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 Prenatal Reproductive Setting and Preimplantation Genetic Testing

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Proprietary

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# Table of Contents

Description and Application of the Guidelines ........................................................................................................ 3  
General Clinical Guideline ........................................................................................................................................ 5  
  Clinical Appropriateness Framework ....................................................................................................................... 5  
  Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions ............................................................... 5  
  Repeat Diagnostic Intervention .................................................................................................................................... 5  
  Repeat Therapeutic Intervention ............................................................................................................................ 6  
Carrier Screening in the Reproductive Setting ............................................................................................................ 7  
  Description and Scope ............................................................................................................................................... 7  
  General Recommendations ........................................................................................................................................ 7  
    Genetic counseling .................................................................................................................................................. 7  
  Clinical Indications .................................................................................................................................................. 9  
  General Requirements ................................................................................................................................................ 9  
    Repeat carrier screening ....................................................................................................................................... 9  
    Standard carrier screening ................................................................................................................................... 9  
    Expanded carrier screening* ................................................................................................................................. 9  
  Condition-specific Requirements ............................................................................................................................ 10  
    Carrier testing based on family history [moved from General to Condition-specific] ............................................. 10  
    Fragile X syndrome carrier testing ...................................................................................................................... 10  
    [PGT transferred to Genetic Testing for Inherited Conditions] ............................................................................. 10  
Exclusions .................................................................................................................................................................... 11  
Background .................................................................................................................................................................. 11  
References ................................................................................................................................................................. 13  
Codes .......................................................................................................................................................................... 13  
History ........................................................................................................................................................................ 16
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. As used by Carelon, the Guidelines establish objective and evidence-based criteria for medical necessity determinations, where possible, that can be used in support of the following: . In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary (i.e., in general, shown to be effective in improving health outcomes and considered the most appropriate level of service)
- 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 advocate for addressing 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. Relevant citations are included in the References section attached to each Guideline. Carelon reviews all of its Guidelines at least annually.

Carelon makes its Guidelines publicly available on its website-twenty-four hours a day, seven days a week. Copies of the Carelon Clinical Appropriateness 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 is not fully established CMS criteria including review and approval process required of Medicare Advantage plans. If requested by a health plan, Carelon will review requests based on health plan medical policy/guidelines in lieu of the Carelon Guidelines.
Pharmaceuticals, radiotracers, or medical devices used in any of the diagnostic or therapeutic interventions listed in the Guidelines must be FDA approved or conditionally approved for the intended use. However, 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

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 Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.

- Based on the clinical evaluation, current literature, and standards of medical practice, 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) be current enough to accurately reflect the clinical situation at the time of the requested service, and b) sufficiently document the contain the elements necessary to determine compliance with guideline criteria without Carelon physician reviewers having to make assumptions or interpretations about an 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. These conversations may also take into account the extent permitted by law.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

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

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

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 on-going 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. For situations wherein ongoing services might be appropriate, requests for subsequent services may be denied until completion of the previously authorized services so that patient response to the previously authorized services can be considered.
Carrier Screening in the Prenatal Reproductive Setting and Preimplantation Genetic Testing

Description and Scope

Genetic carrier screening in the prenatal reproductive setting applies to individuals considering reproduction in the preconception setting, to those individuals who are currently pregnant, and to the reproductive partners of individuals who are currently pregnant. These tests are performed on asymptomatic adults individuals to identify future pregnancies or current pregnancies that are at increased risk for 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 tested for. Carrier screening may be performed before conception or during a pregnancy.

Testing for conditions that are present in the fetus or embryo related to a known condition in one or both of the biological parents of the fetus/embryo is also included in this guideline.

For preimplantation genetic testing and diagnostic prenatal testing, see the Genetic Testing for Inherited Conditions guideline.

For non-reproductive prenatal carrier and diagnostic testing, see the guideline Genetic Testing for Inherited Conditions guideline.

General Recommendations

Genetic counseling

The approach chosen for any prenatal reproductive carrier screening program technique should involve shared decision-making between the patient and the clinician. Genetic counseling is strongly recommended encouraged prior to any prenatal 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 the probability of disease occurrence or recurrence
- Education about inheritance patterns, genetic testing, disease management, prevention, risk reduction, and resources 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
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
• Counseling for the psychological aspects of genetic testing
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. (Burke, 2014, #1) 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. (Resta, 2006, #2)

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. (CDC, 2020, #3)

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. (Borno, 2020, #4) 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. (Borno, 2020, #4, Patch, 2018, #5) Uncovering incidental findings and being overwhelmed with information are important possible consequences to genetic testing, particularly among vulnerable patient subgroups. (Knob, 2010, #6) 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.

Genetic testing is a procedure that involves risk that accompanies its potential benefits. The clinician and the patient should consider the balance of risks and potential benefits before testing is pursued through informed consent. As with any procedure, the clinical utility of the genetic test must be considered along with its psychological and sociologic implications. (Knob, 2010, #6) Genetic counselors provide a patient-centered contribution to the care of individuals who are undergoing genetic testing. Genetic counseling is a communication process aimed at helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. Genetic counselors have advanced training in medical genetics and counseling which helps guide and support patients seeking more information about how inherited diseases and conditions might affect them or their families. This expertise is also applied to interpret genetic test results based on an individual's personal and family history. Genetic counselors are often specialized in prenatal carrier screening.

The current literature demonstrates the clinical value of genetic counselor involvement in service delivery, including improvements in clinical management and positive psychological impact along with increased patient engagement. Physicians have varying levels of knowledge on how to interpret genetic and genomic information, and often express low confidence and high uncertainty in counseling about genetic testing findings. (Gray, 2014, #7) Professional genetic counselors add unique value to the existing care team. For example, a study of the accuracy of routine prenatal genetic screening in patients referred for genetic counseling found that genetic history obtained by the referring provider was missing detail in over half, and of these approximately 40% had their clinical care changed by discovery of this information by a genetic counselor. (Gilstrop Thompson, 2020, #8)

In the past decade, there has been explosive growth in the number of genetic tests available, the number and types of companies involved in providing these tests, diversity of the business models involved, and the diverse settings where genetic tests are accessed by consumers. There is access to some kinds of testing through direct-to-consumer channels, but most of the healthcare-associated testing is from full-service commercial laboratories, for-profit specialized laboratories, or not-for-profit laboratories, such as those associated with academic medical centers. (Scheuner, 2021, #9) While laboratory business models vary widely, there is increasing interest in use of de-identified data from genetic testing for use in research and discovery and other business purposes beyond the application to individual patient care. These other uses of genetic information have partly fueled a trend for broader indications for testing and testing of larger panels of genes. Furthermore, while genetic counselors have traditionally been trained to counsel patients in healthcare settings prior to germline testing for diseases with a Mendelian inheritance pattern, their education and skills can also be readily adapted to other settings. Genetic testing services are now delivered both in person and via telehealth, and counselors may be employed not only by healthcare institutions but also by laboratories working under various distinct business models.

Genomic technologies generate large amounts of data, and this increases the potential for uncertainty in managing and adapting to this information. Clinicians are 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. (Pollard, 2019, #10) Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups. (Borno, 2020, #4) Genetic counseling is an invaluable resource for patients, but there are practical limitations because of the scarcity of genetic counselors relative to the.
current need. Clinicians are often required to
stretch their skillsets and play a role in providing basic counseling about genetic testing and will need more training and skills to do so effectively. Further research is needed regarding the use of clinical practice tools to enhance patient care and uphold the clinical and ethical ideals of medical care in this complicated realm of care delivery.

The use of genetic counseling by professionals not employed by testing laboratories is strongly recommended for a wide variety of common clinical scenarios across all realms of medicine. Genetic counseling is considered mandatory for a subset of clinical scenarios related to germline or somatic testing where the stakes are predictably high in terms of the potential medical and psychological consequences of the testing process. The specific scenarios for which genetic counseling is mandatory and the minimum expected qualifications for genetic counseling providers may vary by health plan.

**Clinical Indications**

**General Requirements**

**Repeat carrier screening**

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

**Carrier screening – standard and expanded**

**Standard carrier screening**

Cystic fibrosis and spinal muscular atrophy

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

- for **all** women who are pregnant individuals or
- a **An individual** considering pregnancy **AND and** their reproductive partners.

**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 (CBC, hemoglobin electrophoresis and/or HBA1/HBA2 and HBB gene analysis) are available for interpretation:

- All pregnant individuals
- An individual considering pregnancy **AND and** their reproductive partner

**Expanded carrier screening**

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

- **At least ONE or more** of the following apply:
  - One or both individuals **have ancestry are members of a population** (e.g., Ashkenazi Jewish, Finnish, French Canadian, Mediterranean, and Southeast Asian, among others) that is known to be at increased risk for certain conditions, other than cystic fibrosis, spinal muscular atrophy, and hemoglobinopathies (e.g., conditions that have a carrier frequency of at least 1% in 100 in that ancestry population)
  - The **individual and their reproductive couple** is **partner are known or suspected to be consanguineous**
  - 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, or other reasons
The genes included in the panel are consistent with the reason for testing.

- The genetic disorders being screened for evaluated have clearly defined gene(s)-disease clinical validity AND and pathogenic variants in the genes are associated with them significant morbidity and/or mortality in affected individuals.
- The test has sufficiently high sensitivity and specificity to guide clinical decision making.
- Alternate biochemical or other clinical tests are not available, have provided an indeterminate result, or are less accurate than genetic testing.
- The natural history of the disease is associated with significant morbidity and/or mortality in affected individuals.
- 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: Expanded carrier screening should be directed toward target genes that are associated with family history and ancestry-ethnicity. Additionally, genes included in the panel should be shown to impact patient management and health outcomes.*

**Condition-specific Requirements**

**Targeted Carrier testing based on family history**

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

**Fragile X syndrome carrier testing**

Fragile X premutation carrier screening-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.

**Preimplantation genetic testing**

Preimplantation genetic testing is considered medically necessary when the embryo(s) is at increased risk of a recognized inherited condition based on ALL of the following:

- The medical condition being tested for would result in significant morbidity and/or mortality.
- The condition is known to result from a single gene (PGT-M) abnormality, or from structural changes of a parent’s chromosome (PGT-SR).
- Biological parents meet ONE of the following criteria:
  - Both parents are known carriers of an autosomal recessive disease.
  - At least one parent is a known carrier of an autosomal dominant, sex.
Prenatal Carrier Screening in the Reproductive Setting and Preimplantation Testing linked, or mitochondrial condition.
Exclusions

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

- **Prenatal testing** for conditions known to have adult-onset including, but not limited to, genetic testing for breast cancer (e.g., BRCA gene testing)
- Cell-free DNA **screening test** 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 screening performance with nonmolecular screening techniques can be used** (e.g., hereditary hemochromatosis has low penetrance when molecular variants are identified)

Background

Genetic screening of prospective parents to detect carriers of specific inherited recessive diseases is part of routine obstetrical practice. 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 other disorders based on self-reported racial/ethnic background. Examples of conditions associated with carrier frequencies of approximately 1 in 100 or higher include, for example, individuals who are African American or of Southeast Asian, Southern European, or African descent are recommended for additional testing for hemoglobinopathies (HBA1, HBA2, HBB), Cajun or French-Canadian ancestry, and some disorders affecting African or Southeast Asian ancestry. The known clinical utility of carrier screening is based on a focused approach that considers 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 behavior, such as risk-mitigating lifestyle changes, in ordering and receiving genetic counseling, and genetic testing. (Haque, 2016, #12) The known clinical utility of carrier screening is based on a focused approach that considers 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 behavior, such as risk-mitigating lifestyle changes, in ordering and receiving genetic counseling, and genetic testing. (Haque, 2016, #12) The American College of Obstetricians and Gynecologists (ACOG) now recommends offering universal screening for hemoglobinopaties 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). (American College of Obstetricians and Gynecologists (ACOG), 2022, #13)

Targeted testing for individuals with a positive family history in first-, second-, or third-degree relatives is an important aspect of the medical management related to reproduction. Additionally, evidence suggests that identification of family history-based risk leads to patient and provider changes in behavior, such as risk-mitigating lifestyle changes, in ordering and receiving genetic counseling, and genetic testing. (Haque, 2016, #12) The American College of Obstetricians and Gynecologists (ACOG) now recommends offering universal screening for hemoglobinopathies 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). (American College of Obstetricians and Gynecologists (ACOG), 2022, #13)

ACOG specifically states that fragile X syndrome carrier screening should only be pursued in the context of personal and/or family history.

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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. (Guo, 2019, #16) 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 expanded carrier screening approaches vs current professional society recommendations is warranted to understand if the results would lead to clinically meaningful differences in outcomes. (Haque, 2016, #12) 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. (Wang, 2023, #17)

Since 2017 (and reaffirmed in 2023), ACOG has taken a neutral stance. (American College of Obstetricians and Gynecologists (ACOG), 2017, #18, American College of Obstetricians and Gynecologists (ACOG), 2023, #19) They do not recommend expanded carrier screening but include it among the acceptable strategies. Fragile X syndrome carrier screening should only be pursued in the context of personal and/or family history. Disorders selected for inclusion on panels should have a carrier frequency of 1/100 or greater. The American College of Medical Genetics and Genomics (ACMG) has previously also 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 the Ashkenazi Jewish population. ACMG Practice Resource statement published in 2021 defined autosomal recessive and X-linked conditions. They calls for an expansion of genetic-carrier screening protocols for all pregnant patients, those planning pregnancy, and their reproductive partners. 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. (Gregg, 2021, #20). Of note, these recommendations were issued as a practice resource, and not ACMG’s more rigorous Clinical Practice Guideline, that requires stronger evidence. In this Ppractice Resource, the 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 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. (Sagaser, 2023, #21) (Sagaser et al. 2023). This controversial clinical topic also has considerable input from industry. A coalition was founded by six laboratories, Myriad, Natera, Progenity, sema4, Thermo Fisher, and Invitae that have business interest in this expansion of carrier screening.

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. In a systematic evidence review 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. (Ramdaney, 2022, #22) 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.

Per the National Society of Genetic Counselors (NSGC) and ACOG, prenatal testing for adult-onset conditions is not recommended if pregnancy or childhood management will not be affected. Per the NSGC, in addition to potential ethical complexities, testing for adult-onset conditions “may deny a child’s future autonomy, and potential for genetic discrimination.” (American College of Obstetricians and Gynecologists (ACOG), 2023, #19) 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. (MacLeod, 2013, #23)
## References

3. CDC. How accessible are genetics providers and how can access be increased? 2020.

## 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

CPT® (Current Procedural Terminology) is a registered trademark of the American Medical Association (AMA). CPT® five-digit codes, nomenclature and other data are copyright by the American Medical Association. All Rights Reserved. AMA does not directly or indirectly practice medicine or dispense medical services. AMA assumes no liability for the data contained herein or not contained herein.
| 81161 | DMD (dystrophin) (eq, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed |
| 81171 | AFF2 (ALF transcription elongation factor 2 [FMR2]) (eq, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eq, expanded) alleles |
| 81172 | AFF2 (ALF transcription elongation factor 2 [FMR2]) (eq, fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (eq, expanded size and methylation status) |
| 81200 | ASPA (asparoacylase) (eq, Canavan disease) gene analysis, common variants (eq, E285A, Y231X) |
| 81205 | BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eq, maple syrup urine disease) gene analysis, common variants (eq, R183P, G276S, E422X) |
| 81220 | CFTR (cystic fibrosis transmembrane conductance regulator) (eq, cystic fibrosis) gene analysis; common variants (eq, ACMG/ACOG guidelines) |
| 81221 | CFTR (cystic fibrosis transmembrane conductance regulator) (eq, cystic fibrosis) gene analysis; known familial variants |
| 81222 | CFTR (cystic fibrosis transmembrane conductance regulator) (eq, cystic fibrosis) gene analysis; duplication/deletion variants |
| 81223 | CFTR (cystic fibrosis transmembrane conductance regulator) (eq, cystic fibrosis) gene analysis; full gene sequence |
| 81224 | CFTR (cystic fibrosis transmembrane conductance regulator) (eq, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eq, male infertility) |
| 81243 | FMR1 (fragile X messenger ribonucleoprotein 1) (eq, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eq, expanded) alleles |
| 81244 | FMR1 (fragile X messenger ribonucleoprotein 1) (eq, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eq, expanded size and promoter methylation status) |
| 81250 | G6PC (glucose-6-phosphatase, catalytic subunit) (eq, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eq, R83C, Q347X) |
| 81251 | GBA (glucosidase, beta, acid) (eq, Gaucher disease) gene analysis, common variants (eq, N370S, 84G, L444P, IVS2+1G>A) |
| 81252 | GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eq, nonsyndromic hearing loss) gene analysis; full gene sequence |
| 81253 | GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eq, nonsyndromic hearing loss) gene analysis; known familial variants |
| 81254 | GJB2 (gap junction protein, beta 6, 30kDa, connexin 30) (eq, nonsyndromic hearing loss) gene analysis, common variants (eq, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)]) |
| 81255 | HEXA (hexosaminidase A [alpha polypeptide]) (eq, Tay-Sachs disease) gene analysis, common variants (eq, 1278insTATC, 1421+1G>C, G269S) |
| 81256 | HFE (hemochromatosis) (eq, hereditary hemochromatosis) gene analysis, common variants (eq, C282Y, H63D) |
| 81257 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eq, alpha thalassemia, Hb Bart hydops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eq, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring) |
| 81258 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eq, alpha thalassemia, Hb Bart hydops fetalis syndrome, HbH disease), gene analysis; known familial variant |
| 81259 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eq, alpha thalassemia, Hb Bart hydops 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) (eq, familial dysautonomia) gene analysis, common variants (eq, 2507+6T>C, R696P) |
| 81269 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eq, alpha thalassemia, Hb Bart hydops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants |
| 81290 | MCOLN1 (mucolipin 1) (eq, Mucolipidosis, type IV) gene analysis, common variants (eq, IVS3-2A>G, del6.4kb) |
| 81291 | MTHFR (5,10-methylenetetrahydrofolate reductase) (eq, hereditary hypercoagulability) gene analysis, common variants (eq, 677T, 1298C) |
| 81302 | MECP2 (methyl CpG binding protein 2) (eq, Rett syndrome) gene analysis; full sequence analysis |
| 81303 | MECP2 (methyl CpG binding protein 2) (eq, Rett syndrome) gene analysis; known familial variant |
| 81304 | MECP2 (methyl CpG binding protein 2) (eq, Rett syndrome) gene analysis; duplication/deletion variants |
| 81312 | PABPN1 (poly[A] binding protein nuclear 1) (eq, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eq, expanded) alleles |
| 81329 | SMN1 (survival of motor neuron 1, telomeric) (eq, spinal muscular atrophy) gene analysis; dosage/deletion analysis, includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed |
| 81330 | SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eq, Niemann-Pick disease, Type A) gene analysis, common variants (eq, R496L, L302P, fsP330) |
ICD-10 Diagnosis

Refer to the ICD-10 CM manual
## History

<table>
<thead>
<tr>
<th>Status</th>
<th>Review Date</th>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised</td>
<td>10/23/2023</td>
<td>06/30/2024</td>
<td>Independent Multispecialty Physician Panel (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. Added required language per new Medicare regulations.</td>
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<tr>
<td>Updated</td>
<td>n/a</td>
<td>01/01/2024</td>
<td>Added CPT code 0400U; Removed 0168U, 0252U, 0253U, 0254U, and 0341U. Description changes for 81171, 81172, 81243, 81244, 81406.</td>
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<tr>
<td>Revised</td>
<td>04/12/2023</td>
<td>11/05/2023</td>
<td>Independent Multispecialty Physician Panel (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.</td>
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<tr>
<td>Created</td>
<td>09/21/2022</td>
<td>02/12/2023</td>
<td>IMPP review. Original effective date.</td>
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