Policy Number	**SUR703.003**
Policy Effective Date	**07/15/2023**
Policy End Date	**12/31/2024**

Brain Tissue Transplantation and Neurotransplantation

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Related Policies (if applicable)
SUR703.001: Organ and Tissue Transplantation (General Donor and Recipient Information)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Brain tissue transplantation or neurotransplantation for all indications, including but not limited to the treatment of Parkinson's disease, **is considered experimental, investigational and/or unproven** when performed by any method, including but not limited to:

- Adrenal-to-brain transplantation with autograft or fetal allograft; or
- Human or xenogeneic fetal mesencephalic transplantation.

Xenotransplantation or heterotransplantation (between different species) such as fetal porcine and/or swine brain cells **is considered experimental, investigational and/or unproven** for all indications, including but not limited to the treatment of Parkinson's disease.

Policy Guidelines

None.

Description

This medical policy primarily addresses brain tissue transplantation and neurotransplantation for the treatment of Parkinson's disease, as there is lack of data for the use in other indications.

Parkinson's disease is a degenerative disease that includes symptoms of resting tremor, rigidity, and bradykinesia. The condition usually appears after age 40 years and progresses slowly over many years. Drug treatment with levodopa can usually restore smooth motor function for up to 5–10 years after onset of Parkinson's disease by permitting surviving dopaminergic cells to bypass a rate-limiting enzyme, tyrosine hydroxylase, and thus produce enough dopamine to maintain adequate motor function. Eventually, more dopaminergic cells die, leading to progressive disability.

In an effort to modify motor disability of advanced Parkinson's disease, embryonic mesencephalic (midbrain) tissue containing dopamine-producing cells is implanted into the caudate and putamen of the candidate's brain.

The transplantation of adrenal medullary tissue to the corpus striatum is intended to ameliorate the motor and postural dysfunctions of Parkinson's disease. Striatal dopamine is depleted in Parkinson's disease patients. The rationale for the procedure is that adrenal tissue may restore dopamine activity in the corpus striatum. Adrenal-to-brain transplantation can involve either autografts or fetal allografts.

Autotransplantation entails simultaneous adrenalectomy and craniotomy with subsequent implantation of adrenal medullary tissue. Adrenal tissue is usually implanted in fragments into the caudate nucleus at the margin of the lateral ventricle, such that the tissue is exposed to cerebrospinal fluid (CSF). Tissue fragments can be anchored in place with surgical staples or with Gelfoam®. Besides the caudate nucleus, the putamen has also been used as an implantation site. Open microsurgical insertion of the tissue has been used in addition to stereotactic localization and implantation using a cannula.

Allografting involves harvesting adrenal tissue from an aborted fetus. The surgical techniques are the same as autotransplantation, with the exception of the adrenalectomy.

Xenotransplantation is the practice of transplanting, implanting or infusing cells, tissues or organs from one species to another. (1) Historically, surgeons used the term heterotransplantation to refer to cross-species transplantation. This term was substituted with the word xenotransplantation in the early 1960s. (2)

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research (CBER), under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. (3)

Rationale

This policy was developed in 2000. It has been updated periodically using the PubMed database. The most recent literature review was performed through December 2022.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care of surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

In 2003, Olanow et al. reported on a double-blind, placebo-controlled trial of fetal-nigral (the layer of gray substance separating the tegmentum of the midbrain from the crus cerebri) transplantation in 34 patients with advanced Parkinson's disease followed prospectively for 24 months. (4) Patients were randomized to one of four donor bilateral transplantation or a placebo procedure. The authors reported no significant difference in overall effect (p=0.244) and persistent dyskinesia in 56% of patients in the transplant group. While a treatment effect was seen in milder patients (p=0.006), the authors concluded the results did not support fetal nigral transplantation as a recommended therapy for Parkinson's disease.

Gordon et al. reported on a double-blind, placebo-controlled RCT, 40 patients with Parkinson's disease were randomized to receive bilateral 4-donor implantation of embryonic mesencephalic cells or a placebo procedure and followed for one year. (6) The authors reported that patients in the National Institute of Neurological Disorders and Stroke (NINDS) trial improved significantly on reaction and movement times twelve months post transplantation (p=0.005) while patients in the placebo group deteriorated. (6) The authors concluded reaction time analyses can be useful in identifying subtle motor performance changes over time.

In 2004, McRae et al. reported on a portion of the NINDS RCT that evaluated QOL of 30 of the 40 study patients at baseline, four, eight, and twelve months post procedure. (7) The authors reported a strong placebo effect, since all patients reported better scores if they believed they had received the transplant.

Trott et al. reported on cognition one-year post-procedure in the NINDS study. (5) The authors reported no significant differences in cognitive performance at follow-up for the transplant or placebo group as performance for most measures remained the same.

In 2010, Ma et al. reported long-term clinical and positron-emission tomography (PET) outcomes from 33 participants who were followed for 2 years after transplantation and 15 of these subjects who were followed for 2 additional years. (8) The authors had previously reported the results of a 1-year double-blind, placebo-controlled study of embryonic dopamine cell implantation for Parkinson's disease. At the end of the blinded phase, they found a significant increase in putamen uptake on ^{18}F-fluorodopa (^{18}F-FDOPA) PET reflecting the viability of the grafts. Nonetheless, clinical improvement was significant only in younger (age $\leq$ 60 years) transplant recipients, as indicated by a reduction in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores. Longitudinal changes in UPDRS motor ratings and caudate and putamen ^{18}F-FDOPA uptake were assessed with repeated-measures analysis of variance (ANOVA). Relationships between these changes over time were evaluated by the analysis of within-subject correlations. The current results expand on the original findings, with the authors now reporting continued clinical improvement at 2 years to nearly twice the degree observed at 1 year. Furthermore, they found that improvement was sustained in the subgroup of transplant recipients who were followed for 4 years after surgery. These long-term findings agree with the results of other open-label studies. In this study, the authors confirmed the previous finding that age significantly affected clinical outcome at 1 year after transplantation. Although, the younger patients still showed relatively better clinical improvement than did the older patients at 2 years after transplant surgery, this group difference was not significant, even with most of the subjects still in the study. Thus, the impact of age on clinical outcome may be time-dependent, with a slower time course of clinical benefit after transplantation in older subjects. Nevertheless, the time course of the age effect on clinical outcome could not be assessed fully because of the predominant dropout of the older subjects by the final time point. The current study included the 5 transplant patients with graft-induced dyskinesia (GID) who were no longer taking dopaminergic medications as reported previously. These subjects all belonged to the young subgroup of transplant recipients and had greater clinical improvement and putamen F-FDOPA uptake at 1 and 2 years than did those who did not develop this complication. That said, similar clinical outcomes and changes in PET signal were seen across the entire cohort whether or not these subjects were included in the analysis. Thus, the therapeutic window for symptom relief after engraftment may not be as narrow as had been previously suggested. Nonetheless, GID remains a major challenge for neural transplantation in Parkinson's disease. Studies are ongoing to develop new surgical approaches to avoid this troubling side effect.

Practice Guidelines and Position Statements

American Academy of Neurology (AAN)

In 2006 (reaffirmed on October 17, 2009, and July 13, 2013), The AAN created a practice parameter on the management of Parkinson's disease relating to neuroprotective strategies and alternative treatments. They stated there is a severe limitation in current studies due to the absence of accepted surrogate endpoints that mirror nigrostriatal dopaminergic neuron loss; reliable and validated surrogated endpoints need to be developed. Secondly, accurate early diagnosis and improved knowledge of disease progression will facilitate clinical trials of potential neuroprotective agents. Another factor for consideration is that by the time of clinical diagnosis, over 70% of dopaminergic cell loss has already occurred. More emphasis needs to be placed on the development of methods to identify presymptomatic patients for clinical trials of potential neuroprotective therapies. In addition, innovative trial designs with long-term follow-up need to be implemented to provide convincing evidence of neuronal protection. Alternative therapies are widely used by patients in Parkinson's disease treatment. Few studies are available to demonstrate safety or effectiveness of these treatments, exposing patients to the possibility of ineffective or possibly harmful treatments. These therapies need to be tested in the same rigorous manner as conventional therapies in order to provide an evidence-based rationale for their use. The AAN practice parameter was retired by the Guideline Subcommittee of the AAN Institute on January 26, 2019. The AAN does not have resources to update the Guideline. (9)

International Parkinson and Movement Disorder Society (MDS)

In 2021, the International Parkinson and MDS updated their position paper on the use of stem cell therapies for Parkinson's disease, reconfirming their earlier conclusion that human fetal cell transplantation remains unproven. The paper concluded that cell-based therapies should demonstrate efficacy and safety particularly lacking adverse immune reactions, tumor formation or dyskinesias. While there have been advances in the research of stem-cell therapy, especially for PD, and clinical trials are ongoing, there is still not enough evidence to support widespread use of cell-based therapies for PD outside of carefully controlled clinical trials. (10)

Summary of Evidence

There is limited data in the published, peer-reviewed scientific literature regarding the current clinical use of adrenal-to-brain transplantation in humans. For individuals diagnosed with Parkinson's disease who receive adrenal-to-brain transplantation the evidence to date is limited to uncontrolled, short term studies with small sample sizes, and case studies. Relevant outcomes are change in disease status, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. Focus has shifted towards fetal mesencephalic transplantation, however at present there is only limited number of controlled trials with small sample sizes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	64999
HCPCS Codes	S2103

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) **does not** have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been **developed** since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
07/15/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. References revised; some removed, and no new references added.
06/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 29, 33-34, 36, and 74-77. Title changed from: Hematopoietic Stem-Cell (HSC) Transplantation (HSCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information).
04/15/2018	Reviewed. No changes.
06/15/2017	Document updated with literature review. Coverage unchanged. The following NOTE was added, Refer to SUR703.001, Organ and Tissue Transplantation for general donor and recipient information.
05/15/2016	Reviewed. No changes.
07/15/2015	Document updated with literature review. Donor lymphocyte infusion and hematopoietic stem-cell boost coverage statements removed from each individual hematopoietic stem-cell transplantation medical policy back to this general donor and recipient informational medical policy; coverage for each procedure remains unchanged. Title changed from Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information).
06/01/2014	Document updated with literature review. The following was added: 1) Genetic modification of donor leukocytes for infusion at any point following any SCS treatment is considered experimental, investigational and/or unproven; 2) Short tandem repeat (STR) markers may be considered medically necessary when used in pre- or post-SCS testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment; and, 3) All other uses of STR markers, including use for a condition that was originally considered experimental, investigational and/or unproven, are considered experimental, investigational and/or unproven.

04/01/2010	Revised/updated entire document. Policy contains criteria for umbilical cord blood donation and storage, prophylactic stem-cell storage, and purging of stem-cells, along with general information regarding stem-cell harvesting, typing, and usage. Medical policy combined with SUR703.022, SUR703.023, and SUR703.024. This policy is no longer scheduled for routine literature review and update.
04/07/2005	CPT/HCPCS code(s) updated (SUR703.022)
11/15/2004	Revised/updated entire document (SUR703.002)
04/01/2003	CPT/HCPCS code(s) updated (SUR703.022)
06/01/2001	CPT/HCPCS code(s) updated (SUR703.022)
05/01/2000	Revised/updated entire document (SUR703.002)
01/01/2000	Revised/updated entire document (SUR703.002)
06/01/1999	Revised/updated entire document (SUR703.002)
05/01/1999	Revised/updated entire document (SUR703.002)
12/01/1998	Revised/updated entire document (SUR703.002)
09/01/1996	New medical document (SUR703.002)
05/01/1996	Medical policy number changed (SUR713.002)
10/01/1994	Revised/updated entire document (SUR703.002)
10/01/1993	Revised/updated entire document (SUR703.002)
07/01/1993	Revised/updated entire document (SUR703.002)
04/01/1993	Revised/updated entire document (SUR703.002)
01/01/1993	Revised/updated entire document (SUR703.002)
07/01/1992	Revised/updated entire document (SUR703.002)
01/01/1992	Revised/updated entire document (SUR703.002)
09/01/1991	Revised/updated entire document (SUR703.002)
05/01/1990	New medical document (SUR703.002)