Corporate Medical Policy

Pre-Implantation Genetic Testing AHS – M2039

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Description of Procedure or Service

Preimplantation genetic testing (PGT) involves the biopsy of a single cell, or a few cells of embryos to facilitate genetic testing for various genetic conditions. These conditions range from aneuploidies to monogenic disorders to structural deformities of the chromosomes themselves (Schattman & Xu, 2024).

Related Policies:
Genetic Testing for Cystic Fibrosis AHS-M2017
General Genetic Testing, Germline Disorders AHS-M2145
General Genetic Testing, Somatic Disorders AHS-M2146
Prenatal Screening (Genetic) AHS-M2179

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will cover preimplantation genetic testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

Please refer to the member's benefit booklet for availability of benefits for in vitro fertilization and infertility services. Assisted reproductive technology (ART) benefits may be limited to persons who are infertile. Some plans may provide no benefits for these services. This medical policy relates only to the services or supplies described herein. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy. Member would also need to meet medical necessity criteria for ART.

When Preimplantation Genetic Testing is covered

Genetic counseling is required for individuals contemplating preimplantation genetic testing.

Preimplantation genetic testing for specific mutation(s) or chromosomal changes that have been associated with a specific disorder is considered medically necessary when one of the conditions below are met:

- Both biological parents are known carriers of an early-onset, autosomal recessive disorder
- One biological parent is a known carrier of an early-onset, autosomal recessive disorder and the other biological parent is unavailable for testing.

- One biological parent is a known carrier of an early-onset, autosomal recessive disorder and together, the biological parents have produced previous offspring affected with the disorder.
- One biological parent is a known carrier of an early-onset, autosomal dominant disorder.
- One biological parent is a known carrier of an early-onset, X-linked disorder.
- One biological parent carries a balanced or unbalanced chromosomal translocation.

When Preimplantation Genetic Testing is not covered

Preimplantation genetic testing for sex selection, in the absence of an early-onset sex-linked disorder is considered not medically necessary.

Preimplantation genetic testing is considered not medically necessary for any of the following situations:

- Preimplantation genetic testing for adult-onset disorders.
- Preimplantation HLA genotyping for purposes of identifying potential tissue or organ donors.
- Routine preimplantation screening for chromosomal abnormalities, including testing based on advanced maternal age.

Preimplantation genetic testing for all other situations not described above is considered not medically necessary.

Policy Guidelines

Preimplantation genetic testing (PGT) in conjunction with assisted reproductive technology (ART) was developed to allow reproductive partners at risk of transmitting a genetic condition to their offspring to have an unaffected child without facing prenatal diagnosis and termination of pregnancy (PGDIS, 2008). Initially offered for diagnosis in couples at-risk for single gene genetic disorders, such as cystic fibrosis, spinal muscular atrophy and Huntington disease, preimplantation genetic diagnosis (PGD) has most frequently been employed in assisted reproduction as preimplantation genetic screening (PGS) for detection of chromosome aneuploidy from advancing maternal age or structural chromosome rearrangements. The Preimplantation Genetic Diagnosis International Society (PGDIS) estimates that nearly 80% of PGT cycles have been performed for aneuploidy screening, 12% for single gene disorders, 6% for chromosome rearrangements and 2% for sibling human leukocyte antigen (HLA) matching (PGDIS, 2008). Both this and the European Society of Human Reproduction and Embryology (ESHRE) surveys confirm that aneuploidy testing is the major indication for PGT (Stern, 2014).

Embryonic genetic material used for PGT can be obtained from any of three sources: polar bodies from oocytes, blastomeres from day two or three, or trophectoderm cells from blastocysts (K. L. Scott et al., 2013). Polar bodies are typically analyzed if the embryo cannot be biopsied. However, polar body analysis is only useful for finding maternally inherited mutations or a cell division error during oocyte development. Furthermore, since genetic changes occur after the polar body develops, test results are of limited use. Additionally, as many as 30% of oocytes will not fertilize successfully, causing the test to fail (Schattman & Xu, 2024).

Blastomeres from day two or three (cleavage stage) were once the preferred practice in in-vitro-fertilization (IVF) as more embryos survived in culture by day three compared to days five or six (blastocyst stage). Despite the greater survival rate of day three embryos, these embryos were found to have a lower survival rate in a sustained implantation compared to day five embryos. Overall, trophectoderm biopsy on day five is preferable as it has no measurable impact on embryo development (Scott et al., 2013). Up to two or three dozen cells can be removed without disrupting development; although, common practice is to remove five to eight cells. Day five and later embryos also provide more DNA for testing compared to other stages of development (Schattman & Xu, 2024). Improved results have been seen with decreasing use of day three blastomere biopsy in favor of day five trophectoderm biopsy (K. L. Scott et al., 2013).

Pre-implantation genetic screening (PGS) is emerging as one of the most valuable tools to enhance pregnancy success with assisted reproductive technologies by assessing embryos for aneuploidy (Brezina et al., 2016).

As the genetic basis of more disorders are identified, increasing demand for and acceptance of the use of PGT for adult-onset disorders, such as Huntington disease, hereditary breast and ovarian cancer and Alzheimer disease, have occurred. Using PGD to screen embryos for diseases or mutations that confer an increased risk for developing a particular disease raises issues of how to weigh the benefits of PGD to the future child against the risks of PGD and ART (Stern, 2014). The Ethics committee for the American Society of Reproductive Medicine (ASRM) found that PGD for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome (ASRM, 2013). The use of PGT for nonmedical sex selection or family balancing continues to be controversial, and the ethics committee has stated that it is acceptable for facilities to offer this service; however, employees wishing to decline participation in these procedures should be allowed to do so (ASRM, 2015).

Women recommended for pre-implantation genetic diagnosis for aneuploidy testing (PGD-A) or PGT for aneuploidy (PGT-A) are those of advanced reproductive age with a history of recurrent miscarriages and/or IVF failures; PGD-A is currently performed on trophectoderm biopsies by 24 different chromosome screening techniques (Vaiarelli et al., 2016). Trophectoderm biopsies are a safe and extensively validated approach with a low margin of error and miscarriage rate as well as a suspected high sustained pregnancy rate (Vaiarelli et al., 2016). However, Alteri et al. (2019) states that while PGT-A allows for an increased implantation rate, current data does not show an increase in successful pregnancy rates. Researchers agree that this technology is imperfect as Ledger (2019) reports that PGD-A can incorrectly designate an euploid embryo as an aneuploid embryo, leading to the unnecessary waste of embryos. These researchers also suggest that this type of screening may only be necessary in women between the ages of 35 and 44, as embryonic aneuploidy rates are low below 37 years of age and "costly screening for aneuploid seems pointless for women over 44 years of age, as almost all embryos are aneuploid" (Ledger, 2019).

The development of whole genome amplification and genomic tools, such as single nucleotide polymorphism (SNP) microarrays and comparative genomic hybridization microarrays, has led to faster, more accurate diagnoses that lead to improved pregnancy and live birth rates (Sullivan-Pyke & Dokras, 2018). Next-generation sequencing has also been used to distinguish between normal and abnormal embryos (García-Herrero et al., 2019). PGD-polymerase chain reaction (PCR) is often used to amplify the obtained DNA from the blastomere biopsy for further analysis (Feldman et al., 2017). Fluorescence In-situ Hybridization (FISH) has also been used for PGD and is an efficient method that may help to decrease IVF failure in infertile patients (Montazeri et al., 2018).

Other researchers are attempting to develop a non-invasive pre-implantation genetic testing technique. Farra et al. (2018) state that circulating cell-free embryonic DNA can be obtained from used culture media from blastocysts and in blastocoel fluid; this can then be used as a non-invasive method to evaluate genetic embryonic properties.

Proprietary Testing

Companies, such as Natera, have developed a preimplantation genetic test for monogenic/single gene conditions called Spectrum™ that includes PGT-A, PGT-M, and PGT-SR. This PGT-A uses SNP microarray technology. "Spectrum's SNP microarray platform typically yields >99% accuracy and allows for simultaneous PGT-M and/or PGT-SR with PGT-A" (Natera, 2022). Simon et al. (2018) studied IVF outcomes with this test when measuring PGT-A and euploid embryo transfer in day five or six embryos. An implantation rate and live birth rate of 69.9% and 64.5%, respectively, was identified (Simon et al., 2018). The authors concluded that "SNP-based PGT-A can mitigate the negative effects of maternal age on IVF outcomes in cycles with transfer, and that pregnancy outcomes from SET [single embryo transfer] cycles are not significantly different from those of double-embryo transfer cycles, and support the use of SET when transfers are combined with SNP-based PGT-A" (Simon et al., 2018).

iGLS Reproductive Genetics developed a PGT-A that uses next generation sequencing (NGS) to analyze thousands of DNA sequences that are unique to each chromosome allowing for the accurate identification of extra or missing chromosomes (iGLS, 2022).

PacGenomics has developed several PGT's for aneuploidies (PGT-A), structural chromosomal rearrangements (PGT-SR) with a subsequent PGT-SR Plus® which is used to differentiate between normal and balanced translocation carrier embryos in translocation cases, and for monogenic/single gene disorders (PGT-M). PGT-A for aneuploidies is performed on embryos created through IVF to screen for chromosomal abnormalities. PGT-SR is a genetic test performed on embryos created through IVF to screen for chromosomal structural rearrangements caused by balanced translocations and inversions. PGT-SR-Plus® can be added to PGT-SR which helps identify translocation carriers in patients who are not initially suspected to be at significant risk. PGT-M is performed on embryos created through IVF that is designed for individuals who know they are at an increased risk of having a child with a specific genetic disorder (PacGenomics, 2022).

Reproductive Genetic Innovations (RGI) developed several PGT tests including PGT-A, PGT-SR, and PGT-M which has similar functions to the other proprietary tests. RGI provides an additional test, PGT-HLA, which identifies embryos that are HLA compatible with a child who needs a bone marrow or cord blood transplant to help treat blood disorders (RGI, 2022).

Clinical Utility and Validity

Dreesen et al. (2014) performed a study assessing the accuracy of diagnoses made based on PGD. A total of 940 cases covering 53 genetic disorders were re-evaluated using a PCR-based test. Of the 940 embryos, 881 (93.7%) of these embryos had two agreeing diagnoses. The first evaluation breakdown was 234 unaffected embryos, 590 affected, and 116 aberrant whereas the re-evaluation's breakdown was 283 unaffected embryos, 578 affected, and 79 aberrant. The sensitivity of this method was 99.2%, and its specificity was 80.2%. Allelic drop-out, mosaicism, and human error were the three most common causes of error (Dreesen et al., 2014).

Ghiossi et al. (2018) performed a study focusing on couples' decisions based on expanded carrier screening. Forty-five couples took a survey of their reproductive decision making after receiving their results, and of those 45, 28 said they would plan IVF with PGD or a prenatal diagnosis in future pregnancies. Of the 19 pregnant respondents, eight chose a prenatal diagnosis route, two planned amniocenteses but miscarried, and nine considered the condition insufficiently severe to warrant invasive testing. Three of the eight that chose the prenatal diagnosis route were affected by a condition, and two pregnancies were terminated. Disease severity was found to be a significant association with changes in decision making. Thirteen respondents did not plan to use the results from the carrier screening and four responses were unclear (Ghiossi et al., 2018).

Kamath et al. (2019) analyzed 207,697 data sets from women undergoing single-embryo transfer after PGT or IVF without PGT between the year 2000 and 2016. Results showed a significantly higher incidence of zygotic splitting following PGT (2.4%) compared to following non-PGT IVF (1.5%); this shows "a likely increased risk of monozygotic splitting following embryo biopsy" (Kamath et al., 2019) and highlights a potential risk with PGT embryonic biopsies.

A new study was published which compared the live birth rates of embryos fertilized without chromosome analysis compared to those analyzed via PGT-A and comprehensive chromosome screening of the first and second polar body (Verpoest et al., 2018). All mothers were of advanced maternal age between 36 and 40 years old. A total of 396 women enrolled in this multicenter, randomized clinical trial. Two hundred and five women had chromosomal screening, and 50 (24%) had a live birth within a year; in the group without intervention, which was comprised of 191 women, 45 (24%) had a live birth within a year (Verpoest et al., 2018). It is important to note that the groups had a slightly different number of participants. This study shows that PGT-A allows for similar birth rates when compared to embryos fertilized without chromosome analysis via intracytoplasmic sperm injection (ICSI). However, the authors warn that "Whether these benefits outweigh drawbacks such as the cost for the patient, the higher workload for the IVF lab and the potential effect on the children born after prolonged culture and/or cryopreservation remains to be shown" (Verpoest et al., 2018).

A meta-analysis focusing on evaluating the effectiveness and safety of PGT-A in women undergoing an IVF treatment was conducted in 2020. Thirteen randomized controlled trials—involving a total of 2794 women—reporting data on clinical outcomes were included. The meta-analysis concluded that there existed insufficient evidence for preimplantation genetic testing for abnormal chromosomes numbers to provide a difference in cumulative live birth rate, live birth rate after the first embryo transfer, or miscarriage rate between IVF with and IVF without PGT-A as currently performed, and therefore "the effect of PGT-A on clinical pregnancy rate is uncertain." The evidence evinced that though the observed cumulative live birth rate (cLBR) was 24% in the control group, the chance of live birth following the results of one IVF cycle with PGT-A is between 17% and

34%. Similarly, trials focusing on IVF with addition of PGT-A boasted an average cLBR of 29% in the control group, but the chance of live birth following the results of one IVF cycle with PGT-A was between 12% and 29%. When PGT-A is performed with FISH, the chance of live births after the first transfer in the control group (31%) fell to between 16% and 29% for those tested. Thus, the authors caution that “Women need to be aware that it is uncertain whether PGT-A with the use of genome-wide analyses is an effective addition to IVF, especially in view of the invasiveness and costs involved in PGT-A”, going so far as to state that “PGT-A using FISH for the genetic analysis is probably harmful” (Cornelisse et al., 2020).

Next generation sequencing can be used for PGS to screen for aneuploidies in IVF scenarios. A study by Yap et al. (2019) analyzed results from a total of 391 IVF pregnancies whose embryos were cultured to the blastocyst stage; a total of 1361 blastocysts were analyzed (Yap et al., 2019). Of the 1361 blastocysts, 423 were identified as aneuploid, 723 as euploid and 216 as mosaic (contained varying cell lines) (Yap et al., 2019). These results show that next generation sequencing can be used to identify mosaic and aneuploid blastocysts and is an effective PGS tool.

Zeevi et al. (2021) studied the clinical validity of Haploseek, a method for preimplantation genetic testing and compared the results to polymerase chain reaction (PCR)-based PGT case results. A total of 151 embryo biopsies from 27 PGT cases were obtained and sequenced using Haploseek to predict the chromosome copy-number variants (CNVs) and relevant variant-flanking haplotypes in each embryo. For each of the 151 embryo biopsies, all Haploseek-derived haplotypes and CNVs were concordant with clinical PGT results. The authors conclude that “Haploseek is clinically accurate and fit for all standard clinical PGT applications” (Zeevi et al., 2021).

Kumar et al. (2022) noted the lack of comprehensive embryo genetic assessment in PGT. The authors used parental genome sequencing and embryo genotyping to create a whole-genome reconstruction. Using a combination of molecular and statistic techniques, the authors could infer inherited genome sequences and model susceptibility to common conditions. The study included 110 embryos from ten couples and investigated 12 common conditions including cancer and autoimmune diseases. The method resulted in “genotype accuracy of 99.0–99.4% at sites relevant to polygenic risk scoring in cases from day-5 embryo biopsies and 97.2–99.1% in cases from day-3 embryo biopsies.” The authors conclude that these results can “inform the discussion of utility and implementation of genome-based PGT in clinical practice” (Kumar et al., 2022).

Guidelines and Recommenations

American College of Obstetricians and Gynecologists (ACOG)

In 2017, the ACOG noted that if a carrier couple (carriers for the same condition) is identified, genetic counselling is encouraged so that options such as preimplantation genetic diagnosis or prenatal diagnosis may be discussed. This guideline was reaffirmed in 2023 (ACOG, 2017).

In 2020, the ACOG published a series of recommendations in their “ACOG Committee Opinion” Number 799. The committee opinion was reaffirmed in 2023. These recommendations are shortened for brevity and reported below:

- “Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered.”
- “To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements (known as PGT-SR) is used. Confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered.”
- “The main purpose of preimplantation genetic testing-aneuploidy (known as PGT-A) is to screen embryos for whole chromosome abnormalities. Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients” (ACOG et al., 2020).

European Society for Human Reproduction and Embryology (ESHRE) PGD Consortium

In 2010, the ESHRE issued detailed guidelines related to technical aspects of PGD, specifically for the use of amplification techniques and for FISH. The ESHRE recommends that "misdiagnosis rates should be calculated for each type of assay and for all assays from a particular Centre." Additionally, they note that "Follow-up of pregnancies (including multiple pregnancy rate and outcome), deliveries, and the health of children at birth and beyond should be attempted and maintained along with the cycle data" (Harton et al., 2010).

In 2020, the ESHRE expanded upon their practice recommendations for preimplantation genetic testing. For the organization of PGT, the ESHRE provided patient inclusion/exclusion criteria. In general, "It is recommended that PGT is only applied when genetic diagnosis is technically feasible, and the reliability of the diagnosis is high. Current procedures in most IVF/PGT centres allow for overall error rates (resulting in misdiagnosis) as low as 1 to 3%. Each centre should be aware of their error rates and include this information in their informed consents and reports in an open communication with the patient.

When considering PGT, safety issues, female age, impossibility to retrieve male or female gametes, body mass index (BMI) and other contraindications for IVF should be considered as possible exclusion criteria.

Furthermore, exclusion from PGT should be considered if the woman has serious signs and symptoms of an autosomal dominant or X-linked disorder (for which PGT is requested), which could introduce medical complications during ovarian stimulation, oocyte retrieval or pregnancy or medical risks at birth. PGT should be carefully considered if one of the partners has serious physical or psychological problems, either linked to the tested disease or due to other conditions."

Different preimplantation genetic testing for specific defects and disorders carried their own caveats and recommendations in terms of inclusion and exclusion of patients:

For *PGT-M, mitochondrial disorders and HLA*: "Cases of genetic variants of unknown significance that are not predictive of a phenotype should be excluded from PGT. PGT testing is inappropriate in case of uncertain genetic diagnosis (for example genetic/molecular heterogeneity), or in case of uncertain mode of inheritance.

For autosomal recessive disorders, where a single pathogenic variant has been diagnosed in the proband and only one parent, it is acceptable to offer PGT if the pathogenic genotype is attributed to a single gene and sufficient evidence from the family pedigree allows identification of the disease-associated haplotypes. Similarly, it is acceptable to offer PGT for known X-linked recessive single gene disorders with a clear unequivocal clinical diagnosis where no pathogenic variant was found in the proband but low- and high-risk haplotypes can be identified based on the family history.

Exclusion or non-disclosure testing can be indicated for late-onset disorders, such as Huntington's disease, to avoid pre-symptomatic testing of the partner with a family history of the disease. Exclusion testing is preferred over PGT with non-disclosure of the direct test results to the couple."

For *PGT for mitochondrial disorders*: "PGT is not indicated in case of homoplasmy. In cases where the causative pathogenic variant of the mitochondrial disease is encoded by nuclear DNA, testing is the same as for other monogenic disorders."

For *HLA Typing*: "When all other clinical options have been exhausted, selection of HLA-matched embryos via PGT is acceptable for couples who already have a child affected with a malignant, acquired disorder or a genetic disorder where the affected child is likely to be cured or life expectancy is substantially prolonged by transplantation with stem cells from an HLA-matched sibling. Testing can be performed for HLA typing alone, if the recurrence risk of the disease is low, or in combination with autosomal dominant/recessive or X-linked disorders."

For *PGT-SR*: "Depending on the technology used (FISH, quantitative real-time PCR (qPCR), comprehensive testing methods [array-based comparative genomic hybridisation (aCGH), single nucleotide polymorphism (SNP) array or next generation sequencing (NGS)]), different inclusion/exclusion criteria may apply. In general, PGT-SR is only recommended if the technique applied is able to detect all expected unbalanced forms of the chromosomal rearrangement. When comprehensive testing strategies are applied, it is acceptable to use information on copy number of nonindication chromosomes to refine embryo transfer strategies."

For *PGT-A*: "For all, but in particular for RIF, RM and SMF couples, a previous karyotype of both partners is recommended since there is a higher chance of structural rearrangements for these indications. If an abnormal karyotype is identified, the technology for the detection of unbalanced abnormalities can differ from the regular PGT-A" (ESHRE PGT Consortium Steering Committee et al., 2020)..

Ethics Committee of the American Society for Reproductive Medicine (ASRM)

The ASRM ethics committee has published several opinion guidelines over the years.

In 2018, the ASRM published a committee opinion on the use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions. These guidelines stated the following:

- "Preimplantation genetic testing for monogenic disease (PGT-M) for adult-onset conditions is ethically justified when the condition is serious and no safe, effective interventions are available."
- "Reproductive liberty arguments ethically allow for PGT-M for adult-onset conditions of lesser severity or penetrance. In the latter cases, the application of the technology hinges on the evidence that PGT-M is a relatively low-risk procedure; this evidence may change."
- "The Committee to strongly recommend that an experienced genetic counselor with knowledge about PGT-M play a major role in counseling patients considering such procedures." (ASRM, 2018).

The ASRM also published an updated committee opinion in July 2023 detailing indications and management of preimplantation genetic testing for monogenic conditions, not limited to adult onset. These recommendations state the following:

- "Suggested categorization of PGT-M indications (derived from table):
    - Childhood-onset, lethal or severe condition
    - Serious adult-onset conditions
    - Mild conditions or indications of limited or questionable risk reduction:
        - Low penetrance or susceptibility genes
        - Mild genetic variants
        - Carrier status for autosomal recessive conditions with carrier manifestations
        - Mild, common, and/or treatable conditions
        - Variants appearing to be de novo in an affected child
        - Variants of uncertain significance
- Indications for which PGT-M is not recommended:
    - Autosomal recessive carrier status without manifestations of symptoms
    - Combination of variants not associated with disease
    - Pseudodeficiency alleles
    - Somatic-only variants"
- "Preimplantation genetic testing for monogenic conditions should be offered if a significant reproductive risk is identified. Acceptance of PGT-M should be optional"

However, with these categorizations, the committee reiterates some key considerations surrounding the application of PGT-M and the ethical arguments in certain situations: "The initial application of PGT-M was primarily to prevent the transmission of severe, untreatable, or life-threatening childhood-onset conditions. Today, however, the use of the technology extends to a much broader range of genetic conditions for which support of PGT-M is less clear or even controversial, including those with mild to moderate phenotypes and later age of onset and of much greater clinical variability and/or reduced penetrance. A survey of laboratory genetic counselors in 2021 found that all participants believed that PGT-M should be allowed for conditions of lower penetrance, citing patient autonomy as a primary consideration. At this time, no guidelines exist to offer direction to those involved in determining when to offer or decline to perform PGT-M, although some ethical arguments exist. As such, physicians, genetic counselors, and PGT laboratories may develop internal policies regarding PGT-M availability within their institution. If certain types of conditions or clinical scenarios are deemed not appropriate for PGT-M, the patient should be informed of the policy as early in the process as possible." (Practice Committee and Genetic Counseling Professional Group of the American Society for Reproductive Medicine, 2023).

Similar guidelines were also published in 2013 by the ASRM regarding the use of PGD for serious adult-onset conditions:

- "Preimplantation genetic diagnosis (PGD) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome.
- For conditions that are less serious or of lower penetrance, PGD for adult onset conditions is ethically acceptable as a matter of reproductive liberty. It should be discouraged, however, if the risks of PGD are found to be more than merely speculative.
- Physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on any developing fetus. Though thought to be without serious side effects, PGD for adult onset diseases of variable penetrance should only be considered after patients are carefully and thoroughly counseled to weigh the risks of what is unknown about the technology and the biopsy itself against the expected benefit of its use.
- It is important to involve the participation of a genetic counselor experienced in such conditions before patients undertake PGD. Counseling should also address the patient specific prognosis for achieving pregnancy and birth through in vitro fertilization (IVF) with PGD" (Ethics Committee of the American Society for Reproductive Medicine ASRM, 2013).

Additional guidelines were published in 2008, which stated the following:

- "Before PGD is performed, genetic counseling must be provided to ensure that patients fully understand the risk for having an affected child, the impact of the disease on an affected child, and the limitations of available options that may help to avoid the birth of an affected child.
- Prenatal diagnostic testing to confirm the results of PGD is encouraged strongly because the methods used for PGD have technical limitations that include the possibility for a false negative result.
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with advanced maternal age.
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with previous implantation failure.
- Available evidence does not support the use of PGS as currently performed to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy" (ASRM, 2008).

Preimplantation Genetic Diagnosis International Society (PGDIS)

In the report from the 2021 PGDIS Expert Consultation on Mosaic Embryo Transfer, the PGDIS published a position statement on the transfer of mosaic embryos, including the following recommendations for clinicians:

- "Patients should continue to be advised that any genetic test based on sampling one or small number of cells biopsied from preimplantation embryos cannot be 100% accurate because of a combination of technical and biological factors, including cell mosaicism;
- Patient information and consent forms for aneuploidy testing should be modified to include the possibility of mosaic results; and
- In general, transfer of blastocysts with a normal euploid result should be prioritized over those with mosaic results unless other indications, such as patient preference, are raised" (Leigh et al., 2022).

American College of Medical Genetics and Genomics (ACMG)

The ACMG has released guidelines on prenatal/preconception carrier screening, primarily when to test:

- "Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
- For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed."
- There must be validated clinical association between the mutation(s) detected and the severity of the disorder" (Grody et al., 2013).

In 2021 the ACMG published recommendations on screening for autosomal recessive and X-linked conditions during pregnancy and preconception. They reference an overlapping, tiered approach to testing defined as:

- Tier 1: Cystic fibrosis, spinal muscular atrophy, and risk based screening.
- Tier 2: "Conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100." (Includes Tier 1).
- Tier 3: "Conditions with a carrier frequency ≥ 1/200." (Includes Tier 2). Includes X-linked conditions.
- Tier 4: "Genes less common than those in Tier 3 and can identify additional at-risk couples." Conditions with a carrier frequency <1/200. (Includes Tier 3).

In terms of what screening approaches should be offered, the ACMG recommends that "all pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening. Tier 4 screening should be considered: when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer); [or] when a family or personal medical history warrants." The ACMG does NOT recommend "Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups [or] routine offering of Tier 4 panels."

In terms of what autosomal recessive conditions are appropriate for carrier screening, the ACMG recommends that "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive and X-linked conditions. Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their partner."

In terms of which X-linked conditions are appropriate for carrier screening, they note that "All XX patients should be offered screening for only those X-linked genes [listed here] as part of Tier 3 screening." The X-linked genes are: *ABCD1, AFF2, ARX, DMD, F8, F9, FMR1, GLA, L1CAM, MID1, NR0B1, OTC, PLP1, PRGR, RS1, SLC6A8*.
Lastly, the ACMG notes the "critical" importance of education and counseling in carrier screening and recommends that "carrier screening counseling should be provided by knowledgeable and appropriately trained health-care professionals and should be performed pre- and post-test" (Gregg et al., 2021).

British Fertility Society (BFS) Policy and Practice Guidelines

The BFS have published guidelines regarding PGS. These guidelines state that "It remains possible that PGS may be of benefit under certain circumstances. However at present patients should be informed that there is no robust evidence that PGS for advanced maternal age improves live birth rate per cycle started, and PGS should preferably be offered within the context of robustly designed randomised trials performed in suitably experienced centres" (Anderson & Pickering, 2008).

Indian Society for Assisted Reproduction (ISAR)

The Indian Society for Assisted Reproduction released consensus guidelines about preimplantation genetic testing in *In vitro* fertilization clinics in India. The recommendations for PGT-A are: "PGT-A is recommended for: advanced maternal age (36–40 years), or repeated pregnancy loss – known etiologies. PGT-A is not recommended for: young, good prognosis patients (<35 years), or unexplained RPL, or low AMH – limited eggs; multiple IVF cycles may be necessary in order to obtain one euploid blastocyst."

The clinical recommendations for genetic testing for monogenic indications are:

- "Can be offered to all patients with single or multiple gene disorders with a positive mutation report
- Cannot be offered for diseases which as multifactorial and nongenetic based diseases
- In case PGT-A is desired, it should be performed on PGT-M screened embryos" (Malhotra et al., 2021).

Applicable State and Federal Regulations

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81228, 81229, 81349, 81479, 0254U, and 0396U

ICD-10 diagnosis codes: Z84.81, Z14, Z15, Q95 and Q99

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 4/2021

Specialty Matched Consultant Advisory Panel 9/2021

Medical Director review 9/2021

Medical Director review 4/2022

Medical Director review 12/2022

Medical Director review 4/2024

Policy Implementation/Update Information

04/14/2020 Notification of new policy given 04/14/2020 for effective date 06/23/2020. Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. (eel)

10/13/2020 Specialty Matched Consultant Advisory Panel review 9/29/2020. No change to policy statement. (eel)

07/01/2021 Reviewed by Avalon 1st Quarter 2021 CAB. Updated Description, Policy Guidelines, and References. No change to policy statement. Medical Director review 4/2021. (bb)

10/1/21 Specialty Matched Consultant Advisory Panel review 9/2021. Medical Director Review 9/2021. No change to Policy statement. (tt/jd)

5/17/22 Reviewed by Avalon 1st Quarter 2022 CAB. Updated Description, Policy Guidelines, Related Policies, and References. When Covered section updated as follows: Reimbursement is allowed for preimplantation genetic testing when ALL of the conditions below are met: 1) Specific mutation(s) or chromosomal changes have been defined to be associated with a specific disorder, AND 2) One of the following conditions are met: Both biological parents are known carriers of an autosomal recessive disorder with early onset, OR, One biological parent is a known carrier of an autosomal dominant early onset disorder, OR, One biological parent is a known carrier of an X-linked early onset disorder, OR One biological parent carries a balanced or unbalanced chromosomal translocation. When not Covered section updated as follows: 1) Reimbursement is not allowed for Preimplantation genetic testing for sex selection, in the absence of a sex-linked early onset disease; Reimbursement is not allowed for preimplantation genetic testing in the following situations: -Preimplantation genetic testing for adult-onset disorders. - Preimplantation HLA genotyping for purposes of identifying potential tissue or organ donors. -Routine preimplantation screening for chromosomal abnormalities including testing based on advanced maternal age. Reimbursement is not allowed for preimplantation genetic testing for all other indications. Medical Director review 4/2022. (tt)

2/7/23 Reviewed by Avalon 4th Quarter 2022 CAB. Updated Description, Policy Guidelines, and References. Related policies section removed. The following bullets added When Covered section: " • One biological parent is a known carrier of an early-onset, autosomal recessive disorder and the other biological parent is unavailable for testing" and "• One biological parent is a known carrier of an early-onset, autosomal recessive disorder and together, the biological parents have produced previous offspring affected with the disorder." Added CPT code 81244 and removed CPT codes 89290 and 89291. Medical Director review 12/2022. (tt)

6/30/23 Added CPT code 0396U to Billing/Coding section, effective 7/1/2023. (tt)

10/24/23 Wording in Policy Statement, When Covered, and/or Not Covered section(s) changed from Reimbursement to Medical Necessity. (tt)

5/15/24 Description, Policy Guidelines, and References updated. Related policies section added. When covered section edited for clarity to indicate that genetic counseling is required however medical necessity criteria is outside the scope of this policy. Updated Billing/Coding section to remove CPT codes 96040, S0265, 81251, 81255, 81257, 81260, 81290, 81326, 81330, 81331, 81332, 81413, 81414, 88245, 88248, 88249, 88261, 88262, 88263, 88264, 88271, 88272, 88273, 82274, 88275, 81161, 81200, 81201, 81202, 81203, 81205, 81209, 81220, 81221, 81240, 81242, 81243, 81244, 81250, 81252, 81253, 81288, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81301, 81303, 81304, 81310, 81321, 81322, 81323, 81324, 81325 and updated to add 81228, 81229, 81349, and 81479. Medical Director review 4/2024. (tt)