

CARRIER TESTING FOR GENETIC DISEASES

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[Instructions for Use](#) ⓘ

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Related Commercial Policies

- [Chemosensitivity and Chemoresistance Assays in Cancer](#)
- [Fetal Aneuploidy testing Using Cell-Free Fetal Nucleic Acids in Maternal Blood](#)

Medicare Advantage Coverage Summaries

- [Genetic Testing](#)
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COVERAGE RATIONALE

Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person. For information regarding noninvasive prenatal screening (nipt) for fetal aneuploidy, refer to the Medical Policy titled [Fetal Aneuploidy Testing Using Cell-Free Fetal Nucleic Acids in Maternal Blood](#).

Ashkenazi Jewish Carrier Screening

Ashkenazi Jewish carrier screening is proven and medically necessary for evaluating the following:

- Individuals who are seeking prenatal care or planning a pregnancy who have had not previously had informative Ashkenazi Jewish carrier screening; and
- At least one of the following additional criteria is met:
 - At least one reproductive partner is Ashkenazi Jewish (this individual has at least one Ashkenazi Jewish grandparent); or
 - The reproductive partners have a previously affected child with one of the genetic diseases included in the Ashkenazi Jewish carrier screening test and the results of this test will inform a current or future pregnancy; or
 - One or both individuals have a first- or second-degree relative who is affected and the results of this test will inform a current or future pregnancy; or
 - One or both individuals have a first-degree relative with an affected offspring and the results of this test will inform a current or future pregnancy; or
 - One of the reproductive partners is already known to be a carrier for one of the genetic diseases included in the Ashkenazi Jewish carrier screening test and the results of this test will inform a current or future pregnancy.

Carrier testing for any additional genetic diseases as part of Ashkenazi Jewish carrier screening is unproven and not medically necessary.

Ashkenazi Jewish carrier screening is unproven and not medically necessary for all other indications.

Expanded Carrier Screening Panel Testing

Expanded carrier screening panel testing is unproven and not medically necessary for all indications.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply

any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
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
81479	Unlisted molecular pathology procedure

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DESCRIPTION OF SERVICES

Carrier screening is performed to detect genetic mutations that may increase the risk of a genetic disorder. This testing may impact the reproductive decision-making for parents or prospective parents.

Carrier screening may be available for autosomal recessive conditions, autosomal dominant less penetrant conditions, X-linked conditions, and certain chromosome abnormalities. In general, carrier screening may be performed 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. For individuals of Ashkenazi Jewish descent (Gross et al., 2008), certain autosomal recessive conditions are more prevalent and many of these disorders are lethal in childhood or associated with significant morbidity.

Diagnostic genetic testing of a heritable disease may also be performed using similar methods as carrier screening. It may be medically necessary to use genetic testing to establish a molecular diagnosis when an individual has clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic) and the result of the test will directly impact the treatment being delivered.

Ashkenazi Jewish Carrier Screening

Carrier screening for individuals of Ashkenazi Jewish descent is focused on identifying reproductive partners who are at risk to have a child with a disorder that has a higher prevalence in this population. For individuals of Ashkenazi Jewish descent, certain autosomal recessive conditions are more prevalent and many of these disorders are lethal in childhood or associated with significant morbidity. The disorders generally screened in this population are Tay-Sachs, Canavan, Cystic fibrosis, Familial Dysautonomia, Fanconi Anemia, Niemann-Pick type A, Bloom syndrome, Mucopolysaccharidosis IV, and Gaucher disease. Since carrier screening includes only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a carrier. If an individual has no mutations detected on a carrier screening test, the individual still has some remaining risk of being a carrier (Gross et al., 2008; ACOG, 2017).

Ashkenazi Jewish carrier screening should include testing for the genetic diseases recommended by American College of Obstetricians and Gynecologists (ACOG) and/or the American College of Medical Genetics (ACMG):

- Tay Sachs disease
- Canavan disease
- Cystic fibrosis
- Familial dysautonomia
- Bloom syndrome
- Fanconi anemia
- Niemann-Pick disease
- Gaucher disease
- Mucopolysaccharidosis IV
- Maple Syrup Urine Disease
- Joubert syndrome
- Glycogen storage disease 1A
- Familial hyperinsulinism

Expanded Carrier Screening Panels

For carrier screening, new technologies, such as next generation sequencing technology or chromosomal microarray, have created the ability to screen for genetic mutations using genetic panels instead of single genes. These expanded genetic panels, typically 5 or more genes, are able to analyze many genes simultaneously, however there is a lack of evidence to establish the clinical utility of gene test panels that include genes that are not associated with a specific inherited disorder (ACOG, 2017). Furthermore, there is a lack of standardization in the genetic panel composition, thus panels for the similar conditions, may evaluate different set of genes. Currently, there are no existing

professional guidelines to support the ordering and evaluation of carrier screening by expanded panels (Grody et al., 2013).

Additionally, for every disorder, the gene/mutation/mutation frequency should be known in the population being tested so that negative test results can be translated into an expected residual risk of the disorder (Grody et al., 2013). Unfortunately, many laboratories are unable to calculate the residual risk as they lack the knowledge of the carrier frequency within the testing population and the proportion of disease-causing mutations on the assay platform.

CLINICAL EVIDENCE

Ashkenazi Jewish Carrier Screening

Shi et al. (2017) genotyped over 3,000 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. However, 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.

Arjunan et al. (2016) at the Center for Jewish Genetics explored the difference between targeted mutation analysis for Tay Sachs disease, plus enzyme analysis, with next generation sequencing (NGS). Blood or saliva samples were collected on 506 individuals who underwent NGS for 84 recessive conditions and targeted genotyping. Two hundred and eighty-eight individuals were carriers of at least one condition, represented by 434 pathogenic variants, and eight couples were carriers for the same disorder. When NGS was compared to traditional screening for the diseases routinely screened for in the AJ population, NGS did not find any additional mutations beyond what would have been found by targeted genotyping. However, NGS and the broader panel identified two carrier at risk couples, and 115 (26%) pathogenic variants that would not be found by routine AJ screening.

Professional Societies

American College of Medical Genetics and Genomics (ACMG) and American College of Obstetricians and Gynecologists (ACOG)

ACMG and ACOG both recommend carrier screening for Ashkenazi Jewish individuals for:

- Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30),
- Canavan disease (1/6,400; 1/40), and
- Cystic fibrosis (1/2,500-3,000; 1/29), and
- Familial Dysautonomia (1/3,600; 1/32).

(Gross et al. 2008)

In addition, the ACMG practice guideline from 2013 recommends that the following also be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy (Gross et al. 2008):

- Fanconi Anemia (group C) (1/32,000; 1/89)
- Niemann-Pick (type A) (1/32,000; 1/90)
- Bloom syndrome (1/40,000; 1/100)
- Mucopolysaccharidosis IV (1/62,500; 1/127)
- Gaucher disease (1/900; 1/15)
- Maple Syrup Urine Disease (1/50,000; 1/81)
- Joubert syndrome (1/33,000; 1 in 92)
- Glycogen storage disease 1A (1/20,000; 1/71)
- Familial hyperinsulinism (1/10,000; 1/52)

If only one member of the couple is Jewish, ideally, that individual should be tested first. One Jewish grandparent is sufficient to offer testing. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be tested for variants associated with that particular disorder (Gross et al. 2008).

Expanded Carrier Screening

Terhaar et al. (2018) retrospectively report on their experience as a commercial laboratory with reproductive carrier screening comparing three panels; 3 genes, 23 genes, or 218 genes. Data was assessed on 75,036 individuals referred by a healthcare provider in the United States. Three genes were assessed in 51,584 samples, and 7.2% had

a positive result. The 23 gene panel was assessed for 19,550 samples, and 13.2% were positive. Finally, 3,902 samples were assessed for 218 genes, and 36% were positive. Overall, 127 conditions came up positive at least once in this group. The authors noted that those that seeking the 218 gene panel were more ethnically diverse when compared to the other groups. It was not reported in this study if any at risk couples were identified. In addition, it was noted that while receiving more genomic information can be beneficial to patients and providers who want a lot of information to inform medical management, this may also place a burden on clinical care. Most of the disorders identified were inherited in a recessive manner, requiring the clinicians to provide counseling and screening for a reproductive partner. Large panels may identify conditions with mild phenotypes. Common diseases like cystic fibrosis may be familiar to clinicians, but rare diseases may not. Educational resources for clinicians and patients are needed in order to ensure informed conversations and decision making.

Wilfond et al. (2018) reported on lessons learned from the NextGen study, a prospective study designed to explore the best approaches to genomic based reproductive carrier screening. The study randomized women who saw a genetic counselor in person who desired carrier screening, and randomized them to those that received genomic sequencing (n=133) and those who received usual care-meaning no additional screening (n=180). If a woman was positive, her male partner was offered genome sequencing to determine the risk of having an affected pregnancy. In the genome sequencing arm, the team chose to report on 728 conditions, and categorized the conditions into five classes that participants could choose to learn about or not. The classes included diseases with a shortened life span, serious conditions, mild conditions, conditions with unpredictable outcomes, adult onset conditions, and medically actionable conditions related to the individual's personal health (secondary to carrier screening.) Overall, 15 at risk couples were identified, and most were for adult onset conditions. Eight were at risk for hereditary hemochromatosis, two for alpha-1-antitrypsin deficiency; one for non-syndromic hearing loss, one for Factor V Leiden homozygous offspring, and the remaining were for X-linked disorders. These included spondyloepiphyseal dysplasia, G6PD deficiency, and hemophilia A. Overall, however, 78% of participants had at least one finding. This leads to concerns about implementation of this approach into clinic workflows. The median time needed to prepare for a follow up visit for positive results disclosure by a genetic counselor was 64 minutes. In this study, 26% of women became pregnant before disclosure, adding additional time sensitivity to developing a genomic based screening program. The authors noted that their study design and size did not allow for a complete analysis of clinical utility, but they highlighted some anecdotal evidence that was collected. It was reported that women did not seek out more mental health or other services compared to those receiving usual care. They did not report more anxiety or depression. One participant declined amniocentesis for chromosome abnormalities because she believed the expanded carrier screening covered that, and this misconception was later corrected. The woman identified as a carrier of hemophilia A did undergo an amniocentesis, and the fetus was male and found to carry the pathogenic variant. This altered the birth plan and allowed the neonatal team to intervene early. The baby did experience a rare subgaleal hemorrhage after birth, which was immediately treated. Finally, the authors noted that their study was small and on an older, more educated population. When asked about what they might pay out of pocket for genome sequencing, participants were willing to pay a little more than a copay, but the amount varied based on income. In conclusion, the authors noted that genomic sequencing as an approach to routine carrier screening could have significant impact on clinical workflow and resources, the optimal gene targets need to be identified, and may not be accessible to low income patients. Additional research is needed to address these issues.

Ghioffi et al. (2017) studied the decision making of 537 couples who were identified to be carriers of the same genetic disease after undergoing expanded carrier screening for 110 genes through their commercial lab. These couples represented 1% of 51,775 couples screened between August 2014 and August 2015. The diseases included in the study were classified to be profound, severe, or moderate in terms of clinical impact. All couples were invited to participate in a survey about reproductive decision making, and 64 completed the survey. Of these, 45 couples had sought screening prior to pregnancy, and 62% reported that they planned to use preimplantation genetic diagnosis or prenatal diagnosis in a future pregnancy. Twenty-nine percent did not plan to alter reproductive decision making and the remaining four survey responses were unclear. Of the 19 pregnant couples, 10 elected to have prenatal diagnosis but two miscarried before testing could occur. Of those that had testing, five pregnancies were unaffected, and three were affected. Two affected pregnancies were terminated. The remaining couples did not think the condition they were at risk for was significant enough to undergo invasive testing. Perceived severity of the disorder appeared to impact decision making, as 76% of couples who were at risk for a profound or severe disorder reported altering reproductive decision making as a result, compared to only 22% of those at risk for moderate conditions. The authors also compared the choices made by the couples by diseases in professional society screening guidelines (20 couples) and diseases not currently in guidelines (22 couples), and found no significant difference in decision making. The authors noted that limitations of the study included the low response rate, lack of random sampling, and possible response bias.

Haque, et al. (2016) created a model of fetal risk based on a commercial laboratories experience with expanded carrier screening. From January 2012 to July 2015, the laboratory screened 346,790 individuals that were referred for testing by their healthcare provider. The expanded carrier screening test offered was for 110 genes, including 94 conditions categorized as severe or profound. Two platforms were utilized. The first was a targeted genotyping

platform for 417 known pathogenic variants, and the second was next generation sequencing for all genes. Healthcare providers could select the testing platform and genes desired for their patient, so not all patients were screened for all conditions. Targeted genotyping was performed on 308,668 patients, and 47,590 carriers were identified, and 279 individuals were homozygous or compound heterozygotes. Next generation sequencing was completed on 38,122 individuals, and 11,088 people were carriers, and 124 were identified as homozygous or compound heterozygous. Results were reviewed in the context of the participant gender and self-reported race/ethnicity. The largest racial mix in the study was "mixed or other Caucasian." The smallest group included in the analysis was SE Asian, although Finnish was the smallest overall and excluded from the final analysis due to small numbers. The authors utilized the results of both platforms to estimate the carrier frequency by ethnic group, and then modeled the carrier frequency, carrier couple frequency for couples of the same ethnicity, and resulting fetal risk. Based on the model, the authors then compared the detection rate of potential at risk couples for diseases included in current professional carrier screening guidelines against the detection rate of all profound and severe diseases in the expanded carrier screening panel. When hemoglobinopathy genes are excluded from analysis, African Americans were noted to have 18% of profound or severe recessive diseases covered by guidelines, and 82% were outside of guidelines, with a calculated cumulative risk of 1 in 1,741 to have a fetus affected by any profound/severe condition in the study. The Ashkenazi Jewish group had 45% within guidelines, and 55% outside of guidelines with a modeled fetal risk on 1 in 255. Mixed or other Caucasian had 32% within guidelines, and 68% outside of guidelines with a modeled fetal risk on 1 in 649. The authors conclude that current guidelines do not perform equally well between self-reported ethnic groups, and currently target diseases prevalent in European populations. Expanded carrier screening may identify couples at risk for other conditions that are important in a diverse population. Limitations identified for the study includes the use of an artificial construct to calculate disease frequencies and fetal resulting from random mating within an ethnic group. Disease frequencies in the general population might vary when compared to the population referred for genetic testing by a healthcare provider. The model doesn't fully address the racial/ethnic admixture possible in the study population or in real world reproductive pairing. Prospective studies comparing current standard of care with expanded carrier screening are needed before expanded carrier screening is fully adopted.

Professional Societies

American College of Obstetricians and Gynecologists (ACOG)

In their 2017 Committee Opinion 690, ACOG states that if an expanded carrier screening test is to be considered, the following consensus driven criteria should be considered:

- Have a carrier frequency greater than 1 in 100
- The condition should have a well defined phenotype, a detrimental effect on quality of life, cause physical or cognitive impairment, and have onset early in life
- Can be diagnosed prenatally to provide opportunities for antenatal intervention to improve perinatal outcomes such as changes in delivery management, and to educate parents about special needs after birth
- Carrier screening panels should not include adult onset conditions

American College of Medical Genetics and Genomics (ACMG)

An ACMG position statement states that although some commercial laboratories offer expanded carrier screening panels, there is little consensus on which disease genes and mutations to include in these panels (Grody et al., 2013; Edwards et al., 2015). Panels for that include multiple carrier screening tests may be useful if they include the diseases that are present with increased frequency in a specific population (i.e., Ashkenazi Jewish Carrier Screening), but do not have clinical utility when they include a larger number of genetic diseases for which the individual does not have an increased risk of being a carrier.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at:

<https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm>.

(Accessed April 17, 2018)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) that specifically addresses carrier testing for genetic diseases such as Ashkenazi Jewish carrier screening or expanded carrier screening panel testing. Local Coverage Determinations (LCDs) exist, see the LCDs for [Biomarkers Overview](#), [MoIDX: Molecular Diagnostic Tests \(MDT\)](#), [Molecular Diagnostic Tests \(MDT\)](#) and [Molecular Pathology Procedures](#).

(Accessed May 28, 2018)

REFERENCES

- American College of Obstetricians and Gynecologists. Committee Opinion No. 690: Carrier screening in the age of genomic medicine. *Obstet Gynecol*. 2017 Mar;129(3):595-596.
- Arjunan A, Litwack K, Collins N, Charrow J. Carrier screening in the era of expanding genetic technology. *Genet Med*. 2016 Dec;18(12):1214-1217.
- Edwards JG, Feldman G, Goldberg J, et al. 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* 2015;125:653–62.
- Ghioffi CE, Goldberg JD, Haque IS, et al. Clinical utility of expanded carrier screening: reproductive behaviors of at-risk couples. *J Genet Couns*. 2017 Sep 27.
- Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. *Genet Med*. 2013 Jun;15(6):482-3.
- Gross SJ, Pletcher BA, Monaghan KG, et al. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008 Jan;10(1):54-6, reaffirmed 2013.
- Haque IS, Lazarin GA, Kang HP, et al. Modeled fetal risk of genetic diseases identified by expanded carrier screening. *JAMA*. 2016 Aug 16;316(7):734-42.
- 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.
- Terhaar C, Teed N, Allen R, et al. Clinical experience with multigene carrier panels in the reproductive setting. *Prenat Diagn*. 2018 Apr 23.
- Wilfond BS, Kauffman TL, Jarvik GP, et al. Lessons learned from a study of genomics-based carrier screening for reproductive decision making. *Health Aff (Millwood)*. 2018 May;37(5):809-816.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none">Reorganized policy template:<ul style="list-style-type: none">Simplified and relocated <i>Instructions for Use</i>Removed <i>Benefit Considerations</i> sectionUpdated coverage rationale; modified language to clarify the listed services are:<ul style="list-style-type: none">Proven and medically necessary (as described)Unproven and not medically necessary (as described)Archived previous policy version 2018T0586C

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.