PHP_4.02.05	Preimplantation Genetic Testing		
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Section:	4.0 OB/Gyn/Reproduction	**Page:**	Page 1 of 31

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- TAR and Non-Standard Benefits List: Codes 90000 thru 99999 (tar and non cd9)
- Presumptive Eligibility for Pregnant People: Billing Codes (presum bill)
- Pathology: Molecular Pathology (path molec)
- Genetic Counseling and Screening (gene coun)

Below is an excerpt of the Genetic Counseling and Screening guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Prenatal Screen Follow-Up and Diagnostic Testing (81228, 81229, 81349, 88271, 88274, 88275)
Medi-Cal covers follow-up services and diagnostic tests for positive or inconclusive prenatal screening test results received through Medi-Cal enrolled licensed clinical laboratories (outside of the California Prenatal Screening Program).

Medi-Cal also covers follow-up services and diagnostic tests if prenatal screening test results (either through the California Prenatal Screening Program or through Medi-Cal enrolled licensed clinical laboratories) are negative or if the member did not receive prenatal screening tests and the member then requires diagnostic tests for other medical reasons. Clinical indications for fetal diagnostic testing may include advanced maternal age, abnormality on fetal ultrasound, family history of genetic or chromosomal abnormality, etc.

Covered benefits for follow-up and diagnostic testing and procedures include the following: 81228, 81229, 81349, 88271, 88274, 88275

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- N/A

Policy Statement

Any criteria that are not specifically addressed in the above Provider Manuals, please refer to the criteria below.

I. Preimplantation genetic *diagnosis* (PGD) may be considered **medically necessary** as an adjunct to in vitro fertilization (IVF) in couples not known to be infertile who meet **one** of the criteria listed below:
   A. For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:
      1. Both partners are known carriers of a single-gene autosomal recessive disorder
      2. One partner is a known carrier of a single-gene autosomal recessive disorder, and the partners have an offspring who has been diagnosed with that recessive disorder
      3. One partner is a known carrier of a single-gene autosomal dominant disorder
      4. One partner is a known carrier of a single X-linked disorder
   B. For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality such as for a:
      1. Parent with balanced or unbalanced chromosomal translocation.

II. Preimplantation genetic *diagnosis* (PGD) as an adjunct to IVF is considered **investigational** in individuals or couples who are undergoing IVF in all situations other than those specified above.

III. Preimplantation genetic *screening* (PGS) as an adjunct to IVF is considered **investigational** in individuals or couples who are undergoing IVF in all situations.

Policy Guidelines

In some cases involving a single X-linked disorder, determination of the sex of the embryo provides sufficient information for excluding or confirming the disorder.

This policy does not address the myriad of ethical issues associated with preimplantation genetic testing that should be carefully discussed between the treated couple and the provider.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

Previous	Updated	Definition
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

See the Codes table for details.

Description

Preimplantation genetic testing involves the analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into 2 categories. Preimplantation genetic diagnosis is used to detect a specific inherited disorder in conjunction with in vitro fertilization (IVF) and aims to prevent the birth of affected children to couples at high-risk of transmitting a disorder. Preimplantation genetic screening may also involve testing for potential genetic abnormalities in conjunction with IVF for couples without a specific known inherited disorder.

Summary of Evidence

For individuals who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization (IVF) who receive preimplantation genetic diagnosis, the evidence includes observational studies and systematic reviews. Relevant outcomes are health status measures and treatment-related morbidity. Data from observational studies and systematic reviews have suggested that preimplantation genetic diagnosis is associated with the birth of unaffected fetuses when performed for detection of single genetic defects and a decrease in spontaneous abortions for patients with structural chromosomal abnormalities. Moreover, preimplantation genetic diagnosis performed for single-gene defects does not appear to be associated with an increased risk of obstetric complications. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have no identified elevated risk of a genetic disorder undergoing IVF who receive preimplantation genetic screening, the evidence includes randomized controlled trials (RCTs) and meta-analyses. Relevant outcomes are health status measures and treatment-related morbidity. Randomized controlled trials and meta-analyses of RCTs on initial preimplantation genetic screening methods (e.g., fluorescent in situ hybridization [FISH]) have found lower or similar ongoing pregnancy and live birth rates compared with IVF without preimplantation genetic screening. There are fewer RCTs on newer preimplantation genetic screening methods, and findings

are mixed. Recent meta-analyses of newer methods have found some benefit in subgroups of patients (e.g., advanced maternal age); however, the evidence is limited, and larger trials specific to these patient populations are needed. Well-conducted RCTs evaluating preimplantation genetic screening in the various target populations (e.g., women of advanced maternal age, women with recurrent pregnancy loss) are needed before conclusions can be drawn about the impact on the net health benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- Reproductive Techniques

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Preimplantation Genetic Testing

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure (see Blue Shield of California Promise Medical Policy: Reproductive Techniques) in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect before implantation of an embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before implantation provides an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic (preimplantation genetic diagnosis) or screening (preimplantation genetic screening). Preimplantation genetic diagnosis is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively, that has a high risk of transmission. Preimplantation genetic screening is not used to detect a specific abnormality but instead uses similar techniques to identify a number of genetic abnormalities in the absence of a known heritable disorder. This terminology, however, is not used consistently (e.g., some authors use preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder), following a terminology change from 'preimplantation genetic screening' to 'preimplantation genetic testing' in 2017.[1]

Biopsy

Biopsy for preimplantation genetic diagnosis can take place at 3 stages: the oocyte, cleavage stage embryo, or the blastocyst. In the earliest stage, both the first and second polar bodies are extruded from the oocyte as it completes the meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the mother is a known carrier of a genetic defect and genetic analysis of the polar body is normal, then it is assumed that the genetic defect was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of 6 to 8 cells (i.e., blastomeres). Sampling involves aspiration of 1 and sometimes 2 blastomeres from the embryo. Analysis of 2 cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form 5 to 6 days after insemination. Three to 10 trophectoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, when they do, there is a short time before embryo transfer needs to take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

Analysis and Testing

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic defects. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay-Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, sex determination, or to identify chromosomal translocations. Fluorescent in situ hybridization cannot

be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (e.g., microdeletions, duplications) and, thus, single-gene defects can be recognized with this technique.

A more recent approach for preimplantation genetic screening is with comprehensive chromosome screening using techniques such as array comparative genome hybridization and next generation sequencing.

Embryo Classification

Three general categories of embryos have undergone preimplantation genetic testing, which is discussed in the following subsections.

Embryos at Risk for a Specific Inherited Single-Gene Defect

Inherited single-gene defects fall into 3 general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo preimplantation genetic diagnosis to deselect embryos harboring the defective gene. Sex selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is no specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, preimplantation genetic diagnosis is used to deselect male embryos, half of which would be affected. Preimplantation genetic diagnosis could also be used to deselect affected male embryos. While there is a growing list of single-gene defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, β-thalassemia, muscular dystrophy, Huntington disease, hemophilia, and fragile X disease. It should be noted that when preimplantation genetic diagnosis is used to deselect affected embryos, the treated couple is not technically infertile but is undergoing an assisted reproductive procedure for the sole purpose of preimplantation genetic diagnosis. In this setting, preimplantation genetic diagnosis may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

Embryos at a Higher Risk of Translocations

Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or those with recurrent spontaneous abortions. Preimplantation genetic diagnosis can be used to deselect embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

Identification of Aneuploid Embryos

Implantation failure of fertilized embryos is common in assisted reproductive procedures; aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, preimplantation genetic screening has been explored as a technique to deselect aneuploid oocytes in older women and is also known as preimplantation genetic diagnosis for aneuploidy screening. Analysis of extruded polar bodies from the oocyte or no blastomeres at day 3 of embryo development using FISH was initially used to detect aneuploidy. A limitation of FISH is that analysis is restricted to a number of proteins. More recently, newer preimplantation genetic screening methods have been developed. These methods allow for all chromosomes' analysis with genetic platforms including array comparative genomic hybridization and single nucleotide variant chain reaction analysis. Moreover, in addition to older women, preimplantation genetic screening has been proposed for women with repeated implantation failures.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that

are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Preimplantation Genetic Diagnosis

The complicated technical and ethical issues associated with preimplantation genetic testing frequently require case-by-case consideration. The diagnostic performance of the individual laboratory tests used to analyze the biopsied genetic material is rapidly evolving, and the evaluation of each specific genetic test for each abnormality is beyond the scope of this evidence review. However, in general, to assure adequate sensitivity and specificity for the genetic test guiding the embryo deselection process, the genetic defect must be well-characterized. For example, the gene or genes responsible for some genetic disorders may be quite large, with variants spread along the entire length of the gene. The ability to detect all or some of these genes and an understanding of the clinical significance of each variant (including its penetrance, i.e., the probability that an individual with the variant will express the associated disorder) will affect the diagnostic performance of the test. An ideal candidate for genetic testing would be an individual who has a condition associated with a single well-characterized variant for which a reliable genetic test has been established. In some situations, preimplantation genetic testing may be performed in couples in which the mother carries an X-linked disease, such as fragile X syndrome. In this case, the genetic test could focus on merely deselecting male embryos. This review does not consider every possible genetic defect. Therefore, implementation will require a case-by-case approach to address the many specific technical and ethical considerations inherent in testing for genetic disorders, based on an understanding of the penetrance and natural history of the genetic disorder in question and the technical capability of genetic testing to identify affected embryos.

Clinical Context and Test Purpose

The purpose of preimplantation genetic diagnosis in individuals who have an identified elevated risk of a genetic disorder undergoing in vitro fertilization (IVF) is to provide an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with an identified elevated risk of a genetic disorder such as a heritable genetic defect or chromosomal abnormality (e.g., translocations) who are undergoing IVF.

Interventions

The therapy being considered is preimplantation genetic diagnosis using methods such as polymerase chain reaction (PCR), array comparative genomic hybridization, gene sequencing, or single nucleotide variant arrays to identify single-gene defects in cells from a preimplantation embryo or an oocyte polar body single-gene defects. Preimplantation genetic diagnosis is performed

at specialized reproductive endocrinology services or clinics where comprehensive evaluation is available. This includes the availability of or referral for genetic counseling for prospective parents.

Comparators

The comparator of interest is IVF without preimplantation genetic diagnosis and prenatal genetic testing.

Outcomes

The outcomes of interest include test accuracy, health status measures, and treatment-related morbidity, including pregnancy and neonatal outcomes such as implantation rates and time to successful implantation, spontaneous abortion or miscarriage rates, length of gestation, live birth rates, birth weight, fetal anomalies, and neonatal outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Lews et al (2018) conducted a systematic review examining the outcomes of preimplantation genetic diagnosis for couples with recurrent pregnancy loss due to structural chromosomal rearrangement.[2] Twenty studies were identified, mostly retrospective and case-control, therefore, a meta-analysis was not performed due to significant heterogeneity among the studies. The primary outcome for the systematic review was live birth rate. The authors identified 3 study types among the 20 studies: (1) 10 evaluated reproductive outcomes for genetic testing with natural conception, (2) 8 compared outcomes after IVF and preimplantation genetic diagnosis, and (3) 2 directly compared differences in live birth rates between couples who conceived naturally versus those who conceived after IVF and preimplantation genetic diagnosis. The pooled total of 847 couples who conceived naturally had a live birth rate of 25% to 71% as opposed to 26.7% to 87% for the 562 couples who underwent IVF and preimplantation genetic diagnosis - a small difference. One strength of this study is the variety of populations included in the selected studies, which encompassed a range of geographic and ethnic groups, thus reducing the risk of selection bias. Also, case reports and case series were excluded, further lessening the risk of bias. However, most of the studies included in this systematic review were retrospective, nonrandomized, and without a well-defined population.

Hasson et al (2017) published a meta-analysis of studies comparing obstetric and neonatal outcomes after intracytoplasmic sperm injection without preimplantation diagnosis compared with intracytoplasmic sperm injection with preimplantation genetic diagnosis.[3] Studies focused on cases with known parental genetic aberrations. Reviewers identified 6 studies, including data published by the investigators in the same article. The pooled analysis found no significant differences between the 2 groups for 4 of the 5 reported outcomes: mean birth weight, mean gestational age at birth, the rate of preterm delivery, and the rate of malformations. There was a significantly lower rate of low birth weight neonates (<2500 g) in the preimplantation genetic diagnosis group than in the non-testing group (relative risk , 0.84; 95% confidence interval [CI], 0.72 to 1.00; p=.04).

Observational Studies

Selected recent observational studies reporting on pregnancy rates or live birth rates are described next. For example, a study by Kato et al (2016) included 52 couples with a reciprocal translocation (n=46) or Robertsonian translocation (n=6) in at least 1 partner.[4] All couples had a history of at least 2 miscarriages. The average live birth rate was 76.9% over 4.6 oocyte retrieval cycles. In the subgroups of young (<38 years) female carriers, young male carriers, older (≥38 years) female carriers, and older male carriers live birth rates were 77.8%, 72.7%, 66.7%, and 50.0%, respectively.

Chow et al (2015) reported on 124 cycles of preimplantation genetic diagnosis in 76 couples with monogenetic diseases (X-linked recessive, autosomal recessive, autosomal dominant).[5] The most common genetic conditions were α-thalassemia (64 cycles) and β-thalassemia (23 cycles). Patients were not required to have a history of miscarriage. A total of 92 preimplantation genetic diagnosis cycles resulted in embryo transfer, with an ongoing pregnancy rate (beyond 8 to 10 weeks of gestation) in 28.2% of initiated cycles and an implantation rate of 35%. The live birth rate was not reported.

A study by Scriven et al (2013) in the United Kingdom evaluated preimplantation genetic diagnosis for couples carrying reciprocal translocations.[6] This prospective analysis included the first 59 consecutive couples who completed treatment at a single center. Thirty-two (54%) of the 59 couples previously had recurrent miscarriages. The 59 couples underwent a total of 132 cycles. The estimated live birth rate per couple was 51% (30/59) after 3 to 6 cycles. The live birth rate estimate assumed that couples who were unsuccessful and did not return for additional treatment would have had the same success rate as couples who returned.

Keymolen et al (2012) in Belgium reported on clinical outcomes for 312 cycles performed for 142 couples with reciprocal translocations.[7] Seventy-five (53%) of 142 couples had preimplantation genetic diagnosis for infertility, 40 (28%) couples for a history of miscarriage, and the remainder had other reasons. The live birth rate per cycle was 12.8% (40/312), and the live birth rate per cycle with embryo transfer was 26.7% (40/150).

Adverse Events

An important general clinical issue is whether preimplantation genetic diagnosis is associated with adverse obstetric outcomes, specifically fetal malformations related to the biopsy procedure. Strom et al (2000) addressed this issue in an analysis of 102 pregnant women who had undergone preimplantation genetic diagnosis with genetic material from the polar body.[8] All preimplantation genetic diagnoses were confirmed postnatally; there were no diagnostic errors. The incidence of multiple gestations was similar to that seen with IVF. Preimplantation genetic diagnosis did not appear to be associated with an increased risk of obstetric complications compared with the risk of obstetric outcomes reported in data for IVF. However, it should be noted that a biopsy of the polar body is considered a biopsy of extra-embryonic material, and thus one might not expect an impact on obstetric outcomes. Patients in this study had undergone preimplantation genetic diagnosis for both unspecified chromosomal disorders and various disorders associated with a single-gene defect (e.g., cystic fibrosis, sickle cell disease).

Section Summary: Preimplantation Genetic Diagnosis

Two systematic reviews of observational studies were identified. One of the systematic reviews found a median live birth rate of 31% after preimplantation genetic diagnosis compared with 55.5% after natural conception. The median miscarriage rate was 0% after preimplantation genetic diagnosis and 34% after natural conception. The findings of this review apply only to patients with recurrent miscarriages. The other systematic review found a significant rate of low birth weight in the preimplantation genetic diagnosis group compared with a non-preimplantation diagnosis group, but no significant differences in other outcomes. Studies in the review focused on parents with known genetic aberrations.

Preimplantation Genetic Screening

Clinical Context and Test Purpose

The purpose of preimplantation genetic screening in individuals with no identified elevated risk of a genetic disorder undergoing IVF is to provide an alternative to amniocentesis, chorionic villus sampling, and selective pregnancy termination of affected fetuses.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with no identified elevated risk of a genetic disorder who are undergoing IVF. Although preimplantation genetic screening may be used in any individual undergoing IVF, in particular, preimplantation genetic screening may be used in individuals with recurrent IVF implantation failure, recurrent early pregnancy loss, and/or of advanced maternal age.

Interventions

The therapy being considered is preimplantation genetic screening. Preimplantation genetic screening includes older methods using fluorescent in situ hybridization (FISH) or newer methods with comprehensive chromosomal screening. Preimplantation genetic diagnosis is performed at specialized reproductive endocrinology services or clinics where comprehensive evaluation is available. This includes the availability of or referral for genetic counseling for prospective parents.

Comparators

The comparator of interest is IVF without preimplantation genetic screening.

Outcomes

The outcomes of interest include test accuracy, health status measures, and treatment-related morbidity, including pregnancy and neonatal outcomes such as implantation rates, spontaneous abortion or miscarriage rates, live birth rates, gestational age, birth weight, and fetal anomalies, and neonatal outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A number of RCTs evaluating preimplantation genetic screening using FISH-based technology have been published, and these findings have been summarized in several systematic reviews and a meta-analysis. Table 1 summarizes included studies in relevant systematic reviews and meta-analyses. The most comprehensive meta-analysis was a Cochrane review by Cornelisse et al (2020), which included RCTs comparing participants undergoing IVF with preimplantation genetic testing for aneuploidies (PGT-A) versus IVF without PGT-A.[1] A total of 13 trials were included (N=2794 women), of which 11 used FISH for the genetic analysis. The Cochrane review also included 2 studies that used genome-wide analysis (Verpoest et al 2018 and Munne et al 2019); however, pooled analyses were not performed due to heterogeneity in testing methods. Of the 13 included RCTs, studies included patients with advanced maternal age (n=7 studies) and repeated IVF failure (n=3 studies), as well as good prognosis patients (n=5 studies). In a pooled analysis of RCTs using FISH for genetic analysis, live birth

rate after the first embryo transfer was lower in patients undergoing PGT-A compared to the control group (odds ratio [OR], 0.62; 95% confidence interval [CI], 0.43 to 0.91; 10 RCTs; n=1680; I^2=54%). No difference in miscarriage rate per woman randomized was observed between PGT-A and control groups (OR, 1.03; 95% CI, 0.75 to 1.41; 10 RCTs; n=1680; I^2=16%); however, rate of miscarriage per clinical pregnancy was reduced in the control group (OR, 1.77; 95% CI, 1.10 to 2.86; 5 RCTs, n=288; I^2=45%). Only 1 study utilizing FISH evaluated cumulative live birth rate per woman, which did not detect a difference in patients undergoing PGT-A compared with the control (OR, 0.59; 95% CI, 0.35 to 1.01; 1 RCT; n=408). Ongoing pregnancy rate (OR, 0.68; 95% CI, 0.51 to 0.90; 5 RCTs; n=1121; I^2=60%) and clinical pregnancy rate (OR, 0.60; 95% CI, 0.45 to 0.81; 5 RCTs; n=1131; I^2=0%) were also reported to be lower in patients undergoing PGT-A compared with the control group. The authors noted a risk of publication bias, a limited quantity of studies and events, inconsistency in estimates between studies, and high heterogeneity for certain analyses (considered I^2 >50).

Shi et al (2021) conducted a systematic review and meta-analysis of 9 RCTs (N=2113) evaluating IVF with or without PGT-A in women of advanced maternal age.[9] Six of the included trials used FISH-based technology while comprehensive chromosomal screening was applied in 3 trials. Overall, PGT-A did not improve the live birth rate (risk ratio [RR], 1.01; 95% CI, 0.75 to 1.35); however, when the analysis was limited to the 3 trials evaluating comprehensive chromosomal screening (see Rubio et al 2017[10], Verpoest et al 2018[11], and Munne et al 2019[12] trials below) the live birth rate was significantly higher in those randomized to IVF with PGT-A than those without PGT-A (RR: 1.30; 95% CI, 1.03 to 1.65). Clinical pregnancy and miscarriage rates were not significantly different between those receiving PGT-A and those without in the general population or subgroups. Although live birth rates were improved in advanced maternal age patients using comprehensive chromosomal screening for PGT-A, studies assessing the overall benefit of PGT-A with newer screening methods are needed. Additional limitations of the individuals trials included in this meta-analysis are noted below.

In a meta-analysis limited to PGT-A with comprehensive chromosomal screening conducted on day 3 or day 5, Simopoulou et al (2021) identified 11 RCTs.[13] In the overall population PGT-A did not improve live birth rates (RR: 1.11; 95% CI, 0.87 to 1.42; 6 trials; n=1513; I^2=75%). However, in a subgroup of patients over 35 years of age, live birth rates improved with PGT-A (RR: 1.29; 95% CI, 1.05 to 1.60; 4 trials; n=629). Clinical pregnancy rates were also not significantly improved in the overall population (RR, 1.14; 95% CI, 0.95 to 1.37; 9 trials; n=1824); however, miscarriage rates were improved with PGT-A (RR: 0.36; 95% CI, 0.17 to 0.73; 7 trials; n=912). The authors concluded that PGT-A with comprehensive chromosomal screening did not generally improve outcomes, but when performed on blastocyst stage embryos in women over 35 years of age, live birth rates were improved.

Adamyan et al (2024) conducted a systematic review and meta-analysis on 5 RCTs and 14 nonrandomized studies evaluating IVF with and without PGT-A for women of reproductive age with the primary outcomes of interest being clinical pregnancy rate and live birth rate.[14] Eight studies reported result on clinical pregnancy rates, defined as the number of clinical pregnancies expressed per 100 initiated, aspirated, or embryo transfer cycles, for women 35 years or older with a relative risk of 1.44 (95% CI, 1.19 to 1.75; p=.0002). When assessing live birth rates, defined as the number of deliveries resulting in at least 1 live birth and is expressed per 100 cycle attempts, the result differed based on age and patients characterized by American Medical Association with poor prognosis (recurrent implantation failure [RIF], recurrent pregnancy loss [RPL], severe male infertility, or elective single embryo transfer). Five studies demonstrated that PGT-A significantly improved live birth rates in women ≤ 35 years old when compared to controls (relative risk:1.32; 95% CI, 1.11 to 1.57; p=.002), however with substantial heterogeneity amongst the studies (I^2:72%). The meta-analysis of live birth rates for women ≤ 38 years of age demonstrated no statistically significant difference with the use of PGT-A (2 studies; I^2:30%), but an analysis of 2 studies assessing PGT-A in women ≥ 35 years of age indicated significant improvements in live birth rates with the use of PGT-A (relative risk:1.65; 95% CI, 1.18 to 2.30; p=.004; I^2: 0%) with no statistically significant difference in live birth rates for women ≤ 35 years old. The effect of PGT-A on the live birth rate in patients with a history of previous miscarriage, RPL, or RIF demonstrated a statistically significant improvement compared to those without a poor

prognosis (relative risk:1.47; 95% CI, 1.14 to 1.90; p=.003), however with substantial heterogeneity amongst the studies (I^2:68%). Secondary analysis evaluated miscarriage rates, defined as the spontaneous loss of intrauterine pregnancy before 22 weeks of gestational age, amongst women of reproductive age and demonstrated that PGT-A had no statistically significant impact on miscarriage rates. Notable limitations include, but are not limited to, lack of clinical studies with a low risk of bias, insufficient number of relevant clinical studies for subgroup analysis, methods for what embryos to be selected for transfer as well as the outcome definition of "per embryo transfer" are still controversial within the field. Overall, the findings suggest that PGT-A may be a valuable tool for improving the reproductive outcomes of assisted reproductive procedures in older women and those with a history of pregnancy complications.

Chamani et al (2025) performed a systematic review and meta-analysis to evaluate whether embryo biopsy for preimplantation genetic testing (PGT) during IVF increases the risk of disorders related to abnormal placental implantation in 8 studies (N=71,768) ranging from RCTs, prospective and retrospective cohort, case-control, and cross-sectional designs with individuals undergoing PGT (n=3668) and those who did not (n=68,118).[15] The primary outcome was placenta accreta spectrum (PAS), while secondary outcomes included placental abruption, placenta previa, preterm premature rupture of membranes (PPROM), and hypertensive pregnancy disorders. No statistically significant difference was observed in the primary outcome of PAS risk associated with PGT (aggregated odds ratio [OR]: 0.78, 95% CI 0.22 to 2.76; p=.70). For the secondary outcomes, only PPROM demonstrated a statistically significant increase reporting an OR of 1.29 (95% CI, 1.04 to 1.60; p=.02) in the meta-analysis. Notable limitations include, but are not limited to, the meta-analysis used retrospective data and other lower quality studies and the PPROM findings were from a single study with questionable validity as noted by the authors.

Table 1. Comparison of Studies Included in Systematic Reviews and Meta-Analyses

Study	Cornelisse et al (2020)[1]	Shi et al (2021)[9]	Simopoulou et al (2021)[13]	Adamyan et al (2024)[14]
Awadalla et al (2022)				●
Blockeel et al (2008)	●			
Debrock et al (2010)	●	●		
Deng et al (2020)				●
Doyle et al (2020)				●
Fiorentino et al (2013)			●	
Hardarson et al (2008)	●	●		
Jansen et al (2008)	●			
Lee et al (2015)				●
Lee et al (2019)				●
Martello (2021)				●
Masbou et al (2019)				●
Mastenbroek et al (2007)	●	●		
Meyer et al (2009)	●			
Munné et al (2019)	●	●	●	●
Namath et al (2021)				●
Ozgur et al (2019)			●	●
Pantou et al (2022)				●
Rubio et al (2013)	●	●		
Rubio et al (2017)		●	●	●
Sanders et al (2021)				●
Sato et al (2019)				●
Schoolcraft et al (2009)	●	●		
Scott et al (2010)			●	
Scott et al (2013a)			●	
Scott et al (2013b)			●	
Staessen et al (2004)	●	●		
Staessen et al (2008)	●			

Study	Cornelisse et al (2020)[1]	Shi et al (2021)[9]	Simopoulou et al (2021)[13]	Adamyan et al (2024)[14]
Sui et al (2020)			●	
Tiegs et al (2021)				●
Treff et al (2011)			●	
Verpoest et al (2018)	●	●		
Werlin et al (2003)	●			
Whitney et al (2016)				●
Yan et al (2021)				●
Yang et al (2012)			●	●
Yang et al (2017)			●	
Zhou et al (2021)				●

[1] Systematic reviews / meta-analyses across the columns.
[2] Primary studies across the rows.

Randomized Controlled Trials

Several RCTs evaluating comprehensive chromosomal screening in patients undergoing PGT-A have been published and are included in the above systematic reviews.[16,17,18,11,12,10] One additional RCT was published in 2021 and was not incorporated in the above reviews.[19] The characteristics of the RCTs are described in Table 2. Two trials (Yang et al [2012]; Rubio et al [2017]) used array comparative genetic hybridization, 2 used quantitative PCR, 1 (Verpoest et al [2018]) used comprehensive chromosome screening, and 2 used next-generation sequencing (Munne et al [2019]; Yan et al [2021]). The majority of trials did not target women of advanced maternal age or women with repeated implantation failure. Instead, the majority of trials targeted good prognosis patients. For example, Yan et al (2021) included good prognosis patients undergoing their first IVF and who were 20 to 37 years of age, Yang et al (2012) included good prognosis patients younger than age 35 with no history of spontaneous abortion, Forman et al (2013) included women younger than age 43, and Scott et al (2013) included women between 21 and 42 years of age with no more than 1 failed IVF attempt. The Rubio et al (2017) and Verpoest et al (2018) trials did target women of advanced maternal age (36 to 41 years). One of the trials (Forman et al [2013]) transferred 1 embryo in the intervention group and 2 embryos in the control group, which might have introduced bias. The majority of studies were superiority trials. Forman et al (2013) and Yan et al (2021) were noninferiority trials.

Table 2. Characteristics of Randomized Controlled Trials Evaluating Comprehensive Chromosomal Screening

Study	Countries	Sites	Dates	Participants	Interventions	
					PGS	*Control*
Yang et al (2012)[16]	China, U.S.	2	NR	Female partner < 35 y with no history of spontaneous abortion and with normal karyotype	• n=56 • Blastocyst biopsy (day 5/6) analyzed via aCGH • Single euploid embryo selected for transfer based on PGS	• n=56 • Single embryo selected for transfer on day 5/6 based on morphologic assessment
Forman et al (2013)[17]	U.S.	1	2011-2012	Female partner < 43 y with no more than 1 failed IVF attempt	• n=89 • Blastocyst biopsy (day 5/6) analyzed via qPCR • Single euploid embryo selected for	• n=86 • 2 embryos were selected for transfer on day 5/6 based on morphologic assessment

Study	Countries	Sites	Dates	Participants	Interventions	
					transfer based on PGS	
Scott et al (2013)[18]	U.S.	1	2009-2012	Female partner between 21 y and 42 y with no more than 1 failed IVF attempt	• n=72 • Blastocyst biopsy (day 5) analyzed via qPCR • Up to 2 euploid embryo(s) were selected for transfer on day 6 based on PGS	• n=83 • 2 embryos were selected for transfer on day 5 based on morphologic assessment
Rubio et al (2017)[10]	Spain	4	2012-2014	Female partner between 38 y and 41 y with normal karyotypes who were on their 1st or 2nd cycle of ICSI	• n=138 • Blastocyst biopsy (day 3) analyzed via aCGH • An unclear number of euploid embryos selected for transfer or vitrification (day 5) based on PGS	• n=140 • Conventional ICSI cycle with morphologic embryo selection at blastocyst stage, unclear how many embryos were selected for transfer
Verpoest et al (2018)[11]	EU, Israel	9	2012-2016	Female partner between 36 y and 40 y with < 3 previously unsuccessful IVF attempts, < 3 miscarriages, and without poor ovarian response or reserve	• n=205 • Polar body biopsy (6 to 9 hr after insemination); analysis method varied by site • Up to 2 euploid embryos selected from transfer on the day of development decided by site policy	• n=191 • Conventional ICSI cycle with up to 2 embryos selected for transfer on the day of development decided by site policy
Munne et al (2019); Single Embryo Transfer of Euploid Embryo (STAR) study; NCT02268786[12]	Australia, Canada, U.S., UK	34	2014-2016	Female partner between 25 y and 40 y with < 2 previously unsuccessful IVF attempts, ≤ 1 miscarriage, and without azoospermia, or severe oligospermia	• n=330 • Blastocyst biopsy (day 5/6); NGS-based assay (Veriseq PGS) • Single euploid embryo selected for transfer based on PGS	• n=331 • Single embryo selected for transfer on day 5/6 based on morphologic assessment

Study	Countries	Sites	Dates	Participants	Interventions	
Yan et al (2021)[a,19]	China	14	2017-2018	Female partner 20 to 27 y undergoing first IVF cycle with ≥ 3 blastocysts of good quality	• n=606 • Blastocyst biopsy (day 5); NGS-based assay (Illumina Next Seq 550 or Ion PGM/Proton) • Single euploid embryo selected for transfer based on PGS	• n=606 • Single embryo selected for transfer based on morphologic assessment

aCGH: array comparative genomic hybridization; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; NGS: Next-Generation Sequencing; NR: not reported; PGS: preimplantation genetic screening; qPCR: quantitative polymerase chain reaction; y: years old.
[a] Two secondary analyses were conducted on the same RCT that expanded on these results.[20,21]

Results of the RCTs are shown in Table 3. Results were mixed for all outcomes reported across studies. Pregnancy rates were higher in 2 of the 7 RCTs with preimplantation genetic screening compared with the control group. The pregnancy rate in preimplantation genetic screening was 37% in the study including women of advanced maternal age and from 70% to 90% in the studies including good prognosis couples. None of the studies provided justification for clinically meaningful improvements in the outcomes reported. Few neonatal or post-delivery outcomes were reported.

Table 3. Results of Randomized Controlled Trials Evaluating Preimplantation Genetic Screening Using Comprehensive Chromosomal Screening

Study	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate (≥24 Wk of Gestation)	Delivery Rate or Live Births	Miscarriage Rate	Multiple Pregnancy Rate
Yang et al (2012)[16]						
N	NR	103	103	NR	NR	103
PGS, %		70.9	69.1		2.6	0
Control, %		45.8	41.7		9.1	0
TE (95% CI); p		NR (NR);.017	NR (NR);.009		NR (NR);.60	
Forman et al (2013)[17]						
N	259[a]	175	175	NR	131[b]	115[b]
PGS, %	63.2	69	60.7		11.5	0
Control, %	51.7	81	65.1		20.0	53
TE (95% CI); p	NR (NR); .08	NR	RD, -4.4 (-18.7 to 9.9); noninferior but p NR		NR (NR);.20	NR (NR); <.001
Scott et al (2013)[18]				Delivery Rate		
N	297[a]	155	NR	155	NR	NR
PGS, %	79.8	93.1		84.7		
Control, %	63.2	80.7		67.5		
RR (95% CI); p	1.26 (1.04 to 1.39);.002	1.15 (1.03 to 1.43);.03		1.26 (1.06 to.1.53);.01		
Rubio et al (2017)[10]				Live Birth Rate		
N	263[a]	205	NR	278	78[b]	78[b]
PGS, %	52.8	37		31.9	2.7	22
Control, %	27.6	39		18.6	39.0	13

Study	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate (≥24 Wk of Gestation)	Delivery Rate or Live Births	Miscarriage Rate	Multiple Pregnancy Rate
OR (95% CI); p	2.9 (1.7 to 5.0); <.001	NR		2.4 (1.3 to 4.2);.003	0.06 (0.008 to 0.48); <.001	NR
Verpoest et al (2018)[11]				Live Birth Rate		
N	396[a]	136	NR	95	41	38
PGS, %	73	31		24	7	7
Control, %	90	37		24	14	13
RR (95% CI); p-value	0.81 (0.74 to 0.89); <.001	0.85 (0.65 to 1.12);.25		1.07 (0.75 to 1.51);.71	0.48 (0.26 to 0.90);.02	NR
Munne et al (2020)[12]						
N	NR	587	587[c]	587	587	NR
PGS, %		89.4	50.0	50.0	9.9	
Control, %		91.7	45.7	45.7	9.6	
p-value		NR	.3177	.3177	.8979	
Yan et al (2021)[19]				Live Birth Rate		
N	NR	1061	993[d]	964	118	24
PGS, %		83.3	79.0	77.2	8.7	1.0
Control, %		91.7	84.8	81.8	12.6	3.0
Rate ratio (95% CI)		0.91 (0.87 to 0.95)	0.93 (0.88 to 0.98)	0.94 (0.89 to 1.00)	0.69 (0.49 to 0.98)	0.33 (0.13 to 0.83)

CI: confidence interval; NR: not reported; OR: odds ratio; PGS: preimplantation genetic screening; RD: risk difference; RR: relative risk; TE: treatment effect; Wk: week.
[a] Analysis performed per embryo transferred.
[b] Analysis performed per pregnancy.
[c] Ongoing pregnancy at 20 weeks' gestation
[d] Ongoing pregnancy at 11 weeks' gestation

Tables 4 and 5 display notable limitations identified in each study.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Yang et al (2012)[16]			2. Only single embryos transferred in control	1. No delivery or postdelivery outcomes 5, 6. No discussion of clinically important difference	1,2. No follow-up of delivery or postdelivery outcomes
Forman et al (2013)[17]				1. No delivery or postdelivery outcomes 6. No justification for 20% noninferiority margin	1,2. No follow-up of delivery or postdelivery outcomes
Scott et al (2013)[18]				1. Few delivery or postdelivery outcomes 6. No justification for 20% clinically important difference	1,2. No follow-up of postdelivery outcomes
Rubio et al (2017)[10]		1. Not clear how many embryos were transferred	1. Not clear how many embryos were transferred	1. Few delivery or postdelivery outcomes 6. No justification for 15% clinically important difference	1,2. No follow-up of postdelivery outcomes
Verpoest et al (2018)[11]				1. Few delivery or postdelivery outcomes	1,2. No follow-up of postdelivery outcomes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Munne et al (2019)[12]	4. Good prognosis patients	4. More embryos of poor quality were biopsied and vitrified because of study participation that otherwise may have been discarded in standard clinic practice		1. Few delivery or postdelivery outcomes; no discussion of clinical importance of 20-week timepoint.	
Yan et al (2021)[19]	4. Good prognosis patients				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Yang et al (2012)[16]	3. Allocation concealment not described		1. Registration not described	5,6. No ITT analysis reported; patients not completing intervention were excluded (1 in PGS, 8 in control)	1. No power calculations described, "pilot study"	4. Treatment effect estimate not provided
Forman et al (2013)[17]		1. Blinding not possible because different no. of embryos implanted in 2 treatment groups			3. Noninferiority margin of 20% may not exclude clinically important differences	
Scott et al (2013)[18]		1. Blinding not mentioned but perhaps not possible because transfer occurred on different days			3. Not clear how the clinically important difference was determined	2. Multiple embryos per patient analyzed as independent

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Rubio et al (2017)[10]	3. Allocation concealment not described	1. Blinding not mentioned		6. ITT analysis not reported for most outcomes, patients were excluded for many reasons (38 in PGS, 35 in control)	3. Not clear how the clinically important difference was determined	
Verpoest et al (2018)[11]	3. Allocation concealment not described	2. Not blinded outcome assessment				
Munne et al (2019)[12]					3. Magnitude of difference that power calculation was based on was unspecified; targeted sample size of 300 transfers in each arm was not achieved	
Yan et al (2021)[19]	3. Allocation concealment not described	1. Blinding not mentioned				

ITT: intention to treat; PGS: preimplantation genetic screening.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Long-Term Outcomes of Preimplantation Genetic Screening

Several RCTs have reported long-term outcomes after preimplantation genetic screening. Beukers et al (2013) reported morphologic abnormalities in surviving children at 2 years.[22] Women included in the trial were 35 to 41 years of age scheduled for IVF or intracytoplasmic sperm injection treatment. Data were available on 50 children born after preimplantation genetic screening and 72 children born without preimplantation genetic screening. Fourteen (28%) of 50 children in the preimplantation genetic screening group and 25 (35%) of 72 children in the non-screening group had at least 1 major abnormality; the between-group difference was not statistically significant (p=.43). Skin abnormalities (e.g., capillary hemangioma, hemangioma plana) were the most common, affecting 5 children after preimplantation genetic screening and 10 children in the non-screening group. In a control group of 66 age-matched children born without assisted reproduction, 20 (30%) children had at least 1 major abnormality.

Schendelaar et al (2013) reported on outcomes when the children were 4 years old.[23] Women included in the trial were ages 35 to 41 years. Data were available for 49 children (31 singletons, 9 sets of twins) born after IVF with preimplantation genetic screening and 64 children (42 singletons, 11 sets of twins) born after IVF without preimplantation genetic screening. The primary outcome was the child's neurologic condition, as assessed by the fluency of motor behavior. The fluency score ranged from 0 to 15, as measured using a subscale of the Neurological Optimality Score. In the sample as a whole, and among singletons, the fluency score did not differ among children in the preimplantation genetic screening and the non-screening groups. However, among twins, the fluency score was significantly lower among those in the preimplantation screening group (mean score, 10.6; 95% CI, 9.8 to 11.3) and non-screening group (mean score, 12.3; 95% CI, 11.5 to 13.1). Cognitive development, as measured by intelligence quotient (IQ) score, and behavioral development, as measured by the total problem score, were similar between groups.

Section Summary: Preimplantation Genetic Screening

Randomized controlled trials and meta-analyses are available. A meta-analysis of preimplantation genetic screening using FISH-based technology found a significantly lower live birth rate after preimplantation genetic screening compared with controls in women of advanced maternal age, and there was no significant between-group difference in good prognosis patients. A meta-analysis in women of advanced maternal age undergoing preimplantation genetic screening including both FISH-based technology and comprehensive chromosomal screening did not find an overall improvement in live birth rates, but when analysis was limited to those trials employing comprehensive chromosomal screening, improved live birth rates were found. Similarly, a meta-analysis limited to comprehensive chromosomal screening found improved outcomes in women over 35 years of age, but there was no difference in live birth rates with preimplantation genetic testing in the general population. Randomized controlled trials assessing newer methods found higher implantation rates with preimplantation genetic screening than with standard care. Randomized controlled trials evaluating newer preimplantation genetic screening methods tended to include good prognosis patients, and results might not be generalizable to other populations. Two of these RCTs included women of advanced maternal age. Moreover, individual RCTs on newer preimplantation genetic screening methods had potential biases (e.g., lack of blinding, choice of noninferiority margin, imprecision). Several RCTs have been completed but have not yet been published, so publication bias cannot be excluded. Well-conducted RCTs evaluating preimplantation genetic screening in a target population (e.g., women of advanced maternal age) are needed before conclusions can be drawn about the impact on the net health benefit.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2020, the American College of Obstetricians and Gynecologists (ACOG) issued Committee Opinion #799 on Preimplantation Genetic Testing.[24] Recommendations are as follows:

- "Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic (known as PGT-M) is targeted to single gene disorders. 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."

The ACOG (2015, reaffirmed 2017) issued an opinion that recommends "[p]atients with established causative mutations for a genetic condition who are undergoing in vitro fertilization and desire prenatal genetic testing should be offered the testing, either preimplantation or once pregnancy is established."[25]

American Society for Reproductive Medicine

In 2013, the American Society for Reproductive Medicine (ASRM) published an opinion on the use of preimplantation genetic diagnosis for serious adult-onset conditions.[26] This opinion was updated and replaced in 2018.[27] The main points from the 2018 update included:
- "Preimplantation genetic testing for monogenic disease (PGT-M) 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 are perceived to be significantly burdensome.
- For conditions that are less serious or of lower penetrance, PGT-M for adult-onset conditions is ethically acceptable as a matter of reproductive liberty."

The opinion also stated that physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on the developing fetus and that experienced genetic counselors should be involved in the decision process.

In 2018, the ASRM issued an opinion on the use of preimplantation genetic testing for aneuploidy which was informed by a literature search for relevant trials. The committee concluded that "The value of preimplantation genetic testing for aneuploidy as a universal screening test for all in vitro fertilization (IVF) patients has yet to be determined."[28] This opinion was updated in 2024, and states that "the value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between PGT-A and conventional in vitro fertilization".[29]

In 2020, the ASRM issued an opinion on the clinical management of mosaic results from preimplantation genetic testing for aneuploidy of blastocytes.[30] This opinion was updated in 2023, and states that "the value of preimplantation genetic testing for aneuploidy (PGT-A) as a universal screening test for all patients undergoing IVF has not been established…[and] it is unclear whether [PGT-A results] can be used to predict prenatal and postnatal risks accurately".[31]

In 2023, the ASRM issued an opinion on indication and clinical management preimplantation genetic testing for monogenic conditions.[32]
Recommendations are as follows:
- "Preimplantation genetic testing for monogenic conditions should be offered if a significant reproductive risk is identified. Acceptance of PGT-M by patients should be optional."

- "Preimplantation genetic testing should not be offered for autosomal recessive carrier status without manifestations of symptoms, combination of variants not associated with disease, pseudodeficiency alleles, or somatic-only variants."
- "Patients should have genetic counseling about the condition and all reproductive options before PGT-M is performed."
- "Patients may also benefit from genetic counseling about PGT-M results, particularly when making embryo transfer decisions."
- "Given technical limitations that may result in embryo misdiagnosis, prenatal testing should be offered for pregnancies conceived using PGT-M to confirm the embryo testing results and screen for other fetal anomalies unrelated to the indication for PGT-M."
- "Although PGT laboratory genetic counselors support providers and patients in the PGT-M process, IVF clinics should consider employing genetic counselors to result in smoother case management, more efficient workflows, and improved patient experiences."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02941965	Preimplantation Genetic Screening in Patients With Male Factor Infertility	450	Jun 2023 (unknown status)
NCT05009745	Preimplantation Genetic Testing for Aneuploidy (PGT-A) in in Vitro Fertilisation (IVF) Treatment: Pilot Phase of a Randomised Controlled Trial	100	Feb 2023 (unknown status)
NCT06887881	Clinical Use of Preimplantation DNA Methylation Screening (PIMS) and Preimplantation Genetics Screening (PGT-A) in Infertile PCOS Patients-A Multicenter, Prospective Randomized Non-inferior Clinical Trial	766	Dec 2028

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - Family history if applicable
  - How test result will impact clinical decision making
- Lab results documenting one/both partners carrier status or genetic disorder
- Provider order for genetic test
- Name and description of genetic test

- CPT codes billed for the particular genetic test

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
	0552U	Reproductive medicine (preimplantation genetic assessment), analysis for known genetic disorders from trophectoderm biopsy, linkage analysis of disease causing locus, and when possible, targeted mutation analysis for known familial variant, reported as low-risk or high-risk for familial genetic disorder
	0553U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, and a mitochondrial DNA score, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, or mosaic, per embryo tested ***(Preimplantation Genetic Testing (PGT) for aneuploidy, ploidy, and additional quality controls by Igenomix USA)***
	0554U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from trophectoderm biopsy for aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal (euploidy), monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested ***(Smart PGT-SR, Igenomix®, Part of Vitrolife Group™, Thermo Fisher Scientific)***
	0555U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using DNA genomic sequence analysis from embryonic trophectoderm for structural rearrangements, aneuploidy, ploidy, a mitochondrial DNA score, and embryo quality control, results reported as normal/balanced (euploidy/balanced), unbalanced structural rearrangement, monosomy, trisomy, segmental aneuploidy, triploid, haploid, or mosaic, with quality control results reported as contamination detected or inconsistent cohort when applicable, per embryo tested ***(Smart PGT-SR Plus, Igenomix®, Part of Vitrolife Group™, Thermo Fisher Scientific)***

Type	Code	Description
	81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis. (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81173	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
	81174	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
	81177	ATN1 (atrophin 1) (e.g., dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81178	ATXN1 (ataxin 1) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81179	ATXN2 (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81180	*ATXN3 (ataxin 3) (e.g., spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles*
	81181	*ATXN7 (ataxin 7) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles*
	81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81183	ATXN10 (ataxin 10) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; full gene sequence
	81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; known familial variant
	81188	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles

Type	Code	Description
	81189	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; full gene sequence
	81190	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; known familial variant(s)
	81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
	81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81209	BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis, 2281del6ins7 variant
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)
	81221	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants
	81222	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants
	81223	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81234	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
	81239	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; characterization of alleles (e.g., expanded size)
	81242	FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A>T)
	81243	FMR1 (fragile X messenger ribonucleoprotein 1) (e.g., fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81247	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; common variant(s) (e.g., A, A-)
	81248	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; known familial variant(s)
	81249	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; full gene sequence
	81251	GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G>A)

Type	Code	Description
	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S)
	81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P)
	81271	HTT (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
	81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
	81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
	81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence
	81289	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; known familial variant(s)
	81290	MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A>G, del6.4kb)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81302	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
	81303	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant
	81304	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; duplication/deletion variants
	81312	PABPN1 (poly[A] binding protein nuclear 1) (e.g., oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

Type	Code	Description
	81320	PLCG2 (phospholipase C gamma 2) (e.g., chronic lymphocytic leukemia) gene analysis, common variants (e.g., R665W, S707F, L845F)
	81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
	81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
	81333	TGFBI (transforming growth factor beta-induced) (e.g., corneal dystrophy) gene analysis, common variants (e.g., R124H, R124C, R124L, R555W, R555Q)
	81336	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence
	81337	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s)
	81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
	81351	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (e.g., 4 oncology)
	81353	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; known familial variant
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

Type	Code	Description
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81479	Unlisted molecular pathology procedure
	88271	Molecular cytogenetics; DNA probe, each (e.g., FISH)
	88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (e.g., for derivatives and markers)
	88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (e.g., for microdeletions)
	88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
	88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
	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
	96041	Medical genetics and genetic counseling services, each 30 minutes of total time provided by the genetic counselor on the date of the encounter
HCPCS	S0265	Genetic counseling, under physician supervision, each 15 minutes

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section

51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

Below is an excerpt of the language taken from California Children's Services Numbered Letter 05-1020.*

*Department of Healthcare Services Numbered Letter 05-1020. Accessed April 21, 2026, from https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf

Policy

A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
B. The CCS Program and GHPP may provide coverage for an investigational service if:
    1. It is approved by the FDA under any Investigational New Drug (IND) Application; or
    2. It is authorized for use under the State of California's Right to Try Act; and
    3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;
C. Additional criteria that will be considered in the adjudication process include:
    1. Conventional therapy will not adequately treat the intended patient's condition;
    2. Conventional therapy will not prevent progressive disability or premature death;
    3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
    4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
    5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
    6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) § 1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into

consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.