Regenerative Medicine: A Proposed Classification for HEOR Based on Therapeutic Strategy and Technology Type

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BACKGROUND

- Many definitions of regenerative medicine are offered by regulatory agencies, health technology assessment (HTA) authorities, and professional societies, which may complicate efforts by those conducting health economics and outcomes research (HEOR). For example:
  - The United States (US) Food and Drug Administration (FDA) defines regenerative medicine therapy to include "cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations."[1]
  - According to the United Kingdom's House of Lords, regenerative medicine is "used to refer to methods to replace or regenerate human cells, tissues, or organs in order to restore or establish normal function. This includes cell therapies, tissue engineering, gene therapy, and biomedical engineering techniques, as well as more traditional treatments involving pharmaceuticals, biologics and devices."[2]
- In general, regenerative medicine products include cell therapies, gene therapies, and tissue-engineered products. Treatments that combine cell therapy and gene therapy have also been developed and are often referred to as cell-based gene therapy products.

OBJECTIVE

- To propose a classification system for regenerative medicine that is standardized based on characteristics potentially more likely to be considered in HEOR

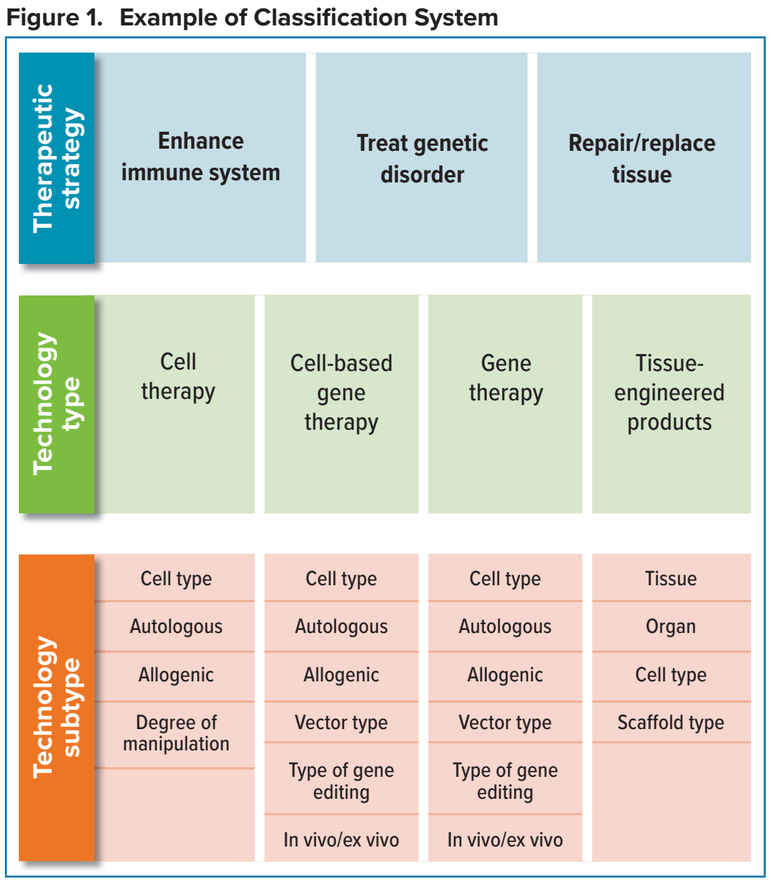
METHODS

- A targeted review was conducted of documentation from government agencies, HTA authorities, and professional societies, as well as published literature, and a classification system was developed to support HEOR.

RESULTS

- The classification system is based on therapeutic strategy and, within that, technology type and subtype (Figure 1).

Figure 1. Example of Classification System



- This classification can help health economists when evaluating regenerative medicine products because the therapeutic strategy, technology type, and technology subtype can impact considerations for an economic model.

Table 1. Examples of Regenerative Medicine Products Approved in the United States and/or European Union by Therapeutic Strategy

Generic Name	Brand Product (Manufacturer)	Technology Type	Technology Subtype	Therapeutic Area
Enhancement of Immune System				
Talimogene laherparepvec	Imlygic (Amgen)[6]	Cell therapy (FDA) Gene therapy (EMA)	Genetically modified virus injected into cancer cells	Cancer: melanoma
Sipuleucel-T	Provenge (Dendreon Corporation)[7]	Cell therapy (cancer vaccine)	Modified autologous immune cells	Cancer: prostate
Tisagenlecleucel	Kymriah (Novartis)[8]	Cell-based gene therapy (ex vivo)	CAR-T (genetically modified autologous T-cells via lentivirus)	Cancer: ALL, DLBCL
Axicabtagene ciloleucel	Yescarta (Gilead)[9]	Cell-based gene therapy (ex vivo)	CAR-T (genetically modified autologous T-cells via lentivirus)	Cancer: DLBCL
Treatment of a Genetic Disorder				
Enriched autologous CD34+	Strimvelis (Orchard Therapeutics)[10]	Gene therapy (ex vivo)	Gene addition (retrovirus vector)	Immunodeficiency: ADA-SCID
Voretigene neparvovec	Luxturna (Spark Therapeutics)[11]	Gene therapy (in vivo)	Gene addition (AAV2 vector)	Ophthalmology: biallelic RPE65 mutation-associated retinal dystrophy
Patisiran	Onpattro (Alnylam Pharmaceuticals)[12]	Gene therapy (in vivo)	Gene silencing (via siRNA)	Hematology: hATTR amyloidosis
LentiGlobin BB305	LentiGlobin (bluebird bio)[13]	Gene therapy (ex vivo)	Gene addition (lentivirus vector)	Hematology: beta-thalassemia
Tissue Repair				
Allogeneic cultured chondrocytes on a bovine collagen matrix	Apligraf (Organogenesis)[14]	Tissue-engineered product	Manipulated cells on a matrix	Wound care: skin ulcers and diabetic foot ulcers
Autologous fibroblasts	Laviv (Fibrocell Technologies)[15]	Cell therapy	Cultured autologous fibroblasts	Cosmetic: nasolabial fold wrinkles
Autologous cultured chondrocytes on porcine collagen matrix	MACI (Verticel Corporation)[16]	Tissue-engineered product	Manipulated cells on a matrix	Orthopedic: cartilage defects of the knee

AAV2 = recombinant adeno-associated virus serotype 2; ADA-SCID = adenosine deaminase deficiency; ALL = acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; EMA = European Medicines Agency; hATTR = hereditary transthyretin-mediated amyloidosis; siRNA = small interfering ribonucleic acid.

- The proposed framework can direct HEOR researchers in identifying key resources, clinical outcomes, and data sources.
  - A gene therapy → risk of off-target mutations as an adverse event
  - Type of gene editing → the more edits that are done (e.g., deleting multiple genes and adding multiple genes), the higher the risk of off-target mutations
  - Use of allogenic versus autologous cells → autologous cells will require resources for the collection of the patient's cells, while allogenic cells have a potential risk of graft-versus-host disease
  - An ex vivo therapy using autologous cells → resource use for the collection of patient cells, and mortality of patients between the time of cell collection and administration of product, which may be several weeks, should be considered
  - A therapy that uses a viral vector → adverse events related to the virus should be considered
  - Tissue-engineered product to replace an organ → source of cell and scaffold material will determine potential clinical outcomes such as the use of long-term immunosuppressants and potential graft-versus-host disease
  - A therapy to treat a genetic disorder → if curative, a lifetime horizon should be modeled, and real-world data from registries may need to be obtained to estimate disease cost avoided
  - A cell-based gene therapy that is a chimeric antigen receptor T-cell (CAR-T) therapy → guidelines on the administration and the grading and management of toxicities of CAR-T therapies are being developed[3-5]
  - A cell therapy that enhances the immune system → therapy may need to be combined with more traditional options such as surgery and/or chemotherapy

DISCUSSION

- Treatments that enhance the immune system, with technology type cell-based gene therapies and subtype of an ex vivo, autologous, modification T-cell receptor as in the CAR-T therapies require the following considerations in an economic model:[8,9]
  - Cost and resource use associated with leukapheresis to collect the patient's cells, as this is an autologous, ex vivo therapy
  - Cost and resource use associated with lymphodepleting chemotherapy that is required for 3 days before treatment, as well as considerations of mortality during this time
  - The reporting of adverse events, such as cytokine release syndrome, has varied between studies. The American Society of Blood and Marrow Transplantation is in the process of developing a toxicity rating system for CAR-T therapies[4]

CONCLUSIONS

- As more regenerative medicine therapies gain marketing authorization, the classification of the therapy strategy, as well as the technology, should be taken into consideration when conducting HEOR.

REFERENCES

Please see handout for references.

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