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PERSPECTIVES

Regenerative Medicine Build-Out

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SUMMARY

Regenerative technologies strive to boost innate repair processes and restitute normative impact. Deployment of regenerative principles into practice is poised to usher in a new era in health care, driving radical innovation in patient management to address the needs of an aging population challenged by escalating chronic diseases. There is urgency to design, execute, and validate viable paradigms for translating and implementing the science of regenerative medicine into tangible health benefits that provide value to stakeholders. A regenerative medicine model of care would entail scalable production and standardized application of clinical grade biotherapies supported by comprehensive supply chain capabilities that integrate sourcing and manufacturing with care delivery. Mayo Clinic has rolled out a blueprint for discovery, translation, and application of regenerative medicine therapies for accelerated adoption into the standard of care. To establish regenerative medical and surgical service lines, the Mayo Clinic model incorporates patient access, enabling platforms and delivery. Access is coordinated through a designated portal, the Regenerative Medicine Consult Service, serving to facilitate patient/provider education, procurement of biomaterials, referral to specialty services, and/or regenerative interventions, often in clinical trials. Platforms include the Regenerative Medicine Biotrust and Good Manufacturing Practice facilities for manufacture of clinical grade products for cell-based, acellular, and/or biomaterial applications. Care delivery leverages dedicated interventional suites for provision of regenerative services. Performance is tracked using a scorecard system to inform decision making. The Mayo Clinic roadmap exemplifies an integrated organization in the discovery, development, and delivery of regenerative medicine within a growing community of practice at the core of modern health care. STEM CELLS TRANSLATIONAL MEDICINE *2015;4:1–7*

SIGNIFICANCE

Regenerative medicine is at the vanguard of health care poised to offer solutions for many of today's incurable diseases. Accordingly, there is a pressing need to develop, deploy, and demonstrate a viable framework for rollout of a regenerative medicine model of care. Translation of regenerative medicine principles into practice is feasible, yet clinical validity and utility must be established to ensure approval and adoption. Standardized and scaled-up regenerative products and services across medical and surgical specialties must in turn achieve a value-added proposition, advancing intended outcome beyond current management strategies.

INTRODUCTION

The urgency for disruptive technologies continues to be underscored by the rising tide of chronic diseases afflicting an aging global population [1]. By 2020, chronic diseases—in particular cardiovascular diseases, cancer, diabetes, and respiratory conditions—will collectively cause more than 70% of all deaths in the world [2, 3]. Moreover, among people 60 years and older, half suffer from disabilities—most frequently visual and hearing impairments, dementia, or osteoarthritis [4]. These trends, in part, reflect success in treating acute conditions, injuries, and congenital anomalies. However, the growth of an increasingly elderly population and the prevalence of age-precipitated degenerative diseases and disabilities impose a pressing mandate to decipher actionable mechanisms underlying disease susceptibility and poor outcome, and in turn develop safe and effective strategies that would limit organ dysfunction and reverse tissue degeneration. In this context, regenerative medicine aspires to repair tissues and assemble replacement organs, offering next-generation solutions in promoting longitudinal wellness while reducing the socioeconomic burden associated with chronic disease management [5].

The respected U.S. Department of Health and Human Services perspective "2020: A New Vision" [6] recognizes regenerative medicine at the forefront of health care. Technological innovation and progress in translating regenerative science into clinical application augur well for a transformative impact inherent to the practice of regenerative medicine. Propelled by success in treating leukemia, lymphoma, or myeloma and more generally by remarkable advances in transplantation, regenerative applications are often considered definitive in purpose and a common framework across practices. Indeed, hematopoietic stem cell transplant is today a life-saving, curative treatment not only for certain hematological malignancies but also for immunodeficiencies, metabolic storage diseases, and in discrete cases extracellular matrix disorders including epidermolysis bullosa. Similarly, solid organ transplantation not only extends life in patients with organ failure but can also improve quality of life. Beyond life-extending measures that are often the last available option, regenerative strategies—agnostic to medical

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or surgical specialties—target functional and structural restoration, offering the prospect of hope and solutions for many of today's incurable diseases.

Multimodal regenerative methods incorporate transplant of healthy tissues, prompt the body to enact a regenerative self-healing response in damaged tissues, and use tissue engineering to manufacture new tissue. Stem cells and derived products are the distinctive active ingredients used in regenerative regimens that leverage their capacity to form de novo tissue and/or promote innate repair [7, 8]. The European Medicines Agency has recently recommended the first advanced therapy medicinal product containing stem cells for treatment for moderate-to-severe corneal limbal stem cell deficiency caused by physical or chemical burns to the eye that can result in blindness [9]. Approval of cellular immunotherapy products, as well as cartilage-derived chondrocytes for repair of symptomatic cartilage defects and mesenchymal stem cell products in graft-versus-host disease, further reflects an ongoing global progress in the conversion of preclinical/clinical trial experiences into bona fide registered therapies [10]. In parallel, advances in materials science and biotechnology offer complementary prospects for growing tissue biografts and for engineering whole organs [11, 12]. Whereas medicine in the 20th century has pioneered treatments to ameliorate/mitigate symptoms of disease, regenerative medicine may be the harbinger of 21st century medicine, wherein the focus is on the root cause of disease and curative options paramount [13, 14].

Statement of Need

Building on the promise of regenerative science and the growing medical and societal needs, there is urgency to design, execute, and validate viable paradigms for translating and implementing regenerative medicine into tangible health benefits that provide value to patients and stakeholders. We here recognize some of the translational challenges while sharing our experience in the build-out of regenerative medicine at Mayo Clinic in the context of a growing community of practice. Engagement and investment by all stakeholders is critical to ensuring success of a comprehensive regenerative medicine blueprint.

Translational Challenges to Industrialization

With the outlook of tangible health benefits and the prospect of challenging rising health care costs, translation of regenerative technologies has the potential to add value and extend current models of care. Notwithstanding, adoption of regenerative medicine in practice requires a fundamental shift in the health care business model to implement distinctive regenerative tenets. Although the transformative power of regenerative medicine is generally recognized by physicians, patients, and payers, the complexity of translating discoveries into new modalities that transform health care is less appreciated. As a working example, patients themselves, in this model, would provide the actual source material that will serve to produce ultimate therapies. Current treatments are constrained either by the supply of source material or the limits associated with the inability to tailor definitive therapeutic solutions to the individual patient. The former is exemplified by donor organ shortage for transplantation, with an estimated 122,553 people needing a life-saving organ transplant in this country today [15]. The latter is exemplified by the needs and risks associated with lifelong immunosuppression in patients receiving a donated organ [16]. Rollout of regenerative solutions in practice will require clinical-grade biotherapies suitable for scale-up and standardized production and application.

The challenges inherent in translating a research-grade method to a reproducible and robust manufacturing process suitable for routine production are significant [17, 18]. Scalability, automation, raw material supply, intermediate and product stability, grade of clean room, process control and general process robustness/failure rate, and the cost of goods all exemplify pertinent issues [19]. The sector has been traditionally subdivided into autologous and allogeneic therapies that are often then served by a decentralized or a centralized production model, respectively, although this distinction has started to evolve with hybrid models emerging [19]. As the industry matures, inclusive supply chain capabilities that integrate sourcing, manufacturing, and care delivery will become the norm [20].

A comprehensive supply chain is essential for the expedited introduction of regenerative medicine products and services into clinical practice. The supply chain for the application of biotherapies requires the development of an array of tools and decision-support processes aimed at a quality-controlled production and delivery of clinical grade products that fulfill patient needs and specifications. At present, the fundamental capabilities required for the manufacture of clinical-grade biotherapies are typically confined to limited applications (e.g., bone marrow stem cell transplant for indications in hematology/oncology), a recognized barrier to the broader introduction of regenerative medicine as a scalable and standardized practice.

The supply chain of patient- and donor-derived regenerative medicine products critically rely on technology industrialization. This multifaceted landscape encompasses the identification of clinical need, patient stratification, procurement of patient materials, production of the therapeutic agent, (re)introduction of the therapeutic agent to the patient, and assessment of response. For the needs of this supply chain to be met in a way that optimally impacts care across a wide range of medical conditions, technical and mechanical advancements are required, as is the creation of an informatics architecture to support and manage the logistics of patient sample collection, scaled manufacturing, product return to provider, and reliable clinical delivery. Considering regenerative medicine in the context of supply chain management highlights essential points of vulnerability and/or scalability that can ultimately constrain translation of the biological revolution or potentiate it into individualized diagnostics and therapeutics for optimized value creation and delivery [20].

Mayo Clinic Blueprint

At Mayo Clinic, "regenerative medicine" is a declared institutional priority—launched by the Board of Governors—underscoring the organizational readiness for knowledge translation in chronic care [21]. The Mayo Clinic Center for Regenerative Medicine serves as a catalyst and coordinator in the discovery-development-delivery cycle established for the express purpose of deploying regenerative solutions across medical, surgical, and laboratory medicine practices [22]. Managing risks and implementing strategy encompasses planning, budgeting, forecasting, and decision support. The Mayo Clinic regenerative medicine blueprint incorporates dedicated patient access, enabling technology platforms and multispecialty delivery (Fig. 1).

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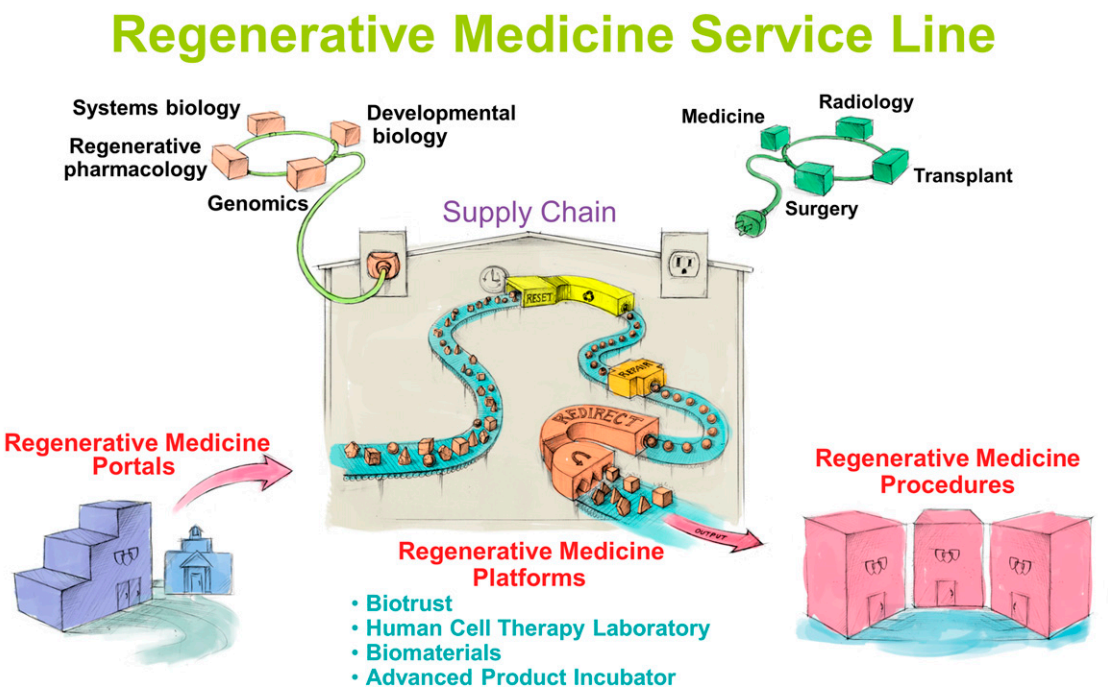

Figure 1. Regenerative medicine blueprint catalyzed by the Mayo Clinic Center for Regenerative Medicine. Powered by advances in fundamental sciences and responding to the unmet patient needs across clinical specialties, the Mayo Clinic regenerative medicine service line build-out incorporates dedicated patient access, enabling technology platforms and multispecialty delivery. Regenerative Medicine Portals refer to a Regenerative Medicine Consult Service (or alternate specialty services) coordinating patient access. Regenerative Medicine Platforms refer to integrated collection, preservation, processing, quality assurance, manufacture, and release of clinical-grade regenerative cellular, acellular, and biomaterial products. Regenerative Medicine Procedures refer to delivery of regenerative therapies across medical and surgical specialties.

Patient Access

Patient access is coordinated, beyond traditional specialty services, via a global portal: the Regenerative Medicine Consult Service (Fig. 1, bottom left). The Regenerative Medicine Consult Service is one of the first dedicated clinical consult services in the U.S. and is operationalized to serve both patients and providers [23]. Indications for a regenerative medicine consult include chronic, degenerative, and congenital disease or other conditions for which the patient or clinician has questions about the value of cell-based or other regenerative therapies. The Regenerative Medicine Consult Service serves as an initial point of care and relies on the expertise of a multispecialty knowledge content board to provide the following services: patient and provider education, procurement of annotated patient biomaterials, referral to standard-of-care services when applicable, and implementation of a regenerative intervention, often in the context of a clinical trial [23]. 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.

Integrated Technology Platforms

The patient experience further integrates collection, preservation, processing, and manufacture of clinical-grade biospecimens for current and future diagnostic and therapeutic use (Fig. 1, center). To this end, the Mayo Clinic Regenerative Medicine Biotrust, a multifunctional repository and refinery, works closely with the Regenerative Medicine Consult Service to source cells and other biospecimens from individual patients. This patient-derived resource provides the foundation for a regenerative theranostics support system to meet anticipated needs. The specific functions of the Regenerative Medicine Biotrust are to generate, process, profile, store, disseminate, and dispense cost-effective, quality-assured patient-derived regenerative products that meet regulatory standards [24]. The Regenerative Medicine Biotrust thus offers a centralized reference and may evolve into a personalized bioinsurance for lifelong disease risk management. Complementing the Biotrust, state-of-the-art current good manufacturing practice (cGMP) facilities have been developed. These include the Human Cell Therapy Laboratory, Biomaterials Resource, and Advanced Products Incubator. Management of manufacturing and quality-control testing in these facilities are carried out according to cGMP requirements, that is, minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packaging of a product. The Human Cell Therapy Laboratory, an enterprise-wide activity embedded within the Department of Laboratory Medicine and Pathology with facilities on Mayo Clinic's campuses in Arizona, Florida, and Rochester, employs cutting-edge know-how to support cell-based clinical applications [25]. This facility has an established track record in cGMP procedures required for the production of bone marrow-derived and non-bone marrow-derived stem cells and an in-depth understanding of the processes required for the provision of these products in a clinical trial environment that is compliant with regulatory agencies including the Food and Drug Administration [26]. The Biomaterials Resource is designed to

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support the manufacture of clinical-grade biologics for biomaterial applications, either alone or in conjunction with cell-based therapy. The Advanced Products Incubator is designed to accelerate the application of novel regenerative products with the focus on developing cell-free biologics-based platforms [27]. Collectively, technology platforms ensure high-quality conformance in consistency, uniformity, and stability as per Food and Drug Administration guidelines.

Delivery

A regenerative medicine model of care challenges traditional tenets associated not only with manufacture but also with the delivery of clinical products and services. Traditional drug therapy is typically self-administered and widely accessible. With regenerative medicine options, selected patients will be treated by specialists, limiting access and requiring advanced training of a new generation of medically qualified personnel and health care auxiliary staff. Moreover, the realization of highly tailored, personalized solutions wherein the patient provides the solution will require a major adjustment in the landscape for provision of health care services. The biotherapeutics, as a patient-derived resource, juxtaposes the patient and provider as never before and significantly alters the lines between production/manufacture and delivery.

Delivery of regenerative medicine at Mayo Clinic is developed in conjunction and embedded within existing medical and surgical specialties. Mayo Clinic leverages its integrated team-based approach and world-class clinical laboratory practice and product manufacturing capabilities to drive the implementation of regenerative therapies and ensure that such treatments achieve standard service-line status.

Although the focus today is on the feasibility, safety, and efficacy of promising regenerative solutions, additional consideration is needed for optimal delivery of regenerative applications across the medical and surgical practice. Mayo Clinic is engaged in the design and development of dedicated interventional suites for the delivery of regenerative products and services—in both inpatient and outpatient settings. Although a number of regenerative procedures can or will increasingly be performed in a customized outpatient setting, the delivery of regenerative medicine products will require specialized facilities equipped with multimodality imaging and advanced visualization technologies and with in-suite capabilities or proximal access to pre/postmanufacturing processing and/or manipulation of biotherapeutics. Across specialties, delivery protocols are developed in conjunction with pre/postdelivery care regimens ensuring seamless integration of a regenerative medicine intervention within patient management plans.

Service Line Build-Out

To establish regenerative medicine service lines, Mayo Clinic has deployed a patient-centered, science-driven practice advancement paradigm deployed across the enterprise. Given this complexity and the diversity of required elements, the precise nature and goals of individual specialty efforts and how these efforts map into a broader vision for the provision of regenerative medicine services must be defined, prioritized, and operationalized. As a designated strategic priority, regenerative medicine is integral to the Mayo Clinic operating plan and jointly overseen by the executive leadership for practice and research. The build-out of service lines is based on the alignment with enterprise clinical priorities, unmet clinical need, capacity to be implemented across Mayo Clinic sites, multidisciplinary expertise, and technological/translational readiness. At Mayo Clinic, clinical trials—launch pads for testing novel therapeutics in humans—serve as a key indicator of technological/translational readiness across service lines (Fig. 2). Of note, the majority of regenerative medicine clinical trials are still at an early stage of development focused on demonstration of feasibility and safety and early indication of efficacy with few reaching at this point the later stages of pivotal clinical trial validation [28–45].

Regenerative medicine has engaged specialties to assess and prioritize current and prospective regenerative service lines aimed to treat and/or alter the course of disease. To facilitate the process, a uniform framework has been developed delineating regenerative medicine activities spanning the discovery-translation-application continuum within each specialty and by clinical condition. For example, molecular and stem cell biology and small-animal-model testing are assigned to the discovery domain, large-animal-model testing and phase I clinical trials are in translation, and phase II/III clinical trials and clinical procedures are assigned to the application domain. A subset of these elements and where on the continuum they are assigned informs the decision process. This framework also enables the identification of gaps and/or barriers to advancing regenerative service lines and assigns principal oversight, that is, research (discovery, early translation) or clinical practice (late translation, application).

Ultimately, viability and success of regenerative medicine will depend on securing regulatory approval and adequate reimbursement. To approach acceptance of regenerative therapies, payers are likely to require robust evidence of safety and efficacy until use becomes common. Site of care (e.g., inpatient or outpatient) is critical to reimbursement strategy, as is the designation of the technology as a biologic, drug, or device. Under existing legislation, cell-based therapies in the U.S. are regulated by the Food and Drug Administration as drugs with rules derived from those developed for chemical drugs. Whether transplantation of a patient's own cells should be regulated as a drug or device or should be treated as a "practice of medicine" is currently a subject of debate. Regulatory designation of regenerative medicine therapies will play a key role in how public and private payers will interpret the therapy for reimbursement purposes and can accelerate or decelerate market access upon market clearance [46].

Scorecard Report System

A set of critical success factors—a regenerative medicine scorecard—has been established by which process and performance within the regenerative medicine space are objectively evaluated. These metrics are provided on a regular basis to institutional leaders and serve as a standing agenda item for review by the Center for Regenerative Medicine leadership team. The scorecard report system ensures the optimal advancement of regenerative science leading to the deployment of regenerative medicine practice that addresses critical unmet patient needs in alignment with institutional priorities. These metrics encompass the declared aims of (a) science-driven practice advancement, (b) education and training of next generation health care scientists and providers, (c) establishment of regenerative medicine and surgery products and service lines, and ultimately (d) rollout of a regenerative medicine

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Regenerative Medicine Clinical Trials

Neurologic	Cancer	Kidney
Parkinson's Disease	Myelodysplastic Syndromes	Renovascular Hypertension
Alzheimer's Disease	Hematological Malignancies	Chronic Kidney Disease
Multiple System Atrophy	Hematopoietic Stem Cell Transplant	Atherosclerotic Renal Artery Stenosis
Amyotrophic Lateral Sclerosis	Myelofibrosis	**Wound Healing**
Hereditary Peripheral Neuropathy	High Risk Myeloma	Pressure Ulcers
Familial Frontotemporal Dementia	Ovarian Cancer	**Urology**
Cardiac	Mandibular Osteoradionecrosis	Stress Urinary Incontinence
Heritable Channelopathies	**Musculoskeletal**	**Surgery**
Hypoplastic Left Heart Syndrome	Knee Osteoarthritis	POP Soft Tissue Repair
Ischemic/Dilated Cardiomyopathy	Hip Decompression	**Ophthalmology**
Left Ventricular Systolic Dysfunction	Osteoarthritis of the Hip	Retinal Disease
Vascular Disease	Rheumatoid Arthritis	**Other**
Lung	Avascular Necrosis	Stromal Cell Donor Bank
Non-Small Cell Lung Cancer	**Liver/GI**	Biomaterial Repository
Lung Obliterans	Fistulizing Crohn's Disease	iPS Cell Bank
Treatment-Refractory Lung Rejection	Liver Disease	

Figure 2. Overview of clinical trials sponsored by the Mayo Clinic Center for Regenerative Medicine. The spectrum of clinical trial categories underscores the multidisciplinary nature of the enterprise-wide endeavor engaging medical, surgical, and laboratory medicine specialties. Abbreviations: GI, gastrointestinal; iPS, induced pluripotent stem; POP, pelvic organ prolapse.

model of care. Pertinent to the "regenerative science scorecard," which focuses on promoting innovative team-based discovery-translation pipelines, the following parameters are monitored: peer-reviewed publications, sponsored grants and awards, research studies/clinical trials, patient enrollment, technology disclosures/patents, and investigational new drug or investigational device exemption portfolio. The "education and training scorecard" focuses on new regenerative science and medicine curricula offered at medical, graduate, and postgraduate levels; targeted career development programs; training and education of health professionals; learning collaboratives; and sponsorship of local, regional, national, and international educational offerings for professionals and the public. The "practice of regenerative medicine scorecard" is built on number and volume of regenerative products and services using the Health Care Common Procedure Coding System established by the Centers for Medicare & Medicaid Services.

Communities of Practice

Mayo Clinic is an integrated not-for-profit organization that closely collaborates with leading regenerative medicine enterprises, both public and private, nationally and internationally. In the U.S., the accelerated development of urgently needed therapies is a declared priority engaging multidisciplinary communities of practice [47]. To address patient and societal needs, clinical development algorithms rely on complementary stakeholders: patients, health care innovators/providers, industry developers, government regulators, and insurers/payers. Synergies generate resources, create infrastructures, and remove barriers to facilitate advancement of innovative therapies into mainstay practice. In this context, the common goal is ensuring the "validity" and "utility" of regenerative therapies to ensure regulatory approval and practice adoption. Uptake mandates a market advantage over available options and appropriate levels of coverage. As treatments with proven efficacy and documented improvement over the current standard of care emerge through clinical development programs, next-generation solutions will be gradually adopted and accepted as reimbursable therapies, ensuring wider patient access. Definitive, curative treatments that alleviate the need for more expensive, long-term, alternative care should in principle provide substantial health care savings and should thus be prioritized as the most promising therapeutic candidates.

Growing public/private initiatives are evolving to expedite the regenerative medicine armamentarium. Case in point, Proposition 71 has established the California Institute for Regenerative Medicine (CIRM), which showcases a regional effort in committing resources toward the goal of advancing stem cell research and emerging therapies toward the clinic. In particular, the CIRM "Alpha Stem Cell Clinics" initiative aims to foster clinical trials, evaluate investigational cell therapies to obtain the evidence needed for establishing safe and effective therapies, and provide access and delivery of proven therapies to patients [48]. This model is in line with the concept of networked clinical research centers, the role of which is to provide clinical trial capacity for those studies involving registration, establishing proven therapies with benefits exceeding the alternative treatments presently available and enabling patients to access proven therapies. Patients who access Alpha Stem Cell Clinics include patients with no therapeutic options seeking experimental treatment and patients seeking standard-of-care treatment. Besides specialized workforce, this endeavor relies on specialized infrastructure, including on/off-site GMP facilities to enable the preparation of cell products and, where appropriate, their purification, storage, modification, expansion, and characterization. Some or all Alpha Stem Cell Clinics may be capable of providing treatments across a spectrum of stem cell applications and be networked to enable the capture of best practices [48].

Furthermore, co-development partnerships in regenerative medicine aim to combine strengths and eliminate deficiencies and are evolving around technological expertise, commercialization, regulatory and/or clinical trial expertise, and financing [49]. The European Union, for example, has formed the Innovative Medicines Initiative to accelerate development of and access to innovative medicines, including regenerative medicine products, and has engaged regulators, researchers, and industry to advance a coordinated innovation agenda in the life sciences [47]. In parallel, new legal frameworks, such as the one allowing for conditional and

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provisional approval for regenerative medical products and technologies enforced recently in Japan under the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, are expected to accelerate safe and fast provision of innovative products to patients with intractable diseases [50]. Notwithstanding, the highest stringency in maintaining the most rigorous standards for safety and efficacy is paramount. Moreover, regulatory harmonization initiatives transcend national and international boundaries and present an opportunity to reduce the costs of new therapy development by streamlining and limiting the requirements for global market approval [47].

In an environment in which price protection is increasingly used in health contracting and in which the risk for treatment failure is still real, the pricing strategy for regenerative medicine interventions will need to be carefully examined. In particular, to improve the alignment between payments and better models of care, fee-for-value—rather than traditional fee-for-service—models with measurable outcomes that consider total cost of care are considered [51]. High pricing creates resistance among payers, consumers, and legislators/policy makers, and although the initial focus is on individual patient benefit and outcomes, ultimate success will be measured by the cost benefit to payers and society as a whole.

Going Forward

Reinstating the physical and functional integrity of a damaged organ in the context of whole-person care is central in realizing the primary objective of regenerative medicine. Experience to date, both nationally and globally, indicates that the translation of regenerative principles into practice is largely feasible and consistently safe in the clinical setting. Regenerative medicine and surgery are, therefore, headed to transition from the ongoing proof-of-principle and proof-of-promise emphasis toward clinical validation and, ultimately, standardization, paving the way for next-generation management algorithms. 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. Adoption of regenerative therapies will require robust clinical evidence, including definitive answers to the long-term benefit of regenerative medicine protocols [52]. Ultimately, the rigor of comparative effectiveness outcome analysis will be needed to determine the value of introducing a regenerative therapy as standardized management.

In the era of precision medicine, regenerative medicine will grow in conjunction with the realization of individualized medicine paradigms to create predictive, personalized, and preemptive solutions for tailored delivery of patient-specific solutions [53]. 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 the processes of optimization [54, 55].

Conclusion

Success in the delivery of regenerative medicine procedures will critically depend on the optimal selection of patient populations and the stratification of disease severity. The initial rollout of regenerative products and services will need to be matched with their value-added proposition, advancing the probability of intended outcome beyond current management strategies. As regenerative applications become increasingly common, the spectrum of patient participation will expand from no-option patients to increasingly include those with 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. Increasingly, regenerative medicine technologies with established safety are also applied in combination interventions as adjuvant therapy to augment the efficacy of standard care. In addition, prophylactic applications of regenerative products in neoadjuvant regimens are considered to offset the dose-limiting adverse effects of aggressive primary therapy. Moreover, in anticipation of or in 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. Thus, knowledge and delivery of regenerative medicine is poised to steadily transform health care service lines to address the unmet needs of patients and populations.

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Author Contributions

A.T., M.A.P., G.J.G., and C.M.H.: conception and design, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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