Kansas City

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Reproductive Techniques

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for assisted reproductive technology (ART) when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Coverage of infertility treatment using assisted reproductive technology is a contract-specific benefit issue. Where benefits are available, all of the services identified by the CPT codes listed below might be considered eligible benefits unless indicated as being investigational.

Some contracts that cover ART treatment may have different member co-pay formulas and limits on these services than for other medical- surgical coverage.

The following reproductive techniques are considered **medically necessary;**

- cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure;
- intracytoplasmic sperm injection;
- blastocyst transfer

The following lists summarize the CPT codes used to describe ART. Those procedures performed in order to **diagnose** infertility, i.e. laparoscopy in the female and semen analysis in the male, are **not** included in this review. Not all steps are routinely done in each case.

Procedures performed on the female:

Code	Description
58321	*Artificial insemination, intracervical
58322	*Artificial insemination, intrauterine
58345	Transcervical introduction of fallopian tube catheter
58350	Chromotubation of oviduct
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method (i.e., GIFT or ZIFT)

* Either intracervical or intrauterine artificial insemination may be performed where there is poor quality cervical mucus, anatomic factors, poor sperm quality or quantity, poor postcoital tests.

Procedures performed on the male: Aside from CPT code 55400, these procedures describe various methods of collection of sperm in men who are unable to produce an adequate ejaculate.

Code	Description
10021	Fine needle aspiration; without imaging guidance
10022	Fine needle aspiration; with imaging guidance
55400	Vasovasostomy, vasovasorrhaphy (i.e., repair of prior vasectomy)
54800	Biopsy of epididymis (may be used to describe epididymal aspiration of sperm in men with obstructive or non-obstructive azoospermia or severe oligospermia)
54500	Biopsy of testis, needle (may be used to describe testicular aspiration of sperm for same indications as above)
55870	Electroejaculation Electroejaculation (may be used in patients who are unable to produce a normal ejaculate due to spinal cord or other nervous system disorder, i.e., diabetic neuropathy)

In Vitro Laboratory Procedures:

Code	Description
58323	Sperm washing for artificial insemination
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
89250	Culture of oocytes(s)/embryo(s), less than 4 days. This CPT code originally described both the culture and fertilization of oocytes, but has been revised to describe only the culture step; the insemination step is now described separately in new CPT code 89268. Note also that this code is limited to culture of less than 4 days. New CPT code 89272 now describes culturing for longer than 4 days.
89253	Assisted embryo hatching, any method. Assisted hatching is a technique performed to enhance the likelihood that the transferred embryo will implant in the uterus and establish a viable pregnancy. The technique involves in vitro disruption of the zona pellucida surrounding the embryo so that the embryo can “escape” and implant into the uterine wall. Assisted hatching has also been referred to as zona drilling and partial zonal dissolution. Assisted hatching is commonly performed as part of an IVF procedure in women over 40 who have a decreased incidence of implantation after embryo transfer and in women with prior failed IVF cycles due to failed implantation.
89254	Oocyte identification from follicular fluid. As part of the oocyte retrieval procedure (58970), follicular fluids are provided to the laboratory. Using microscopic examination and dissection, the oocytes are identified, isolated, classified, and placed in the culture environment. Prior to the introduction of the new CPT code 89254, this laboratory component of the oocyte retrieval process may have been coded as 89399.
89255	Preparation of embryo for transfer. Embryos resulting from ART techniques must be evaluated microscopically for stage of development, cell number, and quality to select the optimal embryo(s) for transfer. The selected embryos are loaded into an embryo transfer catheter, which is introduced by a physician into a patient’s uterus or fallopian tubes. Following the transfer, the catheter is flushed, and the flushings are examined to determine if the embryos(s) have been successfully transferred.
89257	Sperm identification from aspirate. After aspiration of sperm from the epididymis or testis, the fluid undergoes immediate laboratory analysis so that the sperm can be identified and isolated. Prior to the introduction of 89257, this laboratory procedure may have been coded as 89399.
89258	Cryopreservation; embryo. Cryopreservation involves moving the embryo through increasing concentrations of cryoprotectant and loading the embryo into straws or vials for subsequent freezing. The embryos are cooled gradually and then stored for as long as needed. It is estimated that about 20% of couples undergoing ART procedures would have embryos frozen. Prior to the introduction of 89258, this procedure probably would have been coded as 89399.
89259	Cryopreservation; sperm. Sperm are assessed for pre-freeze concentration and motility and viability,

	followed by addition of cryoprotectant agent. Aliquots are loaded into straws or vials, and the sample is cooled and stored. Cryopreservation is indicated for any diagnosis in which chemical or surgical castration is considered appropriate, or in other circumstances that preclude the collection of a semen sample on demand (i.e., paraplegia, ejaculatory dysfunction), following electroejaculation or sperm aspiration, prior to a vasectomy, or in situations in which the male must be absent for long periods of time (i.e., military service). Prior to the introduction of 89258, this procedure probably would have been coded as 89399.
89260	Sperm isolation; simple prep (see 89261)
89261	Sperm isolation; complex. Simple or complex sperm isolation may be performed prior to intrauterine insemination or IVF. The choice of simple or complex preparation is based on a prior semen analysis.
89264	Sperm identification from testis tissue, fresh or cryopreserved. This CPT code describes the dissection of biopsied testicular tissue (i.e., CPT codes 54500-54505) to identify and isolate sperm. This procedure would be typically done in a patient with male factor infertility as part of an intracytoplasmic sperm injection (ICSI) procedure.
89268	Insemination of oocytes. Insemination, or fertilization, used to be included in the original code 89250. However, in 2004, code 89250 was unbundled and separate codes were created for culture and insemination.
89272	Extended culture of oocyte(s) / embryo(s), 4-7 days. This new code is a companion code for 89250 (see above), which describes the length of culture. Culturing beyond 4 days allows the embryo to develop to the blastocyst stage.
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. The above 2 new 2004 CPT codes describe preimplantation genetic diagnosis, which is considered separately in policy No. 4.02.05.
89300	Semen analysis: presence and/or motility of sperm including Hehner test (post coital)
89310	Sperm motility count
89320	Complete sperm count
89321	Semen analysis, presence and/or motility of sperm
89325	Sperm antibodies
89329	Sperm evaluation; hamster penetration test
89330	Cervical mucus penetration test
89335	Cryopreservation, reproductive tissue, testicular. While cryopreservation of ejaculated sperm is the most common technique of preserving male gametes, in cases of azoospermia or where there is blockage of the epididymis, a testicular biopsy may be performed to harvest testicular tissue. Spermatazoa isolated from testicular tissue may then be used in a subsequent IVF procedure, using intracytoplasmic sperm injection. Since IVF is not immediately successful in many cases, additional sperm can be extracted from the cryopreserved tissues for subsequent cycles, thus eliminating the need for sequential testicular biopsies coinciding with the harvest of the oocyte.
89342	Storage, (per year); embryo(s)
89343	Storage, (per year); sperm / semen
89352	Thawing of cryopreserved; embryo(s)
89353	Thawing of cryopreserved; sperm / semen, each aliquot
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
S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
S4016	Frozen in vitro fertilization cycle, 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

When Policy Topic is not covered

The following laboratory procedures are considered **investigational:**

- assisted hatching;
- co-culture of embryos;
- cryopreservation of ovarian tissue, or oocytes; cryopreservation of testicular tissue in prepubertal boys; storage and thawing of ovarian tissue, oocytes or testicular tissue

Code	Description
89251	Culture and fertilization of oocytes less than 4 days; with co-culture of oocytes/embryos. Co-culture techniques involve tissue culture of human embryos in the presence of oviductal, uterine, granulosa, or other cells. The procedure involves the isolation of the substrate cells, culture, plating, and co-culture of these cells with human embryos. The purpose of co-culture is to produce a more viable embryo at the blastocyst stage of development for subsequent transfer to the uterus. Co-culture is not routinely done as part of all IVF procedures; the technique may not be available in all infertility labs.
89335	Cryopreservation of testicular tissue in prepubertal boys.
89344	Storage, (per year); reproductive tissue, testicular / ovarian
89346	Storage, (per year); oocyte
89354	Thawing of cryopreserved; reproductive tissue, testicular / ovarian
89356	Thawing of cryopreserved; oocytes, each aliquot

Description of Procedure or Service

The policy addresses a variety of techniques available to establish a viable pregnancy for couples who have been diagnosed with infertility and for whom assisted insemination is insufficient.

Background

Infertility can be due either to female factors (i.e., pelvic adhesions, ovarian dysfunction, endometriosis, prior tubal ligation), male factors (i.e., abnormalities in sperm production, function, or transport or prior vasectomy), a combination of both male and female factors, or unknown causes. Various reproductive techniques are available to establish a viable pregnancy; different techniques are used depending on the reason for infertility.

Assisted reproductive technologies (ART), as defined by the Centers for Disease Control (CDC) and other organizations, refers to fertility treatments in which both the eggs and sperm are handled. Not included in ART is assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor. In most instances ART will involve in vitro fertilization (IVF), a procedure in which oocytes harvested from the female are inseminated in vitro with sperm harvested from the male. Following the fertilization procedure, the zygote is cultured and ultimately transferred back into the female's uterus or fallopian tubes. In some instances, the oocyte and sperm are collected, but no in vitro fertilization takes place, and the gametes are reintroduced into the fallopian tubes. Examples of ART include, but are not limited to, gamete intrafallopian transfer (GIFT), transuterine fallopian transfer (TUFT), natural oocyte retrieval with intravaginal fertilization (NORIF), pronuclear state tubal transfer (PROST), tubal embryo transfer (TET), zygote intrafallopian transfer (ZIFT), gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy.

The various components of ART and implantation into the uterus can be broadly subdivided into oocyte harvesting procedures, which are performed on the female partner; sperm collection procedures, which are performed on the male partner; and the in vitro component, i.e., the laboratory procedures, which are performed on the collected oocyte and sperm. The final step is the implantation procedure.

The majority of CPT codes describing the various steps in ART procedures are longstanding techniques. This includes codes for oocyte retrieval, sperm isolation, culture and fertilization of the oocyte, and embryo; zygote; or gamete transfer into the uterus or fallopian tubes. Only the relatively new reproductive techniques (i.e., intracytoplasmic sperm injection, assisted hatching, co-culture of embryos) and cryopreservation of reproductive tissue (i.e., testicular, ovarian, or oocytes) will be considered.

Regulatory Status

There are no medical devices or diagnostic tests related to assisted reproductive techniques that require FDA approval or clearance.

Rationale

Literature Review

This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period January 2012 through March 12, 2013. Following is a summary of the key literature to date:

Assisted Hatching

One key component of a successful attempt at in vitro fertilization is implantation of the embryo in the uterus. Although the exact steps in implantation are poorly understood, one critical component is thought to be the normal rupture of the surrounding zona pellucida with escape of the developing embryo, termed hatching. It is hypothesized that during the in vitro component of the in vitro fertilization (IVF), the zona pellucida becomes hardened, thus impairing the hatching process. Alternatively, some embryos may have some inherent inability to induce thinning of the zona pellucida before hatching. In either case, mechanical disruption of the zona pellucida (i.e., assisted hatching) has been proposed as a mechanism to improve implantation rates.

A 2012 systematic review and meta-analysis from the Cochrane collaboration identified 31 randomized controlled trials (RCTs) on assisted hatching with a total of 5,728 individuals. (1) Twelve studies included women with a poor prognosis, 12 studies included women with a good prognosis, and the

remaining 7 studies did not report this factor. Fifteen studies used laser for assisted hatching, 11 used chemical means, and 5 used mechanical means. Live birth rate was reported in 9 studies with 1,921 women. A pooled analysis of data from the 9 studies did not find a statistically significant difference between the groups receiving assisted hatching or a control condition, odds ratio (OR): 1.03, 95% confidence interval (CI): 0.85 to 1.26. The rate of live birth was 313/995 (31%) in the assisted hatching group and 282/926 (30%) in the control group. All 31 trials reported clinical pregnancy rates. In a meta-analysis of all of these trials, assisted hatching improved the pregnancy rate, but the odds ratio just reached statistically significance, OR: 1.13 (95% CI: 1.01 to 1.27).

Previously, in 2008, the Practice Committee of the Society for Assisted Reproductive Technology and the Society for Reproductive Medicine published a comprehensive review and meta-analysis on assisted hatching. (2) The meta-analysis had similar findings to the 2012 Cochrane review, discussed above. (1) The review identified 23 RCTs (n=2,572) with women undergoing assisted hatching during assisted reproduction. A pooled analysis of the 6 studies that reported live birth rates did not find a statistically significant difference in birth rate with assisted hatching compared to a control condition. Nineteen studies reported a clinical pregnancy rate; pooled analysis of these data found a significantly higher rate of pregnancy with assisted hatching compared to control (OR: 1.63, 95%, CI: 1.27-2.09). There was significant heterogeneity among studies. The subgroups with the most benefit from assisted hatching in terms of the pregnancy rate were older women and women who had failed prior attempts with assisted reproductive techniques.

Conclusions: Randomized controlled trials and meta-analyses of these trials have not found that assisted hatching significantly improves the live birth rate compared to a control intervention. Meta-analyses of heterogenous studies have found that the clinical pregnancy rate is improved with assisted hatching.

Embryo Co-Culture

In routine IVF procedures, the embryo is transferred to the uterus on day 2 or 3 of development, when it has between 4 and 8 cells. However, with this approach the implantation rate is estimated to be between 5% and 30%, potentially related to the fact that under normal conditions the embryo reaches the uterus at a blastocyst stage of development. Embryo co-culture techniques, used successfully in domestic animals, represent an effort to improve the culture media for embryos such that a greater proportion of embryos will reach the blastocyst stage, in hopes of improving the implantation and pregnancy rate. In addition, if co-culture results in a higher implantation rate, fewer embryos could be transferred at each cycle, resulting in a decreased incidence of multiple pregnancies. A variety of co-culture techniques have been investigated, involving the use of feeder cell layers derived from a range of tissues, including the use of human reproductive tissues (i.e., oviducts) to non-human cells (i.e., fetal bovine uterine or oviduct cells) to established cell lines (i.e., Vero cells or bovine kidney cells). However, no standardized method of co-culture has emerged, and no controlled trials have evaluated an improved implantation or pregnancy rate associated with co-culture. (3-8) For example, Wetzels and colleagues reported on a study that randomized IVF treatments to include co-culture with human fibroblasts or no culture. (8) Patients in the 2 groups were stratified according to age (older or younger than 36 years) and prior IVF attempts (yes vs. no). The authors reported that fibroblast co-culture did not affect the implantation or the pregnancy rate. Updated literature reviews did not identify any additional published studies that would prompt reconsideration of the relevant policy statement.

Conclusions: There is a lack of controlled trials demonstrating improved outcomes with co-culture, and no standardized method of co-culture has emerged in the literature.

Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue or an entire ovary with subsequent auto- or heterotopic transplant has been investigated as a technique to sustain the reproductive function of women or children who are faced with sterilizing procedures, such as chemotherapy, radiation therapy, or surgery, frequently due to malignant diseases. A variety of articles have focused on the technical feasibility of such an option. There are a few individual case reports of return of ovarian function using this technique. (9, 10) There

are also several case series describing live births using cryopreserved ovarian tissue. (11-13) However, in general, the technique is not standardized and has not been sufficiently studied to determine the success rate. (14, 15) In 2011, Johnson and Patrizio commented on whole ovary freezing as a technique of fertility preservation in women with disease or disease treatment that threaten their reproductive tract function. (16) They concluded, “Although theoretically optimal from the point of view of maximal follicle protection and preservation, the risks and difficulties involved in whole ovary freezing limit this technique to experimental situations.”

Conclusions: This technique has not been standardized, and there is insufficient published data that cryopreservation of ovarian tissue is an effective and safe reproductive technique.

Cryopreservation of Oocytes

Cryopreservation of oocytes was originally investigated primarily as an alternative to embryo cryopreservation due to ethical or religious reasons. More recently, it has been examined as a fertility preservation option for reproductive-age women undergoing cancer treatment, both single women and those who do not want the option of embryo cryopreservation. The mature oocyte is very fragile due to its large size, high water content, and chromosomal arrangement. For example, the mature oocyte is arrested in meiosis, and as such, the chromosomes are lined up in a meiotic spindle. This spindle apparatus is easily damaged both in freezing and thawing. Survival after thawing may also be associated with sublethal damage, which may further impact on the quality of the subsequent embryo. Moreover, due to the large amount of water, when the oocyte is frozen, ice crystals can form that can damage the integrity of the cell. To reduce or prevent ice crystals, oocytes are dehydrated using cryoprotectants, which replace the water in the cell. The most common method of freezing oocytes is a controlled-rate slow-cooling method. A newer technique involves a flash-freezing process known as vitrification. This technique is faster, yet requires a higher concentration of cryoprotectants.

A meta-analysis published in 2006 reported outcomes from 26 reports of IVF with cryopreserved oocytes (1997 to 2005, 354 patients) and compared them with outcomes from IVF with unfrozen oocytes during a similar time period. (17) Live birth rates were reported to be 3% per injected cryopreserved oocyte (vs. 7% for unfrozen oocytes) and 22% (vs. 60%) per embryo transfer. The authors concluded that pregnancy rates appear to have improved, but further studies will be needed to determine the efficiency and safety of this technique.

Two systematic reviews of published literature on outcomes after oocyte cryopreservation were published in 2009. Wennerholm and colleagues searched for studies that reported neonatal information and identified data on 148 children born after slow freezing of oocytes and 221 children born after vitrification (total n=369). (18) Most of these reported limited information on obstetric and neonatal outcomes. Birthweight was reported for 41 infants born after slow-freezing of oocytes and was normal in all cases. For vitrification, 200 of 221 cases were reported in a single study that included 151 singletons and 49 multiples. Eighteen percent of singletons and 80% of multiples were low birth weight, and the congenital anomalies were reported in 2.5% of infants. Noyes searched published literature and meeting abstracts and identified published reports of 609 live births after oocyte cryopreservation. (19) An additional 327 births were identified from communications with fertility centers, for a total of 936 live births. Of these, 532 resulted from slow frozen oocytes, 392 from vitrified oocytes and 12 from a combination of the 2 techniques. There were a total of 12 congenital anomalies, 8 major and 4 minor, for an overall incidence of 1.3%. The incidence in the births from slow frozen oocytes was 6 of 532 (1.1%) and from vitrification births 6/392 (1.5%). The author stated that this compared favorably with the 3% rate of congenital anomalies in the general U.S. population, according to the Centers for Disease Control. The incidence of ventricular septal defects was 0.3% (3 of 936) on the oocyte cryopreservation population and 1 of 125 (0.8%) naturally conceived newborns. The author acknowledges that not all reports were from peer-reviewed publications and limited outcome data were available.

Vitrification and slow-rate freezing were compared in an RCT conducted in Brazil. (20) A total of 230 patients who had concerns with embryo freezing and had greater than 9 mature oocytes retrieved in a

controlled ovarian stimulation cycle participated in the study. Patients were randomly assigned to oocyte slow-rate freezing or vitrification by trained staff using standard methods. Patients who failed to achieve a pregnancy in the fresh *in vitro* fertilization cycle had the option of transferring embryos derived from the cryopreserved oocytes. Seventy-eight patients requested use of the oocytes, 30 of these had been assigned to slow-rate freezing and 48 to vitrification. The authors did not report the amount of time the oocytes had been frozen. Initial survival of oocytes was significantly greater in the vitrification group (81%) than the slow-rate freezing group (67%) ($p<0.001$), and 3 of the 30 couples in the slow-freeze group had no surviving oocytes to inseminate. The clinical pregnancy rate per thawed or warmed cycle was significantly higher in the group that had been assigned to vitrification (18/48, 38%) than those assigned to slow-rate freezing (4/30, 13%), $p<0.02$. Similarly, the clinical pregnancy rate per oocyte thawed or warmed was significantly higher in the vitrification group (18/349, 5.2%) than the slow-rate freeze group (4/238, 1.7%, $p<0.03$). Of the 18 clinical pregnancies resulting after vitrification and warming of oocytes, there were 16 singletons and 2 sets of twins. Of the 4 clinical pregnancies after slow-freezing and thawing of oocytes, 2 resulted in singletons, 1 resulted in twins, and 1 resulted in triplets. In this study, there was greater success after vitrification, but the sample size was too small to draw conclusions about the relatively efficacy and safety of the 2 methods of oocyte cryopreservation.

In 2013, the Practice Committee of the American Society of Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) published an updated guideline on mature oocyte cryopreservation. (21) The guideline cited several European trials showing similar rates of fertilization and pregnancy when fresh oocytes or vitrified/warmed oocytes were used as part of assisted reproduction in young women. The authors noted that these data may not be generalizable to the United States, to clinics with less experience with these techniques or to other populations e.g. older women or cancer patients. The authors stated that data from the United States are available only from a few clinics and report on young highly selected populations. Pregnancy outcomes and rates of congenital anomalies were not discussed in the publication. The guideline included the following 4 recommendations:

- “In patients facing infertility due to chemotherapy or other gonadotoxic therapies, oocyte cryopreservation is recommended with appropriate counseling”

- “More widespread clinic-specific data on the safety and efficacy of oocyte cryopreservation in donor populations are needed before universal donor oocyte banking can be recommended”

- “There are not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women”

- “More data are needed before this technology should be used routinely in lieu of embryo cryopreservation”

Conclusions: There are insufficient published data on the safety and efficacy of cryopreservation of oocytes; data are only available from select clinical settings and select populations.

Blastocyst Transfer

This refers to the extended culture of oocytes/embryos, i.e., for greater than 4 days. The rationale behind blastocyst transfer is that embryos progressing to the blastocyst stage have a much greater chance of implanting successfully in the uterus and resulting in an ongoing pregnancy. Due to the higher probability of implantation, it is thought that fewer blastocysts can be transferred, ultimately resulting in a decreased incidence of triplets and higher-order pregnancies. In 2012, the Cochrane collaboration published a systematic review and meta-analysis of RCTs comparing blastocyst stage transfer (day 5 to 6) to cleavage-stage embryo transfers (day 2 to 3). (22) Twenty-three RCTs were included. Twelve trials reported on the rate of live birth per couple. A pooled analysis of these trials found a significantly higher live birth rate with blastocyst transfer (292/751, 39%) compared to cleavage-stage transfer (237/759, 31%). The OR for live birth was 1.40 (95% CI: 1.13 to 1.74). There was not a significant difference in the rate of multiple pregnancies in the 2 treatment groups (16 RCTs,

OR: 0.92; 95% CI: 0.71 to 1.19). In addition, there was not a significant difference in the miscarriage rate (14 RCTs, OR: 1.14, 95% CI: 0.84 to 1.55).

A meta-analysis published in 2010 identified 15 observational studies that compared transfer of thawed blastocysts that had been frozen either on Day 5 or Day 6 following in vitro fertilization. (23) A pooled analysis of 9 studies found a significantly higher ongoing pregnancy or live birth rate after Day 5 frozen-thawed blastocyst transfer than after Day 6 blastocyst transfer (relative risk [RR]: 1.15, 95% CI:1.01-1.30, p=0.03). However, after controlling for stage of development, a potential confounder, outcomes did not differ in the 2 groups. A pooled analysis of 4 studies that used morphologic criteria to select blastocysts for cryopreservation (rather than simply considering the amount of time after fertilization) did not find a significant difference in ongoing pregnancy/live birth rate between Day 5 and Day 6 blastocyst transfer (RR: 1.08, 95% CI: 0.92-1.27, p=0.36).

A 2010 retrospective cohort study reported on risks associated with blastocyst transfer. Data were taken from the Swedish Medical Birth Register. There were 1,311 infants born after blastocyst transfer and 12,562 born after cleavage-stage transfer. (24) There were no significant differences in the rates of multiple births, which were 10% after blastocyst transfer and 8.9% after cleavage-stage transfer. Among singleton births, the rate of pre-term birth (less than 32 weeks) was 18/1,071 (1.7%) in the blastocyst transfer group and 142/10,513 (1.35%) in the cleavage-stage transfer. In a multivariate analysis controlling for year of birth, maternal age, parity, smoking habits, and body mass index, the adjusted OR was 1.44 (95% CI: 0.87-2.40). The rate of low birthweight singletons (less than 1,500 grams or less than 2,500 grams) did not differ significantly in the blastocyst transfer compared to the cleavage-stage transfer groups. There was a significantly higher rate of relatively severe congenital malformation (e.g., spina bifida, cardiovascular defects, cleft palate, etc.) after blastocyst transfer (61/1,311, 4.7%) than cleavage-stage transfer (509/12,562, 4.1%, adjusted OR: 1.33, 95% CI: 1.01-1.75). The 2 groups did not differ significantly in their rates of low APGAR scores, intracranial hemorrhage, respiratory diagnoses, or cardiovascular malformations. Respiratory diagnoses were given to 94/1,311 (7.2%) infants born after blastocyst transfer and 774/12,562 (6.2%) after cleavage-stage transfer (OR: 1.15, 95% CI: 0.90-1.47). The study was not randomized and, although the investigators adjusted for some potential confounders e.g., age and parity, there may have been other differences in the 2 groups that affected outcomes.

The Practice Committee of the Society for Assisted Reproductive Technology and the Society for Reproductive Medicine issued a Committee Opinion on blastocyst transfer in 2008. (25) They stated that, in trials with good prognosis patients, blastocyst transfer has been found to result in a higher live birth rate compared to transfer of equal numbers of cleavage stage transfer. However, cumulative live birth rates may not differ when frozen and fresh embryos from a given cycle are considered because extended culture yields fewer surplus embryos, and the post-thaw survival rate is lower for blastocysts than for cleavage stage embryos that have been frozen.

Conclusions: According to evidence from RCTs, observational studies and meta-analyses of published studies, blastocyst transfer results in higher live birth rates compared to cleavage stage transfer.

Intracytoplasmic Sperm Injection (ICSI) for male factor infertility

ICSI is performed in cases of male factor infertility when either insufficient numbers of sperm, abnormal morphology, or poor motility preclude unassisted in vitro fertilization. Using ICSI, fertilization rates of up to 76% have been reported, considerably better than the competing technique of sub-zonal insemination (up to 18%), in which sperm are injected into the perivitelline space (as opposed to into the oocyte itself), and by definition better than the negligible to absent fertilization rates seen in patients with male factor infertility. Fertilization rates represent an intermediate outcome; the final outcome is the number of pregnancies per initiated cycle or per embryo transfer, reported in the largest series as 44.7% and 49.6%, respectively. (26-30) These rates are very competitive with those of the standard in vitro fertilization (IVF). A 2012 committee opinion of the American Society of Reproductive Medicine and Society for Assisted Reproductive Technology stated that ICSI is a safe and effective treatment for male factor infertility. (31) The document also stated that ICSI for unexplained fertility, low oocyte yield

and advanced maternal age does not improve clinical outcomes. The opinion included a statement that ICSI may be beneficial for patients undergoing *in vitro* fertilization with preimplantation genetic testing, *in vitro* matured oocytes and cryopreserved oocytes.

Conclusions: There are data indicating that intracytoplasmic sperm injection for male factor infertility has a relatively high rate of successful pregnancy.

Cryopreservation of Testicular Tissue

Testicular sperm extraction refers to the collection of sperm from testicular tissue in men with azoospermia. Extraction of testicular sperm may be performed at the time of a diagnostic biopsy or performed as a subsequent procedure, specifically for the collection of spermatozoa. The spermatozoa may be isolated immediately and a portion used for an ICSI procedure at the time of oocyte retrieval from the partner, with the remainder cryopreserved. Alternatively, the entire tissue sample can be cryopreserved with portion thawed and sperm isolation performed at subsequent ICSI cycles. This technique appears to be a well-established component of the overall ICSI procedure; cryopreservation of either the isolated sperm or the tissue sample eliminates the need for multiple biopsies to obtain fresh tissue in the event of a failed initial ICSI cycle. (32) However, a unique application of cryopreservation of testicular tissue is its use to potentially preserve the reproductive capacity in prepubertal boys undergoing cancer chemotherapy; the typical cryopreservation of an ejaculate is not an option in these patients. It is hoped that re-implantation of the frozen-thawed testicular stem cells will re-initiate spermatogenesis, or alternatively, spermatogenesis could be attempted in vitro, using frozen-thaw spermatogonia. While these strategies have been explored in animals, there are inadequate human studies. (33, 34)

Conclusions: Cryopreservation of testicular tissue in adult men with ozoospermia is a well-established component of the ICSI procedure.

Birth Defects associated with reproductive techniques

Several systematic reviews of the risk of birth defects associated with use of assisted reproductive technologies were published in 2012 and 2013. (35-37) The review with the largest amount of data was published by Hansen and colleagues. (36) They examined 45 cohort studies with outcomes in 92,671 infants born following assisted reproductive technologies (ART) and 3,870,760 naturally conceived infants. In a pooled analysis of the data, there was a higher risk of birth defects in infants born using reproductive techniques (relative risk [RR]: 1.32, 95% CI: 1.24 to 1.42). The risk of birth defects was also elevated when the analysis was limited to the 6 studies that were conducted in the United States or Canada (RR: 1.38, 95% CI: 1.16 to 1.64). A review by Davies and colleagues included data on 308,974 live births in Australia, 6,163 of which followed use of ART. (37) There was a higher rate of birth defects after assisted conception (8.3%) compared to births to fertile women that did not involve assisted conception (5.8%). (Unadjusted OR: 1.47, 95% CI: 1.33 to 1.62). The risk of birth defects was still significantly elevated but was lower in an analysis that adjusted for other factors that might increase risk e.g., maternal age, parity, maternal ethnicity, maternal smoking during pregnancy and socioeconomic status (OR: 1.28: 95% CI: 1.16 to 1.41).

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 4 Physician Specialty Societies and 2 Academic Medical Centers while this policy was under review in 2012. While the various Physician Specialty Societies and Academic Medical Centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the Physician Specialty Societies or Academic Medical Centers, unless otherwise noted. There was general agreement that intracytoplasmic sperm injection and cryopreservation of testicular tissue in adult men with azoospermia as part of an intracytoplasmic sperm injection procedure may be considered medically necessary. Three out of 5 reviewers who responded agreed that co-culture of embryos is considered investigational. In addition, 4 out of 5 reviewers did not agree that blastocyst transfer is investigational; these reviewers considered blastocyst transfer to be medically necessary to decrease multiple gestations. Three out of 6 reviewers agreed with the statement that cryopreservation of ovarian tissue or oocytes is investigational. The other 3 reviewers

had split responses; they thought that cryopreservation of oocytes, but not ovarian tissue, is medically necessary. Clinical input on other policy statements was more variable.

Summary
Intracytoplasmic sperm injection (ICSI) has a relatively high rate of successful live births for treatment of male factor infertility due to low sperm count and/or impaired sperm motility. ICSI for male factor infertility and cryopreservation of testicular tissue in adult men with azoospermia as part of an ICSI injection procedure received support from clinical reviewers. These techniques may be considered medically necessary. Based on evidence from RCTs of a higher live birth rate than cleavage-stage embryo transfer, as well as on supportive clinical input, blastocyst transfer may be considered medically necessary. The evidence is insufficient to permit conclusions concerning the effectiveness of the following reproductive techniques: assisted hatching; co-culture of embryos; cryopreservation of ovarian tissue or oocytes; cryopreservation of testicular tissue in prepubertal boys; and storage and thawing of ovarian tissue, oocytes, or testicular tissue. For these procedures, there is a lack of published data on live birth rates, the incidence of multiples and neonatal and child outcomes, compared to established reproductive techniques. Therefore, these procedures are considered investigational.

Practice Guidelines and Position Statements
In May 2008, Agency for Healthcare Research and Quality (AHRQ) published the evidence report/technology assessment, “Effectiveness of Assisted Reproductive Technology.” (38) The report reviewed the evidence regarding the outcomes of interventions used in ovulation induction, superovulation, and IVF for the treatment of infertility. Short-term outcomes included pregnancy, live birth, multiple gestation, and complications. Long-term outcomes included pregnancy, and post-pregnancy complications for both mothers and infants. Approximately 80% of the included studies were performed outside the United States. The limitations of the review included: the majority of randomized trials comparing techniques were not designed to detect differences in pregnancy and live birth rates; and most trials did not have sufficient power to detect clinically meaningful differences in live birth rates, and had still lower power to detect differences in less frequent outcomes such as multiple births and complications. The authors concluded that interventions for which there was sufficient evidence to demonstrate improved pregnancy or live birth rates included: (a) administration of clomiphene citrate in women with polycystic ovarian syndrome; (b) metformin plus clomiphene in women who fail to respond to clomiphene alone; (c) ultrasound-guided embryo transfer, and transfer on day 5 post-fertilization, in couples with a good prognosis; and (d) assisted hatching in couples with previous IVF failure. There was insufficient evidence regarding other interventions. Infertility itself is associated with most of the adverse longer term outcomes. Consistently, infants born after infertility treatments are at risk for complications associated with abnormal implantation or placentation; the degree to which this is due to the underlying infertility, treatment, or both, is unclear. Infertility, but not infertility treatment, is associated with an increased risk of breast and ovarian cancer. The authors concluded that despite the large emotional and economic burden resulting from infertility, there is relatively little high-quality evidence to support the choice of specific interventions. AHRQ’s conclusion was based primarily on studies that had pregnancy rates as the primary endpoint, not live births. In addition, studies used multiple assisted hatching techniques.

Medicare National Coverage
No national coverage determination.

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Billing Coding/Physician Documentation Information

(See Tables Above)

The following CPT codes describe procedures that would be routinely performed in all ART procedures involving in vitro fertilization (IVF):

- **58970**: Oocyte retrieval
- Either:
  89250: Culture and fertilization of oocyte, less than 4 days; **OR**
  89272: Culture and fertilization of oocyte, greater than 4 days.
- Either
  89268: Insemination of oocytes; **OR**
  89280 / **89281**: Assisted oocyte fertilization, microtechnique, less than or greater than 10 oocytes, respectively
- **89260** or **89261**: Sperm isolation, simple or complex
- **89255**: Preparation of embryo for transfer
- **58974** or **58976**: Embryo, zygote, or gamete transfer, intrauterine or intrafallopian

The following CPT codes describe procedures that would not be routinely performed in all ART procedures involving IVF.

- **89257**: Sperm identification from aspiration. Only performed in patients with oligospermia who have undergone a prior testicular or epididymal aspiration; typically performed as a part of an intracytoplasmic sperm injection procedure (ICSI).

- **89264**: Sperm identification from biopsied testis tissue. Only performed in patients with oligospermia who have undergone a prior testicular biopsy; typically performed as a part of an ICSI procedure.
- **89253**: Assisted hatching. Only performed in women over the age of 40, or in cases in which prior ART attempts resulted in failed implantation.
- **89256**: Preparation of cryopreserved embryos
- **89258**: Cryopreservation of embryos
- **89259**: Cryopreservation of sperm
- **89342**-**89356**: Code range, cryopreservation and thawing of various components

The following CPT codes describe procedures that would be routinely performed as part of an intrauterine or intracervical artificial insemination:
- **58321**: Artificial insemination; intracervical
- **58322**: Artificial insemination; intrauterine
- **58323**: Sperm washing for artificial insemination

Note also that other "S" codes are available (see Coding section, above) that describes in vitro fertilization globally.
- **S4013**: Complete cycle, gamete intrafallopian transfer (GIFT), case rate
- **S4014**: Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
- **S4017**: Incomplete cycle, treatment cancelled prior to stimulation, case rate
- **S4018**: Frozen embryo transfer procedure cancelled before transfer, case rate
- **S4042**: Management of ovulation induction (interpretation of diagnostic tests and studies, non-face-to-face medical management of the patient), per cycle

Additional Policy Key Words

N/A

Policy Implementation/Update Information

10/1/88	New policy.
12/1/01	Added new codes, no policy statement changes.
12/1/02	No policy statement changes.
12/1/03	No policy statement changes.
12/1/04	Added S-codes, no policy statement changes.
12/1/05	Formatting changes, no policy statement changes.
12/1/06	Policy statement revised indicate cryopreservation of testicular tissue in prepubertal boys is investigational (89335).
12/1/07	No policy statement changes.
12/1/08	No policy statement changes.
12/1/09	No policy statement changes. Codes 0058T and 0059T were deleted effective 1/1/2009.
12/1/10	No policy statement changes.
12/1/11	No policy statement changes.
12/1/12	Policy statement changed to include blastocyst transfer as medically necessary.
12/1/13	No policy statement changes.