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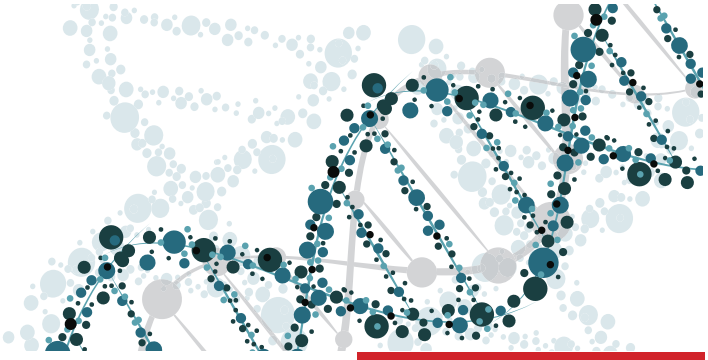
Global Health Brief



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Stem Cell Therapy

Stem cell therapies are becoming increasingly visible and supported in clinical medicine. The U.S. and Canada currently have well-defined stem cell business models and are making significant investments in the field. Japan has also seen new regulations governing regenerative medicine, and stem cell research activities are increasing in Australia and Singapore. With greater frequency of utilization emerging, claims assessors must understand this burgeoning field properly.

Sincerely,
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What Are Stem Cells?

Stem cells are cells in multicellular organisms that have not differentiated into specialized cells with specific functions. In essence, they are the precursor building blocks of tissues and organs, and are used in research and therapies.

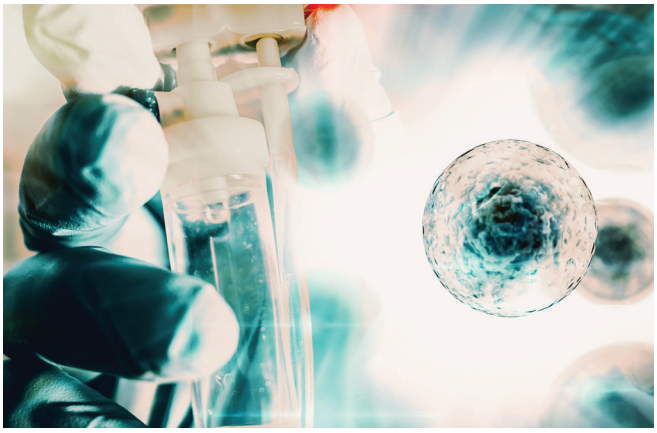
These are the three currently known types of stem cells:

- **Embryonic stem cells** are undifferentiated cells derived from embryos generated and cultured *in vitro* for assisted reproduction that have reached blastocyst stage (not ready for implantation) and legally donated for medical research. (The U.S. and the U.K. have informed consent rules that permit such donations.)
- **Adult stem cells** are undifferentiated cells found within differentiated systems or organs. The two best known adult stem cells are found in bone marrow: hematopoietic (or blood-forming) cells; and mesenchymal cells, which can generate bone, cartilage and fat. Hematopoietic cells can also come from peripheral blood or umbilical cord blood, and for therapies can be autologous (from the patient's own body) or allogeneic (from others). Adult stem cells have also been found in the adult brain and may exist in other organs as well.
- **Induced pluripotent stem cells** (iPSCs) are adult stem cells derived from differentiated cells which have been reprogrammed to assume the basic characteristics of embryonic stem cells. This technology, just over a decade old, won the Nobel Prize for its discoverers in 2012. These cells are useful in drug development and disease modeling and have the highest potential for use in therapies where risk of rejection is high, as they can be made from the cells of the affected individual.

Stem cells demonstrate two principal characteristics: self-renewal/clonality, referring to the cell's ability to reproduce itself over time without differentiation; and potency (sometimes called pluripotency), which is a stem cell's capacity to differentiate.

Stem Cells In Treatment Of Diseases

The term "stem cell therapy" is used to indicate that stem cells are being used as part of a treatment modality. These cells can, for example, be transplanted, infused, or injected into the body. The rationale of using stem cells in treatment is that these cells have a unique ability to repair and replace



specific damaged or abnormal cells arising from certain medical conditions, and could have the potential to cure certain conditions altogether.

Stem cells have already been used successfully since the 1970s to treat blood diseases such as lymphoblastic leukemia, myeloid leukemia, thalassemia, and multiple myeloma. This type of stem cell therapy, known as hematopoietic stem cell transplantation (HSCT), wherein the harvested stem cells are "transplanted" by intravenous infusion, was until recently the only proven clinical use of stem cells.

Stem cell transplantation takes place in three areas of treatment:

- To replace cells damaged either by cancer or by high-dose chemotherapy and radiotherapy treatments
- To provide a patient with a new immune system that would enable the identification and destruction of any remaining cancer cells persisting after chemotherapy or radiotherapy
- To provide limbal (corneal epithelial) cells to help burn patients needing ocular surface reconstruction, or for people with limbal stem cell deficiency

Stem cell transplantation in cancer cases is usually recommended only if certain criteria are met. The criteria may include type and stage of cancer, chance of relapse, sensitivity of the cancer to chemotherapy, and whether there is sufficient scientific evidence to support the treatment.

Several studies have been conducted on the applicability of stem cell therapy to conditions such as stroke and spinal cord injury, Parkinson's disease, Alzheimer's disease, as well as neuromuscular, heart, bone and joint diseases. Many successful trials have been conducted on animals, but only a few on humans. Of these, some have shown promise but only on a relatively small scale and so are not yet considered recommended clinical practices by the medical community.

Experimental Treatment or Not?

Although HSCT is well accepted among clinicians and insurers in cancer treatment, many stem cell therapies are still deemed "experimental treatments." Most policies clearly exclude it, but policy language can often be less than clear in defining what "experimental" means.

This is an example of a policy definition of experimental treatment:

> ***Experimental Treatment*** *shall mean treatment that is not recognized as an established treatment which shall be treatment that has undergone appropriate clinical trial and assessment and where there is sufficient evidence published in medical journals to confirm effectiveness.*

As published clinical evidence can still be debated by the medical profession and interpreting the significance of published evidence is still very much subjective, claims assessors face an uphill task to obtain the necessary information.

There are two ways to approach this:

- Once a treatment is deemed (or commissioned) "acceptable clinical practice" it should no longer be considered experimental. This commissioning is done either by an international body of authority such as the World Health Organization, or by local entities governing clinical practices such as ministries of health or equivalent authorities such as the U.K.'s National Institute of Health and Care Excellence (NICE).
- If a treatment has not been commissioned, insurers should fully engage their medical team and obtain the consensus of their chief medical officers as to whether there is sufficient evidence to determine if it can be accepted as a non-experimental treatment.

Medically Necessary or Not?

At the crux of any debate on stem cell treatments is whether or not these treatments, as a category, can be deemed "medically necessary." Because of the rapid advances in stem cell research for new diseases as well as the increasing ease of harvesting stem cells, insurers today are seeing many more stem cell therapy claims for conditions other than cancers, and it is highly likely more will come in the future.

As many clinical applications of stem cells are still considered experimental, some insurers are opting to include, in addition to the usual "Medically Necessary" and "Experimental Treatment" definitions in their policy wordings, specific provisions or exclusionary language governing stem cells, such as:

- Human bone marrow using hematopoietic stem cells preceded by total bone marrow ablation is covered
- Other stem cell transplants are excluded

Alternatively, an insurer may publish references stating which stem cell treatments it considers "medically necessary" and which "experimental," which would provide both claimants and their treating doctors with clear guidance. The "experimental treatment" language would need to be updated on a regular basis, as various treatments become accepted standards of care.

Or, rather than trying to list all stem cell experimental treatments individually, an insurer may insist that all such treatments except those previously confirmed as "medically necessary" (e.g., HSCT) be pre-authorized, which would allow each treatment to be validated on a case-by-case basis using the latest medical evidence. Because of the complexities of doing so, insurers would need comprehensive guidance in place to determine whether or not certain stem cell treatments are experimental.

Fundamental guidance would ask two questions:

- Does the treatment meet the definition of "medically necessary," which often includes being "in accordance with generally accepted standards of medical practice"?
- Is the treatment excluded as experimental? If so, then it is not considered "in accordance with generally accepted standards of medical practice".

For further guidance, insurers may use material from national medical accreditation bodies such as the U.K.'s NICE, which has now published 52 guidance notes mentioning stem cell therapies.

Underwriting/Claims Considerations

All of this being said, the medical utility of stem cells continues to be an area of debate. The ethics of stem cell therapy are often in the news when advances in science provide the potential for new treatments. Concerns have been raised in respect of how stem cells are obtained and their subsequent use.

On the other hand, interest in the field, as well as with new discoveries related to stem cells' growing therapeutic value, is increasing around the world. Well-defined business models already exist in the U.S. and Canada, where significant investment in research is coming both from governments and private sector companies. Regulatory changes in Japan with respect to regenerative medicine has attracted substantial interest and stem cell research activities in Australia and Singapore are increasing as well. Indeed, the global research firm Transparency Market Research projects that by 2025 the worldwide stem cell market will have attained a compound annual growth rate of 13.8% and will have grown to USD 270.5 billion.

In terms of cost, the main focus for insurers should be to ensure that medical treatments are appropriately provided and that costs meet the policy definition of being "reasonable and customary." This is especially important, as the cost of stem cell treatment can be significant and can also vary substantially from region to region. An autologous bone marrow transplant in the U.S., for example, can cost between USD 250,000 and USD 450,000 but in Asia between USD 50,000 and USD 70,000.

Right now, stem cell therapies are not likely to impact underwriting practices much in the near future. However, once their uses are well-established and the treatments they enable are proven more effective than other treatment modalities, insurers might look at considering seeing claims for stem cell therapies in a better light. ■

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