MEDICAL POLICY

POLICY TITLE	PREIMPLANTATION GENETIC TESTING
POLICY NUMBER	MP-7.009

Effective Date:	7/1/2023

I. POLICY

Preimplantation genetic *diagnosis* (PGD) testing 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 following criteria:

For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:

- Both partners are known carriers of a single-gene autosomal recessive disorder;
- One partner is a known carrier of a single-gene autosomal recessive disorder, and the partners have one offspring that has been diagnosed with that recessive disorder;
- One partner is a known carrier of a single-gene autosomal dominant disorder;
- One partner is a known carrier of a single X-linked disorder; **OR**

For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality such as for a:

- Parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic *diagnosis* as an adjunct to IVF is considered **investigational** in patients or couples who are undergoing IVF in all situations other than those specified above. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Preimplantation genetic *screening* (PGS) as an adjunct to IVF is considered **investigational** in patients or couples who are undergoing IVF in all situations, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

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

This policy does not attempt to address the myriad ethical issues associated with preimplantation genetic testing that should be careful discussed between the treated couple and the physician.

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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 policy updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by 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	Diseased-Associated Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	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

American College of Medical Genetics and Genomics; AMP: Association of 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.

II. Product Variations

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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Preimplantation Genetic Testing

Preimplantation genetic testing describes various adjuncts to an assisted reproductive procedure 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 [PGD]) or screening (preimplantation genetic screening [PGS]). PGD 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. PGS 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 PGD when testing for a number of possible abnormalities in the absence of a known disorder).

Biopsy

Biopsy for PGD 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 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 (e.g., blastomeres). Sampling involves aspiration of one 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. FISH 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 are 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 PGD 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 a specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGD is used to deselect male embryos, half of which would be affected. PGD 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 PGD 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 PGD. In this setting, PGD 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. PGD 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, PGS has been explored as a technique to deselect aneuploid oocytes in older women and is also known as PGD for aneuploidy screening. Analysis of extruded polar bodies from the oocyte or no blastomeres at day three of embryo development using FISH was initially used to detect aneuploidy (PGS version 1). A limitation of FISH is that analysis is restricted to a number of proteins. More recently, newer PGS methods have been developed (version 2). 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, PGS has been proposed for women with repeated implantation failures.

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.

IV. RATIONALE

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Summary of Evidence

For individuals who have an identified elevated risk of a genetic disorder undergoing IVF who receive PGD, 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 PGD 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 PGS, the evidence includes randomized controlled trials (RCTs) and meta-analyses.

Relevant outcomes are health status measures and treatment-related morbidity. RCTs and meta-analyses of RCTs on initial PGS methods (e.g., fluorescent in situ hybridization) have found lower or similar ongoing pregnancy and live birth rates compared with IVF without PGS. There are fewer RCTs on newer PGS methods, and findings are mixed. Recent meta-analyses of newer methods have found some benefit in subgroups of patients (eg, advanced maternal age); however, the evidence is limited, and larger trials specific to these patient populations are needed.Well-conducted RCTs evaluating PGS 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 the effects of the technology on health outcomes.

V. DEFINITIONS

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ANEUPLOIDY is a condition of having an abnormal number of chromosomes for the species indicated.

ASSISTED FERTILIZATION is also referred to as assisted reproduction technology (ART). Refers to the process of aiding or supporting the union of the female egg and the male sperm to achieve conception, including artificial insemination (AI), in vitro fertilization (IVF), gamete intra-fallopian transfer (GIFT), and zygote intra-fallopian transfer (ZIFT).

CHORIONIC VILLUS are the vascular (blood-vessel like) projections from the chorion, which form the fetal portion of the placenta.

DNA is a large nucleic acid molecule, found principally in the chromosomes of the nucleus of a cell that is the carrier of genetic information.

IN VITRO FERTILIZATION-EMBRYO TRANSFER (IVF-ET) is a method of fertilizing human ova outside the body by collecting the mature ova and placing them in a dish with a sample of sperm. After an incubation period of forty-eight hours to seventy-two hours, the fertilized ova are injected into the uterus through the cervix.

OOCYTE refers to the early or primitive ovum (egg cell) before it has developed completely.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any

medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Not medically necessary; therefore not covered

Procedure Codes								
0253U	0254U	0396U						

Covered when medically necessary:

Procedure Codes								
88271	88272	88273	88274	88275	89290	89291		

Additional CPT codes will be required for the genetic analysis. The CPT codes used will vary according to the test and technique used to perform the genetic analysis.

ICD-10-CM Diagnosis Code	Description
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.438	Encounter for other genetic testing of female for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z31.448	Encounter for other genetic testing of male for procreative management
Z31.49	Encounter for other procreative investigation and testing

IX. REFERENCES

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1. *Treff NR, Fedick A, Tao X, et al. Evaluation of targeted next-generation sequencing-based preimplantation genetic diagnosis of monogenic disease. Fertil Steril. Apr 2013;99(5):1377-1384 e1376. PMID 23312231.*
2. *Martin J, Cervero A, Mir P, et al. The impact of next-generation sequencing technology on preimplantation genetic diagnosis and screening. Fertil Steril. Mar 15 2013;99(4):1054-1061 e1053. PMID 23499002.*

3. *Iews M, Tan J, Taskin O, et al. Bedaiwy MA. Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. Reprod Biomed Online. 2018 Jun;36(6):677-685. PubMed PMID: 29627226.*
4. *Hasson J, Limoni D, Malcov M, et al. Obstetric and neonatal outcomes of pregnancies conceived after preimplantation genetic diagnosis: cohort study and meta-analysis. Reprod Biomed Online. Aug 2017;35(2):208- 218. PMID 28576301.*
5. *Kato K, Aoyama N, Kawasaki N, et al. Reproductive outcomes following preimplantation genetic diagnosis using fluorescence in situ hybridization for 52 translocation carrier couples with a history of recurrent pregnancy loss. J Hum Genet. Aug 2016;61(8):687-692. PMID 27193217.*
6. *Chow JF, Yeung WS, Lee VC, et al. Experience of more than 100 preimplantation genetic diagnosis cycles for monogenetic diseases using whole genome amplification and linkage analysis in a single centre. Hong Kong Med J. Aug 2015;21(4):299-303. PMID 26044869.*
7. *Scriven PN, Flinter FA, Khalaf Y, et al. Benefits and drawbacks of preimplantation genetic diagnosis (PGD) for reciprocal translocations: lessons from a prospective cohort study. Eur J Hum Genet. Oct 2013;21(10):1035- 1041. PMID 23386032.*
8. *Keymolen K, Staessen C, Verpoest W, et al. Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: clinical outcome until delivery of 312 cycles. Eur J Hum Genet. Apr 2012;20(4):376- 380. PMID 22071893.*
9. *Strom CM, Strom S, Levine E, et al. Obstetric outcomes in 102 pregnancies after preimplantation genetic diagnosis. Am J Obstet Gynecol. Jun 2000;182(6):1629-1632. PMID 10871489.*
10. *Mastenbroek S, Twisk M, van der Veen F, et al. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. Hum Reprod Update. Jul-Aug 2011;17(4):454-466. PMID 21531751.*
11. *Dahdouh EM, Balayla J, Garcia-Velasco JA. Impact of blastocyst biopsy and comprehensive chromosome screening technology on preimplantation genetic screening: a systematic review of randomized controlled trials. Reprod Biomed Online. Mar 2015;30(3):281-289. PMID 25599824.*
12. *Dahdouh EM, Balayla J, Garcia-Velasco JA. Comprehensive chromosome screening improves embryo selection: a meta-analysis. Fertil Steril. Dec 2015;104(6):1503-1512. PMID 26385405.*
13. *Chen M, Wei S, Hu J, et al. Can comprehensive chromosome screening technology improve IVF/ICSI outcomes? a meta-analysis. PLoS One. Oct 15 2015;10(10):e0140779. PMID 26470028.*
14. *Lee E, Illingworth P, Wilton L, et al. The clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A): systematic review. Hum Reprod. Feb 2015;30(2):473-483. PMID 25432917.*
15. *Natsuaki MN, Dimler LM. Pregnancy and child developmental outcomes after preimplantation genetic screening: a meta-analytic and systematic review. World J Pediatr. 2018 Dec;14(6):555-569. PMID: 30066049.*
16. *Yang Z, Liu J, Collins GS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF*

patients: results from a randomized pilot study. Mol Cytogenet. May 02 2012;5(1):24. PMID 22551456.

17. *Forman EJ, Hong KH, Ferry KM, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril. Jul 2013;100(1):100-107 e101. PMID 23548942.*
18. *Scott RT, Jr., Upham KM, Forman EJ, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril. Sep 2013;100(3):697-703. PMID 23731996.*
19. *Verpoest W, Staessen C, Bossuyt PM, et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. Hum Reprod. 2018 Sep 1;33(9):1767-1776. PMID: 30085138.*
20. *Rubio C, Bellver J, Rodrigo L, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril. May 2017;107(5):1122-1129. PMID 28433371.*
21. *Beukers F, van der Heide M, Middelburg KJ, et al. Morphologic abnormalities in 2-year-old children born after in vitro fertilization/intracytoplasmic sperm injection with preimplantation genetic screening: follow-up of a randomized controlled trial. Fertil Steril. Feb 2013;99(2):408-413. PMID 23127590.*
22. *Schendelaar P, Middelburg KJ, Bos AF, et al. The effect of preimplantation genetic screening on neurological, cognitive and behavioural development in 4-year-old children: follow-up of a RCT. Hum Reprod. Jun 2013;28(6):1508-1518. PMID 23535872.*
23. *Ethics Committee of the American Society for Reproductive Medicine. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril. Jul 2013;100(1):54-57. PMID 23477677.*
24. *Committee on Genetics. Committee opinion no. 643: identification and referral of maternal genetic conditions in pregnancy. The American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015;126(4):e49-e51. PMID 26393459.*
25. *ACOG Committee Opinion No. 430: preimplantation genetic screening for aneuploidy. Obstet Gynecol. Mar 2009, reaffirmed 2014;113(3):766-767. PMID 19300349.*
26. *Cornelisse S, Zagers M, Kostova E, et al. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. Cochrane Database Syst Rev. Sep 08 2020; 9: CD005291. PMID 32898291*
27. *Munne S, Kaplan B, Frattarelli JL, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril. Dec 2019; 112(6): 1071-1079.e7. PMID 31551155*
28. *Amato P, Brzyski R, Braverman A, et al. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril. Jul 2013; 100(1): 54-7. PMID 23477677*
29. *Penzias A, Bendikson K, Butts S, et al. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. Mar 2018; 109(3): 429-436. PMID 29566854*
30. *Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Clinical management of mosaic results*

from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. Fertil Steril. Aug 2020; 114(2): 246-254. PMID 32741460

31. *Preimplantation Genetic Testing: ACOG Committee Opinion Summary, Number 799. Obstet Gynecol. Mar 2020; 135(3): 752-753. PMID 32080047*
32. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 4.02.05 Preimplantation Genetic Testing. September 2022.*

Other:

Taber's Cyclopedic Medical Dictionary, 20th edition

X. POLICY HISTORY

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MP 7.009	**4/22/20: Consensus Review.** Policy statement unchanged. References checked and Updated. FEP variation updated. Coding reviewed with no changes.
	6/14/21 Admin Update. Added new codes 0253U and 0254U (both not medically necessary); effective July 1, 2021.
	10/15/2021 Consensus Review. No change to policy statement. FEP language revised. Background and Rationale updated. References added**.**
	12/29/2022 Consensus Review. No change to policy statement. Updated background, rationale. Coding reviewed, no changes.
	6/15/2023 Administrative update. CPT code 0396U added, Effective 7/1/2023

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