

Infertility Diagnosis, Treatment, and Fertility Preservation

Policy Number: INFERTILITY 008.20
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[➔ Instructions for Use](#)

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Related Policy
<ul style="list-style-type: none"> Preimplantation Genetic Testing and Related Services

Related Optum Clinical Guideline
<ul style="list-style-type: none"> 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
- 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 surgically derived sperm
- Cryopreservation of *mature* oocytes (eggs) for women 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 supernumerary embryos or in the setting where the intent is to freeze all embryos for the purpose of an elective single embryo transfer
- 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
- Post-coital cervical mucus penetration test
- Reactive oxygen species (ROS) test
- Sperm acrosome reaction test
- Sperm capacitation 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)

Note: For eligibility of [Infertility](#) benefits, refer to the member specific benefit plan document.

Benefits are available for [fertility preservation](#) for medical reasons that cause irreversible Infertility such as chemotherapy, radiation treatment, and bilateral oophorectomy due to cancer; check the member specific benefit plan document. For coding associated with fertility preservation for [Iatrogenic Infertility](#) benefit, refer to the [Applicable Codes](#) section below; codes are identified with an asterisk (*).

Medical Records Documentation Used for Reviews

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. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled [Medical Records Documentation Used for Reviews](#).

Definitions

Iatrogenic Infertility: An impairment of fertility by surgery, radiation, chemotherapy, or other medical treatment affecting reproductive organs or processes. (COC, 2018)

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 for those individuals actively looking to achieve a conception may be

justified based on medical history and physical findings and is warranted after 6 months for women age 35 years or older. (ASRM, 2020)

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)

Therapeutic Donor Insemination (TDI): Insemination with a donor sperm sample for the purpose of conceiving a child. The donor can be an anonymous or directed donor. (COC, 2018)

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 may apply.

Coding Clarification: For coding applicable to the [Infertility Services](#) benefit, refer to the Infertility Services Code Grid at the end of the *Applicable Codes* section.

For the fertility preservation for [Iatrogenic Infertility](#) benefit, claims must be submitted with diagnosis code Z31.84 in order for the benefit to apply. Refer to the codes marked with an asterisk (*).

CPT Code	Description
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (e.g., pre-receptive, receptive, post-receptive)
0255U	Andrology (infertility), sperm-capacitation assessment of ganglioside GM1 distribution patterns, fluorescence microscopy, fresh or frozen specimen, reported as percentage of capacitated sperm and probability of generating a pregnancy score
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
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography

CPT Code	Description
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)
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

CPT Code	Description
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
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

CPT Code	Description
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]

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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
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
*Z31.84	Encounter for fertility preservation procedure

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.

Fertility preservation is the practice of proactively helping individuals preserve their fertility chances for future reproduction. Established methods of fertility preservation include embryo cryopreservation for men and women, sperm cryopreservation in men, and oocyte cryopreservation in women. A multidisciplinary team approach is encouraged when working with individuals.

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 plan 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 benefit plan

document provides benefits for Infertility diagnosis and/or treatment. The member specific benefit plan document should be reviewed for applicable benefits, limitations and/or exclusions.

Infertility Services

Check the member specific benefit plan document for benefit eligibility and refer to state mandates.

Services for the treatment of Infertility when provided by or under the care or supervision of a physician are limited to the following procedures:

- Ovulation induction (or controlled ovarian stimulation).
- Insemination procedures: Artificial Insemination (AI) and Intra Uterine Insemination (IUI).
- Assisted Reproductive Technologies (ART).

To be eligible for benefits, the member must meet all of the following:

- The member is not able to become pregnant after the following periods of time of regular, unprotected intercourse or Therapeutic Donor Insemination:
 - One year, if the member is a female under age 35.
 - Six months, if the member is a female age 35 or older.
- The member has Infertility not related to voluntary sterilization or to failed reversal of voluntary sterilization.

For the purposes of this Benefit, "Therapeutic Donor Insemination" means using insemination with a donor sperm sample for the purpose of conceiving a child.

Gestational Carrier or Surrogate

Refer to the member specific benefit plan document for services related to a gestational carrier or surrogate. A member with an Infertility benefit that is using a gestational carrier/surrogate because of the member's known medical cause of Infertility (this does not include a member who has had a voluntary sterilization or a failed reversal of a sterilization procedure) will have coverage for the following services. These services will be paid per the member's coverage:

- Female member's ovary stimulation and retrieval of eggs are covered when a member is using a surrogate (host uterus). **Note:** The implantation of eggs or oocytes or donor sperm into a host uterus is not covered even if the member has the Infertility benefit.
- Male member retrieval of sperm.

Benefit Limitations and Exclusions

When the member's plan includes benefits for Infertility, the following services are not covered:

- Any Infertility services or supplies beyond the benefit maximum [dollars or procedure limit(s)].
- Assisted Reproductive Technologies, ovulation induction and insemination procedures are excluded from coverage unless the member has a benefit for Infertility and the criteria listed in the [Coverage Rationale](#) section has been met.
- Long-term storage (greater than one year) of reproductive materials such as sperm, eggs, embryos, ovarian tissue, and testicular tissue.

Note: Short Term storage under one year may be eligible for benefits.

- Infertility treatment when the cause of the Infertility was a procedure that produces sterilization, e.g., vasectomy or tubal ligation.
- In-vitro fertilization that is not an Assisted Reproductive Technology for the treatment of Infertility. This would include but is not limited to elective fertility preservation, embryo accumulation/banking.

When the member's plan does not include benefits for Infertility, the following services are not covered:

- All health care services and related expenses for infertility treatments, including assisted reproductive technology, regardless of the reason for the treatment.
- In vitro fertilization regardless of the reason for treatment.
- Storage and retrieval of all reproductive materials. Examples include eggs, sperm, testicular tissue, and ovarian tissue.

The following services are excluded on all plans (even when the plan provides benefits for Infertility):

- Donor services for donor sperm, ovum, or oocytes (eggs), or embryos.
 - Donor eggs - The cost of donor eggs, including medical cost related to donor stimulation and egg retrieval is excluded. Cost for fertilization (in vitro fertilization or intracytoplasmic sperm injection), embryo culture, and embryo transfer may be covered if the member has an Infertility benefit that allows for Assisted Reproductive Technology.

- Donor sperm - The cost of procurement and storage of donor sperm is excluded. However, the thawing and insemination are covered if the member has an Infertility benefit that allows for artificial donor insemination.
- Surrogate Parenting: Services and treatments for a gestational carrier of a pregnancy that is not our member and all related services including, but not limited to:
 - Fees for the use of a gestational carrier or surrogate.
 - Pregnancy services for a gestational carrier or surrogate who is not a covered person.
- Self-injectable drugs for Infertility. Refer to the exclusion for self-injectable drugs in the member specific benefit plan document. Refer to the pharmacy benefit administrator for self-injectable medication benefit information.

Additional Information

- Assisted reproductive technology services (IVF, GIFT, ZIFT, PROS, and TET) requested for reasons other than Infertility, must be reviewed in accordance with the member specific benefit plan document (case by case determination).
- As a standard, coverage is provided for maternity services (prenatal, delivery and postnatal pregnancy) for our members. If a female member is pregnant and functioning as a Surrogate, coverage is provided for maternity services. Coverage is not provided for maternity services for a surrogate that is not a member (refer to the member specific benefit plan document).
- Even if a plan excludes Infertility services (AI, ART, IUI, ovulation induction), covered health services include procedures to diagnose Infertility and therapeutic (medical or surgical) procedures to correct a physical condition, which is the underlying cause of the Infertility (e.g., for the treatment of a pelvic mass or pelvic pain, thyroid disease, pituitary lesions, etc.). These diagnostic and therapeutic services are not considered to be Infertility treatments.

Fertility Preservation for Iatrogenic Infertility

Certain plans may include coverage for fertility preservation for Iatrogenic Infertility. Refer to the member specific benefit plan document to determine if this coverage applies.

Benefits are available for fertility preservation for medical reasons that cause irreversible Infertility such as chemotherapy, radiation treatment, and bilateral oophorectomy due to cancer. Services include the following procedures, when provided by or under the care or supervision of a Physician:

- Collection of sperm.
- Cryo-preservation of sperm.
- Ovarian stimulation, retrieval of eggs and fertilization.
- Oocyte cryo-preservation.
- Embryo cryo-preservation.

Benefits for medications related to the treatment of fertility preservation are considered under the Outpatient Prescription Drug benefit or under the Pharmaceutical Products. Check the member specific benefit plan document for inclusion or exclusion.

Coverage Limitations and Exclusions

When the member's plan includes benefits for Fertility Preservation for Iatrogenic Infertility, the following services are not covered:

- Benefits are not available for embryo transfer.
- Benefits are not available for long-term storage costs (greater than one year).
- Benefits are further limited to one cycle of fertility preservation for Iatrogenic Infertility per covered person during the entire period of time he or she is enrolled for coverage under the policy.
- Benefits are not available beyond any applicable dollar maximum listed in the member specific plan document.

Clinical Evidence

Co-Culturing of Embryos

Studies describe different techniques of co-culture, but no standardized method of co-culturing has been defined. Further studies are necessary to support the effects of co-culture on clinical outcomes.

An ECRI (2022) Clinical Evidence Assessment report on endometrial coculture for treating infertility was inconclusive as there is limited studies on assessing its safety. The assessment reviewed all available literature through November 2022 and identified two RCTs, one nonrandomized comparative study, and two case series that reported on 2,684 patients. The conclusion findings suggests that there are insufficient studies to determine whether endometrial coculture improves the

chances of assisted reproduction (AR) to result in a live birth. The controlled studies suggest coculture is not effective, but the findings are at high risk of bias and need validation. In addition, at least one of the studies indicates the procedure may result in multiple pregnancies.

Le Saint et al. (2019, included in the ECRI 2022 Clinical Evidence Assessment) conducted a randomized, double-blind study of 207 patients undergoing an in-vitro fertilization or intracytoplasmic sperm injection (ICSI) protocol, which compared blastocyst quality between autologous endometrial co-culture (AECC) and conventional culture. The study found AECC significantly increased the quality of blastocysts compared to a conventional culture medium. However, the analysis was conducted on embryos rather than patients, there was no follow-up of children born following the treatments, and no significant differences were found in pregnancy and live birth rates.

In a meta-analysis of 17 prospective, randomized trials, Kattal et al. (2008) evaluated the role of coculture 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 coculture 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.

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.

In a 2021 systematic review, Finelli et al. sought to compare results from semen evaluation by both computer-aided sperm analyzers (CASA)-based and manual approaches. After meeting inclusion criteria, 14 articles published within a 10-year period (January 2010 to November 2020) were used in this study. Results concluded that sperm concentration and motility had a high degree of correlation between both approaches, whether manually or by using a CASA system. However, CASA results showed increased variability in low (< 15 million/mL) and high (> 60 million/mL) sperm concentration. Sperm motility analysis was inaccurate in samples with higher concentration or in the presence of non-sperm cells and debris due to difficulties with CASA systems distinguishing between immotile sperm, non-sperm cells and debris. Morphology results was the most difficult parameter to analyze and the least reliable one to assess, due to the high amount of heterogeneity seen between the shapes of the spermatozoa either in one sample or across multiple samples from the same subject. The authors concluded manual semen analysis is considered the gold standard when performed by highly trained competent technologists working in accredited lab and are monitored by external agencies. In addition, the authors suggest CASA systems are a valid alternative for the evaluation of semen parameters specifically for sperm concentration and motility. However, further technological improvements are necessary before these devices replace the human operator.

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

There is insufficient evidence supporting the clinical utility of cryopreservation of immature oocytes (eggs), ovarian tissue, or testicular tissue. Further studies are needed to support improved clinical outcomes measures.

Finkelstein et al. (2024) conducted a systematic review and meta-analysis to investigate the pregnancy outcomes of patients who have undergone ovarian tissue cryopreservation (OTC) for non-malignant indications. Sixteen studies (seven cohort studies and nine case series, with 187 patients) met inclusion criteria and were reviewed in this meta-analysis. The pooled successful pregnancy rate was 23.52 % (16 studies, 95 % CI 6.48 to 44.79 %). When subgroup analysis of study types was performed, the successful pregnancy rate was higher amongst case series than cohort studies. Sensitivity analysis limited to studies at low risk of bias revealed a similar pooled successful pregnancy rate of 23.35 %. The authors concluded one quarter of women who underwent OTC for non-malignant indications had a successful pregnancy. Limitations in the study included small sample size in each study cohort and the studies did not exclusively dedicate their patient cohort to non-malignant indications.

In a 2022 systematic review and meta-analysis, Khattak et al. (2022) sought to review the current evidence of women who received ovarian transplants, including frozen-thawed transplant, fresh or donor graft. The analyzed data included in this

review are 87 studies (n = 735 women). Reproductive outcomes reviewed in this study include pregnancy, live birth and miscarriage rates. For endocrine outcomes, oestrogen, FSH and LH levels were reviewed. The pooled rates for reproductive outcomes after ovarian tissue transplantation, was pregnancy rate of 37% for frozen transplants and 52% for fresh transplants. Live birth rate for frozen transplants was 28% and 45% for fresh transplants. Miscarriage rate for frozen transplants was 37% and 33 % for fresh transplants. The endocrine function after ovarian tissue transplantation pooled mean for pre-transplant oestrogen was 101.6 pmol/l, which increased post-transplant to 522.4 pmol/l. Pooled mean of pre-transplant FSH was 66.4 IU/l, which decreased post-transplant to 14.1 IU/l. The median time to return of FSH to a value < 25 IU/l was 19 weeks. The median duration of graft function was 2.5 years. The authors concluded that ovarian tissue cryopreservation and transplantation show promising results in reproductive and hormonal functions in women. However, due to limitations of small sample size, heterogeneity of the studies, larger samples of well-characterized populations are required to define the optimal retrieval, cryopreservation and transplantation processes. (Author Meirou 2016 which was previously cited in this policy, is included in this systematic review.)

An ASRM guideline covers evidence-based outcomes regarding the efficacy of oocyte cryopreservation (OC) for donor oocyte IVF and planned OC. The ASRM conducted a literature search from 1986 to 2018 that identified 30 relevant studies. The main outcome measures included clinical pregnancy rate, obstetrical and neonatal outcomes, live birth rate and factors predicting reproductive outcomes. Recommendations were developed regarding neonatal outcomes after using fresh vs cryopreserved oocytes in cases of autologous or donor oocytes. Evidence-based recommendations were developed for predicting factors that may impact live birth rates, and predicting the likelihood of live births after planned OC, autologous OC in infertile women, and donor OC. The authors concluded neonatal outcomes appear similar with cryopreserved oocytes compared with fresh oocytes, ongoing and live birth rates appeared to be improved for women who undergo planned OC at a younger vs older age, and there were no significant differences in per transfer pregnancy rates with cryopreserved versus fresh donor oocytes. Additionally, the authors found insufficient evidence to predict live birth rates after planned OC and insufficient evidence that the live birth rate is the same with vitrified versus fresh donor oocytes. The authors recommend future studies that compare cumulative live birth rates with long-term outcomes. (ASRM, 2021c)

A Hayes report (2019; updated 2021) 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 single-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). In Hayes (2022) Health Technology Annual Review, 2 new abstracts were retrieved, including 2 single-arm studies. Based on the impact of the newly published studies, there is no change to the current rating.

In a small, prospective, single center cohort study, Meirou 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.

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. Further studies are needed to support improved clinical outcomes measures.

In a 2022 systematic review and meta-analysis, Heymann et al. sought to determine whether hyaluronic acid (HA) addition to embryo transfer media improves pregnancy outcomes in both autologous and egg donation IVF cycles. Fifteen studies, totaling 4686 participants, were analyzed. In autologous oocyte cycles, live birth increased from 32% to 39% when embryo transfer media contained functional HA concentrations. HA-enriched media increased clinical pregnancy and multiple pregnancy rates by 5% and 8%, respectively. Furthermore, in donor oocyte cycles, HA addition showed little effect on live birth and clinical pregnancy. There was insufficient available information on multiple pregnancy in donor oocyte cycles and on total adverse effects in both groups to draw conclusions. The authors suggest that HA may be valuable in improving the success rate of IVF using autologous oocytes. The combination of HA addition to transfer media in cycles using autologous oocytes and a single embryo transfer policy might yield the best combination, with higher clinical pregnancy and live birth rates, without increasing the chance of multiple pregnancies. Limitations in the study include limited studies with separate data on donor oocyte cycles and limited information on oocyte quality. Additionally, one-third of the included studies did not include the main outcome, live birth rate. (Author Hazlett 2008 which was previously cited in this policy, is included in this systematic review.)

Yung et al. (2021) performed a randomized, double blind, controlled trial, which compared the effects of hyaluronic acid (HA)-enriched transfer medium versus standard medium on live birth rate after frozen embryo transfer (FET). Five hundred and fifty infertile women, age 43 and under, were randomly placed in two groups. The first group used an HA enriched medium (EmbryoGlue), with an HA concentration of 0.5 mg/ml while the control group used the conventional G-2 (Vitrolife) medium with an HA concentration of 0.125mg/ml. The study found that live birth rates in both groups were comparable; however, EmbryoGlue did not improve the live birth rates of FET when compared with standard medium.

In a Cochrane systematic review, Heymann et al. (2020) evaluated whether adding adherence compounds to embryo transfer media could improve pregnancy outcomes, including improving live birth and decreasing miscarriage, in women undergoing assisted reproduction. Twenty-six RCTs with a total of 6704 participants were analyzed. The certainty of evidence was low to moderate overall. Compared to embryos transferred in media containing no or low (0.125 mg/mL) HA, the addition of HA concentrations (0.5 mg/mL) to the transfer media probably increases the live birth rate (RR 1.21, 95% CI 1.1 to 1.31; 10 RCTs, n = 4066; $I^2 = 33\%$). This suggests that if the chance of live birth following no HA addition in media is assumed to be 33%, the chance following HA addition would be between 37% and 44%. The addition of HA may slightly decrease miscarriage rates (RR 0.82, 95% CI 0.67 to 1.00; 7 RCTs, n = 3091; $I^2 = 66\%$). Adding HA to transfer media probably results in an increase in both clinical pregnancy (RR 1.16, 95% CI 1.09 to 1.23; 17 studies, n = 5247; $I^2 = 40\%$) and multiple pregnancy rates (RR 1.45, 95% CI 1.24 to 1.70; 7 studies, n = 3337; $I^2 = 36\%$). The effect of HA added to transfer media on the rate of total adverse events yielded uncertain results. The authors concluded the addition of HA as an adherence compound in embryo transfer media in ART improved clinical pregnancy and live birth rates, adding HA may slightly decrease miscarriage rates, HA had no clear effect on the rate of total adverse events and combining an adherence compound and transferring more than one embryo may increase multiple pregnancy rates. The authors recommend further studies of adherence compounds with single embryo transfers. Limitations include imprecision and/or heterogeneity.

A Cochrane systematic review by Bontekoe et 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 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).

Novoselsky Persky et al. (2021) conducted a retrospective study to compare fertilization and embryo development between standard intracytoplasmic sperm injection (ICSI) and physiologic ICSI (PICSI) in sibling oocytes. Forty-five IVF cycles, in which 257 oocytes were fertilized with PICSI and 294 with standard ICSI, were compared. Both fertilization rates (71% vs. 83%) and transfer eligible embryo rates (38% vs. 51%) were significantly higher in PICSI fertilized oocytes (p = 0.008 and p = 0.01 respectively). Study limitations were identified. First, the retrospective study design prevented inclusion criteria regarding the indication of utilizing both fertilization techniques. Second, the study had a relatively small number of cycles (45) which did not allow the study to define subpopulations that benefitted more than others from PICSI. Finally, the methodology of comparing oocytes, not patients, limited the strength of our pregnancy rates results. The authors concluded PICSI improves fertilization rates and transfer eligible embryo rates in sibling oocytes in a selected study group with previous IVF failures.

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.

Miller et al. (2019) compared success rates of ICSI and hyaluronan-based sperm selection for ICSI (physiological ICSI [PICSI]) for improving livebirth rates among couples undergoing fertility treatment. A parallel, two-group RCT was performed. Between February 2014 and August 2016, 2772 couples were randomly assigned to receive either the PICSI (n = 1387) or ICSI (n = 1385). Compared with standard ICSI, PICSI did not increase the term livebirth rate and there was no difference found in either premature birth or clinical pregnancy. A significant reduction in miscarriage with PICSI was noted when compared to standard ICSI.

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)

A systematic review, conducted by Said and Land (2011), evaluated four advanced sperm selection methods: surface charge, apoptosis, membrane maturity (hyaluronic acid binding) and ultra-morphology. 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.

Vuong et al. (2023) conducted a systematic review to evaluate the effectiveness and safety of in vitro maturation (IVM) compared with conventional ovarian stimulation (COS) in women with predicted hyper-response to gonadotropins. The authors searched for relevant studies comparing any IVM protocol with any COS protocol followed by in vitro fertilization or intracytoplasmic sperm injection. From a total of 1472 potentially relevant records screened, 3 studies (2 RCTs and 1 retrospective cohort study) met inclusion criteria and were used in the analysis. Live birth rate was not significantly lower after IVM vs. COS [odds ratio (95% confidence interval) of 0.56 (0.32–1.01) overall, 0.83 (0.63–1.10) for human chorionic gonadotropin (hCG)-triggered IVM (hCG-IVM) and 0.45 (0.18–1.13) for non-hCG-triggered IVM (non-hCG-IVM)], irrespective of the stage of transferred embryos. Data from nonrandomized studies generally showed either significantly low or statistically comparable rates of live birth with IVM vs. COS. Most studies have not identified any significant difference between IVM and COS with respect to the rates of obstetric or perinatal complications, apart from a potentially higher rate of hypertensive disorders during pregnancy. The development of offspring from IVM and COS with in vitro fertilization or intracytoplasmic sperm injection appears to be similar. The authors concluded data are not yet sufficient to draw definitive conclusions about the relative merits of IVM compared with COS in terms of reproductive outcomes. The authors identified there is a clear need for additional data on IVM to allow more robust comparisons with current ART strategies. (Author Zheng 2022 which was previously cited in this policy, is included in this systematic review.)

In a 2022 single-center, open-label randomized control trial, Zheng et al. sought to assess the effectiveness of in vitro maturation (IVM) in non-inferior cumulative live birth rates compared to those after standard in vitro fertilization (IVF) in infertile women with polycystic ovary syndrome (PCOS). A total of 351 women were randomly selected to receive one cycle of unstimulated IVM (n = 175) or one cycle of standard IVF with a GnRH antagonist protocol and hCG as ovulatory trigger (n = 176). Both groups received a freeze-all and single blastocyst transfer strategy. The researchers concluded that one cycle of IVM without ovarian stimulation to be inferior to IVF with ovarian stimulation for women with infertility and PCOS in terms of 6-month cumulative ongoing pregnancy rates [22.3% vs. 50.6%; rate difference - 28.3%; 95% confidence interval (CI): -37.9% to -18.7%]. To evaluate the effectiveness and safety of other IVM protocols or multiple cycles of IVM compared to IVF, further RCTs should be evaluated due to limitations in the study. The limitations include IVM protocol constraint, decline in patient participation, primary outcome transfer timeframes, and ovarian stimulants.

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.

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.

Post-Coital 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).

Reactive Oxygen Species (ROS) Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. Additional studies are needed to support improved clinical outcomes.

In a 2023 systematic review, Sanyal et al. assessed the clinical utility of available advance sperm function tests in predicting the male fertility potential. A total of 110 articles met the inclusion criteria and were included in this review. The majorly investigated sperm function tests are hypo-osmotic swelling test, acrosome reaction test, sperm capacitation test, hemizona binding assay, sperm DNA fragmentation test, seminal reactive oxygen species test, mitochondrial dysfunction tests, antisperm antibody test, and nuclear chromatin de-condensation (NCD) test. The different advance sperm function tests analyze different aspects of sperm function. The authors concluded any one test may not be helpful to appropriately predict the male fertility potential. Currently, the unavailability of high-quality clinical data, robust thresholds, complex protocols, high cost, are the limiting factors and prohibiting current sperm function tests to reach the clinics. Further multi-centric research efforts are required.

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.

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).

Xu et al. (2018) performed a meta-analysis to determine whether sperm acrosome function scoring can predict fertilization rate in vitro. The study included seven hundred and thirty-seven couples undergoing in-vitro fertilization. Although a significant correlation was found between acrosome function scoring and fertility rate, the study revealed that acrosome function assays were not specific or highly sensitive. Additional studies of sperm functional assays are needed in clinical settings to better predict fertilization outcomes in in-vitro fertilization.

Sperm Capacitation Test

There is insufficient evidence supporting the predictive value or clinical utility of this test. Additional quality studies are needed to support improved clinical outcomes.

A Hayes (2023) Precision Medicine Research Brief examined the published peer-reviewed literature to evaluate the evidence related to the Cap-Score test (Cap-Score) for the evaluation of sperm capacitation. The safety and clinical utility of this health technology cannot be made within this report as there is currently not enough published peer-reviewed literature to evaluate the evidence related to the Cap-Score test for sperm capacitation evaluation in a full assessment.

Sharara et al. (2020) analyzed data in the multicentric, prospective observational study (n = 128, six clinics) to test a previously published relationship between probability of generating pregnancy (PGP) within 3 cycles of intrauterine insemination (IUI) and percentage of fertilization-competent capacitated spermatozoa (Cap-Score). Logistic regression of total pregnancy outcomes (n = 252) assessed fit. Cap-Scores of 2155 men questioning their fertility (MQF) from 22 clinics were compared with those of 76 fertile men in the cohort comparison. New outcomes (n = 128) were rank-ordered by Cap-Score and divided into quintiles (25-26 per group); chi-squared testing revealed no difference between predicted and observed pregnancies (p = 0.809). Total outcomes (n = 252; 128 new + 124 previous) were pooled and the model recalculated, yielding an improved fit (p < 0.001). Applying the Akaike information criterion found that the optimal model used Cap-Score alone. Semen analysis data were available for 1948, Cap-Scores were performed on 2155 men. To compare fertilizing ability, men were binned by PGP ($\leq 19\%$, 20-29%, 30-39%, 40-49%, 50-59%, $\geq 60\%$). Distributions of PGP and the corresponding Cap-Scores were significantly lower in MQF versus fertile men (p < 0.001). Notably, 64% of MQF with normal volume, concentration and motility (757/1183) had PGP of 39% or less (Cap-Scores ≤ 31), versus 25% of fertile men. The authors concluded sperm capacitation prospectively predicted male fertility and many MQFs with normal semen analysis results had an impaired capacitation. Limitations noted include the logistic relationship between Cap-Score and male fertility in the form of PGP as it is predicated upon a fertile female partner. Additionally, the authors state some participating physicians reported modifying their clinical practices when receiving the result of a low Cap-score that could have led to bias. The authors caution of interpretation of outcomes data stratified by maternal age and note that no data regarding comorbidities were included in the MQF group.

Schinfeld et al. (2018) conducted a prospective, observational study to determine whether Cap-Score can predict male fertility with the outcome being clinical pregnancy within ≤ 3 IUI cycles. Initial exclusion criteria for men were having fewer than 10×10^6 motile sperm on initial count. The fertility of female partners was examined, but findings of female factor that did not preclude attempts at IUI were not considered grounds for exclusion. Only couples that pursued IUI were included in the study. A Cap-Score and semen analysis were performed on 208 men, with outcomes available for 91 men. The chance of generating pregnancy was predicted for the men using previously-defined Cap-score ranges, low (n = 47) or high (n = 44). Absolute and cumulative pregnancy rates were reduced in men predicted to have low pregnancy rates versus high [(absolute: 10.6% vs. 29.5%; p = 0.04); (cumulative: 4.3% vs. 18.2%, 9.9% vs. 29.1%, and 14.0% vs. 32.8% for cycles 1-3; n = 91, 64, and 41; p = 0.02)]. The Cap-Score differed significantly between outcome groups. Logistic regression evaluated Cap-Score and semen analysis results relative to the probability of generating pregnancy (PGP) for men who were successful in, or completed, three IUI cycles (n = 57). Cap-Score was significantly related to PGP (p = 0.01). The model fit was then tested with 67 additional patients (n = 124; five clinics); the equation changed minimally, but fit improved (p < 0.001; margin of error: 4%). The authors concluded that the Akaike Information Criterion found the best model used the Cap-Score as the only predictor and that Cap-Score provided a predictive assessment of male fertility. The authors note that further investigation is required to assess the decline in success in the third IUI cycle of men with normal-range Cap-Scores. Limitations include potential variation in IUI techniques and patient characteristics from multiple sites, and minimal tests for female factor infertility were defined.

Cardona et al. (2017) assessed whether G_{M1} localization patterns (Cap-Score™) previously studied in animal models would correspond with male fertility in humans-in two different settings. One study (#1) was a post-hoc association between capacitation and involved couples pursuing assisted reproduction in a tertiary care fertility clinic. The second study (#2) involved fertile men versus those questioning their fertility at a local urology center. In Study 1, various thresholds were examined versus clinical history for 42 patients; 13 had Cap-Scores $\geq 39.5\%$, with 12 of these (92.3%) achieving clinical pregnancy by natural conception or ≤ 3 intrauterine insemination cycles. In Study 2, Cap-Scores of 76 men with known recent fertility were obtained (Cohort 1, pregnant partner or recent father) and compared to 122 men seeking fertility assessment (Cohort 2). Cap-Score values were normally distributed in Cohort 1, with 13.2% having Cap-Scores more than one standard deviation below the mean ($35.3 \pm 7.7\%$). More men in Cohort 2 had Cap-Scores greater than one standard deviation below the normal mean (33.6%; $p = 0.001$). Minimal or no relationship was found between Cap-Score and standard semen analysis parameters. The authors concluded the data provided reference ranges for fertile men that could be used to guide couples toward the most appropriate fertility treatment and Cap-Score testing could be used as a complement to standard semen analysis parameters. Study limitations include small sample sizes.

Sperm DNA Integrity/Fragmentation Tests

There is insufficient evidence supporting the predictive value or clinical utility of this test. Prospective studies directly evaluating the impact of DNA fragmentation testing on the management of infertility are needed.

Lourenco et al. (2023) conducted a systematic review and sought the impact sperm DNA fragmentation (SDF) has on embryos from assisted reproduction techniques (ARTs). The study included 20 articles that met inclusion criteria which were cohort and case-control articles. The SDF increase proved to be a limiting potential for ARTs. In IVF, clinical outcomes such as reduced fertilization rate, blastocyst rate, embryo quality, reduced implantation rate, and increased abortion rates were observed. In intracytoplasmic sperm injection (ICSI), outcomes such as reduced blastocyst production rate, embryo quality, implantation, and live birth rate were verified. Furthermore, in intrauterine insemination (IUI), results of reduced pregnancy rates were observed. However, the mechanisms that lead to these deleterious effects on ARTs still unclear, so more studies are needed to identify the effects of SDF on ARTs. Limitations in the study include the absence of patients as healthy controls and the five-year period limited the number of articles obtained. The authors concluded sperm DNA fragmentation was a potential limiting factor for assisted reproduction techniques.

In a 2022 meta-analysis, Chen et al. sought to analyze the effect of sperm DNA fragmentation index (DFI) on the outcomes of IVF and ICSI. A total of 12 cohort studies (4 retrospective, 5 prospective, and 3 bidirectional cohort studies) between 2005 and 2020 were included and analyzed using the random effects model. The results indicated the high DFI group were statistically inconsequential in comparison to the low FI group with the IVF fertilization rate (RR = 0.94, 95% CI: 0.77-1.14, $p = 0.61$), pregnancy rate (RR = 0.83, 95% CI: 0.57-1.21, $p = 0.32$), and live birth rate (RR = 0.53, 95% CI: 0.16-1.80, $p = 0.31$). The association between DFI and ICSI with the fertilization rate (RR = 0.79, 95% CI: 0.52-1.18, $p = 0.25$), pregnancy rate (RR = 0.89, 95% CI: 0.74-1.06, $p = 0.18$), and live birth rate (RR = 0.89, 95% CI: 0.70-1.14, $p = 0.36$) were also not statistically significant. The authors concluded the study has no significant interrelationship between sperm DFI and assisted reproductive outcomes. Therefore, further studies of multicenter large-sample clinical trials should be carried out to conclusively determine the significance of DNA damage on assisted reproduction outcomes. Several limitations were identified in the study. First, age-considered subgroup analyses were not examined. Second, only SCSA studies using DFI detection were used and introduced biases that do not reflect the overall DFI. Finally, no differences were identified in sperm DFI in assisted reproductive outcomes although the threshold between high and low DFI was 15%-30%, which is relatively large.

Sperm Penetration Assays (SPA)

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

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 such as successful pregnancies with delivery of liveborn children.

Arian et al. (2023) conducted a systematic review and meta-analysis to investigate the impact of endometrial receptivity array (ERA) before frozen embryo transfer in patients undergoing IVF. Eight studies (2,784 patients; n = 831 had undergone ERA and n = 1,953 without ERA) were found to be eligible for this meta-analysis. The live birth or ongoing pregnancy rate for the ERA group was not significantly different compared with the non-ERA group, nor was a difference seen in subgroup analyses based on the number of previous failed ETs. The rates of implantation, biochemical pregnancy, clinical pregnancy, and miscarriage were also comparable between the ERA and the non-ERA groups. After separate analyses according to the study design and adjustment for confounding factors, overall pooled estimates remained statistically nonsignificant. Limitations in the study included the combination of randomized trials with non-RCT studies, separate subgroup analyses, the heterogeneity of different types of ERA kits and testing modalities, different types of endometrial preparations and lack of control for causes of implantation failure. The authors concluded the meta-analysis did not reveal a significant change in the rate of pregnancy after IVF cycles using ERA, and it is not clear whether ERA can increase the pregnancy rate or not. The authors suggested further well-designed RCTs must prove the utility of the ERA testing on clinical pregnancy rates (CPRs) and ongoing pregnancy rate (OPRs) in general and certain subgroups of patients with infertility.

In a 2023 systematic review and meta-analysis, Papanikolaou et al. sought to provide the impact of endometrial scratching (ES) during hysteroscopy before embryo transfer (ET) on pregnancy rates. Twelve studies (n = 2,213) met inclusion criteria and were used in this analysis. The authors identified that hysteroscopy and concurrent ES before ET resulted in a statistically significant improvement in clinical pregnancy rate (CPR) [RR = 1.50, (95% CI 1.30–1.74), p < 0.0001] and live birth rate (LBR) [RR = 1.67, (95% CI 1.30–2.15), p < 0.0001] with no statistically significant difference on miscarriage rate [RR = 0.80 (95% CI 0.52–1.22), p = 0.30]. Limitations in the study included poor quality studies, limited number of studies, timing of the interventions and different instruments used. The authors concluded that hysteroscopy with concurrent ES may be offered in IVF before ET as a potentially improving manipulation. The authors suggested future randomized trials comparing different patient groups would also provide more precise data on that issue, to clarify specific criteria in the selection of patients.

A Hayes (2022) Precision Medicine Research Brief examined the published peer-reviewed literature to evaluate the evidence related to the Endometrial Receptivity Analysis (ERA) test. The safety and clinical utility of this health technology cannot be made within this report as it would require a full-text review of the evidence. A full review of evidence may be justified depending on whether the health technology of interest is emerging, evolving, controversial, or disruptive and the degree to which it is a priority to clients.

Liu et al. (2022) conducted a systematic review and meta-analysis to determine the prevalence of displaced window of implantation (WOI) in infertile women, and the clinical utility of personalized embryo transfer (pET) guided by the endometrial receptivity array/analysis (ERA) on IVF/ICSI outcomes. The study included 11 published articles after meeting inclusion criteria. The estimate of the incidence of WOI displacement based on ERA was 38% in good-prognosis infertile patients (GPP) and 34% in repeated implantation failure (RIF), respectively. There was no difference in ongoing pregnancy rate (OPR)/live birth rate (LBR) between patients undergoing routine ET without ERA test and those who following pET with ERA (39.5 vs. 53.7%, OR 1.28, p = 0.49, 95%CI 0.92–1.77, I² = 0%) in relative GPP. The meta-analysis revealed that OPR/LBR of patients with RIF undergoing pET who had non-receptive ERA increased to the level of to those undergoing standard embryo transfer (sET) with receptive ERA (40.7 vs.49.6%, OR 0.94, p = 0.85, 95%CI 0.70–1.26, I² = 0%). The authors concluded the ERA test as a promising tool. In patients with general good-prognosis ERA may not be beneficial, but personalized embryo transfer guided by ERA significantly increases the chances of pregnancy for non-receptive patients with RIF of endometrial origin. Limitations in the study include small sample size and heterogeneity in the studies and therefore more high-quality RCTS are needed to confirm the clinical utility of ERA.

Van Hoogenhuijze et al. (2021) conducted a non-blinded RCT (SCRaTCH trial) in women with one failed IVF/ICSI cycle to evaluate whether a single endometrial scratch using an endometrial biopsy catheter would lead to a higher live birth rate after the subsequent IVF/ICSI treatment compared to no scratch. Cumulative twelve-month ongoing pregnancy leading to live birth rate was a secondary outcome. The women were randomized between January 2016 and July 2018, in total, 933 participants out of 1065 eligible were included in the study that took place in eight academic and 24 general hospitals. After the fresh transfer, 4.6% more live births were observed in the scratch compared to control group (110/465 versus 88/461, respectively). These data are consistent with a true difference of between 0.7% and p9.9% (95% CI), indicating that while the largest proportion of the 95% CI is positive, scratching could have no or even a small negative effect. Biochemical pregnancy loss and miscarriage rate did not differ between the two groups: in the scratch group 27/153 biochemical pregnancy losses and 14/126 miscarriages occurred, while this was 19/130 and 17/111 for the control group. After 12 months of follow-up, 5.1% more live births were observed in the scratch group (202/467 versus 178/466), of which the true difference most likely lies between 1.2% and p11.4% (95% CI). The authors note that the results of this study are an incentive for further assessment of the efficacy and clinical implications of endometrial scratching and if a true effect exists, it may be smaller than previously anticipated or may be limited to specific groups of women undergoing

IVF/ICSI. The authors concluded that at present, endometrial scratching should not be performed outside of clinical trials and recommend further studies with larger sample sizes. Limitations include non-blinding of participants.

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.

In a Cochrane review, Nastri et al. (2015) conducted a review of RCTs comparing intentional endometrial injury before embryo transfer in women undergoing ART, versus a sham procedure or no intervention. Fourteen trials (n = 1063) were in the intervention groups and (n = 1065) were in the control groups. One study compared endometrial injury on the day of oocyte retrieval versus no injury, thirteen studies compared endometrial injury performed between day seven of the previous cycle and day seven of the embryo transfer (ET) cycle versus no injury. In studies comparing endometrial injury performed between day seven of the previous cycle and day seven of the ET cycle versus no intervention or a sham procedure, endometrial injury was associated with an increase in live birth or ongoing pregnancy rate (RR 1.42, 95% confidence interval (CI) 1.08 to 1.85; P value 0.01). There was no evidence of an effect on miscarriage. Endometrial injury was also associated with an increased clinical pregnancy rate (RR 1.34, 95% CI 1.21 to 1.61; P value 0.002). This suggests that if 30% of women achieve clinical pregnancy without endometrial injury, between 33% and 48% will achieve clinical pregnancy with this intervention. Endometrial injury was associated with increased pain. One study reported pain on a VAS scale, two studies reported the number of pain complaints after the procedure, one recorded no events in either group, and the other reported that endometrial injury increased pain complaints. Results from the only RCT comparing endometrial injury on the day of oocyte retrieval versus no injury, reported that this endometrial injury markedly decreased live birth and clinical pregnancy. The authors concluded the procedure is mildly painful, there is no evidence of effect on miscarriage, multiple pregnancy or bleeding, and reduction of clinical and ongoing pregnancy rates is associated with endometrial injury on the day of oocyte retrieval. Additionally, moderate-quality evidence indicates that endometrial injury performed between day seven of the previous cycle and day seven of the ET cycle is associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous embryo transfers. The authors states that although current evidence suggest benefit of endometrial injury, more evidence from well-designed trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage in the control group, stratify the results for women with and without recurrent implantation failure, and report live birth are needed.

Clinical Practice Guidelines

American Society for Reproductive Medicine (ASRM)

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, 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, 2021a)

An ASRM committee opinion on fertility evaluation of infertile women recommends 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, 2021b)

An ASRM committee opinion on fertility evaluation of infertile women states that the post-coital 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, 2021b)

In ASRM fertility evaluation of infertile women: a committee opinion states that markers of ovarian reserve tests are neither beneficial in predicting the likelihood of unaided pregnancy in women with infertility nor do they predict the reproductive potential among women with undocumented fertility. Markers of ovarian reserve can be useful predictors of oocyte yield but weak independent predictors of reproduction potential and should not be used as a fertility test (ASRM, 2020). Additionally, an ASRM committee opinion regarding fertility evaluation of infertile women states Inhibin B and the clomiphene challenge test are not helpful tools to assess ovarian reserve and are not recommended. (ASRM, 2021b)

An ASRM committee opinion states that ovarian tissue banking is an acceptable fertility preservation technique and is no longer considered experimental. However, data on the efficacy, safety, and reproductive outcomes after ovarian tissue cryopreservation are still limited. Given the current body of literature, ovarian tissue cryopreservation should be considered an established medical procedure with limited effectiveness that should be offered to carefully selected patients. (ASRM, 2019)

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 is an established method
- Embryo cryopreservation is an established method of fertility preservation in women and men
- Cryopreservation of ovarian tissue remains investigational (refer to ASRM, 2019 above for updated information)
- Cryopreservation of testicular tissue in prepubescent males remains investigational

American Society of Clinical Oncology (ASCO)

In an ASCO clinical practice guideline on fertility preservation in patients with cancer, an update summary stated a recommendation for ovarian tissue cryopreservation and transplantation. 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).

American Urological Association (AUA)/American Society for Reproductive Medicine (ASRM)

The AUA/ASRM society guideline on diagnosis and treatment of infertility of men states the following:

- Initial evaluation with reproductive history and semen analysis
- If the initial evaluation is abnormal, then a complete evaluation is recommended with the following:
 - Complete history
 - Physical exam
 - Hormonal evaluation testing (i.e., FSH , testosterone)
- Clinicians should counsel infertile men of the risk factors (i.e., lifestyle, medication usage, health conditions, environmental exposures) associated with male infertility and abnormal sperm production
- Further diagnostic testing and imaging may be suggested based on expert opinion (Schlegel et al., 2021a; Schlegel et al., 2021b)

The AUA/ASRM society guideline on diagnosis and treatment of infertility of men states that sperm DNA fragmentation analysis is not recommended in the initial evaluation of the infertile couple. There are no prospective studies that have directly evaluated the impact of DNA fragmentation testing on the clinical management of infertile couples (Schlegel et al., 2021a; Schlegel et al., 2021b).

An AUA/ASRM guideline on diagnosis and treatment of infertility of men states that patients with pyospermia should be evaluated for the presence of infection. Elevated semen white blood cells may secrete cytokines and generate free radicals in the semen (reactive oxygen species) that may be detrimental to sperm function, this is not a test of fertility (Schlegel et al., 2021a).

National Institute for Health and Care Excellence (NICE)

A NICE clinical guideline addresses the evaluation and management of infertility, including assisted reproductive technology (ART) and recommends:

- 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
- The use of inhibin B testing for predicting any outcome of fertility treatment is not recommended

No recommendation for routine use of post-coital testing of cervical mucus for evaluating infertility because the test has no predictive value on pregnancy rate. (NICE, 2013; updated 2017)

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. Refer to the following website to search for specific products: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed January 11, 2024)

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. Refer to the following website for more information (use product code MQL). Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed January 11, 2024)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2024T0270JJ]

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Policy History/Revision Information

Date	Summary of Changes
01/01/2025	<p data-bbox="337 541 1469 611">Medical Records Documentation Used for Reviews (<i>previously titled Documentation Requirements</i>)</p> <ul data-bbox="337 611 1429 674" style="list-style-type: none"><li data-bbox="337 611 1429 674">• Replaced list of <i>Required Clinical Information</i> with instruction to refer to the protocol titled Medical Records Documentation Used for Reviews <p data-bbox="337 674 662 709">Supporting Information</p> <ul data-bbox="337 709 1019 741" style="list-style-type: none"><li data-bbox="337 709 1019 741">• Archived previous policy version INFERTILITY 008.19

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford 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 Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

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