HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Carrier Screening for Genetic Diseases

Policy MP-046

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Reviewed/Revised Date: 01/17/2024

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Carrier screening is a type of genetic test that is used to identify asymptomatic individuals who may carry a gene variant that has been associated with disease. This type of testing is most commonly used to quantify the risk of having a child with a genetic disorder. Testing can occur before or during pregnancy. The decision to pursue carrier screening is voluntary and can include several different approaches which include: ethnicity-based screening, pan-ethnic screening, and expanded carrier screening (ECS). The American College of Obstetricians and Gynecologists (ACOG) has stated that ethnicity-based, pan-ethnic, and ECS are all acceptable strategies to screen individuals for carrier status prior to and during pregnancy.

The goal of carrier screening is to identify disease-causing variants, the vast majority of which are recessive or X-linked in nature. It is important to note that some autosomal dominant conditions with adult onset may also be included which would have future health implications for both the present and future pregnancies and for the individual themselves being screened.

Targeted carrier screening is a carrier screening approach based primarily on race/ethnicity and personal/family history. Expanded Carrier Screening (ECS) employs a broad approach by simultaneously screening for a large number of genetic conditions irrespective of ethnicity.

Companies that offer expanded carrier screening create their own screening panel of disorders that they test for. Some panels test for more than 100 different disorders.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans COVERS carrier testing for ALL pregnant or individuals considering to become pregnant once per lifetime if the following criteria are met:

A. Testing is for one of the following conditions when done as an individual test or as part of a limited carrier testing NGS panel:

i. Cystic fibrosis
ii. Spinal Muscular Atrophy (SMA)
iii. Fragile X

U of U Health Plans COVERS carrier testing using a limited genetic panel for individuals of Ashkenazi Jewish ancestry once per lifetime when ALL (A-C) of the following are met:

A. Screening is done for the disorders as recommended by the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG). The following conditions reflect the emerging clinical and scientific evidence for carrier testing in this population as of guideline publication dates, and include:

i. Tay Sachs disease;
ii. Canavan disease;
iii. Cystic fibrosis;
iv. Familial dysautonomia;
v. Bloom syndrome;
vi. Familial hyperinsulinism;
vii. Fanconi anemia group C;
viii. Gaucher disease;
ix. Glycogen storage disease type I;
x. Joubert syndrome;
xi. Maple syrup urine disease;
xii. Mucolipidosis IV;
xiii. Niemann-Pick disease;
xiv. Usher syndrome.

B. Medical records document confirmation of Ashkenazi Jewish ancestry and genetic counseling by a medical geneticist, a certified and licensed (where required) genetic counselor not associated with the laboratory performing the testing, or a sub-specialist in maternal-fetal medicine.

C. The individual is currently pregnant or contemplating pregnancy.

U of U Health Plans considers carrier screening for genetic diseases medical necessary in limited circumstances when the following criteria are met (Must meet **ALL** of A through E and one of F)**:**

A. The natural history of the disease is well understood and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous, hemizygous or compound heterozygous state;

B. Definitive diagnosis of carrier state using alternative biochemical or other clinical tests are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing;

C. The genetic test has a carrier detection rate of 95% or higher for most disorders;

D. An association of the marker with the disorder has been established;

AND

E. One of the following:

   i. One or both individuals have a first- or second-degree relative* who is affected; OR

   ii. One individual is known to be a carrier; OR

   iii. One or both individuals are members of a population known to have a carrier rate that exceeds >1% with a family history of risk-based or ethnic predilection for a disease such as Ashkenazi Jewish population.

**First-degree relatives include a biological parent, brother, sister, or child; second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.*

U of U Health Plans does NOT cover expanded carrier screening panels as they are considered unproven.

U of U Health Plans does NOT cover any of the following carrier screening tests to predict the risk of several inherited disorders as they are considered experimental/ investigational. Including but not limited to the following:

23andMe®

Baby Genes by ArcherDX

EGL Genetics

GenPath® Diagnostics

Good Start™ Genetics

Igenomix®

Integrated Genetics®

Macrogen™

Natera Horizon Test®

NextStep® Carrier Screening

Pathway Genomics®

Progenity®

Recombinesm

Academic Medical Center Amsterdam

2. **Medicaid Plans**

   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

   CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

It is important to recognize the impact of carrier screening is only significant if it impacts gestational planning or pregnancy management. Kaback (2000) indirectly demonstrated the value of this testing in one population. In his study, he assessed carrier screening performed in individuals having an increased risk based for conditions that are found in the general population (pan-ethnic), for diseases that are more common in a particular population, or based on family history. Pan-ethnic screening (population screening) for carrier status is done for single-gene disorders that are common in the population. This study demonstrated the effectiveness of ethnicity-based screening in a study based on Tay-Sachs disease, which shows a 90% reduction in the disease following the introduction of carrier screening in the U. S. and Canada during the 1970s.

Notably individuals of Ashkenazi Jewish descent have an increased risk to have a child with certain autosomal recessive conditions. For all Ashkenazi Jews who are pregnant or considering pregnancy, ACOG and ACMG recommend carrier screening for the following disorders as they all have significant health impacts on an affected infant; cystic fibrosis, Canavan disease, familial dysautonomia, Tay-Sachs disease, Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, Gaucher disease, Maple Syrup Urine Disease, Joubert syndrome, Glycogen storage disease and familial hyperinsulinism. When only one member of a couple has Jewish ancestry, carrier screening is still recommended. However, these couples should be made aware that it may be difficult to accurately predict the risk of the majority of these conditions affecting offspring, as the detection rate and carrier frequency for non-Jewish individuals is unknown (ACOG committee opinion #691, 2017; reaffirmed 2020).

The American College of Medical Genetics and Genomics (ACMG) defines expanded carrier screening panels as those that use next-generation sequencing to screen for variants in hundreds of genes, as opposed to gene-by-gene screening that are intended to be used for general population screening. These Panels typically include both diseases that are present with increased frequency in specific populations, as well as a large number of diseases for which any given individual is not at high risk of being a carrier without a known family history. Current ACMG guidelines recommend a tiered genetic carrier testing approach instead of the ethnicity-based panel testing or so-called expanded genetic carrier testing based on that even the most common and severe genetic conditions are found to be less common in certain ethnic populations and below the previously recommended threshold of 1/100 carrier frequency (i.e., Cystic Fibrosis in the African American population has a carrier frequency of 1/105). These recommendations are in line with current National Society of Genetic Counselors/NSGC guidelines. Tier 3 genetic panel testing includes serious early-onset genetic conditions at a carrier frequency of 1/200 or above. This test is now recommended for all women pregnant or considering

pregnancy. This panel currently includes 113 autosomal recessive and X-linked genes, and is subject of ongoing curation with input from the ACMG Committees and Work Groups, additional professional organizations and the lay public as appropriate. Furthermore, per current ACMG guidelines Tier 4 screening (larger panel including serious genetic conditions at a carrier frequency below 1/200) should be considered:

1. When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer);
2. When a family or personal medical history warrants.

Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions when carrier screening is performed simultaneously with their partner. This scenario is common in couples undergoing fertility treatment. [Gregg et al., 2021; Capalbo et al., 2021]

Additive to the AMJC position, the American College of Obstetricians and Gynecologists (ACOG) Committee (ACOG Committee Opinion No. 690, 2017) offered the following summary pertaining to expanded 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”.

In 2017, Shi et al genotyped individuals of self-reported Ashkenazi Jewish (AJ) ancestry to analyze the carrier frequency of 29 recessive genetic diseases to determine if additional disorders should be considered as part of routine carrier screening. The team reviewed the literature and the internal database at their lab to identify the genes that should be screened, and utilized pre-existing, de-identified samples from research participants. There were 2252 AJ individuals tested for 29 recessive disorders, and an additional 1390 AJ and 6813 non-AJ individuals were screened for a subset of 18 recessive disorders. The authors identified seven disorders with a carrier frequency of greater than 1 in 100, nine with a carrier frequency between 1 in 100 and 1 in 200, and four between 1 in 200 and 1 in 500. Nine conditions had a carrier frequency of less than 1 in 500 or were not found. Of the 20 diseases with a carrier frequency higher than 1 in 500, two were eye diseases that the authors felt were not appropriate to be included for reproductive related carrier screening. Of the remaining 18 disorders, the team calculated that the cumulative chance for an individual to be a carrier of one of the 18 diseases was 1 in 6. The authors concluded that the chance that an AJ couple would be carriers of the same disease and be at risk for an affected pregnancy is 1 in 441.

A 2019 study by Peyser et.al, evaluated the efficiency of ECS compared with ethnicity-based screening in identifying carriers. Between the June 2013 and July 2015 a total of 4232 infertility patients underwent ECS, from which carrier rates were calculated. In addition, carrier status was determined for two other screening panels: ethnicity-based guidelines (ethnicity was self-reported) or the ECS panel recommended by the ACOG using ECS results. Carrier rate and carrier couple rates were compared in the overall study population and in each self-reported ethnicity. The ECS panel used to screen the patient population identified 1243 carriers (29.4%). For the same population, ethnicity-based screening and the ACOG panel would have identified 359 (8.5%) and 659 carriers (15.6%), respectively,

representing statistically significant differences. Differences in identifying carriers across self-reported ethnicities varied. In 15 couples (1.2%), both partners carried pathogenic variants for the same genes, 47% of whom would have been missed had screening been ethnicity-based. The authors concluded that some diseases may have late-onset as well as variable phenotypes and ECS may eventually play a pivotal role in preventing genetic disease in fertility clinics.

ACOG has proposed seven criteria in an ECS panel design to ensure that screening for a condition is sufficiently sensitive to identify carriers and reduce residual risk of non-carriers. One of the criteria requires a per-condition carrier rate greater than 1 in 100. Ben-Shachar et.al (2019), assessed the impact of the proposed panel criteria on at-risk couples to see if this threshold corresponds with a loss in clinical detection. Carrier rates and at-risk couple rates were calculated in 56,281 patients who underwent a 176-condition ECS and were evaluated for panels satisfying various criteria. Condition-specific clinical detection rates were estimated via simulation. Different interpretations of the 1-in-100 criterion have variable impact: a compliant panel would include between 3 and 38 conditions, identify 11-81% fewer at-risk couples, and detect 36-79% fewer carriers than a 176-condition panel. If the carrier rate threshold must be exceeded in all ethnicities, ECS panels would lack prevalent conditions like cystic fibrosis. Simulations suggest that the clinical detection rate remains >84% for conditions with carrier rates as low as 1 in 1000. In conclusion, the authors found that the 1-in-100 criterion limits at-risk couple detection and should be reconsidered.

Lastly, even though the conditions/genes most appropriate for prenatal genetic carrier screening (PGCS) remain a matter of debate, estimates of carrier rates across genes are needed to guide construction of carrier screening panels. Guo et.al (2019) worked to identify parents at risk of having a child affected by a recessive condition by using an exome sequencing database (n = 123,136) to estimate carrier rates across six major ancestries for 415 genes associated with severe recessive conditions. The study found that 32.6% (East Asian) to 62.9% (Ashkenazi Jewish) of individuals are variant carriers in at least one of the 415 genes. For couples, screening all 415 genes would identify 0.17-2.52% of couples as being at risk for having a child affected by one of these conditions. Screening just the 40 genes with carrier rate >1.0% would identify more than 76% of these at-risk couples. 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. In conclusion, the results accentuated a high cumulative carrier rate across genes, this emphasizes the need for careful selection of genes for carrier screening panels, to further assist in counseling potential parents.

Applicable Coding

The use of "code stacking" or submitting requests for multiple single genes (instead of using the panel code 81443) will be considered an expanded panel and therefore treated as investigational. Individual genes that might otherwise be approved will not be covered when submitted in this fashion with multiple other CPT codes that indicate a panel is being used. Only 81220 (for CFTR) and 81401 (molecular pathology level 2 used for SMN1 or G0452) can be allowed when requested as separate single gene testing. Other single gene testing is only allowed when all the criteria in the Policy Statement above are met to show high risk for a particular disease.

If CPT tier 1 or tier 2 molecular pathology codes are available for the specific test, they should be used. If the test has not been codified by CPT 81479 should be used.

CPT Codes

81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)
81243	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81336	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2
81412	Ashkenazi Jewish associated disorders (e.g., 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 (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., 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

HCPCS Codes

G0452	Molecular pathology procedure; physician interpretation and report

References:

1. American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion No. 691: carrier screening for genetic conditions. Obstet Gynecol. 2017 Mar;129(3):e41-55. PubMed PMID: 28225426. Reaffirmed 2020.
2. American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion No. 690: carrier screening in the age of genomic medicine. Obstet Gynecol. 2017 Mar, reaffirmed 2023;129(3):e35-40. PubMed PMID: 28225425. Available at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-inthe-age-of-genomic-medicine
3. American College of Obstetricians and Gynecologists (ACOG). "Patient Resources; FAQs; Carrier Screening". Accessed: May 11, 2020. Available at: https://www.acog.org/patient-resources/faqs/pregnancy/carrier-screening
4. Ben-Shachar, R., et al. (2019). "A data-driven evaluation of the size and content of expanded carrier screening panels." Genet Med 21(9): 1931-1939.

5. Capalbo A, Fabiani M, Caroselli S, Poli M, Girardi L, Patassini C, Favero F, Cimadomo D, Vaiarelli A, Simon C, Rienzi LF, Ubaldi FM. Clinical validity and utility of preconception expanded carrier screening for the management of reproductive genetic risk in IVF and general population. Hum Reprod. 2021 Jun 18;36(7):2050-2061. doi: 10.1093/humrep/deab087. PMID: 34021342.
6. Edwards, J. G., et al. (2015). "Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine." Obstet Gynecol 125(3): 653-662.
7. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, Chen E, Sparks TN, Reddi HV, Rajkovic A, Dungan JS; ACMG Professional Practice and Guidelines Committee. 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 Oct;23(10):1793-1806. doi: 10.1038/s41436-021- 01203-z. Epub 2021 Jul 20. Erratum in: Genet Med. 2021 Aug 27; PMID: 34285390; PMCID: PMC8488021.
8. Guo, M. H. and A. R. Gregg (2019). "Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels." Genet Med 21(9): 1940-1947.
9. Hayes, Inc. (2020) Precision Medicine Insights. "Expanded Carrier Screening" August 17, 2020. Accessed January 14, 2022. Available at: https://evidence.hayesinc.com/report/grr.carrier4962
10. Kaback, M. M. (2000). "Population-based genetic screening for reproductive counseling: the Tay-Sachs disease model." Eur J Pediatr 159 Suppl 3: S192-195.
11. Peyser, A., et al. (2019). "Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates." Genet Med 21(6): 1400-1406.
12. Sagaser KG, Malinowski J, Westerfield L, Proffitt J, Hicks MA, Toler TL, Blakemore KJ, Stevens BK, Oakes LM. Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors. J Genet Couns. 2023 Feb 9. doi: 10.1002/jgc4.1676. Epub ahead of print. PMID: 36756860.
13. Shi L, Webb BD, Birch AH, et al. Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants. Clinical genetics. 2017;91(4):599-604.
14. Stevens, B., et al. (2017). "Finding Middle Ground in Constructing a Clinically Useful Expanded Carrier Screening Panel." Obstet Gynecol 130(2): 279-284.
15. Sparks TN. Expanded carrier screening: counseling and considerations. Hum Genet. 2020 Sep;139(9):1131-1139. doi: 10.1007/s00439-019-02080-y. Epub 2019 Nov 2. PMID: 31679051; PMCID: PMC7195224.

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