Infertility Diagnosis and Treatment

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Instructions for Use

Table of Contents Page

Related Commercial Policies
- Infertility Services
- Preimplantation Genetic Testing

Medicare Advantage Coverage Summary
- Infertility Services

Related Optum Clinical Guideline
- Fertility Solutions Medical Necessity Clinical Guideline: Infertility

Coverage Rationale

See Benefit Considerations

For medical necessity reviews, refer to the Clinical Guideline titled Fertility Solutions Medical Necessity Clinical Guideline: Infertility.

The following tests or procedures are proven and medically necessary for diagnosing or treating Infertility:

- Antisperm antibodies
- Antral follicle count
- Clomiphene citrate challenge test
- Cryopreservation of sperm, semen, or embryos for individuals who are undergoing treatment with assisted reproductive technologies or are planning to undergo therapies that threaten their reproductive health, such as cancer chemotherapy
- Cryopreservation of *mature* oocytes (eggs) for women under the age of 42 who are undergoing treatment with assisted reproductive technologies or are planning to undergo therapies that threaten their reproductive health, such as cancer chemotherapy
- Genetic screening tests:
  - Cystic fibrosis gene mutations
  - Karyotyping for chromosomal abnormalities
  - Y-chromosome microdeletion testing
- Hormone level tests:
  - Antimüllerian hormone (AMH)
  - Estradiol
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
  - Progesterone
  - Prolactin

    - Testosterone (total and free)
    - Thyroid-stimulating hormone (TSH)
- Hysterosalpingogram (HSG)
- Diagnostic hysteroscopy
- Diagnostic laparoscopy with or without chromotubation
- Leukocyte count in semen
- Pelvic ultrasound (transabdominal or transvaginal)
- Post-ejaculatory urinalysis
- Scrotal, testicular or transrectal ultrasound
- Semen analysis
- Sonohysterogram or saline infusion ultrasound
- Testicular biopsy
- Vasography

Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for diagnosing or treating Infertility:

- Co-culture of embryos
- Computer-assisted sperm analysis (CASA)
- Cryopreservation of *immature* oocytes (eggs), ovarian tissue, or testicular tissue
- EmbryoGlue®
- Hyaluronan binding assay (HBA)
- In vitro maturation (IVM) of oocytes
- Inhibin B
- Postcoital cervical mucus penetration test
- Reactive oxygen species (ROS) test
- Sperm acrosome reaction test
- Sperm DNA integrity/fragmentation tests [e.g., sperm chromatin structure assay (SCSA), single-cell gel electrophoresis assay (Comet), deoxynucleotidyl transferase-mediated dUTP nick end labeling assay (TUNEL), sperm chromatin dispersion (SCD) or Sperm DNA Decondensation™ Test (SDD)]
- Sperm penetration assays
- Uterine/endometrial receptivity testing
- Treatments to improve uterine/endometrial receptivity (e.g., immunotherapy, endometrial scratching, uterine artery vasodilation)

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Codes*	Required Clinical Information
Infertility Diagnosis and Treatment	
0568T, 58321, 58322, 58323, 58752, 58760, 58970, 58974, 58976, 89250, 89251, 89253, 89254, 89255, 89257, 89258, 89259, 89260, 89261, 89264, 89268, 89272, 89280, 89281, 89290, 89291, 89335, 89337, 89342, 89343, 89344 89346, 89352, 89353, 89354, 89356, S4011, S4013, S4014, S4015, S4016, S4022, S4023, S4025,	Medical notes documenting all of the following: • Initial history and physical • All clinical notes including rationale for proposed treatment plan • All ovarian stimulation sheets for timed intercourse, IUI, and/or IVF cycles • All embryology reports • All operative reports • Laboratory report FSH, AMH, estradiol, and any other pertinent information • Ultrasound report antral follicle count and any other pertinent information • HSG report • Semen analysis

CPT/HCPCS Codes*	Required Clinical Information
Infertility Diagnosis and Treatment	
S4026, S4028, S4030, S4031, S4035, S4037	

**For code descriptions, see the Applicable Codes section.*

Definitions

Infertility: A disease (an interruption, cessation, or disorder of body functions, systems, or organs) of the reproductive tract which prevents the conception of a child or the ability to carry a pregnancy to delivery. It is defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women age 35 years or older.

Preimplantation Genetic Testing (PGT): A test performed to analyze the DNA from oocytes or embryos for human leukocyte antigen (HLA)-typing or for determining genetic abnormalities. These include:

- PGT-A: For aneuploidy screening (formerly PGS)
- PGT-M: For monogenic/single gene defects (formerly single-gene PGD)
- PGT-SR: For chromosomal structural rearrangements (formerly chromosomal PGD)

(Zegers-Hochschild et al., 2017)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0568T	Introduction of mixture of saline and air for sonosalpingography to confirm occlusion of fallopian tubes, transcervical approach, including transvaginal ultrasound and pelvic ultrasound
52402	Cystourethroscopy with transurethral resection or incision of ejaculatory ducts
54500	Biopsy of testis, needle (separate procedure)
54505	Biopsy of testis, incisional (separate procedure)
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymograms, unilateral or bilateral
55530	Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)
55535	Excision of varicocele or ligation of spermatic veins for varicocele; abdominal approach
55550	Laparoscopy, surgical, with ligation of spermatic veins for varicocele
55870	Electroejaculation
58140	Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; abdominal approach
58145	Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; vaginal approach
58146	Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g, abdominal approach
58321	Artificial insemination; intra-cervical
58322	Artificial insemination; intra-uterine
58323	Sperm washing for artificial insemination

CPT Code	Description
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography
58345	Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography
58350	Chromotubation of oviduct, including materials
58545	Laparoscopy, surgical, myomectomy, excision; 1 to 4 intramural myomas with total weight of 250 g or less and/or removal of surface myomas
58546	Laparoscopy, surgical, myomectomy, excision; 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g
58555	Hysteroscopy, diagnostic (separate procedure)
58559	Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method)
58660	Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure)
58662	Laparoscopy, surgical; with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method
58670	Laparoscopy, surgical; with fulguration of oviducts (with or without transection)
58672	Laparoscopy, surgical; with fimbrioplasty
58673	Laparoscopy, surgical; with salpingostomy (salpingoneostomy)
58740	Lysis of adhesions (salpingolysis, ovariolysis)
58752	Tubouterine implantation
58760	Fimbrioplasty
58770	Salpingostomy (salpingoneostomy)
58800	Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); vaginal approach
58805	Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); abdominal approach
58920	Wedge resection or bisection of ovary, unilateral or bilateral
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
74440	Vasography, vesiculography, or epididymography, radiological supervision and interpretation
74740	Hysterosalpingography, radiological supervision and interpretation
74742	Transcervical catheterization of fallopian tube, radiological supervision and interpretation
76830	Ultrasound, transvaginal
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76856	Ultrasound, pelvic (nonobstetric), real time with image documentation; complete
76857	Ultrasound, pelvic (nonobstetric), real time with image documentation; limited or follow-up (e.g., for follicles)
76870	Ultrasound, scrotum and contents
76872	Ultrasound, transrectal
76948	Ultrasonic guidance for aspiration of ova, imaging supervision and interpretation
80415	Chorionic gonadotropin stimulation panel; estradiol response This panel must include the following: Estradiol, total (82670 x 2 on 3 pooled blood samples)
80426	Gonadotropin releasing hormone stimulation panel This panel must include the following: Follicle stimulating hormone (FSH) (83001 x 4) Luteinizing hormone (LH) (83002 x 4)
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)

CPT Code	Description
82397	Chemiluminescent assay
82670	Estradiol; total
83001	Gonadotropin; follicle stimulating hormone (FSH)
83002	Gonadotropin; luteinizing hormone (LH)
83498	Hydroxyprogesterone, 17-d
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84144	Progesterone
84146	Prolactin
84402	Testosterone; free
84403	Testosterone; total
84443	Thyroid stimulating hormone (TSH)
84830	Ovulation tests, by visual color comparison methods for human luteinizing hormone
88182	Flow cytometry, cell cycle or DNA analysis
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (e.g., for ataxia telangiectasia, Fanconi anemia, fragile X)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)
88280	Chromosome analysis; additional karyotypes, each study
88283	Chromosome analysis; additional specialized banding technique (e.g., NOR, C-banding)
88285	Chromosome analysis; additional cells counted, each study
89250	Culture of oocyte(s)/embryo(s), less than 4 days
89251	Culture of oocyte(s)/embryo(s), less than 4 days; with co-culture of oocyte(s)/embryos
89253	Assisted embryo hatching, microtechniques (any method)
89254	Oocyte identification from follicular fluid
89255	Preparation of embryo for transfer (any method)
89257	Sperm identification from aspiration (other than seminal fluid)
89258	Cryopreservation; embryo(s)
89259	Cryopreservation; sperm
89260	Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
89261	Sperm isolation; complex prep (e.g., Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
89264	Sperm identification from testis tissue, fresh or cryopreserved
89268	Insemination of oocytes
89272	Extended culture of oocyte(s)/embryo(s), 4-7 days
89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
89281	Assisted oocyte fertilization, microtechnique; greater than 10 oocytes
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos

CPT Code	Description
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos
89300	Semen analysis; presence and/or motility of sperm including Huhner test (post coital)
89310	Semen analysis; motility and count (not including Huhner test)
89320	Semen analysis; volume, count, motility, and differential
89321	Semen analysis; sperm presence and motility of sperm, if performed
89322	Semen analysis; volume, count, motility, and differential using strict morphologic criteria (e.g., Kruger)
89325	Sperm antibodies
89329	Sperm evaluation; hamster penetration test
89330	Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test
89331	Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)
89335	Cryopreservation, reproductive tissue, testicular
89337	Cryopreservation, mature oocyte(s)
89342	Storage (per year); embryo(s)
89343	Storage (per year); sperm/semen
89344	Storage (per year); reproductive tissue, testicular/ovarian
89346	Storage (per year); oocyte(s)
89352	Thawing of cryopreserved; embryo(s)
89353	Thawing of cryopreserved; sperm/semen, each aliquot
89354	Thawing of cryopreserved; reproductive tissue, testicular/ovarian
89356	Thawing of cryopreserved; oocytes, each aliquot
89398	Unlisted reproductive medicine laboratory procedure [when used for cryopreservation of ovarian tissue or hyaluronan binding assay]

HCPCS Code	Description
J0725	Injection, chorionic gonadotropin, per 1,000 USP units
J3355	Injection, urofollitropin, 75 IU
S0122	Injection, menotropins, 75 IU
S0126	Injection, follitropin alfa, 75 IU
S0128	Injection, follitropin beta, 75 IU
S0132	Injection, ganirelix acetate, 250 mcg
S3655	Antisperm antibodies test (immunobead)
S4011	In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development
S4013	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
S4014	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
S4016	Frozen in vitro fertilization cycle, case rate
S4017	Incomplete cycle, treatment cancelled prior to stimulation, case rate
S4018	Frozen embryo transfer procedure cancelled before transfer, case rate
S4020	In vitro fertilization procedure cancelled before aspiration, case rate

HCPCS Code	Description
S4021	In vitro fertilization procedure cancelled after aspiration, case rate
S4022	Assisted oocyte fertilization, case rate
S4023	Donor egg cycle, incomplete, case rate
S4025	Donor services for in vitro fertilization (sperm or embryo), case rate
S4026	Procurement of donor sperm from sperm bank
S4027	Storage of previously frozen embryos
S4028	Microsurgical epididymal sperm aspiration (MESA)
S4030	Sperm procurement and cryopreservation services; initial visit
S4031	Sperm procurement and cryopreservation services; subsequent visit
S4035	Stimulated intrauterine insemination (IUI), case rate
S4037	Cryopreserved embryo transfer, case rate
S4040	Monitoring and storage of cryopreserved embryos, per 30 days

Diagnosis Code	Description
E23.0	Hypopituitarism
N46.01	Organic azoospermia
N46.021	Azoospermia due to drug therapy
N46.022	Azoospermia due to infection
N46.023	Azoospermia due to obstruction of efferent ducts
N46.024	Azoospermia due to radiation
N46.025	Azoospermia due to systemic disease
N46.029	Azoospermia due to other extratesticular causes
N46.11	Organic oligospermia
N46.121	Oligospermia due to drug therapy
N46.122	Oligospermia due to infection
N46.123	Oligospermia due to obstruction of efferent ducts
N46.124	Oligospermia due to radiation
N46.125	Oligospermia due to systemic disease
N46.129	Oligospermia due to other extratesticular causes
N46.8	Other male infertility
N46.9	Male infertility, unspecified
N97.0	Female infertility associated with anovulation
N97.1	Female infertility of tubal origin
N97.2	Female infertility of uterine origin
N97.8	Female infertility of other origin
N97.9	Female infertility, unspecified
N98.1	Hyperstimulation of ovaries

Description of Services

Both male and female factors can contribute to infertility. Some underlying causes of infertility include ovulatory dysfunction, decreased ovarian reserve, cervical factors, uterine abnormalities, tubal disease and male factors. Once a diagnosis is made, treatment falls into 3 categories: medical treatment to restore fertility, surgical treatment to restore fertility or ART.

Cryopreservation is the process of cooling and storing cells, tissues or organs at very low or freezing temperatures to save them for future use. It is used to preserve sperm, semen, oocytes (eggs), embryos, ovarian tissue or testicular tissue as an option for men and women who wish to or must delay reproduction for various reasons, including the need to undergo therapies that threaten their reproductive health, such as cancer treatment. Cryopreservation is also used to preserve unused gametes or zygotes produced through various artificial reproductive techniques for use at a later time.

Benefit Considerations

Infertility services are always subject to mandate review. Several states mandate benefit coverage for certain Infertility services, but the requirements for coverage vary from state to state. Legislative mandates and the member specific benefit document must be reviewed when determining benefit coverage for Infertility services. Where legislative mandates exist, they supersede benefit plan design. Benefit coverage for testing and treatment of Infertility are available only for the person(s) who are covered under the benefit document, and only when the member's specific plan provides benefits for Infertility diagnosis and/or treatment. The member specific benefit document should be reviewed for applicable benefits, limitations and/or exclusions.

For additional information, refer to the Coverage Determination Guideline titled Infertility Services.

Clinical Evidence

Diagnostic Procedures

An ASRM committee opinion on the diagnostic evaluation for infertility in women addresses several tests and procedures, starting with a comprehensive medical, reproductive and family history, as well as a thorough physical exam. Subsequent evaluation should be conducted in a systematic, expeditious and cost-effective manner so as to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility. Diagnostic tests and procedures include evaluation for ovulatory dysfunction, ovarian reserve, cervical factors, uterine abnormalities, tubal disease and peritoneal factors (ASRM, 2015a).

Professional society guidelines on the diagnostic evaluation for infertility in men state that the initial screening evaluation should include a reproductive history and semen analysis. If the initial evaluation is abnormal, then a complete evaluation is recommended. This includes a complete medical history and physical examination. Other tests and procedures may include endocrine evaluation, post-ejaculatory urinalysis, ultrasound, additional tests on semen and sperm and genetic testing (ASRM, 2015c; American Urological Association (AUA), 2010a).

A comprehensive National Institute for Health and Care Excellence (NICE) clinical guideline addresses the evaluation and management of infertility, including ART (NICE, 2013).

Co-Culturing of Embryos

Studies describe different techniques of co-culture, but no standardized method of co-culturing has been defined. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

In a meta-analysis of 17 prospective, randomized trials, Kattal et al. (2008) evaluated the role of co-culture in human IVF. Primary outcomes measured were implantation rates and pregnancy rates (clinical and ongoing). Secondary outcomes included evaluation of pre-embryo development based on average number of blastomeres per embryo. The pooled data of human trials on co-culture demonstrate a statistically significant improvement in blastomere number, implantation rates and clinical and ongoing pregnancy rates. However, the authors acknowledged that confounding factors such as heterogeneity of cell lines and variability in culture media used limit the conclusions.

Johnson et al. (2008) evaluated whether culture of immature human oocytes with and without autologous cumulus cells (CCs) in standard culture medium would provide additional oocytes for use in IVF procedure in 61 women. This study demonstrated good maturation of metaphase I (MI) oocytes but poor maturation of germinal vesicle (GV) oocytes in standard culture medium. The investigators concluded that these extended culturing techniques were inefficient in maturing and providing additional oocytes/embryos for patient use.

A comparative study evaluated 517 women undergoing cumulus co-culture and cumulus-aided embryo transfer with those who underwent cumulus co-culture but did not undergo cumulus-aided embryo transfer. The study results demonstrated a significant increase in the implantation rate in the study group of 25.6% versus 14.5% in the control group and a significant increase in the pregnancy rate in the study group of 47.6% versus 34% in the control group (Parikh et al., 2006).

Computer-Assisted Sperm Analysis (CASA)

There is insufficient evidence to permit conclusions regarding the use of this sperm function test. Study results to date have demonstrated low specificity, low sensitivity and a high rate of false positives. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

AUA guidelines state that specialized tests on semen, such as CASA, are not required for the diagnosis of male infertility. They may be useful in a small number of patients for identifying a male factor contributing to unexplained infertility, or for selecting therapy, such as ART (AUA, 2010a).

A meta-analysis by Oehninger et al. (2000) used data from 2906 patients in 34 prospective, controlled studies to evaluate the predictive value of four categories of sperm functional assays, including CASA, for IVF outcome. In this analysis, the combined results of 4 studies demonstrated a large degree of variability indicating a poor predictive power for sperm parameters assessed by CASA and IVF results. Predictive statistics demonstrated low specificity and sensitivity and a high rate of false positives.

Cryopreservation

A Hayes report (2019) concluded that a low-quality, limited body of evidence suggests that ovarian tissue cryopreservation and transplantation have the potential to restore ovarian function and may result in preserved fertility in patients who have undergone gonadotoxic cancer treatment. Limitations include an evidence base composed of 2 poor-quality cohort studies, 6 poor-quality singe-arm studies and 1 very-poor-quality cross-sectional study. Better quality prospective studies ensuring that all patients are followed after receiving transplantation would provide better assurance that the effects of ovarian tissue cryopreservation and subsequent transplantation on fertility and pregnancy outcomes are consistent with these findings. Future evidence should evaluate the long-term safety and efficacy in populations who are unable to undergo current standard fertility preservation techniques (i.e., embryo or oocyte cryopreservation).

An American Cancer Society (ACS) document on preserving fertility in women with cancer covers options to consider both before and after cancer treatment. Options prior to treatment include mature oocyte cryopreservation, embryo cryopreservation, fertility-sparing surgery, ovarian suppression, ovarian tissue cryopreservation, ovarian transposition, radical trachelectomy and progesterone therapy for early-stage uterine cancer. ACS considers oocyte cryopreservation an established method of preserving fertility in women, although it has not been used as long as embryo cryopreservation, which is the most established and successful method of preserving a woman's fertility. ACS considers ovarian suppression and cryopreservation of ovarian tissue experimental at this time (ACS, 2016a).

An ACS document on preserving fertility in men with cancer covers options to consider both before and after cancer treatment. Options prior to treatment include radiation shielding and sperm banking. The success rates of infertility treatments using frozen sperm vary and depend on the quality of the sperm after it is thawed, as well as the health and age of the female partner. In general, sperm collected before cancer treatment is just as likely to start a pregnancy as sperm from men without cancer. Sperm banking has resulted in thousands of pregnancies, without unusual rates of birth defects or health problems in the children. Once sperm is stored, it remains good for many years (ACS, 2016b).

NICE makes the following recommendations for people with cancer who wish to preserve fertility:

- When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocytes.
- Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile.
- Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:
    - They are well enough to undergo ovarian stimulation and egg collection and
    - This will not worsen their condition and
    - Enough time is available before the start of their cancer treatment

- In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available (NICE, 2013).

In a small, prospective, single center cohort study, Meirow et al. (2016) reported the results of cryopreserved ovarian tissue in twenty cancer survivors. Patient ages at tissue harvesting ranged from 14 to 39 years. Fifteen women had hematologic malignancies, and two had leukemia. Ten patients were exposed to nonsterilizing chemotherapy before ovarian tissue cryopreservation. After transplantation, the endocrine recovery rate was 93%. Fourteen patients underwent IVF treatments with a fertilization rate of 58%. Sixteen pregnancies were achieved (10 after IVF, 6 spontaneous), resulting in 10 live births, two (twins) after harvesting from the mother at the age of 37. After transplantation, 53% of patients conceived, and 32% delivered at least once. One patient conceived four times. Preharvesting chemotherapy exposure was not associated with inferior outcomes. This study is limited by small patient numbers. Further results from ongoing clinical trials are needed to confirm these findings.

Cil et al. (2013) conducted a meta-analysis to estimate age-specific probabilities of live birth with oocyte cryopreservation in infertile patients undergoing non-donor mature oocyte cryopreservation. Original data from 10 studies, including 2,265 cycles from 1,805 patients, was included. Live birth success rates declined with age regardless of the freezing technique. Despite this age-induced compromise, live births continued to occur as late as ages 42 and 44 years with slowly frozen and vitrified oocytes, respectively. Estimated probabilities of live birth for vitrified oocytes were higher than those for slowly frozen.

In a multicenter retrospective study, Harton et al. (2013) assessed the relationship between maternal age, chromosome abnormality, implantation and pregnancy loss in IVF patients undergoing chromosome screening. Results showed that aneuploidy rates increased with maternal age. Implantation and pregnancy rates were not significantly different between reproductively younger and older patients up to age 42 years. Mounting data suggests that the dramatic decline in IVF treatment success rates with female age is primarily caused by aneuploidy.

Bedaiwy et al. (2008) performed a systematic review of reproductive function after ovarian tissue transplantation (OTT) for fertility preservation in women at high risk of premature ovarian failure (POF). Women with follicle-stimulating hormone (FSH) >30 IU/l at the time of OTT were included in a meta-analysis to evaluate the time to re-establishment of ovarian function (ROF). Secondary outcomes included short-term (<12 months) and long-term (>12 months) ovarian function (OVF) and pregnancy after OTT. Transplantation of ovarian tissue can re-establish OVF after POF; however, the efficacy of OTT using cryopreserved tissues is not yet equivalent to that of fresh grafts. A prospective, controlled multicenter trial with sufficient follow-up is needed to provide valid evidence of the potential benefit of this procedure.

In a meta-analysis, Oktay et al. (2006) studied the efficiency of oocyte cryopreservation relative to IVF with unfrozen oocytes. Compared to women who underwent IVF after slow freezing (SF), IVF with unfrozen oocytes resulted in significantly better rates of fertilization. Although oocyte cryopreservation with the SF method appears to be justified for preserving fertility when a medical indication exists, its value for elective applications remains to be determined. Pregnancy rates using a vitrification (VF) method appear to have improved, but further studies are needed to determine the efficiency and safety of this technique.

EmbryoGlue

There is insufficient evidence supporting the clinical utility of EmbryoGlue. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

A Cochrane systematic review by Bontekoe at al. (2014) assessed whether embryo transfer media containing adherence compounds improved live birth and pregnancy rates in ART. The adherence compounds identified for evaluation were hyaluronic acid (HA) and fibrin sealant. Seventeen studies with a total of 3898 participants were analyzed. One studied fibrin sealant, and the other 16 studied HA. No evidence was found of a treatment effect of fibrin sealant as an adherence compound. For HA, evidence suggests improved clinical pregnancy and live birth rates with the use of functional concentrations of HA as an adherence compound. However, the evidence obtained is of moderate quality. The multiple pregnancy rate was significantly increased in the high HA group. The increase may be the result of use of a combination of an adherence compound and a policy of transferring more than one embryo. Further studies of adherence compounds with single embryo transfer are needed.

In a single center, prospective randomized study (n=224), Hazlett et al. (2008) found that routine use of EmbryoGlue did not significantly improve pregnancy or implantation rates in nonselected patients receiving either a day 3 or day 5 embryo transfer

compared with standard culture media. Future prospective randomized studies are needed to determine whether EmbryoGlue is beneficial in a selected patient population.

In a prospective randomized clinical trial, Valojerdi et al. (2006) evaluated the efficacy of EmbryoGlue. A total of 815 patients were randomly allocated to the test group (embryos were treated with EmbryoGlue prior to intrauterine transfer) (n=417) and the control group (embryos were not treated with EmbryoGlue) (n=398). The clinical pregnancy and implantation rate increased significantly in the test group compared to the control group. More studies are needed to evaluate the effectiveness and safety of EmbryoGlue.

Hyaluronan Binding Assay (HBA)

There is insufficient evidence supporting the clinical utility of HBA testing as an advanced sperm selection technique. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

A Cochrane systematic review by Lepine et al. (2019) evaluated the safety and effectiveness of advanced sperm selection techniques, including the ability to bind to hyaluronic acid, on ART outcomes. Two randomized controlled trials compared the effects of hyaluronic acid selected sperm-ICSI (HA-ICSI) versus ICSI on live birth rates. The evidence suggests that sperm selected by hyaluronic acid binding may have little or no effect on live birth or clinical pregnancy but may reduce miscarriage. However, the quality of the evidence was low. Further high-quality studies, including data from ongoing trials, are required to evaluate whether advanced sperm selection techniques, such as hyaluronic acid binding, can be recommended for use in routine practice.

A systematic review of seven studies concluded that the use of hyaluronic acid binding sperm selection techniques yielded no improvement in fertilization and pregnancy rates. The results did not support routine use of hyaluronic acid binding assays in all ICSI cycles. Identification of patients that might benefit from this technique needs further study (Beck-Fruchter et al., 2016).

An ASRM committee opinion on the diagnostic evaluation for infertility in men states that hyaluronic acid binding tests have a very limited role in the evaluation of male fertility because they have limited clinical utility and typically do not affect treatment (ASRM, 2015c).

A systematic review, conducted by Said and Land (2011), evaluated four advanced sperm selection methods: surface charge, apoptosis, membrane maturity (hyaluronic acid binding) and ultramorphology. The analysis focused on the anticipated benefits of sperm quality and ART outcomes. Sperm quality parameters included motility, morphology, viability, DNA integrity, apoptosis and maturity. ART outcomes assessed included fertilization, embryo quality, pregnancy, abortion and live birth rates. Forty-four studies were included. Preliminary results are encouraging; however, the authors concluded that more clinical studies on safety and efficacy are needed before the implementation of advanced sperm selection methods can be universally recommended in ART.

In Vitro Maturation of Oocytes

Although preliminary results with in vitro maturation are promising, studies to date show that implantation and pregnancy rates are significantly lower than those achieved with standard IVF. Further evidence from well-designed trials is needed to determine the long-term safety and efficacy of the procedure.

A Cochrane review by Siristatidis et al. (2018) compared outcomes associated with in vitro maturation (IVM) followed by vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) versus conventional IVF or ICSI, in women with polycystic ovarian syndrome (PCOS) undergoing ART. Though results are promising, there is still no evidence from randomized controlled trials upon which to base any practice recommendations regarding IVM before IVF or ICSI for women with PCOS. Clinical trials are ongoing.

An ASRM committee opinion on in vitro maturation (IVM) of oocytes states that initial results suggest the potential for clinical application. However, at this time, patients must be made aware that the implantation and pregnancy rates are significantly lower than with standard IVF. Because only a small number of children have been conceived with IVM, information on the safety of the procedure with regard to malformation and developmental outcomes cannot be accurately assessed. IVM should only be performed as an experimental procedure in specialized centers for carefully selected patients (ASRM, 2013b).

Inhibin B

There is insufficient evidence to permit conclusions regarding the use of inhibin B as a measure of ovarian reserve. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children) with the use this test.

An ASRM committee opinion on measures of ovarian reserve states that inhibin B is not a reliable measure of ovarian reserve and routine use is not recommended (ASRM, 2015b).

A NICE clinical guideline does not recommend the use of inhibin B testing for assessing ovarian reserve (NICE, 2013).

Postcoital Cervical Mucus Penetration Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

ASRM guidelines state that the postcoital test of cervical mucus is no longer recommended for evaluating infertility because the test is subjective, has poor reproducibility, rarely changes clinical management and does not predict the inability to conceive (ASRM, 2015a).

A NICE guideline does not recommend the routine use of postcoital testing of cervical mucus for evaluating infertility because the test has no predictive value on pregnancy rate (NICE, 2013).

Reactive Oxygen Species (ROS) Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

An ASRM committee opinion on the diagnostic evaluation for infertility in men states that ROS tests have a very limited role in the evaluation of male fertility because they have limited clinical utility and typically do not affect treatment (ASRM, 2015c).

Chen et al. (2013) studied the influence of ROS on sperm physiology and pathology. Low levels of ROS serve a critical function in normal sperm physiology, such as fertilizing ability and sperm motility. Increased levels of ROS are considered to be a significant contributing factor to male infertility/subfertility due to sperm DNA damage and reduced motility. Some studies have shown that antioxidant therapy significantly improves sperm function and motility; however, the overall effectiveness remains controversial due to non-standardized assays for measuring levels of ROS and sperm DNA damage. Further development of standardized tests is needed.

AUA guidelines state that ROS testing has not been shown to be predictive of pregnancy independent of routine semen parameters nor are there any proven therapies to correct an abnormal test result. There is insufficient data to support the routine use of ROS testing in the management of the male partner of an infertile couple (AUA, 2010a).

Sperm Acrosome Reaction Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

An ASRM committee opinion on the diagnostic evaluation for infertility in men states that sperm acrosome reaction tests have a very limited role in the evaluation of male fertility because they have limited clinical utility and typically do not affect treatment (ASRM, 2015c).

AUA guidelines state that less commonly used specialized tests on semen, such as acrosome reaction testing, are important investigative tools, but are not necessary for the routine evaluation of men with infertility (AUA, 2010a).

Sperm DNA Integrity/Fragmentation Tests

There is insufficient evidence supporting the predictive value or clinical utility of this test. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

After conducting a systematic review of the literature, ASRM developed a guideline stating that there is insufficient evidence to recommend the routine use of sperm DNA integrity tests as current assessment methods do not reliably predict treatment outcomes. The review did not identify any Level I (evidence from at least one properly designed randomized controlled trial) studies and few high quality prospective studies. Most studies were Level II-2 (evidence from well-designed cohort or case-control studies) or less. The majority of studies were hindered by small sample size, non-consecutive recruitment of patients, variable patient populations, lack of control for female factors, weak statistical methodology and use of several different methods for assessing DNA damage (ASRM, 2013a).

AUA guidelines state that there is insufficient evidence in the literature to support the routine use of DNA integrity testing in the evaluation and management of the male partner of an infertile couple. Presently, there are no proven therapies to correct an abnormal DNA integrity test result (AUA, 2010).

Sperm Penetration Assays (SPA)

There is insufficient evidence supporting the clinical utility of this test in lieu of newer technologies for treating male infertility.

An ASRM committee opinion on the diagnostic evaluation for infertility in men states that sperm penetration assays have a very limited role in the evaluation of male fertility. Since intracytoplasmic sperm injection (ICSI) is routinely used during IVF for male-factor infertility, this test is rarely of any clinical value (ASRM, 2015c).

AUA guidelines state that specialized tests on semen, such as SPA, are not required for the diagnosis of male infertility. They may be useful in a small number of patients for identifying a male factor contributing to unexplained infertility, or for selecting therapy, such as ART (AUA, 2010a).

A meta-analysis by Oehninger et al. (2000) used data from 2906 patients in 34 prospective, controlled studies to evaluate the predictive value of four categories of sperm functional assays, including SPA, for IVF outcome. In this analysis, the sperm-zona pellucida binding assay and the induced-acrosome reaction assay had a high predictive value for fertilization outcome. SPA had a relatively high positive predictive value (more than 70%), but the negative predictive value was variable, ranging from 11% to 100%, with most studies reporting NPV less than 75%. The authors noted that this assay was limited by the need for standardization.

Uterine Receptivity Testing and Treatment

There is insufficient evidence supporting the safety and efficacy of uterine receptivity testing and/or treatment. More studies are needed to support improved outcomes (i.e., increased successful pregnancies with delivery of liveborn children).

Lensen et al. (2019a) summarized the current evidence for several add-on treatments suggested to improve endometrial receptivity. Immune therapies, endometrial scratching, endometrial receptivity array, uterine artery vasodilation and human chorionic gonadotropin instillation were included in the assessment. Immune therapies addressed include corticosteroids, intravenous immunoglobulin (IVIG), granulocyte-colony stimulating factor and intralipid. The results suggest there is no robust evidence that these add-ons are effective or safe. Large randomized controlled trials are needed prior to introducing these IVF add-ons into routine practice.

Lensen et al. (2019b) conducted a multicenter, open-label, randomized controlled trial evaluating the impact of endometrial scratching prior to IVF. Participants were randomly assigned in a 1:1 ratio to either endometrial scratching (n=690) or no intervention (n=674). The primary outcome was live birth. The frequency of live birth was 180 (26.1%) in the endometrial scratching group and 176 (26.1%) in the control group (adjusted odds ratio, 1.00; 95% confidence interval, 0.78 to 1.27). There were no significant between-group differences in the rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy or miscarriage.

Studies of uterine receptivity testing indicate that even though integrins may be important markers of endometrial receptivity and provide additional information, more study is needed before uterine receptivity testing can be considered a clinically useful test (Thomas et al., 2003; Lessey et al., 2000).

Therapeutic Procedures

ASRM has published several documents, including a guide for patients that address available therapeutic options for infertility (ASRM, 2019b, 2018b, 2013b, 2012a and 2012c).

AHRQ published a report evaluating the comparative effectiveness and safety of fertility treatment strategies in women who are infertile due to PCOS, endometriosis, unknown reasons or tubal or peritoneal factors, or couples with male factor infertility (2019).

A comprehensive NICE clinical guideline addresses the evaluation and management of infertility, including ART (NICE, 2013).

An AUA practice statement addresses surgical treatment options for males with obstructive azoospermia. The report also addresses sperm retrieval techniques and intracytoplasmic sperm injection (AUA, 2010c).

Professional Societies

American Society for Reproductive Medicine (ASRM)

ASRM (2018) recommends the following with regards to cryopreservation and fertility preservation:

- Sperm cryopreservation is an established method of fertility preservation in men
- Oocyte cryopreservation in women
- Embryo cryopreservation is an established method of fertility preservation in women and men
- Cryopreservation of ovarian tissue remains investigational
- Cryopreservation of testicular tissue remains investigational

Mature Oocytes

After conducting a systematic review of the literature, ASRM developed guidelines (2013c) for mature oocyte cryopreservation. Four randomized controlled trials comparing outcomes with cryopreserved and fresh oocytes in IVF/ICSI cycles were included in the review (Cobo et al., 2008; Cobo et al., 2010; Rienzi et al., 2010; Parmegiani et al., 2011). All studies used a similar open vitrification protocol. Two studies were conducted with oocyte donors and two with infertile couples.

The guidelines state that there is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI using fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI in young infertility patients and oocyte donors. No increases in chromosomal abnormalities, birth defects or developmental deficits have been noted in the children born from cryopreserved oocytes. The guidelines also make the following recommendations:

- In patients facing infertility due to chemotherapy or other gonadotoxic therapies, oocyte cryopreservation is recommended with appropriate counseling (Level B).
- More data on the safety and efficacy of oocyte cryopreservation in donor populations is needed before universal donor oocyte banking can be recommended (Level B).
- There is insufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women (Level B).
- More data is needed before oocyte cryopreservation should be used routinely in lieu of embryo cryopreservation (Level B).

Level B - At least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks.

Success rates with oocyte cryopreservation, using either slow-freezing or vitrification, appear to decline with maternal age consistent with the clinical experience with fresh oocytes (ASRM, 2013c).

Ovarian Tissue

An ASRM committee opinion states that ovarian tissue cryopreservation is an option to preserve reproductive potential in patients who must urgently undergo aggressive chemotherapy and/or radiotherapy or who have other medical conditions requiring treatment that may threaten ovarian function and subsequent fertility. Ovarian tissue cryopreservation may be the only option available to prepubertal girls undergoing such treatments. However, these techniques are still considered to be experimental (ASRM, 2014).

American Society of Clinical Oncology (ASCO)

The ASCO conducted a systematic review of the evidence on fertility preservation for adults and children with cancer. This was an update to a previously published guideline (Loren et al., 2013). A total of 61 new publications were reviewed. ASCO clarified the recommendation for ovarian tissue cryopreservation and transplantation noting that at the time of publication of this guideline, ovarian tissue cryopreservation remains experimental. However, ASCO indicated that ovarian tissue cryopreservation is advancing rapidly and may evolve to become standard therapy in the future. Sperm, embryo and oocyte cryopreservation continue to be standard practice. Testicular tissue cryopreservation is still considered to be investigational (Oktay et al., 2018).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Many tests and procedures used in the diagnosis and treatment of infertility are not subject to FDA regulation. See the following website to search for specific products: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 25, 2020)

For tests regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988, premarket approval from the FDA is not required.

Products and media used for cryopreservation of reproductive tissue are too numerous to list. See the following website for more information (use product code MQL). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 25, 2020)

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for the diagnosis and/or treatment of infertility. Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) exist; see the following LCDs/LCAs:

- Biomarkers Overview
- Category III CPT® Codes
- MolDX: Molecular Diagnostic Tests (MDT)
- Molecular Pathology Procedures
- Noncovered Services
- Noncovered Services other than CPT® Category III Noncovered Services
- Non-obstetric Pelvic Ultrasound
- Services That Are Not Reasonable and Necessary

(Accessed March 4, 2020)

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Policy History/Revision Information

Date	Summary of Changes

01/01/2021	**Documentation Requirements**
	• Updated list of CPT codes with associated documentation requirements to reflect annual edits; removed 0058T
	Definitions
	• Updated definition of "Infertility"
	Applicable Codes
	• Updated list of applicable CPT codes:
	  ○ Removed 0058T*
	  ○ Revised description for 80415*, 82670*, and 89398
	*(*annual edit)*
	Supporting Information
	• Updated *References* section to reflect the most current information
	• Archived previous policy version 2020T0270X

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.