Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: AmeriHealth Caritas Pennsylvania Community Health Choices	**Submission Date**: 7/1/2024
Policy Number: ccp.1543	**Effective Date:** 7/2024 **Revision Date:** June 1, 2024
Policy Name: Expanded carrier screening by genomic sequencing	

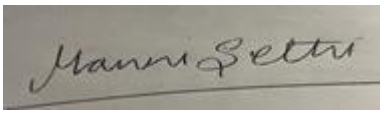
Type of Submission – Check all that apply:

X New Policy
Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

New Policy

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Expanded carrier screening by genomic sequencing

Clinical Policy ID: CCP.1543

Recent review date: 6/2024

Next review date: 10/2025

Policy contains: Autosomal recessive; expanded carrier screening; genetic testing; genomic sequencing; pregnancy; X-linked.

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Expanded carrier screening by genomic sequencing is clinically proven and, therefore, may be medically necessary for estimating the risk of having offspring affected with certain inherited conditions, when all of the following criteria are met (American College of Obstetrics and Gynecology, 2017; Gregg, 2018):

- The member is considering pregnancy or is pregnant.
- There is documentation of genetic counseling prior to testing.
- The test is ordered by an obstetrician-gynecologist or other health care provider with genetics expertise.
- The genomic sequencing panel includes testing for up to 22 autosomal recessive or X-linked conditions identified by the American College of Obstetrics and Gynecology as reasonable to include in expanded carrier screening. These conditions are listed in the Appendix.

Pre- and post-test genetic counseling is clinically proven and, therefore, may be medically necessary for members undergoing or considering carrier testing.

Limitations

Single gene sequencing for an inherited condition that has been performed previously or on the same date of service is not medically necessary for inclusion in an expanded carrier screening panel.

Expanded carrier screening of a member's reproductive partner is investigational/not clinically proven and, therefore, not medically necessary.

Carrier screening for a particular inherited condition generally should be performed only once in a member's lifetime. The decision to rescreen a member for additional genetic variants should be undertaken only with the guidance of a genetics professional who can assess in determining the incremental benefit (American College of Obstetricians and Gynecologists, 2017; Gregg, 2018).

Alternative covered services

Ethnicity-based carrier screening.

Background

In genetics, a carrier is an individual who has inherited a genetic variant associated with a genetic condition. A carrier does not show symptoms or problems associated with the genetic variant but can transmit it to offspring in a sex-linked or autosomal recessive pattern (Veneruso, 2022).

X-linked inheritance refers to genetic conditions associated with genetic variants on the X chromosome. Examples of X-linked conditions are Duchenne muscular dystrophy, hemophilia A, and Charcot-Marie-Tooth disease (Basta, 2023). In autosomal recessive conditions, the genetic variant is located on a numbered (non-sex) chromosome, and two copies of the gene variant, one from each parent, are required for an offspring to be considered affected with the genetic condition. Consanguinity is an important risk factor. Examples of autosomal recessive conditions are cystic fibrosis, thalassemia, sickle cell disease, and Tay-Sachs disease (Gulani, 2023).

Carrier screening analyzes one or more genes associated with specific X-linked or autosomal recessive conditions of infantile or early-childhood onset to determine the risk of having affected offspring. Carrier screening encompasses a variety of laboratory methods such as polymerase chain reaction, Sanger sequencing, multiplex ligation-dependent probe amplification, microarray, and next-generation sequencing. Other methods may be added to identify single nucleotide variants, large-scale structural variants, and copy-number variants (Gregg, 2021).

Carrier screening is typically performed before or during early pregnancy, before gamete donation, and after repeated miscarriages or reproductive failures to assist parents in early reproductive decisions. It complements, but does not replace, family history, race, and ethnicity in overall reproductive risk assessment, other prenatal testing, or newborn screening (Veneruso, 2022).

Traditional carrier screening relies on family history, ethnic background, provider preferences, or patient request. Blood samples are typically required, but saliva and buccal tissue samples may be used depending on the analysis method. Targeted panels look for the most common, known variants for single gene disorders and are usually based on ethnicity. Pan-ethnic carrier screening panels apply microarray technologies to analyze multiple known genetic variants for several conditions through specifically designed probes. However, an incomplete patient ancestry and a screening technology's inability to detect rare or novel variants limit diagnostic sensitivity and accuracy. This may impair the ability to estimate residual risk (the probability an individual is a carrier for a recessive disorder despite a negative carrier screening). Moreover, ethnicity-based carrier screening creates inequity in testing access (Veneruso, 2022).

Expanded carrier screening panels employ next-generation sequencing techniques or a combination of techniques to analyze large genomic regions simultaneously for a wide spectrum of genetic variants responsible for multiple diseases, including known variants found in pan-ethnic panels and variants found in less-studied populations or ethnic groups. Expanded carrier screening offers a more universal approach for estimating

reproductive risk independent of family or ethnic history and may be useful for increasing the carrier detection rate for several genetic diseases.

Molecular testing laboratories determine the composition of and methods for expanded universal carrier screening panels, resulting in variation in the breadth of diseases assayed and depth of the analyses. Many panels include conditions that are not well understood and for which professional guidelines do not exist. Variants of uncertain significance and incidental findings may be detected, making genetic counseling imperative for accurate interpretation of findings (Veneruso, 2022).

The U.S. Food and Drug Administration (2017) has issued 510(k) marketing approval for one direct-to-consumer-genetic test classified as an autosomal recessive carrier screening gene mutation detection system intended for prescription or over-the-counter use — 23andMe Personal Genome Service Genetic Health Risk (GHR) tests (23andMe, Inc., Mount View, California). 23andMe tests for the following 10 diseases or conditions: Parkinson's disease; late-onset Alzheimer's disease; celiac disease; alpha-1 antitrypsin deficiency; early-onset primary dystonia; Factor XI deficiency; Gaucher disease type 1; glucose-6-phosphate dehydrogenase deficiency; hereditary hemochromatosis; and hereditary thrombophilia. However, the manufacturer states 23andMe uses genotyping, not sequencing, and should not be used for medical decision-making (23andMe, 2024).

Findings

Expanded carrier screening panels incorporate numerous autosomal recessive and X-linked genetic conditions that account for a wide range in carrier frequencies existing among at-risk groups and the general population. These include conditions with a very low carrier frequency or with mild or incompletely penetrant phenotypes. The evidence supports improved sensitivity for carrier detection with expanded carrier screening panels over ethnicity-based carrier screening, but the incremental yield of the additional mutations is small for most patients.

Evidence of the clinical utility of expanded carrier screening is limited in terms of improving perinatal, newborn, and infant outcomes; the extent to which individuals or couples make decisions informed by carrier screening; and which factors affect these decisions. The optimal composition of an expanded carrier screening panel has not been determined but should result in a useful carrier pair yield for autosomal recessive diseases appropriate for at-risk reproductive pairs and should be reasonably expected to affect reproductive planning and early neonatal evaluation.

Guidelines vary as to when to offer expanded carrier screening over ethnicity-based approaches preconceptionally and prenatally but trend toward expanded carrier screening as a more equitable and inclusive approach to accessing carrier screening services for reproductive planning. Guidelines emphasize the importance of the informed consent process to facilitate access, including aspects of pre- and post-test counseling that consider incidental findings, variants of uncertain significance, and the implications of the new information on downstream decisions.

Guidelines

A joint statement from the American College of Obstetricians and Gynecologists, the American College of Medical Genetics and Genomics, the National Society of Genetic Counselors, the Perinatal Quality Foundation, and the Society for Maternal-Fetal Medicine recognized the clinical utility of more comprehensive, pan-ethnic carrier screening. The statement provided an approach for health care providers and laboratories for offering expanded carrier screening to their patients but did not provide specifics regarding individual genes (Edwards, 2015).

The American College of Obstetricians and Gynecologists issued recommendations for prepregnancy and prenatal carrier screening and genetics counseling. Ethnicity-specific, panethnic, and expanded carrier screening are acceptable strategies. The appropriate screening approach should be based on the patient's family

history and personal values after counseling. The American College of Obstetricians and Gynecologists recommends (American College of Obstetricians and Gynecologists, 2017; Gregg, 2018):

- Carrier screening for cystic fibrosis and spinal muscular atrophy in all prepregnant or pregnant women, as well as complete blood count and screening for thalassemias and hemoglobinopathies.
- Carrier screening for specific genetic conditions found in some segments of the population — fragile X syndrome, Tay-Sachs disease, and genetic conditions in individuals of eastern and central European Jewish descent.

The choice of conditions to be included in expanded carrier screening panels should achieve a balance between identifying carriers for more common conditions and minimizing the harms of anxiety and additional testing and counseling associated with identifying carriers of extremely rare disorders. The College provides a list of 22 autosomal recessive and X-linked conditions considered reasonable for inclusion in an expanded carrier screening panel, but emphasized that the availability of expanded carrier screening does not preclude the appropriateness of ethnic-based screening or screening based on family history (Appendix; Gregg, 2018).

In general, carrier screening for a particular condition should be performed only once in a person's lifetime. A genetics professional should guide the decision to rescreen based on an assessment of the incremental benefit of repeat testing for additional mutations. For accurate genetic counseling, screening should be offered to the reproductive partner of a woman found to be a carrier for a specific condition. Carrier screening complements, not replaces, other risk-based assessment and newborn screening (American College of Obstetricians and Gynecologists, 2017; Gregg, 2018).

The American College of Medical Genetics and Genomics recommends carrier screening that is ethnic and population neutral and more inclusive of diverse populations. They define the following tiered carrier screening approach based on carrier frequency (Gregg, 2021):

- Tier 1 screening adopts an ethnic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy based on current recommendations from the American College of Medical Genetics and Genomics and those of the American College of Obstetricians and Gynecologists. For other conditions, additional carrier screening is determined after risk assessment.
- Tier 2 carrier screening is based on an American College of Obstetricians and Gynecologists recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100.
- Tier 3 carrier screening is for conditions for any ethnic group with reasonable representation in the United States with a carrier frequency of at least 1/200.
- Tier 4 carrier screening has no lower limit carrier frequency and can greatly extend the number of conditions screened.

These recommendations include Tier 3 carrier screening for all pregnant and preconception patients and Tier 4 carrier screening for consanguineous pregnancies (second cousins or closer) and when a family or personal medical history warrants it. Tier 1 and 2 carrier screening is not recommended because these do not provide equitable evaluation of all racial/ethnic groups. The guidelines also recommend against routinely offering Tier 4 panels.

Similarly, the National Society of Genetic Counselors recommends offering ethnic and population neutral, expanded carrier screening to all who are currently pregnant, considering pregnancy, or might otherwise biologically contribute to pregnancy, taking into account specific features of patients and their preferences and values. The Society considers the risk of mild variant identification through sequencing to be preferable to the risk of variant non-identification through genotyping. Simultaneous expanded carrier screening is preferred to a

consecutive testing strategy, especially prenatally, to avoid delay. The Society does not recommend routinely including variant of uncertain significance in testing results (Sagaser, 2023).

Clinical validity

Several large analyses examined the clinical validity of ethnicity-based and expanded carrier screening in U.S. populations. Carrier screening based on ethnicity may lead to an increased risk for undetected recessive disease. Expanded carrier screening panels as recommended by the American College of Obstetrics and Gynecology provide a reasonable balance between identifying carriers for more prevalent serious inherited conditions and minimizing the harms of anxiety and additional testing and counseling associated with identifying carriers of extremely rare disorders.

For 93,419 individuals undergoing a 96-gene expanded carrier screening panel via next-generation sequencing between January 1, 2014 and September 8, 2016, self-reported ethnicity was an imperfect indicator of genetic ancestry. In 9% of individuals (n = 2,475 carriers), the genetic ancestry component responsible for at least 50% of their ancestry was unexpected and inconsistent with self-reported ethnicity. Concordance was lowest in those who self-reported as Middle Eastern (59.2%), Ashkenazi Jewish (80.2%), or Southern European (84.0%). Relative to expanded carrier screening, ethnicity-based guidelines would have identified only 23% of carriers in the study cohort, with large differences observed across ethnicities (Kaseniit, 2020).

Expanded carrier screening using next-generation sequencing was performed in 381,014 individuals for up to 274 genes meeting clinical utility criteria in current guidelines. Compared to ethnicity-based carrier screening, expanded carrier screening identified additional carriers for diseases associated with Ashkenazi Jewish ancestry, cystic fibrosis, spinal muscular atrophy, and fragile X syndrome, which may impact reproductive decision-making (Westemeyer, 2020).

Investigators assessed the clinical validity for 208 genes and conditions screened on two commercial expanded carrier screening panels — Foresight® Carrier Screen (Myriad Genetics, Salt Lake City, Utah) and GeneAware™ (Baylor Genetics, Houston, Texas). Assessment using the Clinical Genome Resource standardized framework revealed strong evidence of gene-disease association for conditions on the two gene panels. These findings provided support for including conditions on expanded carrier screening panels as recommended by the American College of Obstetrics and Gynecology (Balzotti, 2020).

A single institution study compared the carrier detection rates and carrier couple rates among 4,232 participants at an infertility clinic using three carrier screening panels: an ethnicity-based carrier screening panel; the expanded guideline-based screening panel recommended by the American College of Obstetrics and Gynecology; and a commercial screening panel comprised of 400 variants of 102 genes associated with 100 genetic diseases (Counsyl, now Foresight Carrier Screen). Carrier detection rates for the three panels were 8.5% (n = 659), 15.6% (n = 659), and 29.4% (n = 1,243), respectively. Fifteen couples were identified as carrier couples (1.2%) on the commercial screening panel, seven of whom would have been missed on ethnicity-based screening. For carriers of Hispanic, South Asian, and Middle Eastern ancestry, increasing the carrier screening panel size from ethnicity-based recommendations to the guideline-based screening did not significantly increase the number of carriers (Peyser, 2019).

Clinical utility

A review of 40 articles of varying research methodologies identified potential societal implications of expanded universal carrier screening: unwanted medicalization, stigmatization and discrimination of carriers and people who have the conditions screened, and challenges in achieving equitable access. However, as empirical evidence is scarce, these implications remain largely theoretical (van den Heuvel, 2023).

A systematic review of 108 studies analyzed targeted or universal expanded carrier screening programs for cystic fibrosis, fragile X syndrome, hemoglobinopathies and thalassemia, and spinal muscular atrophy. All but

three studies were noncomparative and retrospective with an overall quality grade of moderate. The proportion of at-risk couples varied considerably among studies, likely affected by participant population, their risk factors, the partner's screening uptake rate, and screening methods. Participants valued the medical benefits from early detection and treatment, associated awareness and preparation, and timely, unbiased information for reproductive decision-making (Ontario Health, 2023).

A companion review of 10 studies examined the implications of a population-based, expanded carrier screening approach on individuals' decisions to have carrier screening in Ontario. It is likely that an increased number of people would consider screening, but the results highlight the need to inform the individual not just on the knowledge carrier screening can provide, but also on how to proceed with the new information. The clinical utility of expanded carrier screening may differ among both patients and providers in terms of whether to undertake carrier screening to obtain clinically actionable results or to inform the individual independent of immediate reproductive decision-making. Information on carrier screening for individuals as a reproductive option should be neutral, non-directive, and, optimally, provided at the preconception stage (Herington, 2021).

A systematic review of 36 studies analyzed the impact of expanded carrier screening on U.S. patients and providers in a prenatal or preconception setting. Although patients expressed desire for expanded carrier screening, clinical uptake and subsequent impact on reproductive decision-making varied. Reproductive care providers, including genetic counselors, also vary in their preference for expanded, guideline-based, or ethnicity-based carrier screening. Providers expressed concerns for the time required for obtaining test results and follow-up counseling with expanded screening and tended to prefer guideline-based screening panels (Ramdaney, 2022).

A systematic review of 10 surveys and two retrospective chart reviews explored interest in expanded carrier screening among individuals and couples in the general population who are not at risk based on their personal or family history. Six of the studies originated from the United States. The sample sizes varied from 80 to 1,669. Interested in a hypothetical test ranged from 32% to 76% of respondents, while actual uptake rates were lower, ranging from 8% to 50%. Uptake rates were highest among pregnant women (50%) and lowest in a preconception population (8% to 34%), except for women preparing for in vitro fertilization (68.7%). The investigators recommend more research to determine if these trends apply to a broader population (Van Steijvoort, 2020).

In a survey of 391 at-risk couples affected by at least one of 176 genetic conditions on the Foresight Carrier Screen panel, expanded carrier screening impacted preconceptional and prenatal reproductive decisions. When screening was offered preconceptionally, 77% planned or pursued actions to avoid having affected offspring. Of respondents screened prenatally, 37% elected prenatal diagnostic testing to inform pregnancy management. In subsequent pregnancies that occurred in both screening groups, 29% pursued prenatal diagnostic testing. The severity of the condition at risk influenced the decision to pursue prenatal testing. Fear of procedure-related miscarriage (35%) and the belief that termination would not be pursued in the event of a positive diagnosis (27%) had the most influence on the decision to decline prenatal testing (Johansen Taber, 2019).

References

On April 2, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Genetic carrier screening" (MAJR), "high throughput nucleotide sequencing" (MeSH), and "carrier screening." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

6/2024: initial review date and clinical policy effective date: 7/2024

Appendix

American College of Obstetricians and Gynecologists: Suggested Expanded Carrier Screening Panel for Autosomal Recessive and X-linked Conditions

The conditions were selected based on the benefits of detection, the accuracy of current screening methods, and the following consensus-determined criteria: 1) The condition has a carrier frequency of 1/100 or greater, which corresponds to a disease incidence of 1/40,000, as a useful threshold. 2) The condition should have a well-defined phenotype and a detrimental effect on quality of life. 3) The condition causes cognitive or physical impairment, requires surgical or medical intervention, or has an onset early in life. 4) The screened conditions should be able to be diagnosed prenatally and demonstrate clinical utility for improving perinatal outcomes, changing delivery management to improve newborn and infant outcomes, and educating parents about post-natal special care needs. 5) Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

- α-thalassemia
- β-thalassemia
- Bloom syndrome
- Canavan disease
- Cystic fibrosis
- Familial dysautonomia
- Familial hyperinsulinism
- Fanconi anemia C
- Fragile X syndrome
- Galactosemia
- Gaucher disease
- Glycogen storage disease type 1A
- Joubert syndrome
- Medium-chain acyl-coenzyme A dehydrogenase deficiency
- Maple syrup urine disease types 1A and 1B
- Mucolipidosis IV
- Niemann–Pick disease type A
- Phenylketonuria
- Sickle cell anemia
- Smith–Lemli–Opitz syndrome
- Spinal muscular atrophy
- Tay-Sachs disease

Source: Gregg (2018).