

# Regenerative Medicine Primer

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For editorial comment, see page 645.

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## Abstract

The pandemic of chronic diseases, compounded by the scarcity of usable donor organs, mandates radical innovation to address the growing unmet needs of individuals and populations. Beyond life-extending measures that are often the last available option, regenerative strategies offer transformative solutions in treating degenerative conditions. By leveraging newfound knowledge of the intimate processes fundamental to organogenesis and healing, the emerging regenerative armamentarium aims to boost the aptitude of human tissues for self-renewal. Regenerative technologies strive to promote, augment, and reestablish native repair processes, restituting organ structure and function. Multimodal regenerative approaches incorporate transplant of healthy tissues into damaged environments, prompt the body to enact a regenerative response in damaged tissues, and use tissue engineering to manufacture new tissue. Stem cells and their products have a unique aptitude to form specialized tissues and promote repair signaling, providing active ingredients of regenerative regimens. Concomitantly, advances in materials science and biotechnology have unlocked additional prospects for growing tissue grafts and engineering organs. Translation of regenerative principles into practice is feasible and safe in the clinical setting. Regenerative medicine and surgery are, thus, poised to transit from proof-of-principle studies toward clinical validation and, ultimately, standardization, paving the way for next-generation individualized management algorithms.

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*There's no finish line in the work of science ... the urgent work of giving substance to hope, of seeking a day when words like 'terminal' and 'incurable' are potentially retired from our vocabulary....*

President Barack Obama<sup>1</sup>

The authoritative outlook “2020: A New Vision,” presented by the US Department of Health and Human Services, places regenerative medicine at the vanguard of 21st century health care.<sup>2</sup> Recognized as the most promising core component of forthcoming

medical and surgical practice, regenerative medicine is considered transformative in scope, poised to add value to and extend the reach of current models of care. By exploiting a growing comprehension of the innate mechanisms of repair, the emergent model of regenerative health care encompasses the discovery, development, and delivery of next-generation management algorithms targeted to address the root cause of disease and to offer the prospect of curative solutions addressing patient needs.<sup>3</sup>

Patient-centric regenerative paradigms aspire to restore the normal structure and function of damaged, dysfunctional, or diseased tissues.<sup>4</sup> Implemented across medical and surgical specialties, and propelled by the success in treating previously incurable disorders such as leukemia, lymphoma, or myeloma, radical regenerative applications are definitive in purpose. Beyond the promise of providing unparalleled health benefits, the disruptive innovation embodied in regenerative technologies offers new approaches to tackle the escalation in inefficient treatments and rising health care costs. To ensure early and proper adoption, the rigor of comparative effectiveness analytics is needed to empower the incorporation of regenerative strategies into mainstream general practices.<sup>5</sup>

### UNMET NEEDS IN THE 21st CENTURY: CHRONIC DISEASE IN AN AGING POPULATION

The World Health Organization recognizes the pandemic of noncommunicable chronic diseases as the leading cause of morbidity and mortality.<sup>6</sup> Globally, chronic diseases are responsible for nearly 40 million deaths per year.<sup>7</sup> Mortality rates for noncommunicable conditions now surpass those associated with communicable, maternal, perinatal, and nutritional conditions combined. By 2020, noncommunicable diseases will account for 7 of every 10 deaths in the world, as they already do in the United States today.<sup>8</sup> By 2030, the 4 most prevalent chronic conditions, spanning the spectrum of cardiovascular diseases, cancer, diabetes, and respiratory diseases, are predicted to be collectively responsible for three-quarters of all worldwide deaths.<sup>9</sup> A critical determinant of such rampant trends is population aging, shaping the evolving global pathodemographic characteristics.

In 2012, there were more than 800 million persons 60 years or older.<sup>10</sup> By 2050, the

number of older persons will reach 2 billion, accounting for a quarter of the global population. By mid-century, for the first time in human history, there will be more older people than children. In part, these megatrends reflect medical progress and the robust success in combating life-threatening acute conditions, injuries, and congenital anomalies. Pertinently, the United Nations and associated organizations have proclaimed increased longevity a triumph of humanity, acknowledging that the longevity dividend mandates that people age in good health.<sup>10</sup>

Even with increased emphasis on health promotion and disease prevention, the overwhelming burden in older persons comes from chronic, degenerative conditions.<sup>11</sup> Advanced age is a major risk factor for chronic diseases and an independent predictor of overall morbidity and disability.<sup>12</sup> Ischemic heart disease, stroke, and chronic lung disease exemplify the main causes of mortality. Visual and hearing impairment, dementia, and osteoarthritis are recognized causes of disability. Worldwide, half of the people 60 years and older have disabilities, a consequence of accumulated health risks across a lifespan of chronic illness. Repeated hospitalizations and premature death, prevalent in this ever-growing population, impose a major unmet need associated with the inability of current, largely palliative therapies to address tissue destruction and organ failure.

With the growth of the elderly population and the prevalence of age-related disabilities, the need to decode the underlying pathobiology (to understand the mechanisms responsible for disease susceptibility and poor outcome) and the aptitude to develop meaningful strategies that limit organ dysfunction and reverse tissue degeneration across the lifespan have never been more urgent.<sup>13</sup> Regenerative medicine, with the potential to repair damaged tissues and the prospect of assembling replacement tissues and whole organs, offers a new frontier in the promotion of longitudinal wellness and the advancement of health care for individuals and populations while reducing the overall expenditure required for chronic disease management.

### REGENERATIVE MEDICINE PROPOSITION

Regenerative medicine draws from the achievements of transplant medicine, which has—along with the development of implantable

medical devices—fundamentally altered the management of chronic conditions and end-of-life situations. Data from the Organ Procurement and Transplantation Network indicate, however, that 117,024 patients were on the national transplant waiting list as of February 10, 2013.<sup>14</sup> Patients fortunate enough to receive a donor organ are at risk for organ rejection and endure lifelong immunosuppressive therapy and its associated morbidity. The scarcity of usable donor organs, compounded by considerable immunosuppression toxicity, imposes the necessity of developing alternatives to meet the demands of end-stage organ failure.<sup>15,16</sup> Equally, few therapeutic options exist today to address severe injuries or congenital absence of complex tissues. The regenerative medicine proposition offers potential solutions. Reinstating the physical and functional integrity of a damaged organ is central in realizing the primary objective of regenerative medicine and surgery aimed at delaying or preventing transplant in patients with acquired or congenital diseases.

Regenerative paradigms are based on the realization that natural, self-renewing processes, collectively referred to as tissue rejuvenation, are innate to organs in the body. Individual genetic variances and environmental influences all contribute to the inherent regenerative potential.<sup>17</sup> Contributing to organ renewal is the continuous division of resident stem cells present in tissues and the migration of stem cells from organs rich in progenitor pools, such as bone marrow, leading to integration in target tissues, acquisition of organotypic signatures, and replenishment of niche structures.<sup>18</sup> Designed to maintain tissue homeostasis and particularly prominent in the young, self-repair mechanisms are often insufficient to salvage a failing organ or disrupt disease progression. Although an endogenous renewal reserve persists throughout adulthood, self-repair efficiency across organ systems is affected by patient age and by comorbidities and concomitant therapies. Estimates extrapolated from the human regenerative map project indicate, for example, that approximately 50% of the heart mass is renewed by age 50 years, with the cardiomyocyte turnover rate slowing with age.<sup>19</sup> Moreover, regenerative competence is regulated by the microenvironment, with hypoxia-inducing factors established as

regulators of stemness. Augmentation of innate regenerative activity is a compelling strategy to achieve therapeutic repair. To this end, activation of endogenous means or introduction of exogenous means to boost reparative mechanisms in a permissive organ are considered key to ameliorate the burden of disease.

Advances in cell, tissue, and organ engineering have led to a variety of regenerative applications in use or having been tested.<sup>20</sup> These advances have come through an improved understanding of developmental biology and embryogenesis and can be applied in the form of stem cell–based products and noncellular preparations of growth factors/cytokines, extracellular matrixes, or small molecules that target regenerative pathways.<sup>21</sup> The capacity of an organ to rejuvenate plausibly reflects the density of operative stem cells, a postnatal remnant of the progenitor pool involved in prenatal development, suggesting that innate rejuvenation represents a revival of atavistic processes inherent to embryo development.<sup>22</sup> There is a presumed overlap between prenatal developmental processes and postnatal regenerative mechanisms, although distinctive pathways may be required for a comprehensive regenerative response. Advancing the knowledge of mechanisms that govern tissue rejuvenation in health and in disease will be decisive in designing the most suitable regenerative therapeutics. Collectively, strategies that promote, augment, and reestablish natural repair are, thus, at the core of translating regenerative principles into practice-conducive protocols.<sup>23</sup>

## STEM CELL AND TISSUE ENGINEERING TOOLKITS

The overarching scope of regenerative therapy is to halt or reverse the progression of disease. Early in disease, the primary therapeutic goal is to salvage the jeopardized organ and prevent remodeling.<sup>24</sup> At later stages of organ dysfunction, the aim is to restore parenchymal integrity, reverse maladaptive remodeling, and ensure improved function.<sup>25</sup> Evolution of the molecular substrate during disease progression requires complementary regenerative strategies capable of preventing progression and treating overt organ failure.

Stem cells function as authentic tissue progenitors and as promoters of tissue repair processes.<sup>26</sup> Initially it was postulated that

transplanted stem cells directly replace nonviable tissue, serving as the sole building blocks for new tissue formation. Recent iterations of the regenerative paradigm suggest a more indirect model of repair whereby interactions between delivered stem cells and the injured/diseased tissue ensure reparative signaling, boosting the regenerative response and promoting endogenous healing.<sup>27</sup> Modern repair models include activation of endogenous progenitor cells, stimulation of cell division, and modification of the tissue niche as contributors to the regenerative outcome. The past decade has realized translation of stem cell–based technology beyond initial indications in hematologic practice to formulate an emergent experimental and clinical experience.<sup>28</sup>

Multiple regenerative platforms that rely on either natural or bioengineered stem cell types, self-supplied (autologous) or donated (allogeneic), have been instituted across specialties. Converting stem cells into functional tissues requires a synchronized sequence of cell fate decisions in a typically heterogeneous mixture of progenitor cells with propensity for diverse lineage specification. Beyond evolutionarily conserved properties encoded in core genetic components, regulatory epigenetic mechanisms and microenvironmental influences refine organogenesis, ultimately defining the structure and function of the resulting organ system.

### NATURAL STEM CELLS

Considered the quintessential stem cell archetype, embryonic stem cells are obtained from embryos that are the product of *in vitro* fertilization.<sup>29</sup> These cells are pluripotent, denoting that they can differentiate into any adult tissue.<sup>30</sup> Accordingly, embryonic stem cells are suitable in deriving tissues that are hard to obtain, such as retinal pigment epithelial cells lost in macular degeneration. Of note, clinical trials have, indeed, been initiated in patients with Stargardt macular dystrophy and dry age-related macular degeneration—the leading cause of blindness in the developed world—to ascertain the safety and tolerability of subretinal transplant of the human embryonic stem cell–derived retinal pigment epithelium.<sup>31</sup> Early reports indicate potential promise because transplant has not been associated with hyperproliferation, tumorigenicity, ectopic tissue formation, or rejection. The eventual goal is to assess the likelihood of

photoreceptor and central visual rescue. Other clinical applications are being considered on the basis of the use of embryonic stem cells and their derivatives to capitalize on the robustness of the repair aptitude documented in preclinical studies.<sup>32</sup>

Perinatal stem cells are derived from umbilical cord blood and are considered multipotent, ie, they can differentiate into many but not all tissue types. As a rich source of primitive hematopoietic stem cells, umbilical cord blood harbors a strong regenerative potential, initially found in stem cell therapy protocols for hematologic disorders.<sup>33</sup> The US Food and Drug Administration has, in fact, approved the first licensed umbilical cord blood stem cell therapy product indicated for use in patients with hematopoietic disorders.<sup>34</sup> A growing number of clinical trials are exploring the usefulness of umbilical cord blood stem cell therapy in non-hematologic diseases.<sup>35</sup> In particular, umbilical cord blood stem cell therapy is being considered in the treatment of inborn metabolic disorders, such as mucopolysaccharide storage disorders, lysosomal storage disorders, and peroxisomal disorder X-linked adrenoleukodystrophy. Although the mechanism(s) of benefit remain(s) uncertain, the observed clinical amelioration in the setting of a multisystem disorder is best documented in the management of Hurler syndrome (also known as mucopolysaccharidosis type I or gargoylism), in which the principle of enzyme delivery by cross-correction to enzyme-deficient host cells is believed to be essential.<sup>36</sup> Compared with embryonic stem cells, umbilical cord blood offers simple procurement that carries no risk and generates limited ethical concerns. In response to the recognized potential of umbilical cord blood stem cell–based therapy and because blood that remains in the placenta after birth is readily collectable, cord blood banks have been increasingly established, although the role of public and private facilities has triggered an ongoing debate.<sup>37,38</sup>

Adult stem cells are clustered in many tissues of the body, including the bone marrow, adipose tissue, and circulating blood.<sup>39</sup> Unlike embryonic stem cells, adult stem cells are considered multipotent, oligopotent, or unipotent because their differentiation potential is more restricted.<sup>40</sup> Clinical trials using adult stem cells have established that this approach

is safe and practical. Indeed, this class of stem cells is best established in clinical practice and is most commonly used for treating lymphoma, leukemia, or autoimmune diseases that require cytotoxic treatments followed by rescue of the hematopoietic lineages and immune system.<sup>41-43</sup> Beyond hematopoietic stem cells that give rise to myeloid and lymphoid lineages, mesenchymal cells, which are also derived from various adult sources, including the bone marrow or adipose tissue, are favored in nonhematologic applications because they are widely accessible and exhibit a recognized differentiation propensity, attractive growth characteristics, and an encouraging safety and efficacy record.<sup>44,45</sup> Notable advances have been made in the study of mesenchymal stem cell differentiation into adipocytes, osteocytes, and chondrocytes. The commitment and differentiation of a mesenchymal stem cell into a specific mature cell type involves the activity of various transcriptional factors, cytokines, growth factors, and components of the extracellular matrix.<sup>46</sup> Homing of mesenchymal stem cells from endogenous or exogenous sources toward a tissue niche implicates migration and incorporation into the microenvironment of the damaged or inflammation site. Mesenchymal stem cells possess potent reparative properties linked to the secretion of paracrine-acting angiogenic, trophic, anti-inflammatory, and immunomodulatory factors and are responsive to the crosstalk with injured tissue and microenvironment.<sup>47</sup> Accordingly, mesenchymal stem cell-based therapies are evaluated in a spectrum of ischemic, inflammatory, and immunologic disorders, specifically for the treatment of graft vs host disease, inflammatory disorders (eg, Crohn disease), musculoskeletal disorders (eg, osteogenesis imperfecta, nonunion fractures, and osteoarthritis), cardiovascular diseases (eg, acute myocardial infarction, ischemic cardiomyopathy, dilated cardiomyopathy, critical limb ischemia, and ischemic stroke), neurologic diseases (eg, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, and multiple system atrophy), liver disorders (eg, cirrhosis), and diabetes (types 1 and 2).<sup>48-53</sup> Building on initial evidence that some patients benefit from mesenchymal stem cell-based therapies, efforts to establish and maintain registries of stem cell-based therapies may prove useful in deciphering the determinants of therapeutic benefit and informing future practices.

Standardization of procedures, including patient selection, is paramount in the quest for optimal outcome. One such strategy is insertion of a lineage orientation step to generate tissue-specified progenitors for guided organotypic regeneration, as recently implemented in clinical trial protocols for optimized heart repair.<sup>54,55</sup>

### BIOENGINEERED STEM CELLS

Complementing the portfolio of native stem cells, regenerative technology also offers bioengineered stem cell counterparts. The differentiation journey from a stem cell to any specialized cell type of the body has been considered unidirectional, yet with the rollout of nuclear reprogramming methods, it is now possible to reverse engineer the biological clock.<sup>56-58</sup> To this end, a handful of stemness genes are required and sufficient to transform a regular somatic cell back into a primordial embryoniclike state.<sup>56-58</sup> Across age groups and underlying pathologic disorders, any somatic cell, such as an adult fibroblast obtained from a dermal biopsy, can be reset to become an induced pluripotent stem (iPS) cell. In turn, iPS cells acquire genuine traits of pluripotent stem cells and the ability to differentiate into all tissue types, offering a renewable source of new tissues derived from the patient's own cell pool.<sup>59</sup> Plasticity in energy metabolism contributes to the propensity of iPS cells to adapt to the divergent demands of self-renewal and lineage specification.<sup>60,61</sup> By eliminating, at least in principle, issues of donor shortage and rejection, the embryo-independent derivation of iPS cells evades traditional bioethical and societal concerns associated with embryonic stem cell use.<sup>62</sup> Accordingly, iPS cells have become a privileged source of progenitor derivation, tissue-specific differentiation, and repair in preclinical studies.<sup>63</sup> Moreover, a hypersensitive apoptotic response to DNA damage has recently been exploited to reduce the risk of dysregulated growth and augment the safety of bioengineered progenitors.<sup>64</sup> Clinical translation of iPS technology will be contingent on securing reprogramming fidelity to ensure normal genetic/epigenetic status and defined immunotolerance for safe transplant.<sup>65</sup> A more immediate application lies in the exploitation of cellular models of disease matched to individual patients.<sup>66,67</sup> Through derivation of patient-specific iPS cells, followed by directed

tissue differentiation, a variety of pathologic conditions have been recapitulated.<sup>68,69</sup> These conditions include a series of neurodegenerative diseases (eg, amyotrophic lateral sclerosis, Alzheimer disease, Huntington disease, Parkinson disease, Down syndrome, spinal muscular atrophy, and familial dysautonomia) and hematopoietic disorders (eg, sickle cell anemia and Fanconi anemia), metabolic conditions (eg, diabetes, progressive familial hereditary cholestasis,  $\alpha_1$ -antitrypsin deficiency, familial hypercholesterolemia, and glycogen storage disease type 1a), cardiovascular disorders (eg, LEOPARD syndrome and long QT syndrome), and others (eg, cystic fibrosis, Duchenne muscular dystrophy, and dyskeratosis congenital). These unparalleled “disease-in-a-dish” diagnostic tools enable patient-specific exploration of underlying disease mechanisms, identification of therapeutic targets, examination of individual response to intervention, and screening for drug efficacy/toxicity, advancing the principles of regenerative theranostics into practice.<sup>70,71</sup>

### REGENERATIVE MATERIAL SCIENCES

Matching advances in cell and developmental biology, recent progress in materials science has unlocked additional prospects for regenerative applications.<sup>72-74</sup> Matrices produced from natural or synthetic sources provide suitable platforms for growing tissue grafts and engineering organs.<sup>75-77</sup> Particularly promising are preclinical and clinical studies that reported the feasibility in decellularizing organs to extract the extracellular matrix backbone.<sup>78-80</sup> To this end, physicochemical and enzymatic methods are used for removal of original cell populations while limiting alterations in the architecture and composition of the native matrix, including the critical maintenance of vascular and lymphatic networks.<sup>81</sup> Repopulation of the heart or lung matrix has been documented as a viable strategy for organ regeneration.<sup>82,83</sup> A decellularized 3-dimensional scaffold provides an inductive support system for progenitor cells to engraft and recreate the structure and function of a desired organ. The matrix serves as a bioactive template around which the recipient rebuilds functional tissue through exogenous provision or recruitment of endogenous replacement cells.<sup>84</sup> The appropriate spatial organization of cells and their maturation in a scaffold is facilitated by

the nurturing environment of the body and is promoted with the use of an ex vivo bioreactor-conditioning step. Beyond the original ex vivo tissue engineering concept, there has been an increased interest in developing in vivo counterparts whereby the human native site serves as an in situ microniche that can be further boosted by permissive and recruiting impulses for maximized outcome.<sup>85</sup> To complete the healing process and boost site-specific regeneration, local or systemic pharmacologic interventions are incorporated to optimize the integrity of tissue-engineered grafts. Although scientific and ethical challenges remain, successful proof-of-principle studies for organs such as the liver, heart, and lung as well as the trachea, esophagus, and skeletal muscle have revealed the substantial promise of such reconstruction strategies that leverage the decellularization/recellularization paradigm.<sup>86</sup> In addition, ensuring the ready availability of an off-the-shelf scaffold that could be recellularized on demand with autologous cells is an attractive proposition for donor shortage. The usefulness of this strategy has been exemplified through the recent application of a synthetic scaffold in a clinical setting of tissue-engineered trachea transplant.<sup>87</sup> Beyond the manufacturing of scaffolds on which cells can grow for later implantation into the body, even more recent technologies enable consideration of in toto fabrication of structures that would map the complex architecture of biological tissues. Specifically, the prospect of bioprinting, which ensures printing and patterning in 3 dimensions of all components that make up a genuine tissue, opens a neoteric dimension of tissue engineering and regenerative medicine for the procurement of organs on demand.<sup>88,89</sup>

### REGENERATIVE MEDICINE AT POINT OF CARE

To address growing interest regarding the utility and applicability of current knowledge in regenerative medicine and surgery, dedicated clinical services are created to offer guidance for patients and families as well as health care professionals. Despite public awareness, there is a general misapprehension regarding stem cell therapies, with medical tourism becoming a common issue in this emerging field.<sup>90-93</sup> Adoption of regenerative therapies will require robust clinical evidence, including definitive answers to the long-term benefit of regenerative

protocols.<sup>94</sup> In this context, a regenerative medicine clinic would serve as a trusted initial point of care to educate patients and clinicians, inform on regenerative medicine needs and services, offer medical/surgical options and subspecialty referral, enable a central data/biospecimen repository, and facilitate enrollment into clinical protocols. At Mayo Clinic, a prototype specialty consult service for regenerative medicine has been launched as a single point of access streamlined through a multidisciplinary team.<sup>95</sup> A central function of the Mayo Clinic Regenerative Medicine Consult Service is to provide medical evaluations for patients with a variety of conditions in which the question has been raised whether a regenerative medicine protocol is appropriate for the individual patient. Indications for a regenerative medicine consultation range from congenital to degenerative diseases about which the patient/family or physician inquire regarding the potential utility of a regenerative therapy.<sup>95</sup> More generally, the consult service is designed to provide expert opinion on the risks and benefits of regenerative approaches and to address the value of available products or services. As appropriate, physicians from the service connect patients with ongoing regenerative medicine protocols and clinical trials. The consult service algorithm begins with a triage system in which operators are equipped with focused questions to determine whether the patient is appropriate for a referral to the service. The next step in the process, in which patient demographic information is collected, is coordinated by the administrative support team. A consult is offered to the patient or physician depending on the nature of the request and the services that are available. Clinical visits are charted in the electronic medical record using the service code "Regenerative Medicine," and episodes of care are documented. Systems and procedures currently in place enable the regenerative medicine consult service to participate in ongoing care plans.<sup>95</sup>

The regenerative medicine patient experience further integrates collection, preservation, and processing of clinical-grade biospecimens for current and future diagnostic and therapeutic needs. A multifunctional repository enables a patient-derived resource for regenerative applications and provides the foundation for a regenerative theranostics support system to meet anticipated demands. A uniqueness of

regenerative biospecimens is the requirement to preserve and maintain the cellular viability to ensure the functionality of derived reagents and biologics for diagnostic and therapeutic development.<sup>96,97</sup> Such a regenerative medicine biotrust functions to enroll patients; to collect and annotate samples; to process, profile, and validate specimens; and, ultimately, to dispense regenerative medicine products that meet regulatory standards. The utility in practice ranges from enabling patient-specific diagnostic disease modeling, target identification, predictive toxicology, and high-throughput molecular screening to clinical therapeutic applications. As an example, a stated purpose of the Mayo Clinic Regenerative Medicine Biotrust includes the banking of umbilical cord blood under Good Manufacturing Practice guidelines required for clinical applications<sup>98</sup> and the refining of pluripotent/lineage-committed cytotypes in a patient-specific manner across disease entities. The regenerative medicine biotrust thus offers a centralized reference and may evolve into a personalized bio-insurance for lifelong disease risk management.

Success in the delivery of regenerative medicine procedures critically depends on the optimal selection of patient populations and the stratification of disease severity. The initial rollout of regenerative products and services needs to be matched with their value-added proposition, advancing the probability of intended outcome with current management strategies.<sup>99</sup> As regenerative applications become increasingly standardized, the spectrum of patient participation will expand from no-option patients to increasingly include earlier stages of disease, ultimately moving toward preemptive interventions for disease prevention. Today, regenerative medicine procedures are largely used in patients with an otherwise dismal prognosis to bridge end-stage organ failure in an attempt to abort or delay high-risk transplant.<sup>100</sup> Increasingly, regenerative medicine technologies with established safety are also applied in combination interventions as adjuvant therapy to augment the efficacy of standard care.<sup>101</sup> In addition, prophylactic applications of regenerative products in neoadjuvant regimens are considered to offset the dose-limiting adverse effects of aggressive primary therapy.<sup>102</sup> Moreover, in anticipation of or response to disease and disability, growing new tissues and organs would offer fit-for-purpose

solutions that can be applied routinely despite age, comorbidities, or disease severity.<sup>103,104</sup> Thus, knowledge and delivery of regenerative medicine steadily transform health care service lines to address the unmet needs of patient populations.

## REGENERATIVE MEDICINE FUTURE

A catalyst in advancing knowledge on disease causes and cures into informed delivery of quality care, regenerative medicine aims to discover, translate, and apply regenerative medicine science into innovative clinical practice. At the core of new medicine and surgery, regenerative principles are poised to leverage understanding of multiplex parameters, defining therapeutic outcome in the setting of individualized management. Insights into the regenerative basis of cell, tissue, and organ function, and their interface with the environment, will increasingly define disease risk, identify processes mediating disease susceptibility, and target mechanism-based therapies, providing unanticipated opportunities for patient-specific disease management. Regenerative medicine will thus grow in conjunction with the realization of individualized medicine paradigms to create predictive, personalized, and preemptive solutions for tailored delivery of patient-specific solutions. Individualized regenerative algorithms will be refined by diagnosis of the inherent reparative potential to identify patients who would particularly benefit from such interventions. Moreover, methods to enhance the propensity for repair outcome will be central in processes of optimization.

## CONCLUSION

Translation of regenerative principles into practice is progressively addressed with demonstration of feasibility and safety in clinical settings. With further development of tools to aid successful delivery, along with advances in the dissection of mechanisms driving repair, regenerative medicine and surgery are poised to transit from proof-of-principle studies toward clinical validation and, ultimately, standardization. In this regard, the multidisciplinary community of regenerative science and practice has provided an extraordinary foundation, paving the way for next-generation therapies. Beyond safety and efficacy, regenerative therapies will be tested for equivalence across distinct socioeconomic and health care settings as an

indicator that these new strategies can potentially reach broader populations in need. Ultimately, the rigor of comparative effectiveness outcome analysis will be required to determine the value of introducing a personalized regenerative therapy as standardized management.

**Abbreviations and Acronyms:** iPS = induced pluripotent stem cell

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