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The Regenerative Horizon: Opportunities for Nursing Research and Practice

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Abstract

Background: Regenerative technologies aim to restore organ form and function. Technological advances in regenerative treatments have led to patients increasingly seeking these therapies. The readiness of nursing to fully contribute to this emerging healthcare field is uncertain.
Purpose: The goal of this discipline-oriented overview is to enhance awareness in the nursing community regarding regenerative science, and to provide suggestions for nursing research contributions and practice implications.
Methods: Evolving and applied cutting-edge therapies, such as regenerative immunotherapies with chimeric antigen receptor expressing T lymphocytes, are highlighted in the context of emerging opportunities for nurses in practice and research.
Discussion: Next generation nurses will increasingly be at the forefront of new therapies poised to make chronic illnesses curable, thus restoring health and function to diverse groups of individuals.
Clinical Relevance: The regenerative care model imposes on the nursing community the imperative to (a) increase research awareness; (a) educate, develop, and deploy a skilled nursing workforce; (c) integrate regenerative technologies into nursing practice; and (d) embrace the regenerative technologies horizon as a future in health care.

Regenerative technologies are emerging on a global scale aimed at achieving therapeutic repair in the context of worldwide aging and the pandemic of chronic degenerative diseases (Cuende, Rasko, Koh, Dominici, & Ikonomou, 2018; Zacchigna & Giacca, 2018). In the United States, the 21st Century Cures Act was designed to help accelerate the next generation of medical innovations to address patient needs (U.S. Congress, 2016). It provided the National Institutes of Health with resources to advance biomedical research, and specifically established the Regenerative Medicine Innovation Project to support clinical research while promoting the highest standards for carrying out scientific research and protecting patient safety (National Institutes of Health, n.d.). We aim here to present the current state of regenerative science in the United States and highlight the opportunities for nursing research and practice to contribute to the improvement of human health with these cutting-edge therapies and technologies.

The Regenerative State of Affairs

Healing From Within

Today, with rapidly changing technology, new treatment options are remarkably transforming the healthcare horizon. One area at the forefront of new treatments and therapies is the field of regenerative technologies. Broadly defined, regenerative technologies are biological repair therapies aimed at achieving tissue or organ rejuvenation, restoration, or replacement (Terzic & Nelson, 2010). Intended to address debilitating or life-threatening conditions, regenerative

technologies are at the vanguard of promoting human health by restituting form and function compromised by disease (Terzic, Pfenning, Gores, & Harper, 2015). Examples of clinically adopted or clinical trial–tested treatments include bone marrow stem cell transplantation for blood malignancies in hematology; nerve reconstruction in neurosurgery; facial reanimation and composite allotransplantation in plastic and microsurgery; hybrid core decompression and osteochondral grafts in orthopedics; platelet-rich plasma interventions in physical and sports medicine; cell therapies for neurodegenerative, cardiac, and kidney disease in neurology, cardiology, nephrology, and vascular surgery; and neo-organogenic regeneration for aerodigestive pathologies in otorhinolaryngology, thoracic, and general surgery. The regenerative medicine perspective to build, rebuild, or repair aims to boost the innate healing capacity, improve tissue injuries, and help the patient reclaim better health (Hargraves, Behfar, Foxen, Montori, & Terzic, 2018).

Knowledge Gap

Patients who receive these cutting-edge treatments require integrated, multidisciplinary science-based care supported by evidence. Because regenerative technologies are new to most healthcare professionals, a period of integrating knowledge of regenerative therapies into practice will be needed. Specifically, it is not known how knowledgeable the global nursing community is about regenerative technologies. Foundational knowledge surrounding regenerative science is essential in order to fully contribute to the health care of these patients. Yet, the prospective contribution of nursing to preclinical assessment, patient-reported outcomes, and clinical practice is vast, albeit largely untapped to date. Accordingly, there is a need to educate and develop a nursing workforce competent in regenerative science and practice, including the identification and management of potential side effects, while paying attention to ethical issues. This article serves to highlight opportunities for nursing scholarship and leadership in the era of regenerative health care.

The Quest for Regeneration

Innovation has led to a growing number of regenerative therapies supported by the rigor of preclinical work, regulatory science, ethics, quality control, and clinical surveillance (Galipeau & Sensebe, 2018; Rosenthal & Badylak, 2016). Regenerative technologies are diverse—from transplant of healthy tissues, to prompting self-healing in damaged tissues, to applying tissue engineering to manufacture new tissue (Terzic & Nelson, 2013). Examples of emerging regenerative therapies are highlighted here (Table 1; Figure 1). Stem cells (and derived products) are the active ingredients most generally used in regenerative regimens that leverage a distinctive capacity to form new tissue or promote innate repair. Stem cells for treatment of corneal limbal cell deficiency caused by burns to the eye is one example (Holmes, 2017). Cartilage-derived chondrocytes for repair of cartilage defects, and mesenchymal stem cell products in graft-versus-host disease, further reflect progress in translation of preclinical and clinical experiences into registered therapies (Saris, de Windt, Vonk, Krych, & Terzic, 2018). In hematology, the inclusion of regenerative immunotherapies in managing blood-related cancers illustrates early adoption of a new class of validated treatments (Lulla, Hill, Ramos, & Heslop, 2018). The prospect of tumor obliteration by chimeric antigen receptor–expressing (CAR-expressing)

Table 1. Examples of New and Emerging Regenerative Therapies and Their Clinical Application

Diagnosis	Regenerative procedure	Type of therapy
Lymphoma	Chimeric antigen receptor T-cell therapy engineered to destroy cancer cells (Neelapu et al., 2018)	Cell and cell based
Heart failure	Intramyocardial administration of bone marrow–derived, lineage-directed, autologous cardiopoietic mesenchymal stem cells (Bartunek et al., 2018)	Cell and cell based
Osteoarthritis	Injection of Phlpp inhibitor-Phlpp gene blocks cartilage regeneration (Hwang et al., 2018)	Cell and cell based
Macular degeneration	Retinal cell replacement therapy in which pluripotent stem cells are instructed to become retinal pigment epithelial cells (Geng et al., 2017)	Cell and cell based
Diabetes type I	Preservation of islet beta cells by targeting antigen-specific T cells (Burrack, Martinov, & Fife, 2017)	Cell and cell based
Neurodegenerative diseases	Intrathecal delivery of autologous adipose-derived mesenchymal stem cells (Staff et al., 2016)	Cell and cell based
Liver failure	Bioartificial liver (Chen et al., 2018)	Bioengineered and hybrid
Kidney failure	Bioengineered vessel grafts for use in hemodialysis (Lawson et al., 2016)	Bioengineered and hybrid
Spinal cord injury	Implantation of acellular injectable peripheral nerve matrix (Cerqueira et al., 2018)	Acellular
Breast cancer	Acellular dermal matrix used for breast reconstruction (Sorkin et al., 2017)	Acellular

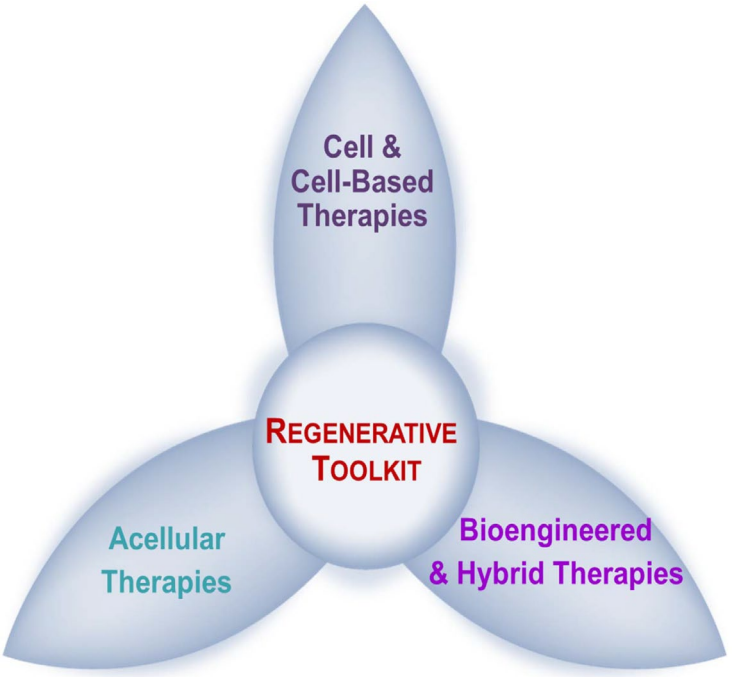

Figure 1. Regenerative technologies toolkit. [Correction added on November 6, 2019 after first online publication: Figure has been updated] [Colour figure can be viewed at wileyonlinelibrary.com]

T lymphocytes technology paves the way for potentially curative options for certain cancers such as B-cell malignancies unresponsive to conventional treatment. Optimized stem cell therapy to treat heart failure utilizes cardioreparative cells developed to target the ailing myocardium (Terzic & Behfar, 2016). Further, advances in materials science and biotechnology offer prospects for growing tissue biografts and for engineering whole organs (Martinod et al., 2018; Murphy & Atala, 2014). Current and emerging regenerative approaches based exclusively on stem cell therapies are steadily enriched with a broader array of biotherapies (Behfar & Terzic, 2019). These include cell-free, bioengineered, or hybrid therapeutic solutions exemplified by exosome-based heart repair therapies, bioprinted cartilage products for joint reconstruction, or hybrid biomaterials for bone regeneration (Behfar & Terzic, 2017; Madl, Heilshorn, & Blau, 2018; see Figure 1). Irrespective of the therapeutic modality and timing of intervention, induction of the body's innate regenerative responses is the common denominator of this healing outlook.

Regenerative Technologies: From Science Fiction to Real-World Practice

While still a nascent notion, regaining form plus function altered by disease or injury is the driving imperative of regenerative technologies (Nelson, Behfar, & Terzic, 2008). Indeed, regenerative technologies have the potential to shape the ongoing healthcare revolution by leveraging diverse mechanisms for endogenous regeneration and repair (Wells & Watt, 2018). In addressing unmet patient needs, the restorative approaches of regenerative technologies are poised to offer therapies that go beyond symptom mitigation. With a deeper understanding of disease causes, it is progressively within reach to consider a therapeutic toolkit targeted on disease underpinnings, not just on symptom relief (Waldman & Terzic, 2018). For example, regenerative therapies have the potential to halt the progression of degenerative joint disease in the knee or the hip. They can also help to improve the pump function of a failing heart or assist in healing damaged tissue in the setting of complex fistula-associated conditions. In so doing, regenerative treatments and therapies profoundly shift the traditional "care" model toward an increasingly "cure" paradigm.

Aligning Nursing With Regenerative Health Care

Aligning with regenerative breakthroughs and the needs of an aging society plagued with chronic illnesses (Terzic & Waldman, 2011), there is urgency to engage nursing broadly in regenerative science and practice (Olshansky, 2018). It is anticipated that nurse scientists will play

an integral role in patient-centered outcomes research and the translation into practice of validated regenerative clinical applications (Perrin et al., 2018). Translating and implementing regenerative paradigms into tangible health benefits that provide value to patients and society is the overarching impetus for collective regenerative technologies success. To meet this need, it is imperative that nursing in the context of current and evolving regenerative health care pursue the generation of new knowledge and the translation of research findings to practice in an expeditious manner (Figure 2).

Opportunities for Nursing Science in Regenerative Health Care

Building a next-generation cadre of nurse scientists to conduct research within the regenerative technologies sphere is urgently needed. The Council for the Advancement of Nursing Science Scientific Committee advocates for the importance of the nursing lens in research to address key aspects that promote health, well-being, and health-related quality of life (Eckardt et al., 2017). This nursing lens assumes the centrality of the individual as a whole (i.e., a holistic systems biology framework) (Founds, 2018); it is imperative that nursing's holistic focus be brought to the science around regenerative technologies. Central to nursing engagement in regenerative science is the iterative development of evidence-based, disease-specific, and regenerative therapy-tailored frameworks to assist and guide providers in the management of patients (Howell et al., 2018; Trounson, DeWitt, & Feigal, 2012). Examples include nursing science–generated practices in the triage and stratification of candidates that best qualify to receive a regenerative therapy; evaluating and establishing at the bedside the safety and effectiveness of a regenerative intervention; long-term surveillance of symptoms and potential adverse outcomes; and offering individualized monitoring to recipients, including prophylaxis from possible complications associated with care-intensive regimens. Of note, recipients of regenerative therapies may suffer from serious comorbidities associated with increased burden of chronic conditions that compromise recovery and overall quality of life. Thus, proactive, rather than reactive, nursing research to measure recovery trajectories including quality of life is warranted (Chow et al., 2016; Ruano, Enninga, Brana Rivera, & Terzic, 2019; Waldman & Terzic, 2019).

Nursing research developed for the express purpose of generating knowledge and proficiency to inform science-based practice, regardless of educational preparation and expertise in regenerative technologies, is important (see Figure 2). Nursing science in regenerative research consists of a spectrum of activities including collection and interventional translation of evidence from clinically relevant preclinical models, followed by design and implementation of clinical trials focused on salient patient outcomes, evaluation of study quality including treatment fidelity monitoring, and establishment of validated safety and efficacy datasets including

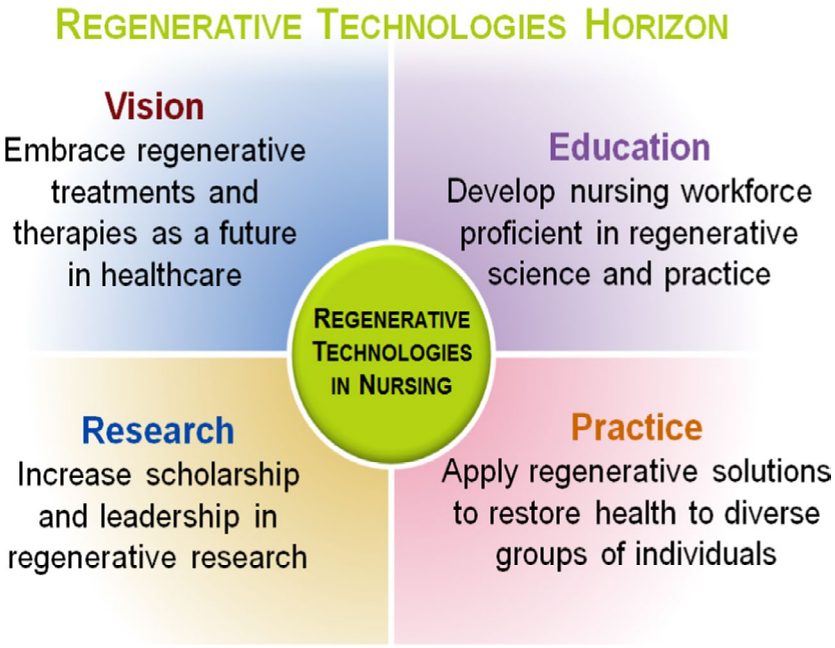

Figure 2. Regenerative technologies horizon in nursing. [Colour figure can be viewed at wileyonlinelibrary.com]

patient-centered outcomes and quality of life (Osier, Pham, Savarese, Sayles, & Alexander, 2016; Santacroce, Leeman, & Song, 2018). Designing databases that include common data elements (CDEs) and Patient-Reported Outcome Measurement Information System (PROMIS) instruments can serve as a global repository for measures and outcomes in regenerative health care. CDEs are variables that are operationalized and measured in identical ways in studies that allow comparisons across studies with large samples that can be aggregated within and across centers and disciplines (Redeker et al., 2015). These types of datasets also facilitate data sharing and secondary data analyses. Big data and data analytics will be essential for the development of databases and registries to capture health outcomes over the lifespan for persons who have undergone regenerative treatments (Waldman & Terzic, 2016).

Research advancing regenerative science from a nursing perspective may focus on evaluating patient experiences, outcomes including symptoms, along with implications for self-management, functional status, emotional well-being, health-related quality of life, economic outcomes, and the impact of these technologies on the family. For example, individuals who receive injections of cell-based therapies for osteoarthritis would be expected to experience improved pain, functional status, and quality of life over time if treatment was successful. Pain prior to, during, and after regenerative cell therapy for chronic osteoarthritis could be measured with the PROMIS Pain scale. The CDE of physical and mental well-being (National Institutes of Health, 2013) in response to regenerative cell therapy could be measured over time using the Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36).

Regenerative technologies offer vast opportunities for nursing science. For example, there may be phenotypic variations among responders and nonresponders to regenerative therapies (Bartunek, Terzic, Behfar, & Wijns, 2018). Given that some regenerative treatments may be costly, it is not known what the immediate and long-term impact is on the health and well-being of individuals, including cost effectiveness expressed in quality-adjusted life years. Further, there is a paucity of knowledge about treatment burden and life-style impact for nonresponders to regenerative therapies. It is imperative that nursing contribute to the design of databases and registries that captures patient outcomes over time, inclusive of side effects and health consequences. This would ensure that measurement of key phenomena in response to regenerative technologies are patient centered and patient reported and inclusive of trajectories of recovery over time.

The National Institutes of Health–supported Innovation Fund awards grants to inform science-based care for patients seeking and experiencing regenerative therapies. The National Heart, Lung, and Blood Institute (NHLBI; n.d.) offers a list of compelling questions and critical challenges corresponding with objectives contained in the strategic vision document. For example, Strategic Vision Objective 6 ("Optimize clinical and implementation research to improve health and reduce disease") envisions the translation of discovery into practice in an accelerated manner through a variety of strategies, including leveraging electronic health records, patient registries, and existing datasets to create an integrative interface between clinical research and practice. Regenerative science is poised to address this vision (Grace & Zumstein-Shaha, 2019).

The National Institute of Nursing Research (NINR; n.d.) supports science to enhance clinical practice, prevent illness, and improve lives of individuals across the lifespan. The NINR's Innovative Questions provide a compass for research funding priorities. One innovative question in the symptom science priority area (1–9) posits, "How can we create a standardized, feasible, valid and relevant data and technology infrastructure to routinely collect and aggregate symptom data from patient health records but also from other types of assessments (biological, physiological, performance) to inform clinical care and research?" This question is directly related to regenerative health care in that databases and registries are needed that comprehensively assess and monitor patients' symptoms across regenerative therapies, including pretreatment, treatment, post-treatment across the lifespan.

Opportunities for Nursing Practice in Regenerative Health Care

There is a need to build nursing practice capacity through education, continuing professional development, and awareness of regenerative technologies in order to provide science-based care prior to, during, and following treatment with a clinically apt workforce (see Figure 2). Implementation of targeted initiatives, such as the state-legislated California Institute of Regenerative Medicine (Trounson et al., 2012) or Minnesota Regenerative Medicine Act (Tolar & Terzic, 2017), contributes to the need for strengthening nursing practice competencies. Similarly, on a more global scale, the translational alliance for regenerative therapies underscores international endeavors for the comprehensive application of regenerative medicinal products (Fernandez-Aviles et al.,

2017) and the development of targeted educational curricula to ensure proficiency of the next-generation workforce (Wyles, Hayden, Meyer, & Terzic, 2019).

While the focus on restoration of health and function are inherent to the practice of nursing, regenerative treatments (Bartunek et al., 2009) may require major changes to care delivery. As new regenerative therapies delay the progression or potentially reverse chronic disease processes, the emphasis by healthcare providers on restoration of health and function will be even more critical (Terzic, Harper, Gores & Pfenning, 2013). Nursing practice will continue to shift from acute care settings to outpatient and community settings (Alleyne & Jumaa, 2007). For example, cell-based therapies to reverse heart failure may result in the need for fewer hospitalizations. However, recipients will need ongoing symptom monitoring and self-management, and will have an array of educational and supportive care needs that can be addressed through outpatient visits, community programs, or home visits. Restoration of physical and psychosocial function will foster creativity and generation of unique nursing interventions. Scientifically based nursing interventions will be needed to provide excellent care to patients in the community, especially for those with health conditions that require ongoing care before, during, and after receiving a regenerative treatment.

As regenerative technologies advance and move into mainstream healthcare settings, it is important for nursing practice to keep up to date on how these innovative treatments may require unique interventions to address human health needs. A prime example is oncology. Cancer treatment has shifted from reliance on destruction of both healthy and malignant cells through chemotherapy and radiation therapy to a restorative approach that focuses on halting growth of the malignancy through preservation, repair, or restoration of normal tissue function, enabling healthier survivorship. The introduction of effective regenerative immunotherapies is unprecedented (McCune, 2018). The development of targeted therapies, beginning in the late 1990s, ushered in a new era in cancer treatments that hold great expectations of better efficacy with fewer side effects since healthy cells would be increasingly spared by regenerative, precision therapies (Afghahi & Sledge, 2015).

An example of how changes in cancer treatment options have also led to challenges and opportunities in nursing practice include administration of cetuximab, one of the first targeted therapies approved for use in metastatic colon cancer. Cetuximab is a monoclonal antibody that targets epidermal growth factor receptors in people with a wild-type KRAS mutant colon cancer (Jarzabek et al., 2015). Treatment with cetuximab results in increased survival; however, it causes a severe acneiform rash that is itchy, painful, and predisposes individuals to infection. Interestingly, the severity of the acneiform rash is correlated with better response to therapy (Kogawa et al., 2015). Oncology nurses were facing a new dilemma in how to manage this side effect, including what education to provide, and what types of pharmacologic and nonpharmacologic treatments were appropriate. Researchers had to first evaluate potential treatments to ameliorate the suffering that patients were experiencing as a result of these dermatologic reactions.

As immunotherapies and targeted therapies continue to evolve in cancer care, nurses will play a key role in monitoring patients' responses to therapy, including identification of side effects, promoting self-care interventions, and providing education to support patients before, during, and after treatment. Nursing practice will need to integrate science-based interventions into standardized patient care. Considering that the evidence needed to guide nursing practice will be developing as new therapies are introduced, it is critical that nurses keep abreast of the latest validated research findings in order to best manage unmet patient needs.

Another area that requires science-based patient care for cutting-edge regenerative therapies is the intensive care unit (ICU). While ICU nurses possess keen assessment and technical skills, additional knowledge is needed when caring for patients who have undergone regenerative treatments in order to anticipate side effects and subtle physiological changes. For example, patients who have received CAR T-cell therapies require an understanding and anticipation of a number of toxicities and complications that must be recognized and managed in a timely manner, including cytokine release syndrome and neurotoxicity (Neelapu et al., 2018). Close monitoring of hemodynamic status, mental status, and laboratory values is paramount, as is the timely administration of supportive treatments such as corticosteroids (Gutierrez et al., 2018). Additionally, delayed adverse responses to post–CAR T-cell therapy can include cognitive impairment or seizures (Boniifant & Curran, 2016). When patients who have received CAR T-cell therapy present to the emergency department or a primary care provider, proper diagnosis and treatment cannot occur without prompt recognition of delayed neurological toxicity associated with a CAR T-cell–based regimen. To prepare nurses for practice settings that offer regenerative treatments, dedicated fellowship programs have been designed and implemented, leading to certification in this specialty area (Diaz, Corbett, & Camiling-Burke, 2018). Indeed, patients treated with regenerative options do need high-quality nursing care so that the treatment actually takes hold.

There is a recognized burden on educators responsible for preparing the next generation of nursing professionals to address the regenerative horizon. Nurses will require foundational knowledge pertinent to regenerative science, including in immunology, cell and tissue biology, genomics, (patho)physiology, as well as pharmacology. Teaching of regenerative science principles can best be addressed by multidisciplinary education teams in an interprofessional format. Readily accessible learning platforms, including at point of care, include web-based modules, virtual classrooms, and seminars. Educational needs will vary based upon individual factors (role, specialty, expertise) and will need to expand as more regenerative technologies make their way into clinical practice. Interprofessional education may provide additional value in enriching curricula and preparing for opportunities in nursing practice.

Summary and Future Implications

Regenerative therapies offer hope to individuals with chronic conditions, and in some cases aim to cure aging-related chronic illnesses (see Table 1 and Figure 1). Notably, regenerative technologies may be limited in availability and not widely accessible to patients. Thus, the responsible, ethical clinical translation of these technologies and therapies is warranted (Shapiro, Smith, Arthurs, & Master, 2019).

It is time to begin a global conversation on how to prepare nursing to meet the needs of persons who receive or seek regenerative therapies. Resources must be present to support restoration of physical, psychological, and role function during acute and long-term phases of treatment, as well as during transition from acute care into outpatient and community settings. Resources to support nursing staff in caring for these patients are essential. Research efforts will need to be directed toward evaluation of short- and long-term effects of new therapies, determinants of success, and measurement of functional, safety, and quality of life–related outcomes across the life-span. Validity (i.e., safety and efficacy), utility (i.e., long-term outcomes), and cost effectiveness of these therapies must be established prior to broad adoption. Ethical issues concerning use of various and expanding regenerative biotherapies (e.g., stem cells, tissue engineering, acellular biologics), along with quality control or assurance, access, and affordability or reimbursement, are ongoing conversations that must take place in the context of societal and personal goals and values.

Opportunities and challenges in caring for these patients will require a pro-active, multidisciplinary perspective. All stakeholders should be involved in the conversation, including healthcare experts, patients and families, patient advocates, regulatory specialists, and funding agencies. An initial step in initiating this conversation could include a global forum in regenerative sciences, similar to the Geroscience Summit held by the National Institutes of Health in 2013, to disseminate knowledge, promote interdisciplinary collaborations, and develop strategies to address healthcare challenges (Burch et al., 2014). The time is now for nursing to contribute to the cutting-edge field of regenerative health care in the pursuit to improve human health, well-being, and quality of life (see Figure 2). The future of health care has arrived in the form of cutting-edge regenerative technologies. It is imperative that the nursing profession educate themselves about the vast array of regenerative technologies that will be making their way into practice and contribute to the science necessary to ensure evidence-based care for patients.

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Clinical Resources

- AABB. Facts about cellular therapies. http://www.aabb.org/aabbcct/therapyfacts/Pages/default.aspx
- Aplastic Anemia and MDS International Foundation. The nurse's role in preparing patients for stem cell transplant. https://www.aamds.org/nurse%E2%80%99s-role-preparing-patients-stem-cell-transplantation
- ONS Voice. Nursing considerations for adverse events from CAR T-cell therapy. https://voice.ons.org/news-and-views/nursing-considerations-for-adverse-events-from-car-t-cell-therapy
- University of Pittsburgh Medical Center. Glossary of regenerative medicine terms. http://www.upmc.com/Services/regenerativemedicine/education/Pages/glossary.aspx

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