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## Description/Scope

This document addresses selected tests that are part of the diagnostic work-up to determine the cause of infertility or manage infertility treatment.

*Note:* In this guideline, the term “male” or “men” is used to refer to genetic or biological men. The term “female” or “women” is used to refer to genetic or biological women.

Note: Please see the following related documents for additional information:

- CG-MED-66 Cryopreservation of Oocytes or Ovarian Tissue
- CG-SURG-34 Diagnostic Hysteroscopy for Infertility
- CG-SURG-35 Intracytoplasmic Sperm Injection (ICSI)

## Position Statement

### Investigational and Not Medically Necessary:

The following tests or procedures are considered **investigational and not medically necessary** for diagnosing or managing infertility:

- Endometrial receptivity analysis;
- Sperm-capacitation test;
- Sperm deoxyribonucleic acid (DNA) fragmentation test;
- Sperm penetration assay; and
- Uterine natural killer (uNK) cells test.

## Rationale

Conception is a complex process that is dependent upon many factors: the production of healthy eggs (ovum) and healthy sperm; patent fallopian tubes that allow the sperm to reach the ova; the sperm’s ability to fertilize the egg; the ability of the fertilized egg (embryo) to implant in the uterus; and sufficient embryo quality. For the pregnancy to continue to full-term, the embryo must be genetically viable and the hormonal and uterine structural environment adequate for its development. A problem with any or several of these steps can result in infertility.

Infertility has been defined by several specialty associations and specialty medical societies. The Centers for Disease Control and Prevention (CDC) and the World Health Organization defines infertility as a disease of the reproductive system which results in a failure to achieve a successful pregnancy within 12 months of regular, unprotected sexual intercourse, in the absence of known reproductive pathology. Similarly, the American College

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of Obstetricians and Gynecologists (ACOG) defines infertility as “failure to achieve pregnancy within 12 months of unprotected intercourse or therapeutic donor insemination in women younger than 35 years or within 6 months in women older than 35 years” (ACOG 2018; CDC, 2021; WHO, 2020). In 2023 the American Society for Reproductive Medicine (ASRM) updated their definition of fertility to read as follows:

“Infertility” is a disease, condition, or status characterized by any of the following:

- The inability to achieve a successful pregnancy based on a patient’s medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors.
- The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos in order to achieve a successful pregnancy either as an individual or with a partner.
- In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older (ASRM, 2023).

It has been estimated that in the United States, of the 15% of couples experiencing infertility, a “male factor” is identified in addition to a “female factor”. In approximately 20% of couples with infertility, a “male factor” is the only identifiable cause (Leslie, 2023).

Both the American College of Gynecologists (ACOG) and ASRM recommend evaluation and treatment of any individual who has infertility or is at high risk of infertility based on history. Females older than 40 years should be offered expedited evaluation and treatment. Immediate evaluation should be offered if either partner has a condition known to cause infertility (ACOG, 2019; ASRM, 2015).

ACOG indicates that the infertility workup might reasonably include laboratory and imaging tests. For the female partner, tests will generally focus on ovulatory function, ovarian reserve, and structural abnormalities. ACOG also advises the following:

Certain fertility tests have a low yield in identifying modifiable diagnoses, do not distinguish women who will and will not become pregnant, add significant expense, or are associated with harms that outweigh demonstrable benefit. Although there may be other reasons for these tests to be done, they are low yield for infertility evaluation. Imaging of the reproductive organs provides valuable information on conditions that affect fertility. Imaging modalities can detect tubal patency and pelvic pathology and assess ovarian reserve (ACOG, 2019).

According to ACOG (2019), the following low-yield infertility tests that should not be routinely ordered include:

- Laparoscopy for unexplained infertility;
- Advanced sperm function tests (e.g., DNA fragmentation testing);
- Postcoital testing;
- Thrombophilia testing;
- Immunologic testing;
- Karyotype;

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- Endometrial biopsy;
- Prolactin.

In the evaluation of the infertile male, ASRM recommends that:

At a minimum, the initial screening evaluation of the male partner of an infertile couple should include a reproductive history and analysis of at least one semen sample. If the initial evaluation is abnormal, then referral to someone experienced in male reproduction is recommended (ASRM, 2015).

This document addresses tests that are generally not considered part of the initial, standard diagnostic work-up to determine the cause of infertility.

### ***Endometrial Receptivity Analysis***

Successful embryo implantation requires an intricate exchange between a competent embryo and a receptive endometrium. Repeated implantation failure (RIF) is the failure of the embryo to implant onto the side of the uterine wall following in vitro fertilization (IVF) treatment. As a rule, this occurs at 6-7 days after conception and involves the embedding of the growing embryo into the mother's uterus. While failed implantation is often ascribed to embryonic factors, when multiple high-quality embryos have failed to implant, non-embryonic factors such as defects in endometrial receptivity should be considered. The endometrium is only receptive during a limited period of time ("window of implantation [WOI]") that coincides with the development of a blastocyst (Cohen, 2020).

The standard of care for endometrial evaluation in IVF is ultrasonographic measurement of endometrial thickness during the follicular phase of the menstrual cycle. However, ultrasound measurements are susceptible to observer variability, have poor predictive value for implantation, and are often normal in the RIF population (Bonilla-Musoles, 2013; Cohen, 2020; Jarvela, 2005). Because of the limitations in ultrasonographic measurements to identify the WOI, researchers are exploring the use of other diagnostic tests, including but not limited to endometrial receptivity analysis, to identify the optimal time for embryo transfer.

The Endometrial Receptivity Assay or ERA (Igenomix, Valencia, Spain) was developed as an objective means to evaluate endometrial receptivity. This genomic test using microarray technology exploits RNA obtained from an endometrial tissue sample to measure the expression of 238 genes and subsequently employs a prediction algorithm (artificial intelligence), to classify the endometrium as "receptive" or "non-receptive" (Díaz-Gimeno et al. 2011).

Simon and colleagues (2020) reported the outcomes of an open-label, multi-center randomized controlled trial (RCT), that assessed if clinical performance of personalized embryo transfer (PET) guided by ERA would differ from frozen embryo transfer (FET) or fresh embryo transfer (ET) in infertile individuals undergoing in vitro fertilization (IVF). This study included a total of 458 participants aged 37 years or younger undergoing IVF with blastocyst transfer at first appointment. The participants were randomized to PET guided by ERA, FET or fresh ET in 16 reproductive clinics. Clinical outcomes by intention-to-treat (ITT) analysis were comparable, but cumulative pregnancy rate (CPR) was appreciably higher in the PET (93.6 %) compared with FET (79.7 %) ( $p=0.0005$ ) and fresh ET groups (80.7 %) ( $p=0.0013$ ). Analysis per protocol revealed that live birth rates (LBRs) at first ET were 56.2 % in PET versus 42.4 % in FET ( $p=0.09$ ), and 45.7 % in fresh ET groups ( $p=0.17$ ). After 12 months, the cumulative LBRs (CLBRs) were 71.2 % in PET versus 55.4 % in FET ( $p=0.04$ ), and 48.9 % in fresh ET ( $p=0.003$ ).

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Pregnancy rates for the first ET in PET, FET and fresh ET arms were 72.5 % versus 54.3 % ( $p=0.01$ ) and 58.5 % ( $p=0.05$ ), respectively. Implantation rates for first ET were 57.3 % versus 43.2 % ( $p=0.03$ ), and 38.6 % ( $p=0.004$ ), respectively. Obstetrical outcomes, type of delivery and neonatal outcomes were similar amongst all groups. While the ITT analysis demonstrated no beneficial effect of the ERA test except for a statistically significant CPR compared with FET and fresh ET, the per protocol analysis demonstrated a significant improvement in pregnancy rates at the first and cumulative rates up to 12 months, and implantation rates at the first attempt, showing the potential of the ERA test to diagnose the endometrial factor in the work-up of the infertile couple. The researchers acknowledged that these findings need to be confirmed in a larger randomized clinical trial.

In a prospective, cohort study, Riestenberg and associates (2021) compared the LBRs between individuals who undergo PET after ERA versus FET with standard timing in first single euploid FET cycles. These researchers also reported the rate of displacement of WOI in an infertile population with no history of implantation failure. Subjects consisted of individuals who had undergone their first autologous single euploid programmed FET between January 2018 and April 2019. Participants underwent endometrial biopsy with ERA followed by PET as indicated. Primary outcome measures included LBR as well as rate of receptive and non-receptive ERA. Of the total 228 single euploid FET cycles included in the analysis, 147 (64.5 %) were ERA/PET cycles, and 81 (35.5 %) were standard timing FET cycles. Endometrial receptivity array was receptive in 60/147 (40.8 %) and non-receptive in 87/147 (59.2 %) participants. Non-receptive ERAs demonstrated pre-receptivity in 93.1 % of cases. The LBR did not differ between the participants who underwent FET with standard timing and those who underwent ERA/PET, 45/81 (56.6 %) and 83/147 (56.5 %), respectively. The authors concluded this study does not support the routine use of ERA in an unselected patient population undergoing first autologous single euploid programmed embryo transfer.

Bergin and colleagues (2021) investigated the impact of the ERA on LBRs in FET cycles by reviewing the records of individuals who had undergone autologous FET cycles between January 1, 2014, and June 30, 2019. Multiple co-variables that impacted outcomes were used for propensity score matching; 133 ERA subjects were matched to 353 non-ERA subjects. Participants were assigned to the ERA group if they had an ERA during treatment and underwent at least one "personalized" FET (PFET) based on the ERA recommendations. Primary outcome measures included LBRs per cycle in the FET cycle following ERA compared with that of matched non-ERA subjects. The LBRs of 49.62% for the ERA cohort and 54.96% for the matched non-ERA group (odds ratio [OR] 0.8074; 95 % confidence interval [CI]; 0.5424 to 1.2018) were not significantly different, nor was a difference observed in sub-analyses based on prior number of FETs or receptivity status. The authors concluded that ERA identified an individual's putative WOI with the objective of improving synchrony with the embryo; thus, attaining higher LBRs. This study used propensity score matching to control for multiple co-variables in a heterogeneous group of participants to compare LBRs. There was no difference in the LBRs in the individuals who underwent ERA compared with that of those who did not.

Eisman and colleagues (2021) conducted a retrospective study to investigate the utility of ERA in women with prior failed ETs. Study participants were women who underwent an ERA test with a subsequent FET. Women were classified according to their indication for an ERA test: one or more prior failed ET (cases), or as a prophylactic measure (controls). A subset analysis of the participants with three or more prior failed ETs was also conducted. Pregnancy outcomes of the subsequent cycle were analyzed, including conception, clinical pregnancy, and ongoing pregnancy/livebirth. A total of 222 participants were included, 131 (59 %) females with one or more prior failed ET and 91 (41 %) controls. Among the 131 subjects with one or more prior failed ET, 20 women (9 %) had three or more prior failed ETs. The proportion of non-receptive ERA tests in the three cohorts were the following: 45 % (one or more prior failed ET), 40 % (three or more prior failed ETs), and 52 % (controls). The results between the

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cases and controls did not differ. The pregnancy outcomes did not differ between the participants with greater than or equal to one prior failed ET and controls. Amongst study participants with greater than or equal to three prior failed ETs, there was a lower ongoing pregnancy/LBR (28 % versus 54 %,  $p=0.046$ ). The authors concluded that the participants with one or more prior failed ET and three or more prior failed ETs had a similar prevalence of non-receptive endometrium compared to controls. Participants with three or more prior failed ETs had a lower ongoing pregnancy/LBR despite a personalized FET, suggesting that there are additional factors in implantation failure beyond an adjustment in progesterone exposure. The authors point out that a limitation of the study involves the control group. The control group was defined as female participants who do not have a history of failed ET, but one-third of the controls did not have a clinical pregnancy in the subsequent FET cycle and ultimately would be reclassified as failed ET cases. Ideally, the control group would be comprised of women with a nonreceptive ERA test, who do not undergo an adjusted progesterone duration for a personalized FET.

The ASRM committee opinion on the diagnosis and treatment of luteal phase deficiency, provides the following cautionary language regarding endometrial receptivity testing:

Because the histologic evaluation of the endometrium is imprecise, many additional biochemical, morphologic, and molecular markers of endometrial function have been proposed to assess endometrial receptivity to implantation. However, no marker of endometrial receptivity has been validated in a RCT or demonstrated the ability to distinguish normal fertile from infertile women. At this time, molecular markers of receptivity remain experimental and are not considered valid clinical diagnostic tools (ASRM, 2021)

### ***Sperm Capacitation Test***

Historically, a comprehensive semen analysis (which measured sperm count, motility and analyzed morphology) was used to determine a man's fertility. However, traditional semen analysis does not test for sperm function and, as such, cannot report on the ability of sperm in that semen sample to fertilize an ovum and has been estimated to identify less than 50% of all male infertility. Most infertile men are believed to have defects in sperm function, which are generally diagnosed after repeated failed cycles of IUI. Tests of sperm function have been explored as a means of assisting healthcare practitioners identify the cause of infertility in males. To this end, sperm capacitation testing is being explored as a means to measure sperm functionality (Moody, 2017).

Sperm capacitation refers to the physiological alterations the spermatozoa must undergo to have the ability to penetrate and fertilize an egg. During capacitation, the head and the tail of the sperm undergo transformations that enable them to begin to move in a hyper-activated swimming pattern. This pattern allows the sperm to successfully maneuver up the fallopian tube and into the egg. In addition, specific enzymes must be released in order for the sperm to pass through the layer of cells that surround the egg.

The Cap-Score™ Sperm Function Test (Androvia LifeSciences, Mountainside, NJ), is an in vitro, laboratory-developed test designed to evaluate sperm function, particularly regarding capacitation. This assay identifies and analyzes the localization patterns of the ganglioside  $G_{M1}$  to evaluate the fertilizing ability of sperm. Conducting a Cap-Score test involves the incubation of sperm in medium containing capacitating stimuli (Cap) and non-capacitating (non-Cap) medium. The sperm that react to the capacitation stimuli are identified by specific  $G_{M1}$  localization patterns. The final data, called the "Cap-Score" reports the proportion of sperm within a sample that display the localization patterns that correspond with capacitation (Moody, 2017)

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Cardona and colleagues (2017) evaluated the data of two separate studies to determine whether the Cap-Score could be used to measure the fertility status of men and if the Cap-Score  $G_{MI}$  localization patterns correlated with any of the standard semen analysis parameters or instead added distinct, complementary information. The first study (Study 1), a post-hoc association between capacitation and fertilization, involved couples pursuing assisted reproduction in a tertiary care fertility clinic. In Study 1, the researchers examined various thresholds versus clinical history for 42 participants; 13 had Cap-Scores  $\geq 39.5\%$ , with 12 of these (92.3%) succeeding at clinical pregnancy by natural conception or  $\leq 3$  IUI cycles. Of the 29 participants scoring  $< 39.5\%$ , only 6 (20.7%) attained clinical pregnancy by natural conception or  $\leq 3$  IUI cycles. The authors point out that one of the limitations of the study is the data being obtained from individuals actively seeking a fertility work-up and treatment at a tertiary care clinic, frequently after a long history of examinations and unsuccessful cycles IUI at other clinics. This resulted in a highly skewed participant base, in terms of both age and need for the majority of the participants to utilize IUI to realize a successful fertilization. Therefore, the values and cut-off in Study 1 would likely not be applicable to a population of fertile individuals and/or a population seeking fertility treatment. The study results are also limited by its small sample size.

The second study (Study 2) involved two cohorts (Groups A and B). Group A consisted of 76 fertile males (as evidenced by recent father or pregnant partner status) at a single urology facility, while group B was comprised of 122 males at a single urology center who were seeking semen analysis because of questions regarding their fertility (potential subfertile/infertile). The Cap-Scores of Group A were compared to Group B. Cap-Score values were normally distributed in Group A with 13.2% having Cap-Scores more than one standard deviation below the mean ( $35.3 \pm 7.7\%$ ). More men in Group B 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 sperm morphology, motility or concentration. The authors concluded the data supplied normal reference ranges for fertile men that can be used to steer couples toward the most appropriate fertility treatment and Cap-Score testing could be used as a complement to standard semen analysis parameters. Limitations include small sample sizes. Also, although Cap-Score population means were compared between Group A and B, because the vast majority of Group B was not vetted for female fertility factor, this population likely represents a rather heterogeneous distribution that includes a number of fertile men.

Schinfeld and colleagues (2018) reported the results on an observational, prospective feasibility trial of utilization of the Cap-Score assay at a small number of urology practices and fertility clinics. The primary outcome was clinical pregnancy within three or fewer IUI cycles. The exclusion criteria included men with less than  $10 \times 10^6$  motile sperm on initial count. Cap-Score and semen analysis were complete on 208 males initially, with the outcomes being available for 91 males. The male participants were predicted to have either low ( $n=47$ ) or high ( $n=44$ ) likelihood of generating pregnancy using previously defined Cap-Score reference ranges. The fertility of female partners was assessed but findings of female factor that did not prevent attempts at IUI were not considered grounds for exclusion. Only couples that chose to pursue IUI were included in the investigation. Absolute and cumulative pregnancy rates were reduced in males 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;  $n=91, 64, \text{ and } 41$ ;  $p=0.02$ ]). The Cap-Score differed substantially between outcome groups. Logistic regression calculated Cap-Score and semen analysis results relative to the likelihood of generating pregnancy for men who were successful in, or completed, three IUI cycles ( $n=57$ ). Cap-Score was correlated to probability of generating pregnancy ( $p=0.01$ ). To overcome the initial limitation of generating the logistic equation with data from a single institution, additional data were added to the analysis representing a total of five facilities, and more than doubling

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the sample size from 57 to 124 males; the equation changed marginally, but fit improved ( $p < 0.001$ ; margin of error: 4%). The authors determined that the likelihood of achieving pregnancy by IUI was about 3-fold higher when sperm with the so-called 'high fertilizing potential' was utilized for insemination. The researchers conclude that the sperm capacitation test could assist clinicians in deciding whether a couple should choose IUI or better move to ART. The authors acknowledged that further investigation is required to evaluate the decline in success in the third IUI cycle of men with normal-range Cap-Scores. The authors recognized study limitations include subject characteristics from multiple sites, potential variation in IUI techniques and minimal tests for female factor infertility.

There is insufficient evidence supporting the predictive value or clinical utility of sperm capacitation testing. The peer reviewed scientific literature evaluating sperm capacitation assays consists primarily of observation or cohort studies; no randomized controlled trials, systematic reviews or meta-analyses were identified. At the time of this review, no professional society position statements or clinical practice guidelines were identified that address sperm capacitation testing. Additional, well-designed studies are needed that demonstrate sperm capacitation testing results in changes in patient management and results in improved clinical outcomes.

### ***Sperm Deoxyribonucleic Acid (DNA) Fragmentation Test***

Sperm DNA integrity is critical to the fertilization and development of healthy offspring. Sperm DNA fragmentation refers to damaged or denatured sperm DNA that cannot be repaired. Sperm DNA damage is more common in infertile men and may be a factor in poor reproductive performance in some couples. DNA sperm fragmentation may occur as the result of numerous clinical and environmental factors. Extrinsic factors that may cause sperm DNA fragmentation include, but is not limited to extrinsic factors heat exposure, smoking, radiation, antiperspirants, environmental pollutants, and chemotherapeutic agents. Intrinsic factors that may cause sperm DNA fragmentation include, but is not limited to advanced paternal age, protamine deficiency, defective germ cell maturation, abortive apoptosis, and oxidative stress (Agarwal, 2020; ASRM, 2015).

The ASRM evaluated the evidence for sperm DNA fragmentation testing (sperm integrity testing) to predict male fertility with natural conception, pregnancy with intrauterine insemination (IUI), pregnancy with in vitro fertilization and pregnancy with IVF and intracytoplasmic sperm injection. The group concluded that:

Existing data do not support a consistent relationship between abnormal DNA integrity and reproductive outcomes. At present, the results of sperm DNA integrity testing alone do not predict pregnancy rates achieved through natural conception or with IUI, IVF, or ICSI. However, further research may lead to validation of the clinical utility of these tests (ASRM, 2013).

In the 2015 committee opinion addressing the diagnostic evaluation of the infertile male, the ASRM states:

Existing data relating to the relationship between abnormal DNA integrity and reproductive outcomes are too limited to routinely recommend any of these tests for the male partner in an infertile couple, but the effect of abnormal sperm DNA fragmentation on the value of IUI or IVF and ICSI results may be clinically informative. Although no treatment for abnormal DNA integrity has been proven to have clinical value, varicocele repair and antioxidant use may affect sperm DNA integrity. Sperm retrieved from the testis tend to have better sperm DNA quality in men with abnormal ejaculated sperm DNA integrity. Because the prognostic clinical value of

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DNA integrity testing may not affect the treatment of couples, the routine use of DNA integrity tests in the clinical evaluation of male-factor infertility is controversial (ASRM, 2015).

Similarly, in a guideline for clinicians, Agarwal and colleagues (2020) concluded that “sperm DNA damage is more common in infertile men and may contribute to poor reproductive performance. However, current methods for assessing sperm DNA integrity do not reliably predict treatment outcomes and cannot be recommended routinely for clinical use” (Agarwal, 2020).

The American Urological Association (AUA) has indicated that sperm DNA fragmentation analysis is not recommended in the initial evaluation of the infertile couple. (Moderate Recommendation; Evidence Level: Grade C). However, for couples experiencing recurrent pregnancy loss, men should be evaluated with karyotype (Expert Opinion) and sperm DNA fragmentation. (Moderate Recommendation; Evidence Level: Grade C) (Schlegel 2020).

According to ASRM:

“For a diagnostic test to be clinically useful the results must be reproducible, applicable to a given patient, and change the management of the patient. For tests of DNA integrity to be clinically important there must be an association of sperm DNA damage with reproductive outcomes” (ASRM, 2013).

At the current time, there is a lack of studies demonstrating that sperm DNA fragmentation testing results in improved clinical outcomes (improves the likelihood of conception).

### ***Sperm Penetration Assay***

The sperm penetration assay (SPA), also known as the “hamster test”, “zona free hamster oocyte test” or “hamster egg penetration test” (HEPT), is a laboratory test to predict the ability of a man’s sperm to fertilize a woman’s egg. During the laboratory procedure, sperm are mixed with hamster ova and gauged for their ability to penetrate the egg. Measuring the sperm’s ability to penetrate the pretreated hamster egg provides information about the sperm’s probability of penetrating a woman’s egg. The SPA does not analyze other aspects of sperm function.

In its recommendations on the diagnostic evaluation of the infertile male, the ASRM: states the following:

Numerous other tests of sperm function have been used predominantly in research studies. Sperm penetration assays may detect defects in sperm fertilizing capacity and could identify patients who would benefit from application of ICSI. However, because ICSI is routinely used during IVF for male-factor infertility couples, this test is rarely of any clinical value (ASRM, 2015).

### ***Uterine Natural Killer Cells***

Uterine natural killer (NK) cells are part of the immune system and form the major leucocyte population in the endometrium at the time of implantation. During pregnancy, NK cells assist in supplying blood to the fetus, and protect the fetus against infection and foreign bodies. It has been hypothesized that uNKs play a significant role in the establishment and maintenance of early pregnancy and that elevated levels of NK cells in the uterus may cause an abnormal immune response to sperm and/or embryos, which could result in infertility. Researchers are

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actively exploring the role of uNK in pregnancy pathology including but not limited to how they may contribute to recurrent miscarriage (RM) and recurrent implantation failure (RIF).

In a systematic review and meta-analysis of natural killer cells in female infertility and recurrent miscarriage, Seshadri and colleagues (2014) reviewed a total of 22 studies related to the levels of NK cells in blood and endometrium in infertile versus fertile women, the association between NK cells and IVF outcome, and the levels of NK cells in blood and endometrium in women with recurrent miscarriage (RM) versus controls. Meta-analysis of studies that evaluated peripheral and uterine NK (uNK) cell percentages in infertile versus fertile women demonstrated no significant difference between the two groups [standardized mean difference (SMD) -0.33; 95% CI, -1.06, 0.4;  $p=0.37$ ; SMD -1.82; 95% CI, -4.80, 1.17;  $p=0.23$  respectively]. Meta-analysis of studies that evaluated uNK cells demonstrated no significant difference in women with RM compared with controls (SMD 0.40; 95% CI, -1.24, 2.04;  $p=0.63$ ). The authors concluded that additional research is needed before NK cell assessment can be recommended as a diagnostic tool in the context of female infertility or RM. The authors also recommended that, “on the basis of current evidence, NK cell analysis and immune therapy should be offered only in the context of clinical research”.

Kuon and colleagues (2016) investigated the association between activated peripheral lymphocytes and uNK by analyzing peripheral NK (pNK) cells and uNK in women with a history of RM and healthy controls. With regards to findings related to uNK, the authors reported uNK numbers did not differ between RM subgroups and did not correlate with pNK. Nevertheless, the rate of highly elevated uNK was increased in iRM compared to non-iRM subjects ( $p=0.04$ ). Further, the data demonstrated higher numbers of CD45+CD3-DR+ ( $p<0.01$ ) and CD45+CD3+CD8+DR+ ( $p=0.04$ ) peripheral lymphocytes were associated with higher uNK numbers. The authors concluded that although pNK and uNK numbers did not correlate, the association between high CD45+CD3-DR+ and CD45+CD3+CD8+DR+ peripheral lymphocytes and uNK might indicate that activated NK, B and T cells provide cytokines for the differentiation of uNK.

In 2016 the reviewed the data relating to uterine NK cells and made recommendations for its use.

Despite intensive research the role of uNK cells in pregnancy remains uncertain, and whether the increased uNK cell numbers reported in association with abnormal pregnancy pathology (RM, RIF or pre-eclampsia) are directly causal or reflect more fundamental problems with the endometrium is not known (RCOG 2016).

In their review and discussion of the role of testing for peripheral (PB) and uNKs, the Royal College of Obstetricians & Gynaecologists (RCOG) offered the following:

The reported increases in uNK cell numbers in RIF or RM has resulted in increasing demand from women with these conditions for measurements of PB NK and uNK cell counts. The relevance of the results of these tests is currently limited for a number of reasons: 1) a lack of consensus on the methods used for measuring and reporting uNK cell numbers; 2) lack of a clear definition of a ‘normal’ range or what constitutes a ‘high’ cell count for either PB NK or uNK cells; and 3) uncertainty that higher levels of NK cells are predictive of an adverse pregnancy outcome.

The way in which uNK cell numbers are reported differs among centres; some centres report the absolute numbers of cells, while others express the numbers as a percentage of total stromal

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cells or total leucocytes.... studies with larger numbers of controls are required to determine the normal range. Since uNK cell numbers vary considerably during the menstrual cycle, the timing of sampling is very important. Endometrial tissue sampling is usually carried out during the mid-secretory phase (the peri-implantation period). The steep increase in uNK cell numbers during this phase of the cycle means that a difference in sampling time as few as 1 to 2 days will make a large difference to the number of uNK cells reported. It is therefore important that the biopsy is timed precisely according to the luteinizing hormone surge and preferably taken 7 days post surge (RCOG, 2016).

The RCOG offers the following opinion regarding the role of uterine NK cells in human fertility:

Despite intensive research the role of uNK cells in pregnancy remains uncertain, and whether the increased uNK cell numbers reported in association with abnormal pregnancy pathology (RM, RIF or pre-eclampsia) are directly causal or reflect more fundamental problems with the endometrium is not known. Despite this, a number of women are requesting and being offered analysis of either PB NK or uNK cells and the value of these measurements remains controversial. In response to patients who wish to discuss or request NK cell testing, clinicians should be aware that:

- uNK cells are different from PB NK cells, and that measurements of the latter are of limited value in aiding our understanding of the role of uNK cells in reproductive failure.
- There is no indication to offer routine uNK cell testing in women presenting with infertility or seeking IVF treatment; uNK cell testing in women with RM and RIF is still a matter for debate pending further evidence and should be regarded, for the time being, as within the realm of experimental medicine.
- The measurement of uNK cells must be standardised and the definition of 'normal' and 'high' levels based on established reference ranges derived from standardised methodology.
- Women undergoing uNK cell testing should understand that there is, as yet, no proven effective treatment for those with what may be considered abnormal results, although preliminary data suggest a possible positive effect of prednisolone.
- In planning RCTs, the need to standardise uNK cell measurement cannot be overemphasised. Resolution of this issue should be made a priority in order to provide answers to the points above and to give clarity to both clinicians and patients (RCOG, 2016).

Although several clinical studies have suggested that peripheral blood (PB) natural killer (NK) cells and/or uNK cells are increased in women with RM and RIF, a meta-analysis and systematic review failed to provide conclusive data because of significant heterogeneity across the studies arising from the use of different methods to quantify NK cells. An understanding of the role of these cells in reproductive failure and their value in clinical practice will not be established until a consensus is reached on how they should be measured (RCOG 2016).

Understanding the function of uNK cells is certainly a major challenge in human reproduction. However, until more is known about their role in normal pregnancy, a consensus is reached on how they should be measured, a standard normal range of uNK is determined, and there are well designed studies that show uNK testing results in

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improved patient outcomes, definitive conclusions cannot be made about the role of uNK testing in women experiencing recurrent miscarriage or infertility.

## Background/Overview

The most frequent cause of female infertility is a problem with ovulation. The most frequent cause of male infertility is a problem with sperm cells and how they function. Other causes that may affect fertility include age, health conditions and lifestyle (ACOG 2020).

Tests for infertility generally include laboratory tests, imaging studies, and certain procedures. Imaging tests and procedures examine the reproductive organs and how they work. Laboratory tests frequently involve testing samples of semen or blood (ACOG, 2020).

Treatments for infertility can range from medications to embryo implantation using assisted reproductive technology (ART). There are treatments that are specifically for women or for men and some that involve both partners. Occasionally no cause of infertility is found. Unexplained infertility may be diagnosed in as many as 30% of infertile couples (ACOG, 2020).

## Definitions

ART: Artificial reproductive techniques.

DNA fragmentation: The breaking down or separation of DNA strands into pieces; Denatured or damaged sperm DNA which cannot be repaired.

Fecundability: The probability of conceiving during a given menstrual cycle.

Fecundity: The ability to produce an offspring.

Female factor: causes of infertility associated with individuals of a biological female sex, including ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage and other fallopian tubal abnormalities and hyperprolactinemia.

Follicular phase: The phase of the menstrual cycle when the cells are multiplying and spreading, estrogen levels rise and the endometrium thickens. Also known as the proliferative phase of the menstrual cycle.

Infertility is a disease of the female or male reproductive system defined by the inability to get pregnant (conceive) after one year (or longer) of regular, unprotected, sexual intercourse (CDC, 2021; WHO, 2020).

Male factor: causes of infertility associated with individuals of a biological male sex, including hypogonadism, post-testicular defects, seminiferous tubule dysfunction.

Window of implantation (WOI): The time during which endometrium is receptive to blastocyte implantation.

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## Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

### When services are Investigational and Not Medically Necessary:

For the following procedure and diagnosis codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

#### CPT

86357 Natural killer (NK) cells, total count

#### ICD-10 Diagnosis

N96 Recurrent pregnancy loss

N97.0-N97.9 Female infertility

### When services are also Investigational and Not Medically Necessary:

For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

#### CPT

89329 Sperm evaluation; hamster penetration test

89330 Sperm evaluation; cervical mucus penetration test, with or without spinnbarkeit test

89398 Unlisted reproductive medicine laboratory procedure [when specified as a sperm DNA fragmentation test]

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 (eg, pre-receptive, receptive, post-receptive) ERA® (Endometrial Receptivity Analysis), Igenomix®, Igenomix® USA

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 Cap-Score™ Test, Androvia LifeSciences, Avantor Clinical Services (previously known as Therapak)

#### ICD-10 Diagnosis

All diagnoses

## References

### Peer Reviewed Publications:

1. Bergin K, Eliner Y, Duvall DW Jr, et al. The use of propensity score matching to assess the benefit of the endometrial receptivity analysis in frozen embryo transfers. Fertil Steril. 2021; 116(2):396-403.

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## Selected Tests for the Evaluation and Management of Infertility

2. Bonilla-Musoles F, Raga F, Osborne NG, et al. Endometrial receptivity: evaluation with ultrasound. *Ultrasound Q*. 2013; 29(1):3-20.
3. Bostofte E, Bagger P, Michael A, Stakemann G. The sperm penetration test (P-test) can predict fecundability in the male partner from infertile couples. *Andrologia*. 1992; 24(3):125-129.
4. Cardona C, Neri QV, Simpson AJ, et al. Localization patterns of the ganglioside GM1 in human sperm are indicative of male fertility and independent of traditional semen measures. *Mol Reprod Dev*. 2017; 84(5):423-435.
5. Chiokadze M, Kristesashvili J. On the issue of standardization of uterine natural killer cell measurement in patients with recurrent pregnancy loss. *Georgian Med News*. 2019; (294):31-36.
6. Diaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, et al. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. *Fertil Steril*. 2011; 95(1):50-60.
7. Eisman LE, Pisarska MD, Wertheimer S, et al. Clinical utility of the endometrial receptivity analysis in women with prior failed transfers. *J Assist Reprod Genet*. 2021; 38(3):645-650.
8. Jarvela IY, Sladkevicius P, Kelly S, et al. Evaluation of endometrial receptivity during in-vitro fertilization using three-dimensional power Doppler ultrasound. *Ultrasound Obstet Gynecol*. 2005; 26(7):765-769.
9. Kuon RJ, Vomstein K, Weber M, et al. The "killer cell story" in recurrent miscarriage: Association between activated peripheral lymphocytes and uterine natural killer cells. *J Reprod Immunol*. 2017; 119:9-14.
10. Lash GE, Bulmer JN, Li TC, et al. Standardisation of uterine natural killer (uNK) cell measurements in the endometrium of women with recurrent reproductive failure. *J Reprod Immunol*. 2016; 116:50-59.
11. Moffett A, Regan L, Braude P. Natural killer cells, miscarriage, and infertility. *BMJ*. 2004; 329(7477):1283-1285.
12. Moody MA, Cardona C, Simpson AJ, et al. Validation of a laboratory-developed test of human sperm capacitation. *Mol Reprod Dev*. 2017; 84(5):408-422.
13. Rafael BZ. Endometrial Receptivity Analysis (ERA) test: an unproven technology. *Hum Reprod Open*. 2021; 2021(2).
14. Riestenberg C, Kroener L, Quinn M, et al. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. *Fertil Steril*. 2021; 115(4):1001-1006.
15. Ruiz-Alonso M, Blesa D, Diaz-Gimeno P, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril*. 2013; 100(3):818-824.
16. Schinfeld J, Sharara F, Morris R, et al. Cap-Score™ prospectively predicts probability of pregnancy. *Mol Reprod Dev*. 2018;85(8-9):654-664.
17. Seshadri S, Sunkara SK. Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis. *Hum Reprod Update*. 2014; 20(3):429-438.
18. Simon C, Gomez C, Cabanillas S, et al. ERA-RCT Study Consortium Group. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. *Reprod Biomed Online*. 2020; 41(3):402-415.
19. Tuckerman E, Mariee N, Prakash A, et al. Uterine natural killer cells in peri-implantation endometrium from women with repeated implantation failure after IVF. *J Reprod Immunol* 2010; 87:60-66.
20. Zini A, Boman JM, Belzile E, Ciampi A. Sperm DNA damage is associated with an increased risk of pregnancy loss after IVF and ICSI: systematic review and meta-analysis. *Hum Reprod* 2008; 23:2663-2668.

### Government Agency, Medical Society, and Other Authoritative Publications:

1. Agarwal A, Majzoub A, Baskaran S, et al. Sperm DNA Fragmentation: A New Guideline for Clinicians. *World J Mens Health*. 2020; 38(4):412-471.

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## Selected Tests for the Evaluation and Management of Infertility

2. Centers for Disease Control and Prevention (CDC). Infertility FAQs. Last reviewed April 26, 2023. Available at: [Infertility | Reproductive Health | CDC](#). Accessed on January 29, 2024.
3. Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. Obstet Gynecol. 2019; 133(6):e377-e384.
4. Leslie SW, Soon-Sutton TL, Khan MAB. Male Infertility. [Updated 2023 Mar 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK562258/>. Accessed on January 29, 2024.
5. Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Diagnosis and treatment of luteal phase deficiency: a committee opinion. Fertil Steril. 2021; 115(6):1416-1423.
6. Practice Committee of the American Society for Reproductive Medicine. Definition of Infertility: A Committee Opinion (2023). Available at: <https://www.asrm.org/globalassets/asrm/practice-guidance/practice-guidelines/pdf/definition-of-infertility.pdf>. Accessed on June 26, 2024.
7. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015; 103(3):e18-e25.
8. Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020; 114(6):1151-1157.
9. Practice Committee of the American Society for Reproductive Medicine. The clinical utility of sperm DNA integrity testing: a guideline. Fertil Steril. 2013; 99(3):673-677.
10. Royal College of Obstetricians & Gynaecologists. The Role of Natural Killer Cells in Human Fertility. 2016. Available at: [PCrown\\_A\(rcog.org.uk\)](http://Pcrown_A(rcog.org.uk)). Accessed on January 29, 2024.
11. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. J Urol. 2021 Jan;205(1):36-43.
12. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part II. J Urol. 2021; 205(1):44-51.
13. World Health Organization (WHO). Infertility April 3, 2023. Available at: <https://www.who.int/news-room/fact-sheets/detail/infertility>. Accessed on January 29, 2024.

## Websites for Additional Information

1. ACOG FAQs. Evaluating infertility. Last reviewed: August 2022. Available at: <https://www.acog.org/womens-health/faqs/evaluating-infertility>. Accessed on January 29, 2024.

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## Document History

Status	Date	Action
	06/28/2024	Revised Discussion/General Information and Reference sections.
Revised	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Reformatted the "Position Statement" section. Updated review date, Rationale, References, Websites for Additional Information and History sections.
Reviewed	02/16/2023	MPTAC review. Updated review date, Rationale, References and History sections.
New	02/17/2022	MPTAC review. Initial document development.

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