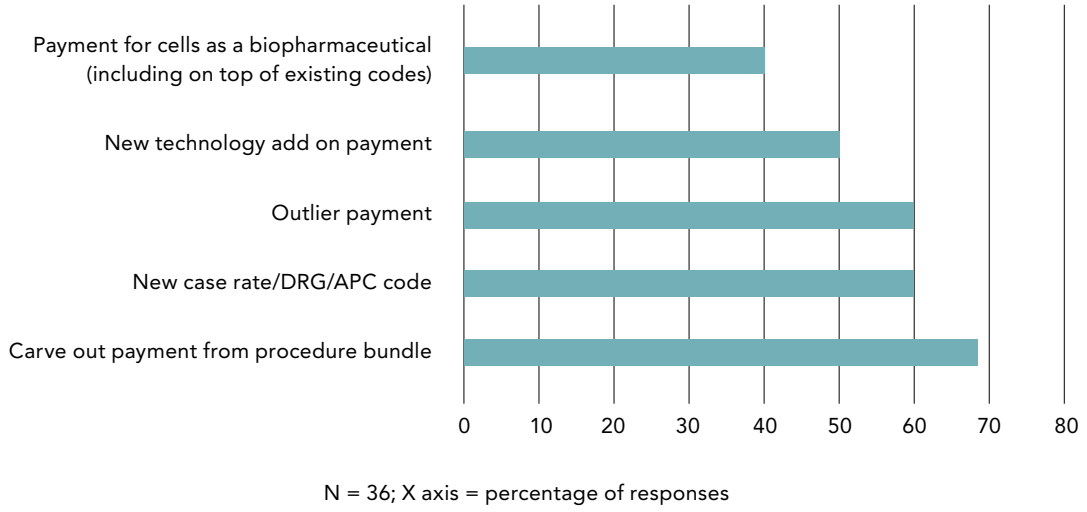
• Almost one-third of the survey sample anticipated that **reinsurance** could defray the cost impacts of these therapies, but anticipated this as a stopgap approach. Reinsurance is geared toward addressing unanticipated outlier events, to help the health plan address acute cost issues that may impact plan financial operations. Reinsurance scenarios may apply to the first few regenerative and advanced therapies, assuming reinsurer plan language would allow it, but is an unlikely long-term solution (under current models) as regenerative and advanced therapies enter the market in greater number/become more common. Broader use would require restructuring of conventional reinsurance models to accommodate transformative therapies *en masse*.

• Of all the options, payers in the workshop viewed a **high-risk pool model** as being the best option from a managed care perspective. However, only around 45 percent of survey respondents suggested that this was the most feasible option. High-risk pool models were thought to enable access, while defraying impacts to an individual plan. Models drawing from Medicaid end-stage renal disease (ESRD) approaches were advanced as a starting point and payers indicated that such models will be better received if they are familiar and implementation effects on the plan can be predicted or characterized. Payers indicated that reinsurers had to be part of this dialogue as well.

The potential for a high-risk pool to have unintended consequences was also discussed. Rules for what treatment scenarios would be "in" or "out" of the pool was noted as a potential risk for excluding some patients that may benefit from a regenerative and advanced therapy that does not technically meet predefined risk pool inclusion criteria. Also, payers viewed such models as opening the door to other therapies, depending on whether definitions of concepts like transformative or curative were included as part of such a risk pool model. In this sense, whether inclusion is based on (a) *degree or effect* (i.e., transformative or curative), (b) *technology type* (i.e., cell and gene or other regenerative or advanced therapies), or (c) *regulatory designation* (i.e., RMAT or ATMP) would have substantial implications for patient access to technologies in a risk pool model. Payer respondents in the workshop were reluctant to provide specific feedback on inclusion or exclusion criteria, but did acknowledge that the success of such models would hinge on definitions. They also viewed that a government-administered model would be easiest, although low per-member per-month funding from commercial plans was also raised as a potential model, if the high-risk pool is numerically large.

In the absence of such a model, when faced with a scenario of claims for a regenerative and advanced therapy "hitting their desk tomorrow," payers indicated that the most likely scenarios were single-time upfront payment or rejection of the therapy as investigational (even with regulatory approval, unless

Figure 9: Most Likely Payment Models Anticipated for Inpatient Regenerative and Advanced Therapy Scenarios



N = 36; X axis = percentage of responses

the therapy is in a protected class) where treatments could be viewed as having insufficient evidence.

Figure 9 reflects feedback from survey respondents on the most likely approaches for securing sufficient payment under U.S. managed care models for inpatient therapies. Some of these have been considered more broadly at the global level.[10] It was acknowledged that inpatient payment under DRG models can be particularly problematic for regenerative and advanced therapies that do not fit under existing DRG payment rates. The ability of providers or health systems to "be made whole" for the cost of delivering regenerative and advanced therapies was highlighted as a critical uptake driver on the provider side. Under scenarios where providers would not be profitable, payers anticipated that therapies may be rejected altogether where other more affordable alternatives exist. Payers were mixed in regard to the best way forward for new reimbursement, and approaches like new case rates, add-on payments, carve-outs, and outlier payments were all discussed. This suggests that manufacturers must consider multi-pronged approaches in establishing appropriate payment in the inpatient setting, given variability among stakeholder systems and limited precedent for regenerative and advanced therapies. Preparation of a clear value story was viewed as the most important preparation to make a case for any of these options, as well as the importance of alignment with provider champions and patient advocacy groups.

Further, extension of bundling models beyond typical DRG settings to account for episodes of care relevant to regenerative and advanced therapies was also acknowledged as a potential way forward. Such vehicles are relevant in existing models, such as bone marrow transplant and a host of other medical procedures that include medical technologies as part of the patient solution. While bundling models may improve certainty and clarity of the reimbursement pathway, the cost of the cell or gene therapy component must then "fit" in the context of the bundle. On the one hand this would make pricing this component outside of the bundle difficult and on the other hand, if the cost of these therapies decreases over time, this would limit the ability of payer systems to redistribute any cost efficiencies. A bundling option also does not solve aggregate cost concerns acknowledged by payers in the workshop.

On a broader level, payers recognized the promise that this area offers, but acknowledge that significant hard work will be required to develop structures for consistent uptake of regenerative and advanced therapies. Payers also acknowledged that managed care is reactive, and not proactive, and that competition among U.S. health plans may inhibit advancing solutions for regenerative and advanced therapies prior to a number of these therapies emerging on the marketplace. Other factors such as cost shifting with higher copays, higher maximum out-of- pocket values, institutional/system blocks, and prescriber risk models are also relevant to consider in driving acceptance and uptake of these 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 regenerative and advanced therapy 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 do point to trends in payer and provider views on regenerative and advanced therapy.

VI. Conclusions

It was clear from the ARM and NAMCP joint meeting that payers view the regenerative and advanced therapies industry as still in early stages of evolution. Managed care executives were excited by the prospect of technology that may yield truly transformative care results, but also concerned about the affordability of such therapies entering the patient care environment in number. Because these therapies are truly novel and managed care plans anticipate that they are likely to be more costly than predecessor therapies, the following conclusions are critical to preparing the health care marketplace for the regenerative and advanced therapy era.

• Prepare for education and market preparation to be a journey and not a destination.

At present, there is much uncertainty and heterogeneity in the understanding of regenerative and advanced therapies. The range of different platform approaches were viewed as more complex to explain in terms of implications for benefits and risks versus conventional pharmaceuticals. The industry should plan to invest in consistent educational activities to help prepare the range of stakeholders that will soon access regenerative and advanced therapies. Characterizing patient and physician perspectives and acceptance scenarios and drivers will also be important as many of these technologies may offer more permanent/durable effects different from conventional biopharmaceutical models. Underestimating the importance of such education could complicate commercial launch activities and hamper patient access to these innovative therapies.

• Lead with value and think transformatively.

Payers in both the survey and workshop were clear that the most important area that regenerative and advanced therapy developers can focus on is developing compelling evidence of value. Further, in scenarios where costs of therapies would be significantly above that of most conventional therapies, regenerative and advanced therapies must demonstrate transformative benefit. Payers indicated that technologies bringing only marginal improvements at high cost would face difficulties in achieving coverage (including being viewed as experimental/lacking sufficient evidence) or, if covered, experience severe access restrictions. During the discussion, payers had a difficult time coming up with a singular definition of transformative, noting that relative benefit is scenario-dependent, including a variety of factors such as unmet need, availability of alternatives, their effectiveness, and costs.

This suggests that regenerative and advanced therapy manufacturers should take a comprehensive view of value demonstration and focus on not only superiority, but rather the transformative benefit. Lack of a clear patient population, non-inferior pivotal designs, focus on surrogates, and key gaps in evidence could weaken acceptance and patient access to these new therapies.

• Payers viewed existing value frameworks to be sufficient, with some exceptions.

Payers in the workshop anticipated existing technology assessment frameworks to be generally sufficient for evaluation of regenerative and advanced therapies. Managed care executives indicated that existing processes accommodate the magnitude of effect, even if transformative. There were two key exceptions noted in discussion: (a) expectations for demonstrating duration of effect and (b) demonstrating curative effect.

Payers indicated that duration of effect influences acceptance potential at the time of market entry. In scenarios where the evidence of duration is more like that of conventional products in terms of 6 to 18 month outcomes, arguments about duration would be questioned and could therefore potentially weaken pricing position. One exception could be conditional reimbursement and/or managed entry plans supported by downstream evidence development in markets where such arrangements are possible. However, payers in the workshop indicated that existing U.S. commercial models have few provisions for coverage with evidence development. They did, however, suggest to collect patient follow-up data on patients at the earliest trial stages to have as much evidence as possible at the time of launch, understanding that it may be difficult in practice to collect the desired 2 to 5 years of data indicated as ideal.

Existing payer models also do not typically have to deal with what could be considered a curative therapy. Currently, coverage models do not have special considerations for therapies that would be curative. If numerous regenerative and advanced therapies do emerge that are curative, payers noted that HTA processes or policy provisions may need to adapt.

• Anticipate heterogeneity in reimbursement models, as the health care system was not built for most regenerative and advanced therapies.

Another key area of discussion is the recognition that existing reimbursement systems were not built with regenerative and advanced therapies in mind. While therapies used in in-patient settings were anticipated to face more significant challenges if the cost of the cell or gene therapy put providers at financial risk in a bundled environment, payers did confirm that if the therapy were viewed as transformative, that many commercial payers would have the potential to develop new case rates to cover the cost of the therapy. This process, however, requires "bottom up" discussions with payers, involvement of providers under the plan to present the evidence package supporting the case rate, and often involves engagement at the CFO-level of many plans. Payers indicated that new DRG or APC codes covering the therapy could help broaden acceptance and make it more uniform in a manner similar to bone marrow transplant or other in-patient procedures versus the variable commercial uptake scenarios associated with a route dependent on new case rate development. In general, while not an insurmountable hurdle, this barrier was noted as critical to achieving broad patient access.

• There is a strong need for novel payment models, but prepare for today's market realities.

One of the key areas that payers noted as problematic is that existing U.S. health care systems are not geared to absorb the financial impact on cash flows of single administration models for very high-cost therapies. Payers further indicated that some of the more recent costly therapies are placing plans under strain and aggregate costs may challenge the financial viability of certain plans. In the absence of a means to address this dilemma, payers anticipated that therapies without a strong value proposition may face non-coverage and, in the long-term, innovative payment models must emerge to address the financial implications of this scenario. In the interim, payers counseled manufacturers to prepare for the fact that commercial uptake will require careful planning, time, and sufficient resources.

Evolution of new payment models will be necessary, but in the short-term products are likely to face heterogeneity in uptake. The options noted as most likely, aside from one-time payment included (a) payment in 2 to 3 installments with stopping provisions and/or clawback contractual provisions, (b) development of a high-risk pool, or (c) bundled or inclusive/bundled models such as payment for chronic kidney disease. While payer respondents generally preferred a high-risk pool model, defining the model and developing broadly acceptable inclusion and exclusion criteria should be carefully considered to avoid unintended consequences (e.g., denied access to patients for treatments that do not meet eligibility criteria). This may require, for example, defining transformative and or curative as a vehicle to support policy as payers indicated they may be less likely to define special benefit budgets/pools based on technology type (i.e., regenerative and advanced therapies) or determining another means to gauge pool eligibility such as linking the pool to therapies that fall under the Regenerative Medicine and Advanced Therapy (RMAT) FDA regulatory designation.

Other elements of the pool may require further evolution of benefit design, payout models, and other factors, and may be a longer-term goal. Such a pool could also incorporate longer-term value demonstration as a means of fully characterizing therapy value as a condition of participation. Such a model under this vehicle would help address current commercial payer challenges in executing conditional coverage models, while enabling promising technologies to rapidly enter the market with value demonstration and final reimbursement criteria for a particular therapy evolving with the technology evidence base.

Next-generation payment models for regenerative and advanced therapies would likely incorporate elements of risk pooling/sharing, along with provisions for scenarios to protect stakeholders when patients change health plans. While this could be accommodated by government models, it will be critical to engage the full range of stakeholders, including payers, reinsurers, providers, patients, and policy makers. Payers also raised possibilities like chronic kidney disease (CKD) payment where costs are integrated and models like the East India Trading Company model, which enable financial risks to be spread more broadly.

This open dialogue between managed care and the regenerative and advanced therapy industry has surfaced several areas where stakeholders must work collaboratively to help ensure that regenerative and advanced therapies that deliver on their promise for transformative benefit will be available to patients with health needs not yet sufficiently addressed by the U.S. health system. The findings of this study lay the groundwork for active engagement around the most critical issues of definitions/expectations for value, reimbursement, pricing, and, most importantly, appropriate access to novel innovation with the potential to alter care practices and health outcomes as we know them today.

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References:

1. Faulkner E, Ransom J, Clark G. Is managed care prepared for regenerative and advanced therapy? Early landscape and reimbursement considerations. *Journal of Managed Care Medicine*, 2017:(20)1:52-67.

2. Pettitt D et al. An assessment of the factors affecting the commercialization of cell-based therapeutics: a systematic review protocol. *Syst Rev.* 2017 Jun 26;6(1):120.

3. Faulkner E, Ransom J, Clark G. Is managed care prepared for regenerative medicine? Early landscape and reimbursement considerations. *Journal of Managed Care Medicine*. (20)1:2017:52-67.

4. Iyengar S, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. *PLoS Med*. 2016 May 31;13(5):e1002032.

5. Faulkner E. Critical Success Factors for Navigating Regenerative Therapies Through the Maze of Market Access Uncertainty. International Society for Cellular Therapy. London, England. March 2017.

6. Exploring the assessment and appraisal of regenerative and advanced therapies and cell therapy products. CRD and CHE Technology Assessment Group, University of York. 2015.

7. Aetna: Eteplirsen (Exondys 51) Coverage Policy 0911. 2016. BCBS of Florida Eteplirsen Coverage Policy 09-J2000-29. 2016.

8. Carr DR, Bradshaw SE, Faulkner E. Critical Success Factors for Navigating Regenerative Therapies Through the Maze of Market Access Uncertainty. International Society for Cellular Therapy. London, England. March 2017.

9. Faulkner E. What value do we place in a cure? Implications for regenerative medicine technologies. Phacilitate Cell and Gene Therapy Meeting 2015. Washington DC. January 2015.

10. Driscoll D, Farnia S, Kefalas P, Maziarz RT. Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access. Stem Cells Transl Med. 2017 Aug;6(8):1723-1729.

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