Test Specific Guidelines

Expanded Carrier Screening Panels

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Introduction

Expanded carrier screening panels are addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Ashkenazi Jewish Genetic Disorders Sequencing	81412
ASPA Targeted Mutation Analysis	81200
BCKDHB Targeted Mutation Analysis	81205
BLM Targeted Mutation Analysis	81209
Carrier Screening Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
CFTR Targeted Mutation Analysis	81220
CFTR Deletion/Duplication Analysis	81222
CFTR Sequencing	81223
DMD Deletion/Duplication Analysis	81161
FANCC Targeted Mutation Analysis	81242

Procedures addressed by this guideline	Procedure codes
FMR1 Expansion Analysis	81243
FMR1 Methylation Analysis	81244
G6PC Targeted Mutation Analysis	81250
GBA Targeted Mutation Analysis	81251
Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders, 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)	81443
GJB2 Sequencing	81252
GJB6 Targeted Mutation Analysis	81254
HBA1/HBA2 Targeted Mutation Analysis	81257
HBA1/HBA2 Sequencing	81259
HBA1/HBA2 Deletion/Duplication Analysis	81269
HBB Targeted Mutation Analysis	81361
HBB Deletion/Duplication Analysis	81363
HBB Sequencing	81364
Hemoglobin Electrophoresis	83020
HEXA Targeted Mutation Analysis	81255
IKBKAP Targeted Mutation Analysis	81260
MCOLN1 Targeted Mutation Analysis	81290
SERPINA1 Targeted Mutation Analysis	81332
SMN1 Gene Analysis; Dosage/Deletion Analysis (eg, carrier testing), includes SMN2 Analysis, if performed	81329
SMPD1 Targeted Mutation Analysis	81330

What Are Expanded Carrier Screening Panels?

Definition

Expanded carrier screening panels, also known as multiplex carrier screening panels, are designed to identify carrier status or predict risk for multiple genetic diseases in a single test. It is typically offered to individuals planning a pregnancy or currently pregnant.

Prevalence

The genetic diseases that are tested for range in severity from lethal in infancy to so mild an affected individual may never develop symptoms. Some conditions are quite common, especially in certain ethnic groups, while others are rare.

It is generally believed that all people carry several recessive gene mutations. An estimated 1 in 580 births has an autosomal recessive condition and 1 in 2000 have an X-linked condition.[1]

Inheritance

Expanded carrier screening panels may include autosomal recessive and X-linked conditions.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with expression of the X chromosome carrying the mutation can influence the degree of severity.

Common Uses

Expanded carrier screening is most commonly done for reproductive planning, to identify couples at risk for having a child with a recessive inherited disorder. In most cases, couples who have a child with a recessive inherited disorder have no family history of that disorder or any other risk factors.

Carrier screening for a specific disorder may be indicated when there is a positive family history, when a reproductive partner is a carrier of or affected with a recessive disorder, or when there is a known increased risk based on ethnicity or other factors.

Test Information

Introduction

Expanded carrier screening panels determine carrier status for numerous genetic conditions simultaneously for the purposes of reproductive planning.

Expanded Carrier Screening Panels

Several expanded carrier screening panels are available. Each test has a unique set of diseases included in novel and proprietary genetic testing platforms. The number of mutations tested varies considerably by condition, ranging from a single mutation for rare conditions to over 100 mutations for cystic fibrosis. Complete testing information, including a list of all conditions screened, can be found at a laboratory's website.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to expanded carrier screening.

American College of Obstetrics and Gynecology

The American College of Obstetrics and Gynecology (ACOG, 2017)[2] published a committee opinion that stated the following regarding Expanded Carrier Screening:

"Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. After counseling, a patient may decline any or all carrier screening." "Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth."

- **"Carrier screening panels should not include conditions primarily associated with a disease of adult onset."**

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2021) released an educational practice resource on carrier screening.[3] This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic. To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of >1/200 was suggested. ACMG generated a list of 113 genes meeting these criteria.

Concerns with Large Panels

Although the number of large panels being offered by laboratories is increasing, most of the included tests are not indicated for each person being tested.

Issues with expanded carrier screening include:

Many included tests have not been recommended for population-based carrier screening and should therefore only be performed when there is a specific known increased risk, such as a family history of the condition.

Some conditions included in expanded carrier screens are exceedingly rare except in certain ethnicities, or the carrier frequency in teh general population may not be known. Therefore, the residual risk for an individual after a negative expanded carrier screen may not be provided by the laboratory.[3]

Mutation analysis may not be the preferred initial screening test for some conditions. For example, a CBC with RBC indices is the initial screening test for beta-thalassemia followed by hemoglobin analysis for individuals with microcytic anemia.[4,5] Measuring hexosaminidase A activity may be preferable to mutation analysis for Tay-Sachs carrier screening, especially in non-Jewish populations.[5]

Some expanded carrier screens include testing for conditions that are relatively mild, treatable, or have onset in adulthood.

- **Depending on ethnicity, current expanded carrier screening panels are expected to identify up to 40% of people tested as carriers of a recessive gene mutation. Therefore, if this screening is routinely offered, many patients will require counseling for a positive result, and partner testing must be offered. The most complete partner testing is often by full gene sequencing. Availability of partner testing, cost, turnaround time, and the possibility of identifying a variant of unknown significance by sequencing make this a complex clinical scenario to manage in the routine reproductive setting.**

Criteria

Introduction

Requests for expanded carrier screening panels are reviewed using these criteria.

Individually Billed Gene Tests

Individual gene tests included in expanded carrier screening panels that will be separately billed should be evaluated based on the medical necessity criteria for each gene test.

Any gene tests that are separately billed and do not meet medical necessity criteria are not a reimbursable service. It will be at the laboratory, provider, and patient's discretion to determine if a multi-gene panel remains the preferred testing option, recognizing that only a portion of the panel may be reimbursed by insurance.

Single Panel Code Billed

Panel will be billed with a single procedure code, 81443, to represent all genes being sequenced.

No single gene components of the panel have been performed and reimbursed previously, or billed separately on the same date of service, AND

- **Medical necessity must be established for full gene** sequencing **of at least two conditions included in the panel. This does not include:**

targeted mutation testing (i.e. cystic fibrosis carrier testing performed by a panel of mutations, or known familial mutation testing), or

molecular methodologies other than sequencing (i.e. fragile X testing; deletion/duplication analysis of any gene by MLPA or similar platform), or

- **non-molecular methodologies (i.e. hemoglobin electrophoresis for hemoglobinopathies)**

Billing and Reimbursement Considerations

The following conditions should not be billed as part of 81443 and should not count toward the requirement of two conditions meeting medical necessity requirements:

Spinal muscular atrophy carrier testing should be billed separately using 81329

- **Fragile X testing should be billed separately using 81243**

Carrier testing performed due to the sole indication of Ashkenazi Jewish ancestry will be redirected to 81412.

Coverage Guidance

This table describes coverage guidance around the most commonly performed carrier screening tests. It also includes the test types addressed by population-based carrier screening guidelines. When the test is not addressed in this table, refer to the general guideline: Genetic Testing for Carrier Status. For these

additional tests to be medically necessary, there will generally need to be a specific known increased risk for that condition such as a known family history or a reproductive partner who is known to be a carrier of or affected with the condition.

Coverage Guidance for Genes Included in Expanded Carrier Screening Multi-Gene Panels

Condition groups	Condition	Gene	CPT Code	Required Claim Code	Coverage
Pan-Ethnic Conditions	Cystic fibrosis	CFTR	81220	NONE	MOL.TS.158
			81222	NONE	MOL.TS.158
			81223	NONE	MOL.TS.158
	Spinal muscular atrophy	SMN1/ SMN2	81329	SMN1SMN2	MOL.TS.225
	Fragile X syndrome	FMR1	81243	NONE	MOL.TS.172
			81244	NONE	MOL.TS.172
	Ashkenazi Jewish genetic disorders ** —				MOL.TS.129
	Bloom syndrome	BLM	81209	NONE	MOL.TS.132
	Canavan disease	ASPA	81200	NONE	MOL.TS.145
	Dihydrolipoamide dehydrogenase deficiency	DLD	81479	DLD	MOL.CU.110
	Familial dysautonomia	IKBKAP	81260	NONE	MOL.CU.110
	Familial hyperinsulinism	ABCC8	81401	ABCC8	MOL.CU.110
	Fanconi anemia, type C	FANCC	81242	NONE	MOL.CU.110

Condition groups	Condition	Gene	CPT Code	Required Claim Code	Coverage
	Gaucher disease, type 1	GBA	81251	NONE	MOL.TS.173
	Glycogen storage disease, type 1A	G6PC	81250	NONE	MOL.CU.110
	Joubert syndrome, type 2	TMEM216	81479	TMEM216	MOL.CU.110
	Maple syrup disease, type 1B	BCKDHB	81205	NONE	MOL.CU.110
	Mucolipidosis, type IV	MCOLN1	81290	NONE	MOL.CU.110
	Nemaline myopathy, type 2	NEB	81400	NEB	MOL.CU.110
	Niemann-Pick disease, type A	SMPD1	81330	NONE	MOL.TS.207
	Tay-Sachs disease	HEXA	81255	NONE	MOL.TS.226
	Usher syndrome, type 1F	PCDH15	81400	PCDH15	MOL.CU.110
	Usher syndrome, type 3	CLRN1	81400	CLRN1	MOL.CU.110
Hemoglobinopathy screening	Hemoglobinopathies	NONE	83020	NONE	Cover without review
	Sickle cell anemia, Thalassemia	HBB	81361	HBB	MOL.TS.308
			81363	HBB	MOL.TS.308
			81364	HBB	MOL.TS.308
	Alpha thalassemia	HBA1/HBA2	81257	NONE	MOL.TS.308
			81269	HBA1HBA2	MOL.TS.308
			81259	HBA1HBA2	MOL.TS.308

Note **The single Ashkenazi Jewish Carrier Screening guideline should be sufficient to assess the appropriateness of all tests in this category in most circumstances. The available individual gene test policies are provided should additional information be useful.

References

Introduction

These references are cited in this guideline.

Thompson MW, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 5th ed. Philadelphia: Saunders; 1991.

ACOG Committee Opinion. Number 690, March 2017. Carrier screening in the age of genomic medicine. *Obstet Gynecol*. 2017;129(3):595-596.

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):1793-1806. doi: 10.1038/s41436-021-01203-z

ACOG Practice Bulletin. Number 78, January 2007. Hemoglobinopathies in pregnancy. *Obstet Gynecol*. 2007 Jan;109(1):229-37.