4.02.06	Uterus Transplantation for Absolute Uterine Factor Infertility		
Original Policy Date:	June 1, 2022	**Effective Date:**	June 1, 2022
Section:	4.0 OB/Gyn/Reproduction	**Page:**	Page 1 of 12

Policy Statement

Uterus transplantation for absolute uterine factor infertility is considered investigational.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following codes may be used for this procedure:

- **0664T:** Donor hysterectomy (including cold preservation); open, from cadaver donor
- **0665T:** Donor hysterectomy (including cold preservation); open, from living donor
- **0666T:** Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
- **0667T:** Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor
- **0668T:** Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
- **0669T:** Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
- **0670T:** Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each

Description

Absolute uterine factor infertility is a condition in which an individual is unable to achieve pregnancy due to an absent or non-functioning uterus. Uterus transplantation may present a childbearing option that is an alternative to existing family planning pathways, including adoption, foster parenting, and gestational carrier pregnancy. Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner.

Related Policies

- Laparoscopic and Percutaneous Techniques for the Myolysis of Uterine Fibroids

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Restorative or life-enhancing uterine vascularized composite allograft (VCA) procurement and transplantation falls under the oversight of the Organ Procurement and Transplantation Network (OPTN).[22,]

Rationale

Background

Absolute Uterine Factor Infertility

Absolute uterine factor infertility (AUFI) refers to infertility that is attributable to an absent or non-functional uterus due to congenital, surgical, anatomical, or acquired factors that prevent embryo implantation and term pregnancy. AUFI is estimated to impact 1 in 500 females of childbearing age.[1,2,]

Uterine agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome results in the congenital absence of the uterus or presence of a rudimentary solid bipartite uterus. MRKH syndrome accounts for less than 3% of all müllerian malformations with an estimated prevalence of 1 in 4500 females.[3,4,] Individuals with MRKH syndrome type I present with 2 kidneys and are considered ideal candidates for uterine transplantation. Individuals with MRKH syndrome type II presenting with a single kidney have a higher risk of medication-induced nephrotoxicity and associated obstetric complications (e.g., severe preeclampsia).[5,]

Hysterectomy is the most common cause of acquired AUFI, with 240,000 procedures taking place in females under age 44 in the United States.[6,] In one clinical trial screening study of 239 individuals at the Cleveland Clinic, indications for uterus transplantation included prior hysterectomy (64%) and congenital anomalies (32%). Among individuals with prior hysterectomy, 50% were performed for benign indications, 25% for malignancy, and 25% for obstetric complications.[7,]

Uterus Transplantation

Uterus transplantation may provide a unique fertility restoration option for individuals desiring to carry and birth a child.[8,] Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner. Once screening and consent is established for all involved parties, in-vitro fertilization is performed prior to transplantation to ensure fertilization and normal embryo development.[9,] The transplantation surgery involves radical hysterectomy in the donor to ensure long vascular pedicles for transplantation;[10,] however, several cases of robot-assisted laparoscopic approaches have been reported.[11,12,] An advantage of uterus procurement in a deceased donor involves freedom to transect ureters, but this convenience is balanced by the potential for prolonged uterus ischemic time.[13,] The surgical approach in the recipient is dictated by underlying pelvic anatomy which may be impacted by AUFI etiology. For example, in individuals with Asherman syndrome, a traditional total hysterectomy must first be performed in the recipient. Immunosuppression is initiated at the time of transplantation and protocol and for-cause cervical biopsies enable monitoring for organ rejection.[14,15,] After 6 to 12 months of immunosuppression, embryo transfer, pregnancy, and cesarean delivery may follow. When childbearing has been deemed complete, the

transplanted uterus is removed to avoid lifelong immunosuppression. Thus, uterus transplantation is the first form of organ transplantation intended to be temporary.[1,9,]

The first human uterus transplant was performed in 2000 in Saudi Arabia with a 46 year old living donor and 26 year old recipient with acquired AUFI due to hysterectomy for prior post-partum hemorrhage. Due to the development of acute vascular thrombosis at 3 months post-transplant, graft hysterectomy was required.[16,] The first successful live birth occurred in 2014 in Sweden in a 35 year old recipient with MRKH syndrome via a living, 61 year old, two-parous donor. The recipient was admitted with preeclampsia at 31 weeks, and a healthy male child was born 5 days later via cesarean delivery.[17,] The first live birth in the United States occurred in 2017 in a 29 year old recipient with MRKH syndrome via a living, 32 year old, two-parous donor.[18,] According to the Organ Procurement and Transplantation Network (OPTN), 35 uterus transplants have been performed in the United States via 13 deceased and 22 living donors as of March 2022.[19,]

Literature has explored the implications of uterus transplantation in transgender women, identifying several theoretical medical issues in genetic males meriting further investigation. These include creation of adequate de novo uterine vascularization, administration of appropriate hormone replacement therapy, and placement of the donor uterus in a nongynecoid pelvis.[20,21,]

Literature Review

Evidence reviews 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, 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 1 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 or 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. Randomized controlled trials 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.

Due to the nature of absolute uterine factor infertility (AUFI), there are no RCTs directly comparing uterus transplant with alternatives. Systematic reviews are based on case series. Studies comparing surgical technique, infection prophylaxis, and immunosuppressive regimens are not germane to this evidence review.

Uterus Transplantation

Clinical Context and Therapy Purpose

The purpose of uterus transplantation in individuals who have AUFI is to provide a unique childbearing option that is an alternative to or a desired improvement on existing family planning pathways.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with AUFI due to an absent or non-functioning uterus. Most congenital cases of uterine agenesis are due to Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Individuals with uterine factors contributing to, but not exclusively causing, infertility are generally not considered candidates for uterus transplantation unless established medical or surgical therapeutic options (e.g., hysteroscopic adhesiolysis, myomectomy) have failed. These factors may include müllerian malformations, intrauterine adhesions or Asherman syndrome, radiation injury, poor endometrial receptivity, or uterine leiomyoma(s) of submucosal or intramural type. Most acquired cases of AUFI are due to prior hysterectomy for malignancy, obstetric complications, or uterine fibroids.

Interventions
The therapy being considered is uterus transplantation. Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner. Uterus transplantation is the first organ transplantation procedure intended to be temporary, concluding with graft hysterectomy to avoid the need for lifelong immunosuppression once childbearing is deemed complete. Pregnancy in the transplanted uterus is achieved through in-vitro fertilization (IVF) and embryo transfer.

Comparators
The relevant comparators are alternative family planning pathways, such as adoption, foster parenting, or gestational carrier pregnancy.

Outcomes
The general outcomes of interest are health status measures, perinatal outcomes, quality of life, treatment-related morbidity, and treatment-related mortality. Benefits and harms should be considered for the donor, recipient, developing fetus, and newborn. Several years of follow-up may be required to fully observe outcomes through all stages of the procedure from procurement through graft removal.

In 2020, the United States Uterus Transplant Consortium issued guidelines for standardized nomenclature and reporting in uterus transplantation trials, identifying 7 progressive stages with milestones of success: (1) technical, (2) menstruation, (3) embryo implantation, (4) pregnancy, (5) delivery, (6) graft removal, and (7) long-term follow-up.[23,] Primary outcomes of interest include recipient posttransplant survival, graft survival, and the transplant success rate, defined as the delivery of a child per transplanted recipient reported at 2-year intervals for the duration of the transplant. Secondary outcomes of interest for recipients include onset of menstruation or withdrawal bleeding, clinical pregnancy, failed embryo transfer, miscarriage, rejection episode(s), stricture, acute kidney injury, adjusted live birth rate, preeclampsia, malignancy, metabolic wellness, health of the newborn, and health of the child. The primary outcome of interest for living uterus donors is patient survival at 1 and 2 years after donation. Secondary outcomes for the living donor include complications (e.g., ureteral complications), hospitalizations, and adverse renal events.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Brannstrom etl al (2021) published a systematic review of all published clinical uterus transplantation data and major interim results from 2000 through 2019.[1,] Of 62 uterus transplants identified for the review, the overall technical success rate defined as subsequent regular menstruation, was 76%. Technical success rates for living and deceased donor procedures were 78% and 64%, respectively. Rates of serious postsurgical complications were 18% for living donors and 19% for recipients. Most uterus transplantation procedures to date have involved living donors (51/62; 82%). Complications in living donors have included ureteric laceration, urinary bladder hypotonia, unplanned bilateral oophorectomy, vaginal dehiscence, fecal impaction, and unilateral pyelonephritis and hydronephrosis. Postoperative complications in recipients have included vaginal anastomotic stenosis and treatable episodes of minor to severe graft rejection.

The cumulative live birth rate per transplant attempt, and per surgically successful uterus transplant is estimated to be >60% and >80%, respectively, as based on 24 published live birth accounts from interim data. High rates of preterm birth (19/24; 80%) and respiratory distress syndrome in the newborn (9/24; 38%) have been observed across cases. Obstetric complications have included preeclampsia, gestational hypertension, and several cases of placenta previa and gestational diabetes. Newborns had an Apgar score of 8 or higher at 5 minutes. One minor malformation in a female newborn involving an anteriorly caudally displaced urethra was reported, which was surgically corrected at 11 months. The reviewers concluded that "the modest success rate and the fairly high complication rate among [living donors], indicate that further research and development under strict governance are needed before this option should be widely offered."

Case Series

Characteristics and interim results from select case series are summarized in Tables 1 and 2.

Table 1. Summary of Key Case Series Characteristics

Study	Country (Years)	LD Criteria	Recipient Criteria	Participants
Johannesson et al (2021);[24,] Putman et al (2021)[25,]	United States (2016-2019)	NR	Women with AUFI and intact native ovaries and of childbearing age 20 to 35, negative history of or prior vaccination for HPV, and meets physiological criteria	Median age, 30 years (range, 20 to 35); 17 MRKH type I 1 MRKH type II 2 prior hysterectomy for leiomyoma(s) Mean donor age, NR 18 LD UTx; 2 DD UTx
Fronek et al (2021)[26,]	Czech Republic (2016-2018)	Female 18 to 60 years of age, ≤4 childbirths, ≤1 cesarean section, good general health	Female 18 to 40 years of age, AUFI based on congenital or acquired uterus absence, desire for a child, having a male partner, and good general health	Mean recipient age, 28±3 years; 9 MRKH type I; 1 MRKH type II; Mean donor age, 46±14 years; 5 LD UTx (all related); 5 DD UTx; 5 postmenopausal; 2 nulliparous

AUFI: absolute uterine factor infertility; DD: deceased donor; HPV: human papillomavirus; LD: living donor; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; NR: not reported; UTx: uterus transplant.

Table 2. Summary of Key Case Series Results

Study	Survival	Embryo Transfers, total (range)	Clinical Pregnancy, total (n)	Live Births, total (n)	Live Birth Success Rate	Complications
Johannesson et al (2021);[24] Putman et al (2021)[25]	Graft: 14/20 (70% at 3 years)	30 (1 to 6)	19 (14)	13 (12); 11 LD and 1 DD; 10 MRKH type I; 1 MRKH type II; 1 prior hysterectomy	Overall: 60%; With surgical success: 86%	acute rejection, gestational hypertension, preeclampsia, gestational diabetes mellitus, placenta previa, preterm delivery
Fronek et al (2021)[26]	Graft: 7/10 (70% at 1 year); Recipient: 10/10 (100% at 2 years)	40 (4 to 11)	7 (5)	3 (3); 2 LD and 1 nulliparous DD	Overall: 30%; With surgical success: 43%	vaginal stenosis, leukopenia, UTI, acute rejection, CMV replication, graft HSV infection, *C. difficile* infection; HLA mismatch, CKD

CKD: chronic kidney disease; CMV: cytomegalovirus; DD: deceased donor; HLA: human leukocyte antigen; HSV: herpes simplex virus; LD: living donor; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; UTI: urinary tract infection.

Section Summary: Uterus Transplantation

Case series of uterus transplantation for AUFI have predominantly enrolled individuals with MRKH syndrome type I. A systematic review of interim trial data has reported live birth success estimates exceeding 60% overall and 80% among transplant attempts with surgical success. Slightly higher technical success rates have been reported for living donor compared to deceased donor procedures (78% vs. 64%, respectively). Rates of serious complications are high among both recipients (19%) and living donors (18%). High rates of preterm birth (80%) and episodes of acute respiratory distress syndrome in the newborn have been reported. Long-term health outcomes in children born via uterus transplantation and recipients following graft hysterectomy continue to accumulate in ongoing trials.

Summary of Evidence

For individuals with AUFI who receive uterus transplantation, the evidence includes a systematic review and case series. Relevant outcomes are health status measures, perinatal outcomes, quality of life, treatment-related morbidity, and treatment-related mortality. One systematic review of 62 uterus transplants has reported 24 published live birth accounts, with an estimated overall live birth success rate exceeding 80% among surgically successful transplants. Surgical success rates have ranged from 64% to 78% for deceased and living donor procedures, respectively. Complications have been reported in 19% of recipients and 18% of living donors. High rates of preterm birth (80%) and episodes of acute respiratory distress syndrome in the newborn have been reported. Data for individuals with acquired AUFI are lacking. Further study is necessary to increase success rates, decrease complications and preterm births, and assess long-term outcomes in recipients and their children. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2018 (reaffirmed 2020), the American College of Obstetricians and Gynecologists (ACOG) Committee on Adolescent Health Care issued a Committee Opinion (Number 728) on the diagnosis, management, and treatment of müllerian agenesis.[27,] Regarding future fertility options, the opinion states that while live births have resulted from uterine transplantation, "given limited data, this procedure currently is considered experimental and is not widely available."

American Society for Reproductive Medicine

In 2018, the American Society for Reproductive Medicine (ASRM) issued a position statement recognizing uterus transplantation as the first successful medical treatment for absolute uterine factor infertility, emphasizing its experimental nature.[28,] The statement recommends that the procedure should be performed within an Institutional Review Board-approved research protocol, with recommendations for the composition of "well-coordinated and multidisciplinary" uterus transplantation teams and suggested recipient inclusion and exclusion criteria.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02741102	Uterine Transplant in Absolute Uterine Infertility (AUIF)	10	Jan 2023 (not yet recruiting)
NCT02573415	Uterine Transplantation for the Treatment of Uterine Factor Infertility	10	Oct 2023 (enrolling by invitation)
NCT03252795	Uterus Transplantation From a Multi-organ Donor: A Prospective Trial	20	Dec 2023 (recruiting)
NCT04244409	INvestigational Study Into Transplantation of the Uterus (INSITU)	10	Feb 2024 (recruiting)
NCT05089513	Uterus Transplantation by Robotics and in Donor and Recipient (Robot2)	5	Aug 2024 (recruiting)
NCT03689842	Feasibility Study of Uterine Transplantation From Living Donors in Terms of Efficacy and Safety in Patients With Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH)	20	Jun 2025 (recruiting)
NCT04026893	Deceased Uterine Transplant in Absolute Uterine Infertility	250	Oct 2025 (not yet recruiting)
NCT03277430	Uterus Transplantation From Live Donors and From Deceased Donors - Clinical Study (UTxLD/DBD)	20	Dec 2025 (recruiting)
NCT03581019	Uterus Transplantation From Deceased Donor - Gothenburg III	8	Dec 2025 (enrolling by invitation)
NCT02656550	Uterine Transplantation and Pregnancy Induction in Women Affected by Absolute Uterine Infertility	20	Jan 2026 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03307356	The University of Pennsylvania Uterus Transplant for Uterine Factor Infertility Trial (UNTIL)	5	Jul 2029 (enrolling by invitation)
NCT05263076	Uterine Transplantation and Pregnancy Induction in Women Affected by Absolute Uterine Factor Infertility	10	Dec 2030 (not yet recruiting)

NCT: national clinical trial

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor

Type	Code	Description
	0665T	Donor hysterectomy (including cold preservation); open, from living donor
	0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
	0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor
	0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
	0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
	0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2022	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New Policy **Policy Statement:** N/A	**Uterus Transplantation for Absolute Uterine Factor Infertility 4.02.06** **Policy Statement:** Uterus transplantation for absolute uterine factor infertility is considered **investigational**.