

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 Setting and Preimplantation Genetic Testing

Proprietary

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Table of Contents

Description and Application of the Guidelines	3
General Clinical Guideline	4
Clinical Appropriateness Framework	4
Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions	4
Repeat Diagnostic Intervention	4
Repeat Therapeutic Intervention	5
Carrier Screening in the Prenatal Setting and Preimplantation Genetic Testing	6
Description and Scope	6
General Recommendations	6
Genetic counseling	6
Clinical Indications	7
General Requirements	7
Repeat carrier screening	7
Carrier screening – standard and expanded	7
Standard screening	7
Expanded screening	7
Targeted carrier testing based on family history	8
Preimplantation genetic testing	8
Condition-Specific Requirements	8
Fragile X syndrome	8
Exclusions	9
Background	9
References	10
Codes	11
History	13

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. 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 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 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. 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. 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. 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 should outweigh any potential harms that may result (net benefit).
- 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.

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 supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

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.

Carrier Screening in the Prenatal Setting and Preimplantation Genetic Testing

Description and Scope

Genetic carrier screening in the prenatal setting applies to individuals considering reproduction, to those who are currently pregnant, and to the reproductive partners of individuals who are currently pregnant. These tests are performed on asymptomatic adults to identify pregnancies at increased risk for single gene disorders.

This testing is generally performed on individuals who have not been diagnosed with, or 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 non-prenatal carrier and diagnostic testing, see the guideline for Inherited Conditions.

General Recommendations

Genetic counseling

The approach chosen for any prenatal carrier screening technique should involve shared decision-making between the patient and the clinician. Genetic counseling is strongly recommended prior to any prenatal carrier screening that involves genetic testing and should include **ALL** of the following components:

- Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence
- Education about inheritance, genetic testing, disease management, prevention, risk reduction, and resources
- Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition
- Counseling for the psychological aspects of genetic testing
- Post-test counseling for any positive screening test

Rationale

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.¹ 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.² 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.³ 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.⁴

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.⁵ 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.⁶ Uncovering incidental findings and being overwhelmed with information are important barriers to genetic testing, particularly among vulnerable patient subgroups.⁷ 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 screening

Standard screening for cystic fibrosis (CFTR testing) and spinal muscular atrophy (SMN1 testing) using standard mutation panels is considered **medically necessary** for all women who are pregnant or considering pregnancy and their reproductive partners.

Expanded screening

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

- The genetic disorders being screened for have clearly defined gene(s) and pathogenic variants associated with them
- 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
- At least **ONE** of the following apply:
 - One or both individuals are members of a population (e.g., Ashkenazi Jewish, Mediterranean, and Southeast Asian, among others) that is known to be at increased risk for certain conditions (e.g., conditions that have carrier frequency of at least 1% in that population)
 - The reproductive couple is known or suspected to be consanguineous
 - One or both individuals do not have access to a biological family history due to adoption, use of reproductive donor, or other reasons

Note: Expanded carrier screening should be directed toward genes that are associated with family history and ethnicity. Additionally, genes included in the panel should be shown to impact patient management and health outcomes.

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

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 parents' 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-linked, or mitochondrial condition
 - At least one parent is a carrier of a balanced structural chromosome rearrangement
 - At least one parent is a reproductive donor with unknown carrier risk

Condition-Specific Requirements

Fragile X syndrome

Fragile X premutation carrier screening 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

Exclusions

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

- Prenatal testing for conditions known to have adult onset
- Cell-free DNA testing 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
- Conditions for which screening performance with nonmolecular screening techniques (e.g., hereditary hemochromatosis has low penetrance when molecular variants are identified)

Background

Genetic testing 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 test each individual for cystic fibrosis (CFTR gene), spinal muscular atrophy (SMN1), and a limited number of individual diseases based in part on self-reported racial/ethnic background. 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 descent would trigger additional testing for Tay-Sachs disease (HEXA). Ashkenazi Jewish descent would trigger additional testing for Tay-Sachs disease (HEXA), Bloom syndrome (BLM), Canavan disease (ASPA), Familial dysautonomia (IKBKAP), Fanconi anemia type C (FANCC), Gaucher disease (GBA), mucopolipidosis IV (MCOLN1), and Niemann-Pick disease type A (SMPD1).⁸ The known clinical utility of carrier screening is based on a focused approach based on self-reported racial/ethnic categories.

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 would be 1/8 or 12.5% for the latter, which 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 behavior, such as risk-mitigating lifestyle changes, ordering and receiving genetic counseling, and genetic testing.⁹ The American College of Obstetrics and Gynecology (ACOG) Committee Opinion No. 478 (reaffirmed in 2020) 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 "...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."¹⁰

Multiplex platforms simultaneously assaying many potentially pathogenic variants on each sample have become 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.¹¹ 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.⁸

Since 2017 (and reaffirmed in 2023), ACOG has taken a neutral stance.^{12, 13} 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 (ACMG) has 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 2016 calls for an expansion of genetic carrier screening protocols for all pregnant patients, those planning pregnancy, and their reproductive partners.¹⁴ Of note, the recommendations were issued as a Practice Resource, and not ACMG's more rigorous Clinical Practice Guideline, that requires stronger evidence. In this practice 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. 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.¹⁵ 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."¹³ 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.¹⁶

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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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81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
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)
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)
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) 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)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
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
81290	MCOLN1 (mucopolipin 1) (eg, Mucopolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
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
81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
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)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
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)
81333	TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
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)
81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81344	TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
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)
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, cytogenomic array analysis for neoplasia)
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
0168U	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma without fetal fraction cutoff, algorithm reported as a risk score for each trisomy
0252U	Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy

History

Status	Review Date	Effective Date	Action
Revised	04/12/2023	11/05/2023	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.
Created	09/21/2022	02/12/2023	IMPP review. Original effective date.