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**Regenerative Cell Therapy Reimbursement:  
Lessons From a Survey of Global Health Technology  
Assessments**

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LEADING RESEARCH...  
MEASURES THAT COUNT

## Agenda

- Perceived differences between regenerative cell therapies and biologic drugs
- How these differences are scrutinized in health technology assessments (HTAs)
- Lessons for innovators to increase the likelihood of achieving reimbursement

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What are the perceived differences between regenerative cell therapies and biologic drugs?

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### Expectations of Cell-Based Therapies and Biologic Drugs

Characteristic	Biologic	Cell-Based Therapy
Site of care	Outpatient or self-administered	Outpatient or inpatient
Clinician skill required	Low to moderate	High
Supply of source/skilled providers	Sufficient	Sometimes insufficient
Chronicity of use/number of administrations	Chronic/ semi-chronic/ multiple administrations	Single-dose to few-dose administration
Dosing basis	mg or mg/kg	Cell count
Duration of effect per dose	Short to medium-term	Long to very long
Clearance from body	Rapid	Slow to nonexistent in most cases (ideally)
Diffusion from site of administration	Typically broad diffusion	Localized to some diffusion (although migration may take cells far, e.g., cell homing to site of injury such as the brain)
Efficacy vs. alternatives	Better (could be an add-on therapy)	Best (ideally replaces other therapies)
Mechanism	Various molecular targets	Tissue regenerative/ reparative
Cost/cost concentration	Moderate	High
Trial design	Double-blind RCTs	Full blinding not always possible
Safety/adverse effects	Varying	Infection from allogeneic sources/ complications of concomitant immunosuppression/ risk to donor/ cancer from uncontrolled cell growth

## Expectations of Cell-Based Therapies and Biologic Drugs

Characteristic	Biologic	Cell-Based Therapy
Site of care	Outpatient or self-administered	Outpatient or inpatient
Clinician skill required	Low to moderate	High
Stability of source/ skilled providers	Stable	Sometimes inpatient
Chronicity of use/ number of administrations	Chronic/ semi-chronic/ multiple administrations	Single-dose to few-dose administration
Dosing basis	mg or mg/kg	Cell count
Duration of effect per dose	Short to medium-term	Long to very long-term
Clearance from body	Rapid	Slow to non-existent in most cases (steady)
Diffusion from site of administration	Typically broad diffusion	Localized to some diffusion (although migration may take cells far, e.g., cell homing to site of injury such as the brain)
Efficacy vs. alternatives	Better	Best (ideally replaces other therapies)
Mechanism	Various molecular targets	Tissue regenerative/ reparative/ curative
Cost/cost concentration	Moderate	High
Trial design	Double-blind RCTs	Full blinding not always possible
Safety/adverse effects	Varying	Infection from allogeneic sources/ complications of concomitant immunosuppression/ risk to donor/ cancer from uncontrolled cell growth

## How are these perceived differences scrutinized in HTAs?

- Characteristics of cell-based therapies (and their clinical trials) most scrutinized
- Key criteria most concerning to HTA agencies
- Important trends and lessons

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## Health Technology Assessment Research Approach

Searched HTA Web sites for English-language appraisals for regenerative cell therapies—focused on indications other than immune reconstitution for cancer (e.g., hematologic malignancies)

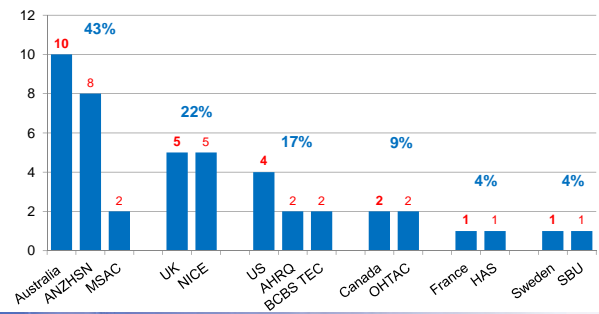
- **Australia**
  - Australia and New Zealand Horizon Scanning Network (ANZHSN)
  - Medical Services Advisory Committee (MSAC)
  - Pharmaceutical Benefits Advisory Committee (PBAC)
- **Canada**
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Ontario Health Technology Advisory Committee (OHTAC)
- **France**
  - Haute Autorité de Santé (HAS)
- **Germany**
  - Institute for Quality and Efficiency in Health Care (IQWiG)
  - Federal Joint Committee (G-BA)
- **Sweden**
  - Swedish Council on Health Technology Assessment (SBU)
  - Dental and Pharmaceuticals Benefits Agency (TLV)
- **United Kingdom**
  - National Institute for Health and Clinical Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
- **United States**
  - Agency for Healthcare Research and Quality (AHRQ)
  - BlueCross BlueShield Technology Evaluation Center (BCBS TEC)

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## Health Technology Assessments Reviewed

23 HTAs identified providing 26 assessments on different technologies/indications



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### Health Technology Assessments Identified—Most Regenerative Cell Therapies Reviewed Were Autologous

Technology/Indication	Cell Type	HTA Agencies
Chondrocyte implantation (Carticeel)	Autologous	HAS, MSAC, NICE, SBU
Hematopoietic stem cell therapy for regeneration of islet cells for type I diabetes	Autologous	ANZHSN
Bone marrow/stem cells for treatment of myocardial infarction/ischemic disease	Autologous	ANZHSN, BCBS TEC
Bone marrow cells for treatment of heart failure	Autologous	ANZHSN
Fibrin sealant derived from blood (Vivostat)	Autologous	ANZHSN
Vaccination for advanced stage III melanoma (M-Vax)	Autologous	MSAC
Islet cell transplant for type I diabetes	Autologous	NICE, OHTAC
Limb cell transplant for limb cell deficiency	Autologous	OHTAC
Limb cell transplant for limb cell pterygium	Autologous	OHTAC
Vaccination for advanced prostate cancer (sipuleucel-T [Provenge])	Autologous	AHRQ, BCBS TEC
Blood injection for tendonitis	Autologous	NICE
Islet cell transplantation for type I diabetes	Allogeneic	AHRQ, ANZHSN, NICE, OHTAC
Limb cell transplant for limb cell deficiency	Allogeneic	NICE, OHTAC
Apligraf for diabetic foot and venous leg ulcers	Allogeneic	ANZHSN
Apligraf for burn injuries	Allogeneic	AZNHSN
Alloderm for burn injuries	Allogeneic	ANZHSN

### Health Technology Assessments: General Findings

- In contrast to the situation with biologic drugs, most HTAs reviewing regenerative cell therapies were not manufacturer/sponsor initiated
  - 22 of 23 (96%) HTAs identified were initiated by HTA agencies and were forward-looking horizon scans, multitechnology reviews, or reviews of non-intellectual-property-based technologies/services

Technology Assessment Decisions		
Positive	Negative	Not Provided
6 (23%)	13 (50%)	7 (27%)

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### Health Technology Assessments: Key Data Reviewed

Criteria	% of assessments in which the		% of assessments with the concern in which the		
	Issue was examined	Issue was a concern	Technology was Rejected	Technology was Recommended	Technology was NOT Recommended*
Trial design/endpoints chosen/inclusion criteria or reporting/number of studies/study quality	100% (26/26)	85% (22/26)	45% (10/22)	18% (4/22)	82% (18/22)
Duration of effectiveness/need for readministration/retreatment	77% (20/26)	69% (18/26)	56% (10/18)	17% (3/18)	83% (15/18)
Safety/adverse events	92% (24/26)	69% (18/26)	56% (10/18)	22% (4/18)	78% (14/18)
Effectiveness/efficacy vs. alternatives or standard of care	100% (26/26)	65% (17/26)	59% (10/17)	6% (1/17)	94% (16/17)
Cost/cost concentration/cost-effectiveness	62% (16/26)	35% (9/26)	56% (5/9)	33% (3/9)	67% (6/9)
Sufficiency of cell source/skilled providers	42% (11/26)	35% (9/26)	44% (4/9)	44% (4/9)	56% (5/9)
Reproducibility/reliability of cell dosing/cell count and composition	27% (7/26)	12% (3/26)	0% (0/3)	0% (0/3)	100% (3/3)
Mechanism of action	19% (5/26)	4% (1/26)	100% (1/1)	0% (0/1)	0% (0/1)

\*Not Recommended = Rejected + No Decision Provided  
= All Assessments - Recommended

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### Health Technology Assessments—Major Concerns Included Study Quality, Safety, Effectiveness Versus Alternatives, and Long-Term Outcomes

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Mechanism of action	19% (5/26)	4% (1/26)	100% (1/1)	0% (0/1)	0% (0/1)

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### Health Technology Assessments—Demonstrating Effectiveness (If Not Superiority) Versus the Relevant Standard of Care May Be Critical

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Mechanism of action	19% (5/26)	4% (1/26)	100% (1/1)	0% (0/1)	0% (0/1)

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### Health Technology Assessments—Top Criticisms

**Top criticisms from HTA agencies:**

- **Suboptimal study design and inclusion of key endpoints (85% of assessments)**
  - Lack of blinding, proper randomization or controls
  - Lack of appropriate or most relevant endpoints
  - Consistency/comparability among enrolled patients, protocols and outcomes reported
- **Lack of long-term follow-up/insufficient trial duration (69% of assessments)**
  - Most HTAs wanted efficacy/safety outcomes for 1-5 years or more
- **Safety/incidence or severity of adverse events (69% of assessments)**
  - Safety to patients
  - Safety to allogeneic donors
- **Effectiveness/efficacy versus standard of care (SOC) (65% of assessments)**
  - No significant difference from comparators
  - Uncertain effectiveness versus alternatives or missing comparators

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### Lessons for Innovators

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## Recommendations For Reimbursement and Market Access

- **Expecting that innovative therapies will have a high burden of proof, it is important to align evidence development with HTA agency/payer requirements**
  - Innovators should do their homework early to determine what evidence key stakeholders will require for acceptance—not a one size fits all situation
- **Because many innovative therapies will be poorly understood, longer-term data may be required to demonstrate efficacy, safety and cost-effectiveness**
  - Studies should be well-designed (preferably RCTs), include homogeneous patient populations to reduce complexity in data interpretation whenever possible, and should focus on comparators and outcomes relevant to decision makers
  - At minimum, where established comparators exist, study designs should allow indirect comparison when possible
- **Economic analyses should capture the full cost of the treatment/episode of care (e.g., including everything from cell collection through implantation and product-specific aftercare)**
  - For pricing inpatient hospital-based therapies, in many cases innovators may be constrained by diagnosis-related group (DRG)-based bundled payment rates
- **Targeting small subpopulations with the greatest unmet need may somewhat reduce the evidence threshold for acceptance**



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## Thanks for your attention!

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