

15 Nov 2016 | Analysis

Curative Regenerative Medicines: Preparing Health Care Systems For The Coming Wave

by Faraz Ali

We may be at the dawn of a new era of curative regenerative therapies, but their inherent nature may create barriers to adoption. The Alliance for Regenerative Medicine frames the opportunities and challenges for the industry, arguing that policy makers must begin to understand the ways that these therapies represent value for money.

- More than 700 companies are working on new gene, cell and tissue engineering therapies that have the potential for profound and durable responses in patients with a diverse array of serious and costly conditions, many of which lack current treatments.
- The health care market is grappling with ways to articulate and assess the value of these potential curative treatments, some of which may be administered only once or a few times.
- There are a number of proposed alternative reimbursement and financing models to address the potential uncertainty and economic disincentives that may be associated with curative therapies.

Emily Whitehead was diagnosed with an aggressive form of cancer called acute lymphoblastic leukemia (ALL) at the tender age of 5 in 2010. She had relapsed twice after chemotherapy and was out of options and near death when she was treated with an experimental chimeric antigen receptor T cell (CAR-T) gene therapy at Children's Hospital of Philadelphia (CHOP) that saved her life. Emily's story was published on the front page of the *New York Times* in December 2012.

Three years later at the *American Society of Hematology Annual Meeting*, pharmaceutical giant [Novartis AG](#) revealed that Emily was not alone. More than 90% of patients with relapsed refractory ALL treated with the same CAR-T therapy – being developed in a large multi-site clinical study including CHOP that is now sponsored by Novartis – had their disease go into complete remission.

Additional companies using similar approaches for other malignancies have reported exciting early results, prompting many to dare speak of a “cure” for cancer. In fact, when US Vice President Joe Biden called for a “moonshot” effort to “end cancer as we know it,” he did so fully aware of the promise of such gene and cell therapies already under development and rapidly approaching the marketplace.

But treatments for cancer are only the tip of the iceberg.

We are at the cusp of a global revolution in medicine. Medical researchers and product developers are now poised to bring forward new gene, cell and tissue engineering therapies that hold out the promise of profound and durable responses – often with just a single treatment – for patients with a diverse array of serious and costly conditions, many of which lack current treatments.

The shared mission of these technologies is to establish – or restore – the healthy functioning of human cells in patients with cellular dysfunction. Some of the new technologies also represent the highest form of personalized medicine, requiring the treatment to be highly tailored and specific to the patient’s genetic background, and often utilizing the patient’s own cells to create the necessary therapies. The term “regenerative medicine” also includes exciting developments in the use of gene editing technologies to replace or correct genetic material with unprecedented precision.

A handful of regenerative medicine products have been approved in various countries around the world; many other new therapies are nearing the market, currently in mid- to late-stage clinical trials. We expect that several will enter the market within the next few years. (*See Exhibit 1.*)

Exhibit 1

| Company/Treatment | Indication | Status |
|--|--|--|
| <i>uniQure NV</i> /Glybera | Lipoprotein lipase deficiency (LPLD), a rare and often fatal metabolism disorder | Approved by the EMA in 2012. First approval of a gene therapy using adeno-associated viruses (AAVs) |
| <i>Amgen Inc.</i> /Imlygic | Melanoma | Approved by the FDA in 2015. First approval of a gene therapy based on oncolytic virus technology |
| <i>Chiesi Farmaceutici SPA</i> / Holoclar | Repair corneas and restore sight in patients with burns to the | Approved by the EMA in 2015. |

| | | |
|---|--|--|
| | eyes | First approval of a tissue engineered medicinal product derived from stem cells |
| <i>GlaxoSmithKline PLC</i> /Strimvelis | Specific form of severe combined immunodeficiency (ADA-SCID) | Approved by the EMA in 2016. First approval of a gene therapy based on <i>ex vivo</i> autologous retrovirus technology |
| <i>Mesoblast Ltd. & JCR Pharmaceuticals Co. Ltd.</i> /TEMCELL | Acute graft-versus-host disease in children and adults | Launched in Japan Feb. 2016 |
| <i>Spark Therapeutics Inc.</i> /SPK-RPE65 | Gene therapy using AAV for a form of inherited blindness called Leber's congenital amaurosis (LCA) | FDA submittal 2016; potential approval 2017 |
| <i>Kite Pharma Inc.</i> /KTE-C19 | CAR-T cell therapy for advanced non-Hodgkin lymphoma | BLA filing early 2017; commercial launch anticipated 2017 |
| Novartis AG /CTL019 | CAR-T technology for relapsed/refractory pediatric ALL | FDA submittal 2016; potential approval 2017 |

Source: Alliance for Regenerative Medicine

These diverse examples are just a glimpse of the depth, breadth and potential of the regenerative medicine industry. ([*Also see "Gene Therapies: Waiting To Emerge From The Bottle"*](#) - Scrip, 6 Sep, 2016.) After decades of work – and some noteworthy early setbacks – the fields of cell therapy, gene therapy, tissue engineering and broader regenerative medicine are progressing through the clinic with great promise. As of mid-2016, we identified more than 700 companies working on regenerative medicines, and 728 clinical trials ongoing for such therapies, with 66 potential therapies already in active Phase III (or equivalent) late-stage clinical trials, almost doubling the count over the previous year. (*See Exhibit 2.*)

Exhibit 2

Gene And Cellular Therapies And Other Regenerative Medicine Products:

CLINICAL TRIALS

728

{ Ph. I: 223
Ph.II: 439
Ph.III:66



+40%

of current clinical trials are in **oncology**

12%

of current clinical trials are in **cardiovascular**

Source: Alliance for Regenerative Medicine

Regenerative medicines represent a wave of innovation coming to the shores of our health care system that is approaching much faster than most realize. With the assistance of groups like the Alliance for Regenerative Medicine (ARM, www.alliancerm.org), policy makers, payers, physicians and patients are beginning to become familiar with the technologies involved and with the opportunities and challenges facing their introduction to the market.

The Sovaldi Effect

One curative therapy outside the regenerative medicine area – *Sovaldi* (sofosbuvir) developed by [Gilead Sciences Inc.](http://www.gilead.com) for hepatitis C – has been in global headlines in recent years. Most of the headlines have been negative and have focused primarily on issues of price, pharmaceutical company profits, health care costs and patient access. Noticeably less media – and political – attention has been devoted to the clinical efficacy of Sovaldi or the fact that as a curative therapy it may also be cost-effective because of the prevention of the costly long-term consequences associated with hepatitis C.

Without debating the merits of the case here, the Sovaldi experience has undoubtedly helped pour fuel on a broader fire raging against biopharmaceutical drug pricing and the growing costs

of health care. In doing so, it may have also unintentionally tainted the optimism and excitement that should be attached to the development of curative therapies, and caused policy makers to fear that the new era of regenerative medicine represents an era of Sovaldi-sized problems.

We are concerned that political rhetoric may turn into broad policy and legislation that may fail to recognize the uniquely high value of curative regenerative medicines and that may instead inadvertently create significant impediments to their funding, development and adoption.

Against this backdrop, it is therefore critical for major stakeholders in the emergence of curative regenerative medicines to engage on the following key issues:

- What lessons can the health care system learn from past experience with other curative therapies such as Sovaldi?
- In what ways will the coming wave of regenerative medicines be different from Sovaldi?
- How should the value of curative therapies be measured and benefits distributed among major stakeholders?
- Do health care systems around the globe need to change their policies to accommodate curative therapies and if so, how?
- How can innovators in the biopharmaceutical industry be better partners to the stakeholders involved?

This article – as well as planned subsequent papers – is an early effort of ARM to help frame the opportunities and the challenges of potentially curative gene and cell therapies and to spark a conversation about specific policy proposals that will benefit patients, the health care system and ultimately, society.

What Is a Pound of Cure Worth?

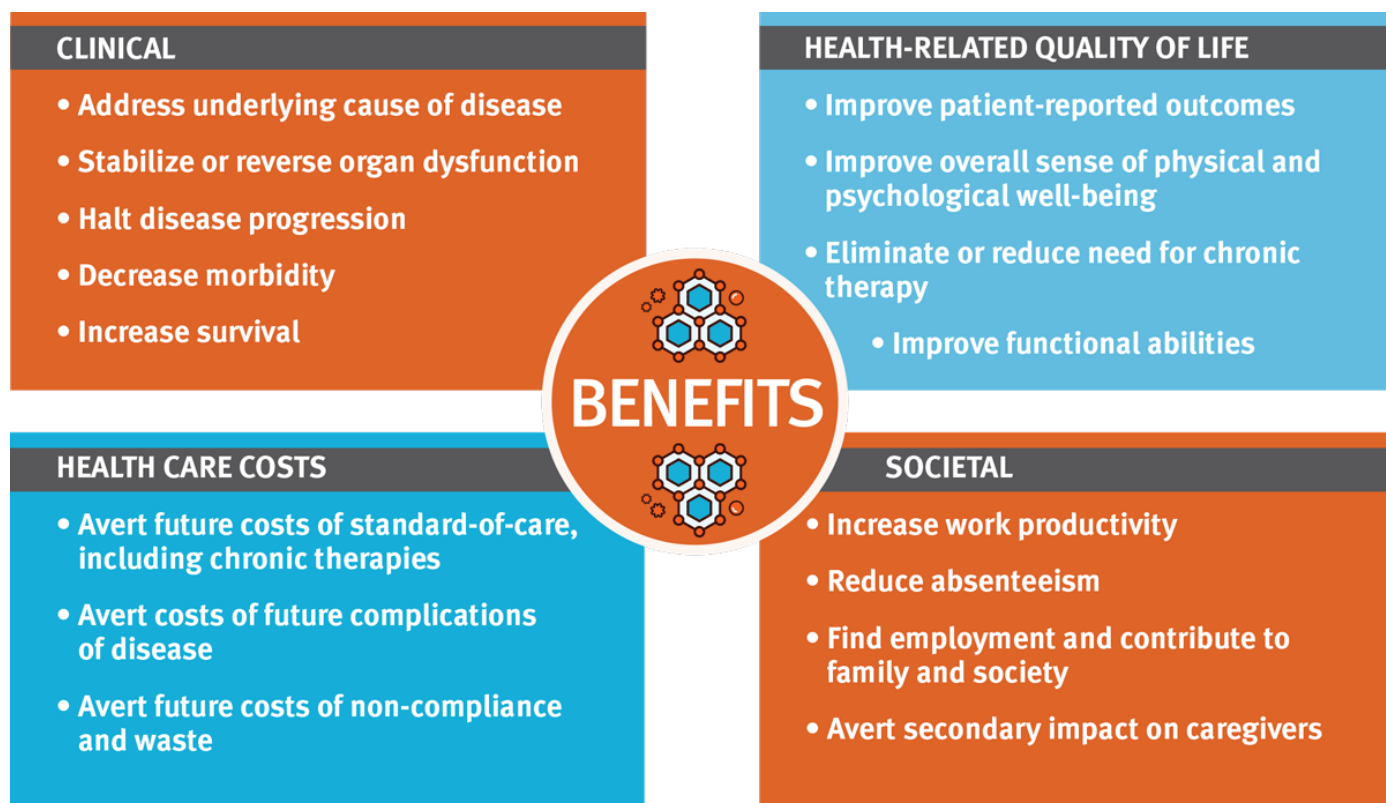
Many stakeholders will intuitively appreciate the uniquely high value of potentially curative therapies. However, any detailed discussion about the value of biopharmaceutical innovation is fraught with challenges. This is true for so-called conventional therapies that are administered – and paid for – chronically over time (potentially over the lifetime of a patient). It is also equally if not more challenging when trying to articulate the value of potential curative therapies that may be administered only once or a few times.

Part of what makes such a discussion challenging is that there is no universally accepted or standardized methodology to assess the value of biopharmaceutical innovation across advanced economies with nationalized single-payer health care systems, or even across public and private payers within fragmented multi-payer health care systems like the US.

There have been commendable recent efforts by various groups to attempt to develop new frameworks to evaluate the value of biopharmaceutical products. Such efforts include the American Society of Clinical Oncology (ASCO) Value Framework, the Institute for Clinical and Economic Review (ICER) Value Assessment Framework and the Memorial Sloan Kettering Cancer Center's *DrugAbacus* project, as well as numerous tools developed by for-profit firms. (*Also see "Drug Pricing: With "Value" Debate In Full Swing, ICER's Influence Grows"* - In Vivo, 2 Nov, 2016.) However, even these attempts have been criticized and are at odds with each other, and none of them formally address unique attributes of potentially curative therapies that should contribute to an appropriate assessment of their value.

We therefore lack a common vocabulary even to begin a conversation about the value of curative therapies. And yet, it is critically important for policy makers to begin to understand all the ways in which potentially curative regenerative medicine therapies may represent value for money. We introduce here a simple framework with four distinct categories to describe the potential value of regenerative medicines. (See *Exhibit 3*.)

Exhibit 3



Source: Alliance for Regenerative Medicine

1. **Clinical Impact:** In part because of the nature of the technologies involved, such therapies

may have a transformative impact on the underlying diseases at many levels. The impact of curative regenerative medicines may be felt in different ways:

- **Quality of the effect.** Conventional therapies often manage the symptoms of the disease, whereas regenerative medicines have unique mechanisms of action that may target the underlying cause of the disease. For example, many gene therapies directly target the underlying genetic defect leading to the disease in a manner that other therapeutic modalities cannot, enabling treatment of previously untreatable conditions.
 - **Magnitude of the effect.** As a result of their mechanism of action, curative therapies may not only halt but even reverse disease manifestations, that could significantly decrease disease morbidity and extend lifespan.
 - **Duration of the effect.** Conventional therapies often need to be administered chronically to be effective. Conversely, curative therapies often aim to treat the patient with a single intervention or a series of interventions with long-term and even potentially lifetime impact (a phenomenon sometimes referred to as “one and done”).
1. **Quality of Life:** Increasingly important to patients, physicians and payers is not just extension of life, but also improvement in objective health-related quality of life (HR-QOL) measures and other patient-reported outcomes (PROs). The impact of curative regenerative medicines may be felt in different ways:
 - If curative therapies live up to the expectations for high clinical impact as described earlier, commensurate improvements in patient QOL are to be expected, as has been already demonstrated in other curative settings (e.g., stem cell transplantation).
 - Patient QOL may benefit from the ability to discontinue chronically administered therapies that are often inconvenient and may require frequent travel to specialist locations.
 - Improvements in QOL may not be restricted to patients, but may also extend to other caregivers involved, depending on the disease.
 1. **Health Care System Cost Savings:** Curative therapies have the potential to offset significant costs to the health care system. The impact of curative regenerative medicines may be felt in different ways:
 - Averting the costs associated with the downstream complications of disease progression and complications including hospitalizations, especially for diseases without existing therapies.
 - Eliminating or replacing the direct costs of existing chronically administered therapies.
 - Eliminating the downstream costs associated with the side effects of existing chronically administered therapies.

- Eliminating the significant costs of non-compliance with conventional therapies, as well as the costs of programs to encourage compliance.

Based on ARM analysis, the current pipeline of regenerative medicines as described earlier are indeed addressing some of the costliest disease areas and conditions currently driving US health care costs. (See *Exhibit 4*.)

1. *Societal Benefits* : Societal benefits are often underappreciated in the evaluation of the value of new therapies. The impact of curative therapies may be felt in different ways:
 - Increased productivity and reduced workplace absenteeism for patients.
 - Employment for patients who previously have not been able to work.
 - Reduced burden on caregivers of patients.

Exhibit 4

| Disease Area | Estimated Annual Cost of Disease Area to US Economy | Selection of Indications Targeted by Cell and Gene Therapies |
|------------------------------|---|---|
| Musculoskeletal | >\$874bn | Wound care, neuropathic pain, stress urinary incontinence, osteoarthritis, cartilage defects, spinal disorders, avascular necrosis, bone fracture and other rare genetic muscle disorders |
| Cardiovascular | >\$316bn | Congestive heart failure, ischemic stroke, critical limb ischemia, ischemic heart disease, peripheral artery disease |
| Central Nervous System (CNS) | >\$245bn | Spinal cord injury, ALD, multiple sclerosis, Friedreich's ataxia, neuro-muscular disorders and various neurological conditions including Alzheimer's disease, Parkinson's disease, Huntington's disease, etc. |
| Ophthalmological | >\$139bn | Inherited eye diseases, blindness, corneal transplantation |
| Oncology | >\$124bn | Renal cell carcinoma, |

| | | |
|---------------------------|--------|--|
| | | mesothelioma, prostate cancer, head and neck cancer, nasopharyngeal cancer, non-small cell lung cancer, ovarian cancer, leukemia, lymphoma, skin cancer, brain cancer, hematologic malignancy, graft vs. host disease, cytomegalovirus infection due to malignancy |
| Inherited Blood Disorders | >\$7bn | Sickle cell disease, hemophilia A & B, beta thalassemia |

Source: Alliance for Regenerative Medicine

While the broad categories of value described are not unique to regenerative medicines, what is unique is the incremental benefit expected over and above what can be achieved with conventional therapies across a patient's lifetime, and the potential ability to generate such long-term benefit with a single or a limited number of applications of therapy.

There is a slowly growing but encouraging body of evidence that some payers and health technology assessment bodies globally are beginning to recognize the potential value of regenerative medicine, and the need for change:

- Private and public payers interviewed for a study commissioned by the California Institute of Regenerative Medicine (CIRM) in 2009 acknowledged that potentially curative therapies would be paid for in the near term with premium increases, *"although the premiums would be reduced if the curative treatments generate long-term cost savings."*
- In the UK, the field of regenerative medicine was elevated to one of "Eight Great Technologies" that will propel future growth. As part of an assessment of the impact of regenerative medicines in 2013, the UK government also expressed the need *"to devise suitable models that give appropriate consideration to the long-term savings sometimes offered by high up-front cost [regenerative medicine] treatments."*
- The UK's National Institute for Clinical Excellence (NICE) health technology assessment (HTA) organization published in 2016 a formal review of its models as applied to potentially curative cell or gene therapies, and determined that *"where there is a combination of great uncertainty but potentially very substantial patient benefits, innovative payment methodologies need to be developed to manage and share risk to facilitate timely patient access while the evidence is immature."*
- A [2016 publication](#) by Eric Faulkner et al. provides summaries of surveys of US managed care

payers and physicians, illustrating that roughly 30% think regenerative medicines will be transformative and about 60% felt that a regenerative medicine therapy that permanently cured a disease could merit a significant (>50%) increase in payment over existing alternatives.

Although these are encouraging early signals, recent history suggests that stakeholders may not automatically understand all the sources of value associated with biopharmaceutical products, and that they tend to focus on price, cost and budget impact. It is therefore critical that regenerative medicine innovators engage in the public discourse on this topic and help inform payers and policy makers.

Even If You Build It, They May Not Come

Acknowledging the potential value of curative regenerative medicines is an important first step. However, it is equally important to acknowledge the potential challenges such therapies may pose to the current health care system, which may in turn introduce undesirable barriers to their adoption to the detriment of patients in need.

A preliminary assessment by ARM has identified several potential challenges that fall under four categories:

Uncertainty

- While gene and cell therapies have been under development for three decades and have been studied in thousands of patients, we must acknowledge that their successful clinical application is still a fairly recent phenomenon. Regulatory approvals are sparse and real-world experience is limited.
- For some diseases, it may be decades before we know if the clinical impact has been as profound and as durable as hoped for at the time of regulatory approval.
- Stakeholders therefore may feel they have no guarantee the products will live up to their promise, which may encourage a “wait and see” approach to adoption, to the detriment of patients.

Economic Disincentives

- There is an inherent disconnect between the timing of payment for potentially one-time curative medicines and the savings to the health care system that may result, but that may only be realized over decades after the therapy is administered. Current insurance coverage policies, mechanisms and economics are not designed to consider the benefits of particular interventions over a long period of time. Most health coverage policies address the costs of

patients on an annual basis and are not structured to take into account offsetting benefits of specific therapies that are realized outside of this annual window. This concern is exacerbated in more fragmented health care systems, as is the case in the US, where patients move around between plans over time and may only be with any given plan on average for two to three years.

- Some regenerative medicines may represent cures for serious and progressive diseases such as congestive heart failure, Alzheimer's disease or diabetes that affect large populations waiting for better alternatives. Approval of such therapies may create extreme near-term budget impact issues for public and private payers driven by high and acute demand that cannot be covered by temporary, incremental premium increases.
- The US health care system is already shifting a higher burden of cost-sharing onto patients in the form of higher deductibles and co-pays for their therapies. Patient co-pays that are set as a percentage of potentially high one-time price may be prohibitively expensive for patients seeking curative therapies.

Product Complexity

- Some regenerative medicines – particularly *ex vivo* autologous therapies that involve the extraction and manipulation of patients' own cells – are highly complex and involve different procedures separated over time, care settings and even geography, which may challenge health care systems that are set up around more conventional therapies.
- New technologies may cut across traditional boundaries. Something that was previously not considered a product or device (e.g., a patient's own cells) may become so with specific manipulation. There may not be adequate frameworks to value and reimburse such therapies.
- Payment codes may simply not exist to represent payment for the full spectrum of product, materials and processes used to deliver a cell or gene therapy, and creating and introducing new codes may be more difficult than for more conventional medicines.

Reimbursement Paradigms

- Health care systems are generally not configured to pay for new products in a manner other than a price per unit (vial, treatment, procedure), exacerbating the divergence in timing of product cost and benefits generated by the product for one-time therapies.
- There may be legal or statutory barriers – such as specific coverage or payment rules set by CMS – that pose reimbursement challenges for regenerative medicine products.

While no single barrier on its own may be problematic, the totality of these considerations may create challenges for stakeholders and policy makers, impeding coverage, coding, valuation,

reimbursement and, ultimately, adoption of regenerative medicines.

Toward a New Paradigm

There is a growing crescendo of proposed solutions to address some of the potential barriers associated with curative regenerative medicines. (*See Exhibit 5.*) Based on our early assessment, most proposals focus on alternative reimbursement and/or financing models, and are intended to address the potential uncertainty and economic disincentives that may be associated with curative therapies.

- Risk-sharing agreements: An agreement between payers and innovators to ensure that payers' exposure is limited or eliminated if a patient fails to respond to an expensive regenerative medicine.
- Value-based contracting: Also known as “pay-for-performance,” an agreement between payers and innovators that ties the amount of payment provided to the degree of value realized (clinical, economic or other).
- Annuities: An agreement between the innovator and the payer to spread payments over time to reduce the cost intensity of potentially expensive one-and-done curative therapies. This could be combined with risk-sharing agreements or value-based contracting as described to also include a performance component.
- Re-insurance: A financial arrangement that limits insurers exposure to the risk of an expected volume of high-cost procedures. Re-insurance was successfully introduced and adopted to address high-cost solid organ and stem cell transplantation procedures.
- Payer financing: Lease-like financing provided by makers of expensive medical imaging equipment to hospitals. Financial intermediaries could provide similar loans to payers to address situations where there is an issue of near-term but temporary budget affordability in response to the approval of a new cure.
- Consumer health care loans: Mortgage-like financing provided by financial intermediaries that allow consumers to take out loans to finance large co-payments or possibly to pay outright for cures in situations where there is inadequate coverage.
- Co-payment reform: Reconsideration of coverage for out-of-pocket expenses incurred by patients who have to travel to centers of excellence for highly specialized curative therapies and that may involve long stays for families near such centers.

Exhibit 5

Alternative Reimbursement Models

Primarily intended
to address uncertainty

**Cost Sharing
Agreements**

**Risk Sharing
Agreements**

**Value-Based
Payments**

**Cure Pools
Reinsurance
License Fee
Annuities**

Alternative Financing Models

Primarily intended
to address affordability

Supplier Credit
(for payers)

Bonds
(for governments)

**Consumer Health
Care Loans**
(for individuals)

Source: Alliance for Regenerative Medicine

There has been a tendency to jump to a particular solution from this list of proposals as the silver bullet that will address all or most of the potential barriers associated with regenerative medicines. Pay-for-performance and annuity models appear to generate particularly high levels of support. We believe that it is still too early – and ultimately may not be helpful – to try to pick any one proposed solution. The health care system may need to be prepared to adopt multiple solutions that are tailored to the specific attributes of the disease and regenerative medicines involved, and to the preferences of the local health care system. In addition, what is still missing is a comprehensive inventory of such solutions, supported by rigorous analysis, modeling and weighing of the pros and cons from the perspective of different stakeholders. This work is critical, and has been prioritized by ARM and others.

Reason For Hope

Although most discussion of curative therapies today focuses on the experience with Sovaldi, less attention is paid to the fact that the global health care system has already been working with curative therapies for more than three decades in the form of solid organ and stem cell transplantation procedures. These procedures were – and are still today – among the most expensive medical interventions (a Milliman research report from 2014 estimated average billed charges for heart transplants and allogeneic stem cell transplants at around \$1 million per procedure). At the time of their introduction, there was a considerable amount of technological and clinical uncertainty related to utilization and long-term outcomes. There was also concern then about the ability of the health care system to absorb the costs of these procedures. Re-insurance was successfully introduced as an alternative model to address issues related to uncertainty and affordability. This pairing of medical and financial innovation has allowed the field of transplantation to flourish over the decades and to benefit millions of patients across the globe facing life-threatening conditions. There are many lessons to be learned from this experience that may have parallel applications to the coming wave of regenerative medicines.

Conclusions

We are on the brink of a new era in medicine. Regenerative medicine, including cell and gene therapy and other similar advanced therapy products have already begun to demonstrate the potential to deliver on their promise to treat or cure a range of diseases. The pipeline of such therapies is robust. The potential social, clinical and economic value of these treatments is significant and may require a serious rethink of the current focus on costs and price. It is critical to ensure successful development

of these products by creating a reimbursement environment that rewards innovation when value is demonstrated or can be reasonably anticipated.

Getting there will not be straightforward. There are complex issues to be discussed, barriers to be confronted, solutions to be considered and even some societal choices to be made. This will likely require a uniquely broad coalition of diverse stakeholders working together proactively and productively years in advance of this wave of innovation.

This is the first of a series of papers presented by ARM and its member organizations in the US and EU that are intended to support the necessary dialogue. (See sidebar, "About ARM.") Subsequent reports will describe the potential reimbursement barriers as well as assess the potential solutions to the challenges described in this article with far more rigor. This work will

About ARM

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The Alliance for Regenerative Medicine is partnering with representatives from other organizations engaged in multi-stakeholder initiatives to prepare the health care system for curative and/or regenerative medicines.

[Read the full article here](#)

culminate in specific policy proposals and recommendations for legislative change that may be necessary to unlock the full potential of curative regenerative medicines. Society – and innumerable patients like Emily Whitehead in need of life-saving regenerative medicines – will judge us on our success.

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