

Approval and implementation dates for specific health plans may vary. Please consult the applicable health plan for more details.

## Clinical Appropriateness Guidelines

# Genetic Testing

## Appropriate Use Criteria: Carrier Screening in the Reproductive Setting

**Proprietary**

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## Description and Application of the Guidelines

The Carelon Clinical Appropriateness Guidelines (hereinafter “the Carelon Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. The Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To address patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The Carelon guideline development process complies with applicable accreditation and legal standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Resources reviewed include widely used treatment guidelines, randomized controlled trials or prospective cohort studies, and large systematic reviews or meta-analyses. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website. Copies of the Guidelines are also available upon oral or written request. Additional details, such as summaries of evidence, a list of the sources of evidence, and an explanation of the rationale that supports the adoption of the Guidelines, are included in each guideline document.

Although the Guidelines are publicly available, Carelon considers the Guidelines to be important, proprietary information of Carelon, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of Carelon.

Carelon applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The Carelon Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines, and in the case of reviews for Medicare Advantage Plans, the Guidelines are only applied where there are not fully established CMS criteria. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines. Use of an FDA approved or conditionally approved product does not constitute medical necessity or guarantee reimbursement by the respective health plan.

The Guidelines may also be used by the health plan or by Carelon for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

# General Clinical Guideline

## Clinical Appropriateness Framework

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Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention is likely to outweigh any potential harms, including from delay or decreased access to services that may result (net benefit).
- Widely used treatment guidelines and/or current clinical literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- There exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

Providers may be required to submit clinical documentation in support of a request for services. Such documentation must a) accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the ordering provider's clinical intent.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would justify a finding of clinical appropriateness. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account to the extent permitted by law.

Genetic tests not specifically mentioned in the guidelines are considered not medically necessary.

## Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

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Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

## Repeat Diagnostic Intervention

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In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues

- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

## **Repeat Therapeutic Intervention**

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In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered. Requests for ongoing services may depend on completion of previously authorized services in situations where a patient's response to authorized services is relevant to a determination of clinical appropriateness.

# Carrier Screening in the Reproductive Setting

## Description and Scope

Genetic carrier screening in the reproductive setting applies to individuals in the preconception setting, individuals who are currently pregnant, and reproductive partners of individuals who are currently pregnant. These tests are performed on asymptomatic individuals to identify future pregnancies or current pregnancies that are at increased risk for autosomal recessive or X-linked single gene disorders.

This testing is generally performed on individuals who have not been diagnosed with, and do not show clinical characteristics of, the condition being evaluated.

*For preimplantation genetic testing and diagnostic prenatal testing, see the Carelon Guidelines [Genetic Testing for Inherited Conditions](#).*

*For non-reproductive carrier and diagnostic testing, see the Carelon Guidelines [Genetic Testing for Inherited Conditions](#).*

## General Recommendations

### Genetic counseling

The approach chosen for any reproductive carrier screening program should involve shared decision-making between the patient and the clinician. Counseling is encouraged prior to any reproductive carrier screening that involves genetic testing and should include **ALL** of the following components:

- Interpretation of family and medical histories to provide a risk assessment for disease occurrence or recurrence
- Education about inheritance patterns, disease severity of conditions being screened for, and the potential need for prenatal diagnosis for confirmation of an affected fetus should the couple be found to be both carriers of the same condition
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
- Counseling for the psychological aspects of genetic testing
- Counseling for carrier screening should include the following details:
  - Positive/carrier results are common and will not usually have an impact on one's own health
  - Carrier screening of the individual's partner is recommended if the individual is found to be a carrier of an autosomal recessive condition
  - Carrier screening may rarely uncover incidental findings, such as a possible diagnosis and/or personal health risks
  - A negative result reduces, but does not eliminate carrier risk

*Note: Post-test counseling should be performed for any at-risk individuals/couples.*

### Rationale

It should be stressed that carrier screening is a screening modality, as opposed to a diagnostic one. Additionally, the approach chosen for any genetic screening technique should involve shared decision-making between the patient and the clinical team. Like any other genetic screening test, carrier screening is a process that involves risk that accompanies its potential benefits and, therefore, the clinical team and the prospective parents should consider the balance of risks and potential benefits before screening is pursued through informed consent. Furthermore, the clinical utility of a genetic screening test must be considered along with its psychological and sociological implications.<sup>1</sup> Counseling, either by a genetic counselor and/or team clinician, provides a patient-centered approach to the care of individuals who are undergoing a genetic screening test.<sup>2</sup>

It is also recognized that the accessibility to genetic counselors is limited by available resources as well as other social determinants of health. Therefore, as it relates to screening, the importance should be placed on counseling in a general sense, such as informed consent, as noted above.<sup>3</sup>

As with any genetic test, whether for screening or diagnosis, genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information.<sup>4</sup> The clinical team is tasked with accurately interpreting and communicating information about test validity and the reliability of test results, as well as the probability for individual patient benefit.<sup>4, 5</sup> Uncovering incidental findings and being overwhelmed with information are important possible consequences to genetic testing, particularly among vulnerable patient subgroups.<sup>6</sup> Counseling is an invaluable resource for patients undergoing genetic screening testing, but there are practical limitations because of the scarcity of resources relative to the current need, as noted above.

## Clinical Indications

### General Requirements

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#### Repeat carrier screening

Carrier screening is limited to adults and may be performed only once per lifetime for a given condition.

#### Standard carrier screening

##### Cystic fibrosis and spinal muscular atrophy

Standard screening for cystic fibrosis (CFTR testing) and spinal muscular atrophy (SMN1 testing) using accepted gene variant sets is considered **medically necessary** in the following scenarios:

- All pregnant individuals
- An individual considering pregnancy

##### Hemoglobinopathies

Standard screening for hemoglobinopathies (HBA1/HBA2 and HBB testing) using hemoglobin electrophoresis or molecular genetic testing is considered **medically necessary** in the following scenarios **IF** no prior testing results (hemoglobin electrophoresis and/or HBA1/HBA2 and HBB gene analysis) are available for interpretation:

- All pregnant individuals
- An individual considering pregnancy

#### Expanded carrier screening

Multigene carrier screening (i.e., multigene testing) is considered **medically necessary** when **ALL** of the following criteria are met:

- **ONE** or more of the following apply:
  - One or both individuals have ancestry (e.g., Ashkenazi Jewish, Finnish, French Canadian, among others) known to be at increased risk for certain conditions, other than cystic fibrosis, spinal muscular atrophy, and hemoglobinopathies
  - One or both individuals do not have access to a biological family history due to reasons such as adoption or use of a reproductive donor as documented in the member's medical record
  - The individual and their reproductive partner are known or suspected to be consanguineous as documented in the member's medical record
- The conditions on the multigene panel have at least a 1 in 100 carrier frequency\*
- The genetic disorders being evaluated have gene-disease clinical validity **AND** pathogenic variants in the genes are associated with significant morbidity and/or mortality in affected individuals

- The test has sufficiently high sensitivity and specificity to guide clinical decision making
- Knowledge of the pathogenic variant(s) may be used for management of either the pregnancy or the potentially affected fetus or child, or for family planning

**\*Note:**

*Conditions on multigene panels can have carrier frequencies less than 1 in 100 for a consanguineous partnership.*

## Exclusions

The following tests and clinical scenarios are considered **not medically necessary**:

- Carrier screening for autosomal dominant conditions
- Carrier screening for conditions known to have adult-onset
- Cell-free DNA screening for single gene disorders, microdeletions, or other indications not otherwise specified
- Variants with high allele frequencies and low penetrance of a phenotype (e.g., methylene tetrahydrofolate reductase variants)
- Whole exome or whole genome assays for the purpose of carrier screening
- Molecular screening for conditions where nonmolecular screening techniques can be used (e.g., hereditary hemochromatosis has low penetrance when molecular variants are identified)

## Condition-specific Requirements

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### Carrier testing based on family history

Condition-specific carrier testing is considered **medically necessary** when **ANY** of the following criteria are met:

- The individual has a previously affected child with the genetic condition being evaluated
- Either partner has a first-, second-, or third-degree relative who is affected with the genetic condition being evaluated
- The reproductive partner of the individual being tested has a pathogenic variant in the gene associated with the condition being evaluated

### Fragile X syndrome carrier testing

Fragile X premutation carrier testing is considered **medically necessary** in **EITHER** of the following scenarios:

- Women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome who are pregnant or considering pregnancy
- Women with unexplained ovarian insufficiency or failure, or an elevated follicle-stimulating hormone (FSH) level prior to age 40

## Background

Preconception or prenatal genetic screening of prospective parents to detect carriers of specific inherited recessive diseases is part of routine obstetrical practice. Carrier screening should ideally be offered during the preconception period because it allows for the most reproductive options for people and the most time to make decisions, compared with the prenatal period.<sup>7</sup> Longstanding recommendations by professional organizations have been to screen each individual for cystic fibrosis (CFTR gene), spinal muscular atrophy (SMN1), and a limited number of individual diseases based on self-reported ancestry associated with carrier frequencies of approximately 1 in 100 or higher.<sup>8</sup> For example, Cajun or French-Canadian ancestry would warrant additional screening for Tay-Sachs disease (HEXA) and other conditions. Ashkenazi Jewish ancestry would



warrant additional screening for Tay-Sachs disease (HEXA), Canavan disease (ASPA), Gaucher disease (GBA) among other conditions.<sup>9</sup> The 1 in 100 carrier frequency threshold aims to provide a balance between identifying carriers for more common conditions and minimizing anxiety associated with identifying carriers of extremely rare disorders.<sup>10</sup> The known clinical utility of carrier screening is based on a focused approach based on self-reported ancestry.<sup>11</sup> Given that approximately 1 in 66 people in the United States have a hemoglobinopathy trait, ACOG now recommends offering universal hemoglobinopathy testing to individuals planning pregnancy or at initial prenatal visits if no prior testing results are available for interpretation. Hemoglobinopathy testing may be performed using hemoglobin electrophoresis or molecular genetic testing (e.g., expanded carrier screening that includes sickle cell disease and other hemoglobinopathies).<sup>12</sup>

Targeted testing for individuals with a positive family history in first-, second-, or third-degree relatives, when cascade screening or results are not available from the affected individual(s), is important, as the a priori risk is 1/8 or 12.5% for the latter. This is significantly higher than the population-carrier risk for most autosomal recessive conditions. Identification of high-risk individuals based on family history has the potential to be a valuable strategy to maximize the potential for medical management related to reproduction. Additionally, evidence suggests that identification of family history-based risk leads to patient and provider changes in ordering and receiving genetic counseling and genetic testing.<sup>13</sup> The American College of Obstetrics and Gynecology (ACOG) Committee Opinion No. 478 (reaffirmed in 2023) states that as it relates to family history, "...history plays a critical role in assessing the risk of inherited medical conditions and single gene disorders...[and] recommends that all women receive a family history evaluation as a screening tool for inherited risk." Lastly, ACOG states that the "...family history information should be reviewed and updated regularly...[and] where appropriate, further evaluation should be considered for positive responses, with referral to genetic testing and counseling as needed."<sup>14</sup> ACOG specifically states that fragile X syndrome carrier screening should only be pursued in the context of personal and/or family history.<sup>8</sup> This statement is supported by prevalence data from a large prospective general population study that found an FMR1 premutation carrier frequency of 1 in 548 and an intermediate carrier frequency of 1 in 86.<sup>15</sup> In addition, another study reported FMR1 prevalence data in the United States indicating a 1 in 257 premutation carrier frequency in women with no known risk factors for fragile X syndrome, a 1 in 86 premutation carrier frequency in women with a family history of intellectual disability and a 1 in 57 intermediate allele carrier frequency.<sup>10</sup> These studies highlight the higher rate of premutation carriers in individuals with a family history of intellectual disability and the higher intermediate allele carrier frequency compared to the premutation carrier frequency even in women with a family history of intellectual disability.

Multiplex platforms that simultaneously assay many potentially pathogenic variants on each sample have been available since 2009, allowing rapid expanded carrier screening (ECS) for a large number of conditions. In an effort to estimate carrier rates across genes to guide construction of ancestry specific multi-gene panels or panethnic panels, Guo and colleagues leveraged an exome sequencing database (n=123,136) to estimate carrier rates across six major ancestries for 415 genes associated with severe recessive conditions. This study found that an ancestry-specific panel designed to capture genes with carrier rates >1.0% would include 5 to 28 genes, while a comparable panethnic panel would include 40 genes.<sup>16</sup> Another retrospective modeling study conducted by Haque and colleagues evaluated 346 790 expanded carrier screenings, suggesting that between 94.5 and 392.2 fetuses per 100 000 would be affected by 1 of 94 single-gene disorders, with variation depending on self-reported racial/ethnic background. The authors concluded that prospective evaluation of panethnic ECS approaches vs current professional society recommendations is warranted to understand if the results would lead to clinically meaningful differences in outcomes.<sup>9</sup> A systematic review and meta-analysis of the clinical utility of reproductive carrier screening for preconception and pregnant couples for multiple genetic conditions (3-176) found the prenatal diagnosis rate among pregnant, high-risk couples to be 0.644 (95% CI = 0.364, 0.923), the pregnancy termination rate among affected pregnancies to be 0.714 (95% CI = 0.524, 0.904), and the rate of in-vitro fertilization with preimplantation genetic testing to be 0.631 (95% CI = 0.538, 0.725). The rates of undertaking prenatal diagnosis and pregnancy termination significantly (p-values <0.05) decreased as the number of screened conditions increased.<sup>17</sup>

Since 2017 (and reaffirmed in 2023), ACOG has taken a neutral stance.<sup>7,18</sup> They do not recommend expanded carrier screening but include it among the acceptable strategies. American College of Medical Genetics and Genomics (ACMG) has previously defined standards of care for common single gene autosomal recessive conditions, i.e., cystic fibrosis and spinal muscular atrophy, and a panel of single gene autosomal recessive conditions for individuals with Ashkenazi Jewish ancestry. The ACMG Practice Resource published in 2021 described a four-tier system of autosomal recessive and X-linked conditions. They recommend offering their Tier 3 carrier screening (97 autosomal recessive and 16 X-linked conditions [including fragile X]) to all pregnant individuals and individuals planning a pregnancy as well as offering Tier 3 carrier screening for the 97 autosomal recessive conditions to their male partners.<sup>19</sup> Of note, these recommendations were issued as a practice resource, and not ACMG's more rigorous Clinical Practice Guideline that requires stronger evidence. In the Practice Resource, ACMG notes that positive predictive value (PPV) and negative predictive value (NPV) can be determined for a population by modeling or by actual measure. Furthermore, they specify that one can establish PPV on a population basis (e.g., all women of a certain age) or individually (using information that is patient-specific). In addition, the ACMG chose not to include cost efficacy or cost utility studies when making recommendations, stating that such studies use a high degree of modeling and assumptions that are at risk for systematic and random bias. In addition, National Society of Genetic Counselors (NSGC) conditionally recommends the use of ECS for all reproductive-aged individuals who desire knowledge regarding the risk of infantile or early-childhood onset disease in their offspring following informed consent, acknowledging that ECS provides the opportunity to

identify risks for a greater number of conditions compared to alternative ethnicity-based DNA screening options. They defined ECS as carrier screening for specific autosomal recessive and X-linked conditions (ten to hundreds) with onset in infancy or early childhood.<sup>20</sup> For perspective, currently in Canada where all residents have reasonable access to medically necessary healthcare, carrier testing is publicly funded for cystic fibrosis, fragile X syndrome, hemoglobinopathies and thalassemia, and spinal muscular atrophy based on indications of increased risk (e.g., personal or family history, ethnic background, clinical manifestations of the condition in the individual, or in the fetus during pregnancy). Canadians may pursue privately paid carrier screening testing if they are not at increased risk or if they wish to gain information about their carrier status for other genetic conditions.<sup>11</sup>

Overall, the use of ECS remains an area of academic and industry controversy, as prospective studies comparing current standard-of-care carrier screening with expanded carrier screening in at-risk populations are lacking. This controversial clinical topic has had considerable input from industry. In a systematic evidence review designed to identify ECS publications describing client-, provider-, and test-related outcomes, clinical uptake of ECS and impact on reproductive decision-making was found to be variable. Although genetic counselors seem to be comfortable with ECS, most other reproductive care providers seem to prefer minimal guideline or ancestry-based screening due to perceived barriers, such as time needed for ECS results disclosure and follow-up, as well as the desire to have panels set by professional society recommendations.<sup>21</sup> The controversy will likely continue until prospective clinical research is conducted evaluating how this strategy affects reproductive outcomes and indicating whether or not the potential benefits of this approach exceed the potential harms.

There are limited scenarios where multigene carrier screening panels may be considered medically necessary. One example includes couples with consanguinity. Approximately 8% of first-cousin couples are at risk of being carriers of the same AR condition<sup>22</sup> compared to a reported 1%-4% in non-consanguineous couples.<sup>23,24</sup> ACOG recommends that couples with consanguinity should be offered genetic counseling to discuss the increased risk of recessive conditions being expressed in their offspring and the limitations and benefits of carrier screening.<sup>8</sup> ACMG recommends Tier 4 screening (autosomal recessive conditions with < 1 in 200 maximum carrier frequencies) when a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer).<sup>19</sup> Some researchers recommend whole exome-based carrier screening for couples with consanguinity.<sup>25,26</sup>

Per NSGC and ACOG, prenatal testing for adult-onset conditions is not recommended if pregnancy or childhood management will not be affected. Per NSGC, in addition to potential ethical complexities, testing for adult-onset conditions “may deny a child’s future autonomy, and potential for genetic discrimination.”<sup>7</sup> Examples of such adult-onset testing include, but are not limited to, Huntington disease and Alzheimer disease—such as HTT and APOE variants, respectively. The ACMG and World Federation of Neurology consider this type of predictive testing more appropriate for adults and not recommended in pregnancies and for minors, as results will neither directly affect pregnancy nor accurately predict progression of behavioral symptoms.<sup>27</sup>

## References

1. Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;81:9.15.1-9..8.
2. Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. 2006;15(2):77-83.
3. CDC. How accessible are genetics providers and how can access be increased? 2020.
4. Borno HT, Rider JR, Gunn CM. The Ethics of Delivering Precision Medicine-Pretest Counseling and Somatic Genomic Testing. *JAMA Oncol*. 2020;6(6):815-6.
5. Patch C, Middleton A. Genetic counselling in the era of genomic medicine. *Br Med Bull*. 2018;126(1):27-36.
6. Knob AL. Principles of genetic testing and genetic counseling for renal clinicians. *Semin Nephrol*. 2010;30(4):431-7.
7. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. *Obstet Gynecol*. 2023;129(3):e35-e40.
8. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 691: Carrier Screening for Genetic Conditions. *Obstetrics & Gynecology*. 2023;129(3):e41-e55.
9. Haque IS, Lazarin GA, Kang HP, et al. Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening. *Jama*. 2016;316(7):734-42.
10. Cronister A, Teicher J, Rohlf's EM, et al. Prevalence and instability of fragile X alleles: implications for offering fragile X prenatal diagnosis. *Obstet Gynecol*. 2008;111(3):596-601.
11. Carrier Screening Programs for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2023;23(4):1-398.
12. American College of Obstetricians and Gynecologists (ACOG). Hemoglobinopathies in Pregnancy, ACOG Practice Advisory 2022.
13. Ginsburg GS, Wu RR, Orlando LA. Family health history: underused for actionable risk assessment. *Lancet*. 2019;394(10198):596-603.
14. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 478: Family history as a risk assessment tool. *Obstet Gynecol*. 2011 (2020);117(3):747-50.

15. Lévesque S, Dombrowski C, Morel ML, et al. Screening and instability of FMR1 alleles in a prospective sample of 24,449 mother-newborn pairs from the general population. *Clin Genet*. 2009;76(6):511-23.
16. Guo MH, Gregg AR. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. *Genet Med*. 2019;21(9):1940-7.
17. Wang T, Kiss D, McFadden K, et al. Clinical utility of reproductive carrier screening for preconception and pregnant couples for multiple genetic conditions: a systematic review and meta-analysis. *Expert Rev Mol Diagn*. 2023;23(5):419-29.
18. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions. *Obstet Gynecol*. 2017;129(3):597-9.
19. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(10):1793-806.
20. Sagaser KG, Malinowski J, Westerfield L, et al. Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors. *J Genet Couns*. 2023;32(3):540-57.
21. Ramdaney A, Lichten L, Propst L, et al. Expanded carrier screening in the United States: A systematic evidence review exploring client and provider experiences. *J Genet Couns*. 2022;31(4):937-48.
22. Hamamy H, Antonarakis SE, Cavalli-Sforza LL, et al. Consanguineous marriages, pearls and perils: Geneva International Consanguinity Workshop Report. *Genet Med*. 2011;13(9):841-7.
23. Arjunan A, Litwack K, Collins N, et al. Carrier screening in the era of expanding genetic technology. *Genet Med*. 2016;18(12):1214-7.
24. Bristow SL, Morris JM, Peyser A, et al. Choosing an expanded carrier screening panel: comparing two panels at a single fertility centre. *Reprod Biomed Online*. 2019;38(2):225-32.
25. Monies D, Abouelhoda M, Assoum M, et al. Lessons Learned from Large-Scale, First-Tier Clinical Exome Sequencing in a Highly Consanguineous Population. *Am J Hum Genet*. 2019;104(6):1182-201.
26. Santos CMdAd, Heller AH, Pena HB, et al. A Protocol for Preconceptional Screening of Consanguineous Couples Using Whole Exome Sequencing. *Frontiers in Genetics*. 2021;12.
27. MacLeod R, Tibben A, Frontali M, et al. Recommendations for the predictive genetic test in Huntington's disease. *Clin Genet*. 2013;83(3):221-31.

## Codes

The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

### CPT/HCPCS

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#### May Be Medically Necessary When Criteria are Met

Code	May Be Medically Necessary When Criteria are Met
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
81173	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
81174	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)

Code	May Be Medically Necessary When Criteria are Met
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81238	F9 (coagulation factor IX) (eg, hemophilia B), full gene sequence
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB2 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, 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) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81286	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence
81289	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s)
81290	MCOLN1 (mucopolipin 1) (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)

Code	May Be Medically Necessary When Criteria are Met
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 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 (eg, > 10 SNP's 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 (eg, 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)
81404	Molecular pathology procedure, Level 5 (eg, 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 (eg, 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 (eg, 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 (eg, 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)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucopolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
81479	Unlisted molecular pathology procedure
0449U	Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)
S3844	DNA analysis of the connexin 26 gene (gjb2) for susceptibility to congenital, profound deafness

### Not Medically Necessary

Code	Not Medically Necessary
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
0400U	Genesys Carrier Panel from Genesys Diagnostics Inc. Using a blood or buccal (cheek) swab specimen from a prospective parent, the test evaluates 145 genes to identify variants that may indicate the person is a carrier of a mutation that could result in a rare inherited disorder that could be passed on to a child, such as cystic fibrosis.

### ICD-10 Diagnosis

Refer to the ICD-10 CM manual

## History

Status	Review Date	Effective Date	Action
Revised	07/16/2024	03/23/2025	Independent Multispecialty Physician Panel (IMPP) review. Revised standard carrier screening (expansive – removed CBC from the list of acceptable prior testing restrictions for hemoglobinopathy screening) and expanded carrier screening (expansive – allow for multigene panels to include conditions with less than 1 in 100 carrier frequencies for consanguineous partnership, removed requirement that alternate biochemical tests not available). Updated references.
Revised	10/23/2023	06/30/2024	IMPP review. Removed preimplantation testing criteria (transferred to Genetic Testing for Inherited Conditions) and retitled guideline to Carrier Screening in the Reproductive Setting. Standard carrier screening: expanded testing to include standard hemoglobinopathy screening for all pregnant individuals or an individual considering pregnancy. Updated references.
Updated codes 03/17/2024	n/a	Unchanged	Split codes into those considered medically necessary when criteria are met (MNWCM) and not MN. Added CPT codes 81173, 81174, 81188, 81189, 81190, 81209, 81238, 81242, 81286, 81289, 0449U (MNWCM). Added HCPCS code S3844 (MNWCM). Removed CPT codes 81302, 81312, 81331, 81333, 81343, 81344. Added required language to General Clinical Guideline per new Medicare regulations.
Updated	n/a	01/01/2024	Added CPT code 0400U; Removed 0168U, 0252U, 0253U, 0254U, and 0341U. Description changes for 81171, 81172, 81243, 81244, 81406.
Revised	04/12/2023	11/05/2023	IMPP review. Expanded targeted screening to include third-degree relatives. Excluded whole exome and whole genome assays for carrier screening. Changed structure for clarity. Added references.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.