Regenerative Therapies: Are We Ready for a Cure? Key Value and Policy Considerations to Facilitate Access

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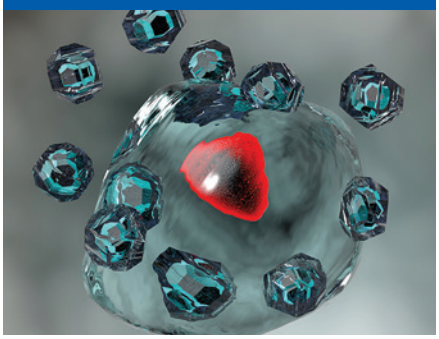
KEY POINTS . . .

Regenerative therapies are expected to bring the next generation of transformative improvements in patients through potentially curing and preventing disease conditions rather than living with these conditions.

Regenerative therapies may offer unique solutions to bring efficiencies and resolve several of the issues that the health care system currently faces.

Uniqueness of regenerative therapies may allow customized solutions to be explored to facilitate access, respect innovation, and provide better care in a financially sustainable way.



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We are at the brink of a new era of medicine

Regenerative therapies replace or regenerate affected human cells, tissue or organs to restore or establish normal function. This represents a new paradigm in human health, transforming the practice of medicine by addressing the underlying causes and altering the fundamental mechanisms of disease. While significant advances to medicine have been propelled through small molecules and biologics, the next phase of transformation is expected from regenerative therapies bringing the next generation of improvements in patients through curing and preventing disease conditions rather than their living with these conditions [1,2].

Regenerative therapies are key to the future of the life sciences. They may be considered especially for diseases for which there are no current effective treatments, those with a known cause such as a defective gene, those that have failed to improve or have become resistant to conventional therapy, and/or cases where current treatment involves long-term administration of a burdensome therapeutic agent or an invasive procedure [2]. A wave of approximately 700 cell, gene, and immunotherapies are working their way to market, with the initial vanguard of entrants already emerging in the marketplace in the area of blood cancers (CAR-T), hemophilia, and the recent European Commission approval of Strimvelis, the first ex vivo stem-cell gene therapy to treat patients with a rare genetic condition, ADA-SCID.

Regenerative therapy might need to be administered only once or just a few times for a lasting benefit [1]. This raises new reimbursement and access policy issues that the global marketplace has not yet addressed. The definition of what constitutes a cure and the associated value demonstration requirements, as well as new patient management and payment models, need to be considered. While these potentially curative therapies offer tremendous promise, are we prepared to absorb them?

A new approach to integrating science and product development

Regenerative therapies represent a paradigm shift in the way therapies are developed and delivered to patients. While traditional drug development with small molecules and biologics acts on specific cellular targets to modify function of persistently defective organ and tissue systems, regenerative therapies transform defective tissues into "normal" cells or tissues.

• *Individualized manufacturing:* Current approaches for regenerative therapies come in the form of living tissues manufactured specifically for the unique needs of an individual patient. This truly personalized nature means that the treatment is not transferable between patients. Manufacturing and delivery involves a sophisticated process and a dedicated logistical chain of custody to reach the patient.

• *More integrated approach to product development:* The semi-sequential approach that is seen with small molecules and biologics (e.g., discrete phases in the journey from translational research to full development) is very different from the more integrated approach with regenerative therapies where science and product development are much more closely intertwined.

• *More integrated approach to manufacturing and commercialization:* Manufacturing and commercialization are highly codependent processes and do not exist in the sequential, isolated ecosystem in which small molecules and biologics can exist. Regenerative therapies focus on continuous improvement through an ongoing collaboration between science, engineering, and operations. This collaboration yields a constant feedback loop that helps drive optimization of quality, efficiency, and scalability. Advancements of these therapies require a concerted approach of integrating science, development, and delivery of care.

Administration of regenerative therapies

Manufacturing and delivery of regenerative therapies is different from the relatively simple processes seen with small molecules or traditional biologics. A typical process is described in Figure 2. The truly personalized

nature of regenerative therapies adds a layer of sophistication to delivery of care through specialized manufacturing and centers of excellence.

Potential impact of regenerative therapies

Regenerative therapies have the potential to deliver high value impact to health systems [4]. The benefit of potentially curative therapies to the patient and to society is anticipated to accrue from long-term health benefits and savings from avoiding future interventions [5]. Payers are reluctant to absorb the high upfront costs unless there is convincing evidence for potential benefits and cost offsets in the future. Innovation through regenerative therapies is uniquely positioned to mitigate some of these risks and manage uncertainties through unique patient-specific manufacturing and treatment management. However, regenerative therapies come with numerous unique challenges that we must consider to facilitate use in clinical practice.

Access and reimbursement considerations of regenerative therapies

Regenerative therapies are fundamentally different from traditional therapies on a number of dimensions. This necessitates navigating a number of pricing and reimbursement considerations that need to be leveraged to enable wider usage of regenerative therapies (Table 1).

a. Treatment regimen and effect: Regenerative therapies are intended as one-time or short-term treatments that avoid future costs seen with chronic treatments. This also means potential avoidance of the burden of medication nonadherence seen with chronic therapies and medication wastage — touted to be around $3 billion in cancer alone in the United States. However, this challenges the traditional commercial model where payments are made for recurring treatments over a prolonged duration. Is the system ready to recognize the benefits of one-time upfront intervention that potentially could avoid future burden of disease and treatment?

b. Funding and pricing decisions/policy: There are no specific policies or processes for funding or reimbursement of regenerative therapies and the environment continues to evolve. In the United Kingdom, the NICE Regenerative Medicines Evaluation Group published a report on their assessment as to whether NICE's health technology appraisal methods are suitable for regenerative medicines and cell therapies. While uncertainty exists currently, there is tremendous opportunity for policy makers and manufacturers to collaborate with key stakeholders to co-create effective solutions to bring these therapies to patients. A true partnership needs to be facilitated to jointly shape the environment and realize the benefits to society.

c. Manufacturing and logistics: Regenerative therapies currently are manufactured through an individualized, sophisticated process with customized logistics where every "single patient" represents a "batch of single manufacturing process." This means substantial cost of goods needs to be covered by price to avoid financial loss. Albeit more complex, individualized manufacturing uniquely offers a solution for readily tracking treatment and follow-up of care delivery, thereby minimizing waste and mitigating uncertainty around treatment adjudication. This should also facilitate exercising value and payment by indication — something that both payers and policy experts propose as a solution.

d. Available data for filing: Health authorities have recognized the potentially substantial benefits with regenerative therapies and have qualified many of these therapies with breakthrough or accelerated approval status. Given the urgency to bring these potentially life-saving therapies to patients who have no other options, it is anticipated that pivotal data for approval will come typically from phase II single-arm and short-term studies. However, this does pose challenges in meeting payers' demands for data on long-term survival and comparative effectiveness, especially considering both potential uncertainties of parameter estimate and uncertainty of decisions. Bringing these therapies to patients rapidly requires all stakeholders to fully appreciate the innovation and form partnerships to share risks and manage clinical and financial implications through novel approaches.

e. Real-world experience: There are currently very few marketed regenerative therapies and the degree of commercial success is varied. While a great deal of interest exists, payer response to marketed therapies has been mixed. Unless we leverage existing

Table 1: Uniqueness of regenerative therapies and implications on access and reimbursement

Dimension	Traditional Therapies	Uniqueness of Regenerative Therapies	Access and Reimbursement Implications
Treatment Administration & Effect	Certain treatment duration, cycles or chronic	One-time/short-term treatment with long-term benefits	No recurring use or payment after one treatment; minimize waste and uncertainty
Funding & Pricing Decisions/Policy	Well-established pathway and decision-making process	No specific policy/process in place yet	Uncertainty in process but opportunity to co-create the environment
Manufacturing & Logistics	Mass production Simpler logistics	Individualized production and complex logistics	Substantial cost of goods; financial risk/reward; ability to track patients by indication
Available Data for Filing	Mostly phase III with comparator and survival data	Phase II single-arm, short-term results given dire patient needs and limited alternatives	Challenge to meet payers' survival and comparative data requirements
Experience	Strong track record and experience	Limited, inconsistent experience across markets	Create user-based best practice network; explore innovative approaches
Treatment Process	Individual physicians	Treatment pathway vs single touchpoint	Institution-level decision; ability to track patient outcomes through registries

knowledge, develop a user-based best practice network, and explore innovative partnership approaches, patients and society will not stand to benefit from technological progress and innovation.

f. Treatment process: Regenerative therapies require multiple touchpoints and multiple decision makers through specialized settings for delivery of care and follow-up. Clearly, a high level of decision complexity in terms of care coordination and execution is inherent, along with potential long-term safety monitoring (possibly 15 years). This provides opportunities for integrated care and institution-level decision making and for tracking patients through long-term registries, enabling outcomes-based execution of care.

What do we need to be ready?

In order to facilitate rapid progress and adoption of regenerative technologies to deliver potential benefits to patients, four considerations need to be addressed from a health care systems perspective.

a) Valuation of regenerative therapies: While value frameworks are evolving, current methodologies and pricing benchmarks are not designed to value the benefits of regenerative therapies accurately. First, payers may rely on clinical comparators that may not exist in the context of regenerative therapies. Second, smaller single-arm trials may mean greater dependence on the totality of data (e.g., duration of response, overall survival, response rates, etc.) versus single outcomes. Third, long-term outcomes uncertainty makes benefit/risk assessment at launch difficult for decision makers. Finally, clinical trials cannot capture the total length or magnitude of potential benefits, making real- world evidence more imperative. Current technology-assessment methods may still be fit for purposes of evaluating regenerative therapies but only with special considerations. An "individualized patient valuation" mechanism, with different values per patient or by indication, may be appropriate to account for differential benefits in patients. Balancing uncertainties and potentially substantial patient benefits may require facilitation of alternative partnership approaches for rapid patient access as the evidence matures.

b) Funding and reimbursement needs to be an investment: Regenerative therapies have multiple touch points of care requiring funding the treatment pathway. While the cost of care is mainly front loaded, most payers work with annual funding cycles, which may prevent them from absorbing large one-time impacts on their budgets. Health care budget siloes make it challenging for one part of the system to absorb costs although there could be offsets in another. While long-term benefits may be captured across localities or regions as patients move from one system to another, the original cost still has to be absorbed by one region or local budget. Alternative payment models are a solution to manage these issues, but these models require channels and safeguards to mitigate risks to providers and payers, and there may be secondary implications on other programs (e.g., best price implications for CMS). Special considerations and changes to the current systems must be made to facilitate access to regenerative therapies. Regenerative therapies offer the simplest way to explore indication-based approaches, avoiding the need for extensive administrative burden.

c) Manufacturing and logistics: With regenerative therapies, balancing manufacturing capacity and meeting patient demand are critical. The logistical chain is time sensitive and requires close communication between providers and manufacturers, and contingencies must be in place to manage disruptions in the logistical supply chain. There is an opportunity to reframe and reward care delivery to include a package of services to support optimal care and patient access.

d) Delivery of regenerative therapies: Treatment needs to be delivered in specialized settings (academic medical "centers of excellence") with highly trained clinicians and sophisticated logistical capabilities to organize and deliver care. Patients will be required to travel across state/regional/country borders for care. While these "centers of excellence" are a winning solution for payers (more control) and patients (higher quality treatment and management), this may create an additional funding challenge for patients' out-of-pocket costs. Institution-level decision making and partnership with patients and referring physicians offer a way to simplify the complex decision making and delivery of care.

Conclusions

Regenerative therapies represent a paradigm shift in the development of medicines with the potential to bring significant transformational change to the way we treat diseases. While the potential benefits to health care systems and patients are immense, innovative approaches towards defining value, identifying solutions to mitigate risks to different stakeholders, funding and rewarding innovation, and fundamental systems reforms are needed to enable regenerative therapies to reach patients efficiently. Considering the dire needs of these patients, risk-sharing partnerships between all stakeholders are required to foster innovation. New financing models can be developed to secure the right incentives for different health care system stakeholders. Amortization, pay-for-performance, social impact bonds, and centralized purchasing funds are potential options. The uniqueness of regenerative therapies may allow customized solutions to be explored to facilitate access, respect innovation, and provide better care in a financially sustainable way. In this truly complex valuation and delivery ecosystem, a true partnership between manufacturers, payers, and providers is needed to leverage synergies to bring these much-needed therapies to patients.

References

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Additional information:

The preceding article is based on an issues panel given at the ISPOR 21st Annual International Meeting.

To view Dr. Thomas' presentation, go to: http://www.ispor.org/Event/ReleasedPresentations/2016Washington#issuepanelpresentations