Carrier Testing Panels for Genetic Diseases

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policies

- Cell-Free Fetal DNA Testing
- Preimplantation Genetic Testing and Related Services
- Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)

Community Plan Policy

- Carrier Testing Panels for Genetic Diseases

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Pretest genetic counseling is strongly recommended to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Reproductive Carrier Screening

Reproductive Carrier Screening panels of up to six genes are proven and medically necessary.

Reproductive Carrier Screening panels of up to 15 genes are proven and medically necessary when an individual and/or their reproductive partner meet at least one of the following criteria:

- Ashkenazi Jewish ancestry (individual/reproductive partner has at least one parent or grandparent of Ashkenazi Jewish descent); or
- A biological First-Degree Relative or Second-Degree Relative has been affected by one or more of the conditions evaluated by the panel

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Reproductive Carrier Screening panels comprising 16 or more genes
- Carrier Screening for all other indications

Note: It is strongly recommended that reproductive Carrier Screening panels include screening for cystic fibrosis (*CFTR*) and spinal muscular atrophy (*SMN1*).

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Medical Records Documentation Used for Reviews

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. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Carrier Screening: Genetic testing that is performed on an individual who does not have any symptoms of a genetic disorder to determine whether that individual may have a genetic variant associated with a certain disorder that could be passed to biological children (American College of Obstetricians and Gynecologists, 2017a; reaffirmed 2025).

First-Degree Relative: First-Degree Relatives include parents, siblings, and children [National Comprehensive Cancer Network® (NCCN®), 2026].

Gene Panel: Testing panel that looks for genetic changes/variants in more than one gene in the same test (Centers for Disease Control and Prevention, 2024; MedlinePlus, 2021).

Second-Degree Relative: Second-Degree Relatives include half-siblings, aunts, uncles, grandparents, grandchildren, and nieces/nephews (NCCN, 2026).

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 guidelines may apply.

CPT Code	Description
0400U	Obstetrics (expanded carrier screening), 145 genes by next generation sequencing, fragment analysis and multiplex ligation dependent probe amplification, DNA, reported as carrier positive or negative
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

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Description of Services

Carrier Screening is used to identify individuals or reproductive partners who are at risk of having a child with clinically significant autosomal recessive or X-linked conditions; screening results may impact reproductive decision-making. The use of modern technology such as next-generation sequencing enables the use of Gene Panel tests, which analyze multiple genes at the same time (Gregg et al., 2021).

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 (ethnic based), or based on family history. The American College of Obstetricians and Gynecologists (ACOG) (2022, 2017b; both reaffirmed 2025) recommends screening for

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cystic fibrosis (CF), spinal muscular atrophy (SMA), and hemoglobinopathies in all women who are considering pregnancy or are currently pregnant.

Carrier Screening for Individuals of Ashkenazi Jewish Descent

Certain autosomal recessive conditions are more prevalent in individuals of Ashkenazi Jewish (AJ) descent. Some of these disorders are lethal in childhood or are associated with substantial morbidity. Carrier Screening for individuals of AJ descent is focused on identifying reproductive partners who are at risk of having a child with a disorder that has a higher prevalence in this population. The majority of individuals of Jewish ancestry in North America are of AJ descent and therefore have an increased risk of having a child who has one of these disorders (ACOG, 2017b; reaffirmed 2025).

AJ Carrier Screening panels may include testing for some or all the genetic diseases below:

- Tay-Sachs disease
- Canavan disease
- CF
- SMA
- Familial dysautonomia
- Bloom syndrome
- Fanconi anemia
- Niemann-Pick disease
- Gaucher disease
- Mucolipidosis IV
- Maple syrup urine disease
- Joubert syndrome
- Glycogen storage disease 1A
- Familial hyperinsulinism
- Usher syndrome 1F and III

Pan-Ethnic Carrier Screening Panels

Historically, Carrier Screening has focused on specific ethnic populations that are known to be at an elevated risk of certain clinically significant disorders (e.g., individuals of AJ descent). However, it has become progressively more difficult to classify an individual's true ancestry in today's multiracial society. As such, the likelihood of being a carrier for a certain disorder may be inconsistent with previous assumptions regarding disease prevalence in the ethnic or racial group with which an individual identifies; this has led to consideration of pan-ethnic screening. Pan-ethnic screening offers panel testing for certain disorders to all individuals who are pregnant or considering pregnancy, irrespective of ethnicity (ACOG, 2017a; reaffirmed 2025).

Carrier Screening panels have the capacity to analyze large numbers of genes simultaneously, but there is currently a lack of standardization in conditions screened and Carrier Screening panel composition. Thus, marketed panels may include many more genes than would be recommended on an individual basis. 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 knowledge of the carrier frequency within the testing population and the proportion of disease-causing mutations on the assay platform. ACOG suggests panels targeting conditions with a carrier frequency of at least one in 100, which correlates with a disease incidence of one in 40,000 (ACOG, 2017a; reaffirmed 2025). The American College of Medical Genetics and Genomics' 2021 practice resource (Gregg et al.) recommends the adoption of a tier-based system built on carrier frequency, with Tier 3 Carrier Screening that includes conditions with carrier frequencies of at least one in 200 plus CF, SMA, and risk-based screening offered to all individuals who are pregnant or planning a pregnancy.

Genetic counseling is strongly recommended prior to Carrier Screening to inform persons being tested about the advantages and limitations of testing as applied to a unique person. For information regarding noninvasive prenatal testing, refer to the Medical Policy titled Cell-Free Fetal DNA Testing.

Clinical Evidence

Carrier Screening for Individuals of Ashkenazi Jewish Descent

Shi et al. (2017) genotyped over 3,000 participants 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 laboratory to identify the genes that should be screened and used preexisting, deidentified samples from research participants. There were 2,252 AJ participants tested for 29 recessive disorders, and an additional 1,390 AJ and 6,813 non-AJ participants were screened for a subset of 18 recessive disorders. The authors identified seven disorders with a carrier frequency of greater than one in 100, nine with a carrier frequency between one in 100 and one in 200, and four between one in 200 and one in 500. Nine conditions had a carrier frequency of less than one in 500 or were not found. Of the 20 diseases with a carrier frequency higher than one 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 a participant to be a carrier of one of the 18 diseases was one in six. However, the chance that an AJ couple would be

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carriers of the same disease and be at risk for an affected pregnancy is one in 441. A noted limitation is the use of a restricted, predefined variant panel and platforms that are unable to detect novel mutations, along with very low detection rates for several conditions, which may reflect sample size–related underdetection. In addition, because ancestry was self-reported, the findings may be affected by potential ancestry misclassification and may not fully represent the broader AJ population's genetic diversity.

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 from 506 participants who underwent NGS for 84 recessive conditions and targeted genotyping. Overall, 288 participants 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 with 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 at-risk carrier couples and 115 (26%) pathogenic variants that would not be found by routine AJ screening. The study is limited by its focus on a predominantly AJ, self-selected, and highly motivated high-risk population, which reduces generalizability to more diverse groups. It also lacked detailed family history data and found no additional mutations detected by NGS compared with genotyping for conditions commonly screened in this population, although the authors noted that expanding AJ panels and increasing genetic heterogeneity make the use of NGS increasingly important.

Pan-Ethnic Carrier Screening

Aul et al. (2025) developed a position statement in consultation with the Canadian College of Medical Geneticists (CCMG), drawing on multidisciplinary expert opinion. Currently, expert recommendations broadly agree that pan-ethnic and expanded carrier screening (ECS) panels should prioritize genes associated with severe, childhood-onset conditions with well-defined phenotypes. However, the concept of severity is subjective and continues to evolve as new treatments become available and gene-disease relationships are refined. Although there is consensus that individuals should have access to information about their reproductive risks, there is no agreement on which specific genes should be included in ECS panels, leaving these decisions to private companies, which results in substantial variation in clinical practice. The CCMG statement recommends offering pan-ethnic reproductive carrier screening (RCS) through provincial or territorial programs but restricting it to a small panel of relatively common, severe, childhood-onset genetic conditions, specifically cystic fibrosis (CF), fragile X syndrome, spinal muscular atrophy (SMA), hemoglobinopathies, and founder mutations associated with Tay-Sachs disease, Canavan disease, and familial dysautonomia. This guidance emphasizes the importance of coordinated oversight, appropriate resourcing, and comprehensive education for both individuals and providers during implementation. It further supports maintaining regional ethnicity-based screening programs where clinically appropriate. Importantly, the CCMG concluded that population-level ECS is not recommended at this time due to limited evidence supporting broad application within the Canadian context. The authors noted that although the recommendations were developed using the best-available evidence, a formal systematic review was not conducted due to the low strength of the appraised evidence; the recommendations are based on expert opinion in collaboration with Canadian professional organizations, including the CCMG and the Canadian Association of Genetic Counsellors.

Gruzin et al. (2025) conducted a large-scale, genomic data–modeling and validation study using ClinVar and gnomAD v4.1.0 to evaluate RCS gene panels, with the goal of maximizing clinical utility. Professional organizations such as the American College of Medical Genetics and Genomics (ACMG), American College of Obstetricians and Gynecologists (ACOG), and European Society of Human Genetics have developed criteria for selecting genes for carrier screening based on analytical validity, carrier frequencies, genotype-phenotype correlations, disease severity and age at onset, available prenatal care options, treatment availability, and clinical management considerations. However, the optimal number of genes needed for a clinically useful, equitable, pan-ancestry screening panel remains undetermined. The ACMG currently recommends a panel of 113 "one-size-fits-all" genes (Tier 3 screening) for all pregnant individuals. This study identified significant inconsistencies in the ACMG carrier screening gene lists, particularly related to test performance among underrepresented ancestry groups due to reliance on older and less diverse population datasets. Using their modeling framework, the researchers estimated that increasingly larger, data-driven carrier screening panels would yield progressively higher detection of at-risk couples (ARCs) by capturing a broader distribution of pathogenic variants across ancestries, with panels of 152, 248, 531, and 725 genes achieving approximately 90%, 95%, 99%, and 99.7% modeled positive yields, respectively. These modeled predictions were then validated using real-world data from more than 63,000 screened couples, confirming that optimized panels improve detection across diverse ancestries. When the investigators reevaluated the ACMG Tier 3 list using updated population data, they found that 44 autosomal recessive genes in the original ACMG list no longer met the ACMG's own inclusion criteria, while 19 previously excluded genes now met the threshold for inclusion. This reevaluation demonstrates that the composition of the ACMG Tier 3 panel is highly sensitive to the population data on which it is based and that the use of outdated or ancestry-limited datasets can result in panels that no longer reflect true carrier frequencies or equitable detection across diverse populations. The authors noted that their analyses are limited by small sample sizes in several gnomAD ancestry groups and by modeling assumptions

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that simplify real-world genetic and reproductive complexity. They also reported potential conflicts of interest, as several contributors are affiliated with organizations involved in commercial carrier screening services, which may influence interpretation of the findings. Despite these limitations, the study provides a valuable, data-driven framework that better aligns with contemporary population genetics than the more static ACMG model. These findings underscore the need for carrier screening panels that incorporate regularly updated population data and flexible, evidence-based criteria to better support equitable and clinically meaningful detection across ancestries.

A 2024 Hayes Precision Medicine Insight found minimal support for the use of ECS in healthy populations to guide reproductive decision-making. Per Hayes, ECS involves testing parents for variants in many genes that can be associated with a variety of recessive disorders. The Hayes conclusion was based on a review of six abstracts of publications addressing the clinical utility of ECS for informing clinical or reproductive decisions. Four professional guidelines addressing ECS were also identified; these guidelines did not show distinct agreement regarding which genes should be included in ECS but generally recommend limiting testing to genes with known clinical impact in terms of reproductive planning. In addition, risks related to ECS, including identification of variants of unknown significance and diseases that have a wide range of phenotypic expression, reduced penetrance, or adult onset, were identified. Of the four guidelines reviewed, only one was based on a formal evidence review process.

Wang et al. (2023a) sought to evaluate the clinical utility of RCS in a systematic review and meta-analysis. The assessment included 11 studies, which incorporated screening for a minimum of three to a maximum of 176 conditions. Across these studies, RCS led to the identification of one to 24 high-risk couples per 1,000 individuals screened. Based on pooled estimations, the prenatal diagnosis rate in pregnant high-risk couples was 0.644 (95% CI, 0.364-0.9230), the termination rate for affected pregnancies was 0.714 (95% CI, 0.524-0.904), and the rate of in vitro fertilization with preimplantation genetic testing (PGT) was 0.631 (95% CI, 0.538-0.725). The data analysis revealed a statistically significant reduction in the rate of individuals undergoing prenatal diagnosis and termination as the number of conditions in the screening test increased. In addition, carriers who were found to have conditions with greater clinical severity were more likely to terminate pregnancy or choose in vitro fertilization with PGT. The authors concluded that while the number of conditions screened and the severity of those conditions appear to impact the reproductive decisions of high-risk couples, additional study is required to more clearly define clinical utility and provide evidence to assist with the design of appropriate screening panels. The researchers also highlighted the importance of genetic counseling in conjunction with RCS. This review is limited by potential omissions due to varying definitions of clinical utility, restriction to English-language studies, and the exclusion of panels that screened fewer than three conditions. Additionally, the small number of eligible studies and wide variation in screened conditions may have biased pooled estimates and limited the ability to evaluate certain outcomes. The publication by Ghiossi et al. (2018), previously discussed in this policy, was included in the Wang et al. systematic review and meta-analysis.

Wang et al. (2023b) evaluated gene content as well as the most common genes/conditions included in 22 existing carrier panels in a comprehensive evaluation of currently marketed carrier screening panels. The number of genes in each panel varied greatly (44-2,054 per panel). Overall, 2,205 cumulative unique genes were included in the 22 panels. Overall, 15 genes (0.7%) with associated conditions that could be considered severe (despite some conditions having only mild or moderate symptoms, depending on the specific pathogenic variants in the associated genes) were included in all 22 of the panels. However, the carrier frequency of the 15 genes varied widely (one in 49 to less than one in > 500), suggesting that carrier frequency was likely not the primary factor guiding gene or condition selection across the 22 panels. In total, 17% (374) of the 2,205 genes were present in 10 or more of the panels, and 73.6% were present in five or fewer panels. Approximately one-third of the genes [695 (31.5%)] were present in one panel only. These findings demonstrate the significant variation in gene inclusion among manufacturers of carrier gene panels. The authors highlighted the lack of consensus on the design of carrier screening panels while acknowledging the increasing availability of genomic data and sequencing information contributing to the rapidly developing industry of carrier panel screening. They underscored the importance of the development of consistent and reliable carrier screening to better serve both individuals undergoing testing and the health care providers ordering and interpreting the test results. The evaluation was limited by the rapidly evolving nature of screening technologies, which may quickly render findings to be outdated. Additionally, carrier frequency and condition severity were not systematically collected for all 2,205 genes, which the authors noted may weaken the strength of their conclusions.

Johansen Taber et al. (2022; included in the 2024 Hayes report) conducted a study of the carrier screening results of 460,608 individuals who had been tested using an NGS panel that screened for up to 176 conditions in an effort to ascertain a carrier screening panel design that is consistent with existing carrier screening recommendations published by ACOG (2017b) and the ACMG (2021). Individuals with a family or personal history of disease or reported consanguinity were excluded, and 11 races/ethnicities were represented. Overall, 40 conditions had carrier frequencies of at least one in 100, and 75 conditions had carrier frequencies of at least one in 200. A well-defined phenotype was present for 175 of the conditions, and at least one severity criterion and onset early in life were met for 165 conditions. Overall, 37 conditions

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met conservative thresholds (including carrier frequency of at least one in 100), and 74 conditions met more liberal thresholds (including carrier frequency of at least one in 200). In a panel that tests for 37 conditions, all seven conditions currently recommended by both ACOG and the ACMG for screening in at least one race/ethnicity would be included; this panel would detect 63% of carriers and 84.6% of ARCs (compared with a 176-condition panel). In a more liberal panel testing for 74 conditions, 81.4% of carriers and 96.6% of ARCs would be detected. The authors concluded that panels that include screening for either the 37 conditions based on the conservative threshold or the 74 conditions based on the more liberal threshold would both be consistent with established guidelines. A noted limitation is that conditions beyond what were included in this study may meet ACOG or ACMG guideline criteria. In addition, although the researchers took steps to ensure the accuracy of carrier frequency data, which were based on self-reported ethnicity, there is potential for over- or underestimation. The development of transparent and consistent panel design that aligns with evidence-based guidelines is recommended.

Ramdaney et al. (2022) conducted a systematic evidence review to evaluate the client and provider experiences with ECS. The authors reviewed literature between January 1, 2003, and May 31, 2021, and found 36 articles that fit the inclusion criteria. Overall, 16 of the articles evaluated test outcomes, 10 articles evaluated provider outcomes, and 20 articles evaluated client outcomes. For the evaluation of client outcomes, the authors focused on the uptake rates of ECS, the yield of carrier couples, and the influence on reproduction decision-making. It was noted that the uptake rate in clients in the general population was 39%, which was consistent with that in other studies. The uptake of ECS among partners varied between 42% and 77%, and the main impacting factors were presence of the partner at the initial appointment, disease severity, and ease of logistical factors. The yield of carrier couple rates ranged from 0.1% to 16.9%; however, the specific populations, panels used, and conditions/genes/mutations assessed varied widely. When evaluating in silico studies using modeled data for yield of carrier couples, it was noted that screening for only CF and SMA would have missed at least 881 of 966 ARCs. The authors noted that decision-making following actual carrier screening results varied greatly depending on whether the clients were preconception or already pregnant. With preconception, most clients elected to pursue or indicated interest in PGT to minimize the risk of an affected pregnancy. For those clients who received PGT and did not pursue or take direct action given the results, some clients noted benefit from a planning and preparation standpoint. For those clients who were already pregnant, ARCs were less likely to alter their reproductive plans than those clients who received results during the preconception period. The authors evaluated the provider influence on reproduction decision-making and noted that more than half of the provider groups analyzed did not offer ECS to their clients; additionally, many of the studies were conducted before newer guidelines regarding ECS were published. It was also noted that the time required for proper education and follow-up was a concern for genetic counselors. Limitations include the significant inconsistency in methodologies and population, which limited the ability to assess the impact of ECS in the United States. There was a lack of studies documenting outcomes with minimal guideline-based carrier screening compared with ECS. Additionally, most of the studies included were observational, and the majority were rated poor/very poor quality or had a high risk of bias.

Leung et al. (2021) developed a method of calculating disease prevalence, ethnic carrier frequency, detection rate, and recurrence risk (RR) metrics across four autosomal recessive conditions (*ABCC8, ASPA, GAA*, and *MMUT*), using CF as proof of concept. A step-by-step approach for calculating detection rate and RR was based on the sum of disease allele frequencies of pathogenic variants found in the literature. CF guidelines were followed, and carrier frequencies for five ethnicities were gathered from published studies and public databases. If no specific carrier frequency was available, they were derived from the Hardy-Weinberg equation. If neither were available, a default carrier frequency of one in 500 was used. The disease allele frequencies of the four genes were compared among three laboratories, and possible reasons of discrepancy were explored. The study revealed that multiple laboratories testing the same genes demonstrated a wide range of detection rates and RRs. Possible explanations for this discrepancy include differences in calculation method for detection rate; differences in definitions for detection rate or laboratories calculating a detection rate that is more consistent with the definition of analytical sensitivity (which may increase RR); known technical challenges of NGS that may limit detection of variants; and timing of publications that may also lead to discrepancies in reported carrier frequencies. The authors emphasized that accurate detection rate and RR statistics are critical for reproductive decision-making and stated that there is a need for professional societies to offer official recommendations to avoid laboratories using disparate criteria in setting their preferred lowest detection rate.

Kauffman et al. (2021) conducted a randomized controlled trial examining the effects of disclosing negative (normal) ECS results compared with usual care in an effort to address concerns regarding the impact of ECS on health care utilization. The authors assessed differences between women randomized to ECS (n = 127) and usual care (177) by evaluating utilization of mental health services, including outpatient, inpatient, and medication use; utilization of outpatient primary care, outpatient specialty care, and inpatient and outpatient mental health services in the year following randomization; and utilization of pregnancy-related services in the 5 years prior to and at any point following randomization with a documented pregnancy. The authors did not find any evidence of harms or increased health care utilization in women who had a negative ECS. There were no significant differences in outpatient mental health service use between study arms in

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the period between randomization and results disclosure or in the 12-month follow-up period after results disclosure. Additionally, there were no significant differences in the use of primary care and specialty care services in the year following results disclosure and no significant differences in utilization of pregnancy-related services following ECS. Of the 304 participants who had data analyzed, there were only two cases noted in which ECS led to inappropriate health care utilization: one participant misunderstood the carrier result and sought treatment for hemochromatosis, and one participant attempted to refuse first trimester prenatal screening because she did not understand how it differed from ECS. Limitations of this study include the possibility of refusals of standard-of-care treatment that were not documented, a lack of racial/ethnic and socioeconomic diversity, and exclusion of male partners. The authors noted that future studies should continue to evaluate the possibility of harms of screening, specifically for non-White and low-income populations.

Kaseniit et al. (2020) quantitatively examined the efficacy and equity of ethnicity-based carrier screening in capturing disease risk for recessive conditions. A 96-gene ECS panel was performed in 93,419 participants; correspondence was assessed among carrier status, self-reported ethnicity, and a dual-component genetic ancestry calculated from sequencing data. The authors reported that a substantial and disproportionate risk for recessive disorders is not detected when carrier screening is based on ethnicity, which leads to inequitable reproductive care. This conclusion was made after establishing that self-reported ethnicity was an inaccurate predictor of genetic ancestry, with 9% of participants having > 50% genetic ancestry from a lineage inconsistent with self-reported ethnicity. Self-reported ethnicity resulted in missed carriers in at-risk populations; for 10 ECS conditions, participants with intermediate genetic ancestry backgrounds who did not self-report the associated ethnicity had a significantly elevated carrier risk. For seven of 16 conditions included in current screening guidelines, most detected carriers were not from the population that the guideline was aiming to serve. The algorithm from this study can be used across laboratories when considering genes for ECS panel inclusion, according to the authors.

Arjunan et al. (2020) used a published algorithm that stratifies diseases into four classes of severity (mild, moderate, severe, and profound) for 176 genes screened by ECS; objective severity classifications were then assigned. Previous reports from ACOG/the ACMG have not defined how to interpret severity criteria for genes included in ECS. Severity categories based on disease traits were mapped to four severity-related ECS panel criteria from ACOG. Four medical geneticists and eight genetic counselors applied the severity algorithm to subsets of 176 genes. A group consensus was made on how disease traits mapped to ACOG severity criteria. Overall, 39% (n = 68) of genes were classified as profound, 40% (n = 71) as severe, 20% (n = 36) as moderate, and 1% (n = 1) as mild. Of 176 total genes, 170 (96.6%) met at least one of the four criteria, 129 (73.3%) met at least two, 73 (41.5%) met at least three, and 17 (9.7%) met all four. The authors noted that the medical geneticists and genetic counselors who reviewed the conditions for this study may not be replicated in practice by clinicians with either similar or different expertise. In addition, the medical geneticist reviewers were not blinded to the genetic counselors' final classifications, so it is possible that they were influenced by the genetic counselors' reviews. Lastly, the genes in the study were based on what is available in the current literature, which may skew toward more severe presentation, especially for rare diseases.

Balzotti et al. (2020) used a ClinGen framework to determine the clinical validity of a gene-disease relationship for 208 autosomal recessive and X-linked conditions offered in commercially available ECS panels by Myriad Women's Health (Foresight) and Baylor Genetics (GeneAware). All conditions met the evidence threshold for supporting a gene-disease association. Overall, 98% of conditions (203/208) reached the strongest (definitive) level of gene-disease association; of the remaining five, four were classified as having moderate evidence, and one was classified as having limited evidence. In total, 21 gene-disease pairs were curated independently by Myriad and Baylor to determine the level of concordance of classification between the two laboratories. The authors surmised that the majority of ECS panel conditions have demonstrable support for gene-disease association, which is a crucial component of ECS clinical validity and ACOG-recommended inclusion criteria for ECS panels. Limitations include potential inconsistencies in how conditions were categorized (potentially skewing results) and the possibility of the emergence of new evidence that may change the classifications used.

Rosenblum et al. (2020) performed a retrospective study to compare the carrier detection rate between a pan-ethnic panel (87 disorders) and an AJ ethnic-specific panel (an 18-disorder subset of the pan-ethnic panel) in 2,398 patients who self-identified as being of AJ descent, with no personal or family history of a genetic disorder. The pan-ethnic panel, which assessed 434 targeted, predefined variants in 87 genes that cause 87 disorders, was tested in 1,150 patients, and the AJ-specific panel, assessing a subset of 147 variants in 18 genes that cause 18 disorders, was tested in 1,248 patients. The pan-ethnic panel identified 431 patients (37.5%) as carriers of at least one disorder, and 87 of these (76%) were carriers of two or more disorders. For the AJ panel, 319 patients (25.6%) were determined to be carriers of at least one disorder, and 60 (4.8%) of these patients were carriers for multiple disorders. The researchers also reanalyzed the pan-ethnic data for the 18 genes in the AJ-specific panel in those patients who were found to be a carrier of one of the 87 genes in the pan-ethnic panel. The carrier detection rate would have been 24.3% (280/1,150); the researchers stated that 151 patients would have been missed for carrier detection. The researchers concluded that these data may contribute to further

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professional discussion on the clinical utility of ECS. However, the study was retrospective and relied on self-reported AJ ancestry, introducing the potential for misclassification, and the two cohorts were screened using different panels at different times, limiting the ability to control for population variation. In addition, because the design focused only on these targeted panels, it was unable to capture the impact of larger NGS-based or whole-gene assessments.

Westemeyer et al. (2020) performed a retrospective analysis of data from a cohort (n = 381,014) receiving ECS of up to 274 genes. The cohort included mostly women [339,739 (89.17%)] and various ethnicities: 148,828 Caucasian patients (39.06%), 62,626 Hispanic patients (16.44%), and 52,454 African American patients (13.77%). The remaining 117,106 patients (30.74%) were either of other races/ethnicities or did not provide information. The majority of patients (374,911) were tested for CF, and 14,229 (3.8%) were found to have a pathogenic or likely pathogenic variant yielding a one in 26 carrier frequency. For CF, 44.0% (6,260/14,229) of carriers identified had a variant not on the standard genotyping panel. Similarly, 344,407 patients were screened for SMA, and 14,606 [one of 24 (4.24%)] were found to be carriers or at-risk silent carriers. Of the 14,606 carriers for SMA, 8,763 [one of 39 (2.54%)] were at risk for being silent carriers, which was not detected by standard screening. In addition, for AJ disorders, 81.6% of carriers identified did not disclose AJ ancestry. For the largest gene panel (274 genes), 60,052 patients were tested, and 38,300 (63.78%) were positive for at least one disorder. The researchers also noted the carrier rates for this large, 274-gene panel compared with those in the literature. Of the 274 genes screened, 117 had a carrier rate that differed from what was expected. The researchers concluded that with the assumption of random pairing across the study population, approximately one in 175 pregnancies would be affected by a disorder in the 274-gene screening panel. Of note, this retrospective study may have been affected by ascertainment bias, as patients opting for screening may differ from the general population, and race/ethnicity data were incomplete or potentially inaccurate, limiting subgroup analyses. In addition, underreporting of accurate family history restricts the generalizability of the findings.

Guo and Gregg (2019) conducted an analysis of exome sequencing data (n = 123,136) to determine the carrier rates for six major ancestries (African/African American, Hispanic, AJ, East Asian, non-Finnish European, and South Asian). The study examined 415 genes that are associated with severe recessive conditions and started with determining the variant carrier rates to then be able to estimate the gene carrier rates (GCRs). Across the ancestries, the highest GCR for a single gene was determined to be for African/African American individuals at 12% for *HBB*. The carrier rates declined for most ancestries; only 30 of the genes in the AJ group had a carrier rate of > 1%. Likewise, in the Hispanic population, only six of the genes had a GCR of > 1%. Overall, the researchers found that 32.6% (East Asian) to 62.9% (AJ) of individuals are variant carriers; however, screening all 415 genes would only identify 0.17% to 2.52% of couples as at risk. This study relied on gnomAD exome data, which is not a true population-based cohort and likely has biases due to socioeconomic status and ancestry, limiting the accuracy of estimated carrier and at-risk couple rates in the general population. Additionally, results may be affected by variable sequencing quality, ancestry misclassification, and exclusion of conditions with uncertain pathogenicity, which could bias gene- and variant-level estimates.

Johansen Taber et al. (2019; included in the Wang et al., 2023a, systematic review and meta-analysis above) reported on survey results from female partners of 391 ARCs who participated in ECS of 176 genetic conditions. The cohort was identified from over 270,000 individuals who underwent screening via the laboratory's ECS panel from September 1, 2015, to December 31, 2017. Female individuals were identified from the database who (1) were found to be carriers of a pathogenic or likely pathogenic variant conferring risk for at least one of 176 autosomal recessive or X-linked conditions currently included in the laboratory's ECS panel; (2) were aged 18 years or older; (3) had consented to being contacted about participating in research at the laboratory; and, for those carrying pathogenic or likely pathogenic variants associated with autosomal recessive conditions, (4) had reproductive partners meeting the same eligibility criteria and were confirmed by the laboratory as being carriers of a pathogenic variant in the same gene. Couples carrying only variants known to cause mild presentations of biotinidase deficiency (D444H), *NPHS2*-related nephrotic syndrome (R229Q), and 21-OH–deficient congenital adrenal hyperplasia (*CYP21A2* gene duplication) were excluded. The 1,701 ARCs invited to complete the survey were geographically dispersed and encompassed 15 ethnicities and more than nine religions. The ARCs reported being at risk for 53 different conditions, with 10% indicating that they were at risk for two conditions and 1.8% reporting being at risk for three conditions. The actions taken by the ARCs were broken down into those receiving preconception ECS results and those receiving the results during the prenatal period. ECS was performed in 235 preconception ARCs; 77% of these couples indicated that they planned or pursued pregnancy management options to avoid having an affected child. Of the 154 ARCs who received the ECS results while pregnant, 37% reported pursuing prenatal diagnostic testing (PNDx). Of them, 36% had affected pregnancies; 40% of affected pregnancies resulted in termination. Of the 63% of cases that did not report PNDx, 75% resulted in live birth; postnatal testing was planned or had been pursued in 62% of those. In addition, 2.1% terminated the pregnancy without PNDx. The authors also surveyed the ARCs for actions and outcomes in subsequent pregnancies. Of those who pursued PNDx through chorionic villus sampling or amniocentesis, 29% had affected fetuses, and 75% of them terminated their pregnancies. Limitations of the study include the accuracy of the individuals' recollection of actions, possible response bias, and a larger number of ARCs whose current or future pregnancies were at risk for conditions that occur more often in the

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population, such as CF and fragile X syndrome. However, the authors tried to decrease these effects by analyzing results in aggregate and by condition severity. Overall, this study represents the largest cohort of at-risk and diverse couples screened to date. The authors asserted that the study's results indicate that ECS directs changes in pregnancy management that can lead to fewer births of children with clinically significant genetic diseases and suggested that there may be clinical value in screening for diseases that have not traditionally been assessed for in prenatal/preconception screens.

Peyser et al. (2019) compared the efficiency of ECS with that of ethnic-based screening to identify carriers. A cohort of 4,232 participants seeking fertility treatment was studied. ECS was performed at one genetic testing laboratory in participants seen between June 2013 and July 2015. Ethnicity was self-reported. Carrier rates based on ECS were calculated. Carrier rates were also determined for the ACOG-recommended ECS tests (ACOG-based screening) and ethnicity-based screening (ACOG and ACMG ethnicity panel recommendations). The ECS test under study was made up of 400 variants of 102 genes associated with 100 genetic conditions. Fragile X CGG repeat size and *SMN1* exon 7 copy-number status for SMA screening were also included in the ECS panel. Carrier rates were calculated for the overall study population and for each ethnic subpopulation and then compared to determine the differences between carrier identification rates by each panel. The ECS panel did not screen for α-thalassemia and maple syrup urine disease 1A (MSUD1A), two conditions included in the ACOG-based screening panel. Therefore, the carrier rate for the ACOG-based screening was calculated without including these two conditions. Overall, 4,232 participants were tested [2,880 female (68.1%); 1,352 male (31.9%)] for carrier status using ECS. Applying ethnic-based screening recommendations would have resulted in 359 of 4,232 participants (8.5%) being identified as carriers. With application of the ACOG-based screening guidelines, 659 of 4,232 (15.6%) would have been identified as carriers. With the ECS panel, 1,243 of participants (29.4%) were identified as carriers. A large and highly significant difference was found between carrier rates when each panel was applied to the population and then compared to each other. The authors also looked at the data from subpopulations based on self-reported ethnicity. The number of carriers identified increased with the increasing panel size across the total study cohort and in all but three of 14 self-reported ethnicities. In the Southeast Asian and Native American populations, the only increase was seen from ACOG-based screening to ECS, resulting in identification of additional carriers. However, the identification of carriers did not change, regardless of the panel for the Pacific Islander cohort. Further, with observation of the overall population and five subpopulations, carrier rates were statistically different in all three comparisons: mixed or other Caucasian, Southern European, Northern European, unknown/not reported, and AJ. In three subpopulations (Hispanic, South Asian, and Middle Eastern), significant differences were observed in ethnic-based screening vs ECS and ACOG-based ethnic screening vs ECS but not the ethnic-based screening vs ACOG-based screening. Ethnic-based screening vs ECS only provided statistical differences in the African or African American population. However, in two subethnic populations, East Asian and Southeast Asian, the carrier numbers for each panel were not statistically significant. Overall, 1,206 couples were screened using the ECS panel; 15 (1.2%) were identified as carrier couples. In revealing the ethnicity of each partner, eight of 15 (53%) would have been recognized through ethnic-based screening guidelines. In addition to carrier couples, 73 women were found to be carriers of fragile X, with variation in repeat numbers identified and thus variation in classification of the reproductive risk. In conclusion, the authors presented data that show that ECS is superior to ethnic-based genetic screening at identifying genetic disease carriers and carrier couples. The authors argued that their study provides additional evidence that ECS provides a larger amount of preconception information. The study did have noted limitations; study participants who were seeking ECS due to a family history of a specific disorder were included in the analysis, which could have elevated the rate of carrier couples found in the study. In addition, learning carrier status for diseases with late onset or variable phenotypes could lead to increased anxiety and confusion for those undergoing ECS.

Terhaar et al. (2018) examined outcomes of three unique multigene RCS panels in a retrospective analysis. Panel sizes varied; genes associated with a minimum of three diseases (trio) to a maximum of 218 diseases (global) were analyzed. Data were reviewed for 75,036 patients referred by a health care provider in the United States. Trio screening was applied to 51,584 samples, and 7.2% of those yielded a positive result. A 23-gene panel (standard) was used for the assessment of 19,550 samples, with a 13.2% positive rate. Finally, 3,902 samples were assessed with the global panel; 35.8% were positive. Overall, 127 conditions were identified at least once in this group. The authors noted that those seeking the global panel were more ethnically diverse than the other groups. It was not reported in this study if any ARCs were identified. The researchers speculate that although receiving more genomic information can be beneficial to individuals 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. In addition, large panels may identify conditions with mild phenotypes. Common diseases like CF may be familiar to clinicians, but rare diseases may not be. Educational resources for clinicians and individuals are needed to ensure informed conversations and decision-making. The study was limited by its retrospective design and its use of three commercial panels from a single laboratory that relied on targeted genotyping, which may miss pathogenic variants. In addition, because results were derived from individuals who were referred for commercial testing, the positivity rates may reflect referral bias and may not generalize to the broader population.

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Wilfond et al. (2018) reported on lessons learned from the NextGen study, which was a prospective study designed to explore the best approaches to genomics-based RCS. The study enrolled women interested in carrier screening, randomizing them to either receive genomic sequencing (n = 133) or receive usual care (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, categorizing the conditions into five classes that participants could opt to learn about. The classes included diseases resulting in a shortened life span, serious conditions, mild conditions, conditions with unpredictable outcomes, adult-onset conditions, and medically actionable conditions related to the participant's personal health (secondary to carrier screening). Overall, 15 ARCs were identified; most were at risk for adult-onset conditions. Eight were carriers for hereditary hemochromatosis, two were carriers for α_1-antitrypsin deficiency, one was a carrier for nonsyndromic hearing loss, one was a carrier for factor V Leiden homozygosity, and the remaining were carriers for X-linked disorders. These included spondyloepiphyseal dysplasia, G6PD deficiency, and hemophilia A. Overall, 78% of participants had at least one finding. This leads to concerns about implementation of this approach into clinical workflows. The median time needed by a genetic counselor to prepare for a follow-up visit for positive results was 64 minutes. In this study, 26% of women became pregnant before disclosure, adding additional time sensitivity to developing a genomic sequencing–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 receiving genomic sequencing–based screening did not seek out more mental health or other services than those receiving usual care. They also did not report more anxiety or depression. One participant declined amniocentesis for chromosome abnormalities because she believed that the ECS assessed that; this misconception was later corrected. The participant who was identified as a carrier of hemophilia A did undergo amniocentesis; the fetus was male and found to carry the pathogenic variant, which altered the birth plan and allowed the neonatal team to intervene early. In conclusion, the researchers noted that genomics-based carrier screening could have a significant impact on clinical workflow and resources, but the optimal gene targets need to be identified. Additional research is needed to address these issues. Of note, the study population limits generalizability, as participants were older, were more educated, had higher income, were less racially/ethnically diverse, and were all covered by a large commercial insurer. Additionally, only participants who had already undergone preconception carrier screening were recruited. Lastly, the trial produced very few high-risk couples, providing limited ability to assess reproductive decision-making or downstream actions among those at highest risk.

Shraga et al. (2017) reported on the reliability of self-reported ethnicity vs genetic ancestry for clinical decision-making in the context of genetic carrier screening. Overall, 9,138 participants were referred by a variety of health care providers such as fertility specialists, obstetricians/gynecologists, and genetic counselors from the United States and Spain. The carrier screening test offered consisted of 311 autosomal recessive and X-linked conditions. Ethnicity information was gathered two times, first at the time that the test was ordered and second when self-recorded on the test requisition form. The couples were asked to choose all applicable ethnicities from the following list of options: African, East Asian, European, French Canadian, Jewish, Latin American, Mediterranean, Middle Eastern, Native American, South Asian, Southeast Asian, and/or other. For the option "other," participants could write in the self-identified ethnicity. All "other" responses were mapped to appropriate categories when applicable (e.g., Caucasian/White mapped to European). The second self-report was obtained during the posttest appointment with a genetic counselor. During the family history portion of the consultation, participants were asked to identify their race/ethnicity or where their family originated from. For situations in which participants did not participate in counseling or were unreachable, a family history ethnicity was not generated, and these participants were not considered in that part of the analysis. However, they were still included in the comparison between requisition form ethnicity and genetic ancestry. A set of single-nucleotide polymorphisms (SNPs) was selected that could accurately determine continental genetic ancestry in the participant population. SNP frequencies were obtained from the ALFRED database, and through a repetitive process, a set of SNPs that could separate the continental groups was selected. Six of the eight continental groups were determined to be well separated. The Middle Eastern and Central Asian groups are closely related to the European and South Asian groups, respectively, and require an extra set of markers to properly estimate population separations. For this reason, it was decided not to use these two groups as separate ancestral populations, and they were removed from the ultimate estimation. The authors also validated the genetic ancestry model by applying a set of 2,504 samples with known origin from the 1000 Genomes project. This test showed that the set of 1,142 SNPs was able to correctly estimate continental ancestry in the included populations. The results also validated the approach of using precommuted population allele frequencies. A comparison of the self-reports in the two situations was then performed. First, the ethnicity reported on the requisition form was compared with that provided during the genetic counseling session. For each ethnic group, counts were generated for (1) each participant who selected it on the requisition form; (2) each participant who identified it during consults; and (3) each participant who did both. Those who selected "other" on the requisition form were excluded. Consistent patterns were seen in self-reported identification in both situations. For example, 97.7% of participants who selected East Asian on the requisition form identified as East Asian during the genetic counseling session, while 99.2% of participants who identified as having East Asian ancestry during the consult also selected East Asian on the requisition form. However, for ethnicities such as Mediterranean, Native American, and Southeast Asian, the responses between the two sources of self-report

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were different. Another observed difference was between self-reported ethnicity on the requisition form and genetic ancestry in South Asian participants and Southeast Asian participants. However, these differences were diminished when obtaining ethnicity during the genetic counseling session. The differences indicate that there is confusion about the meaning of different labels, which indicates that self-reporting of ethnicity cannot be relied on. When calculating genetic reproductive risk, inaccurate reporting of ethnicity results in inaccurate calculation of risk. Admixed populations were also looked at, and results indicate that carrier rates and residual risks are dependent on genetic ancestry in these populations. For example, the carrier rate for CF varies from 1.6% to 3.67% in the Latin American population, depending on the percentage of European ancestry, and the carrier rate for sickle cell anemia varies from 1.3% to 4.6%, depending on the amount of African ancestry. Thus, it cannot be assumed that the genetic risk to admixed populations occurs in a consistent manner. The source of ethnic background can have an impact on estimating carrier and RR and providing appropriate testing and can impact decision-making. The authors suggested that to mitigate these risks and ensure that serious genetic disorders are not missed, ECS panels should be used. Despite the disadvantages of ECS, given that self-reporting of ethnicity is unreliable and can lead to the provision of an incomplete picture of risks to couples, ECS provides a comprehensive approach. The authors also concluded that genetic ancestry should be determined by appropriate clinical testing rather than self-reporting to provide accurate carrier rates, detection rates, and residual risks. The retrospective nature of this study is one of its limitations. Another is that self-reported ethnicity could have been incorrectly entered in the database or modified. A third limitation is that the ancestry model used is based on allele frequency estimates from a small sample size and assumes that assembling people by continent provides meaningful estimates of origin. Additional studies that include larger cohorts are needed to improve the ancestry model and to measure the relationship between carrier rates and genetic ancestry for more diseases. Additional work is also needed to understand the factors leading to self-identified ethnicity. In conclusion, self-reported ethnicity is shown to be unreliable, leading to the possibility of inaccurate calculation of carrier rates and residual risk. To decrease the risk of ordering the incorrect testing panel, the authors recommended the use of pan-ethnic ECS panels. In addition, to accurately estimate carrier rates and residual risks, they recommended the use of a genetic ancestry model in clinical genetic testing.

Haque et al. (2016) created a model of fetal risk based on a commercial laboratory's experience with ECS. From January 2012 to July 2015, the laboratory screened 346,790 individuals who were referred for testing by their health care provider. The ECS panel test that was offered analyzed 110 genes, including 94 conditions categorized as severe or profound. Two platforms were used. The first was targeted genotyping for 417 known pathogenic variants, and the second was NGS for all genes. Health care providers could select the testing platform and genes desired for their patient, so not all individuals were screened for all conditions. Targeted genotyping was performed in 308,668 individuals, and 47,590 carriers were identified, of whom 279 individuals were homozygous or compound heterozygous. NGS was completed in 38,122 individuals; of them, 11,088 individuals were carriers, and 124 were identified as homozygous or compound heterozygous. Results were reviewed in the context of the individuals' 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 Southeast Asian; Finnish was the smallest overall and was excluded from the final analysis due to small numbers. The authors used the results of both platforms to estimate 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 ARCs for diseases included in current professional society carrier screening guidelines against the detection rate of all profound and severe diseases in the ECS panel. When hemoglobinopathy genes are excluded from analysis, African American individuals were noted to have an 18% risk of profound or severe recessive diseases covered by guidelines and an 82% risk outside of guidelines, with a calculated cumulative risk of one in 1,741 to have a fetus affected by any profound/severe condition in the study. The AJ group had a 45% risk within guidelines and 55% risk outside of guidelines, with a modeled fetal risk of one in 255. Mixed or other Caucasian had 32% risk within guidelines and 68% risk outside of guidelines, with a modeled fetal risk of one in 649. The authors concluded that current guidelines do not perform equally well between self-reported ethnic groups and currently focus on diseases prevalent in European populations. ECS may identify couples at risk for other conditions that are important in a diverse population. Limitations identified for the study include the use of an artificial construct to calculate disease frequencies and fetal results from random mating within an ethnic group. Disease frequencies in the general population might vary when compared with the population referred for genetic testing by a health care provider. The model does not fully address the racial/ethnic admixture possible in the study population or in real-world reproductive pairing. Prospective studies comparing the current standard of care with ECS are needed before ECS is fully adopted.

Clinical Practice Guidelines

American College of Obstetricians and Gynecologists (ACOG)

In a 2022 (reaffirmed 2025) practice advisory, ACOG updated their recommendations on hemoglobinopathies in pregnancy, noting that previous recommendations for testing were based on race/ethnicity. This strategy is no longer recommended because self-reported race/ethnicity is not always accurate in terms of genetic ancestry. Since approximately one in 66 individuals in the United States have a trait related to hemoglobinopathy, ACOG recommends

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offering hemoglobinopathy testing (which may be performed using hemoglobin electrophoresis or molecular genetic testing) to all individuals planning a pregnancy or at the first prenatal visit if no prior testing for hemoglobinopathies has been performed. Following this model, individuals who are at risk can receive important counseling regarding their genetic risk, explore potential options, and make informed decisions.

In *Committee Opinion No. 690* (2017a; reaffirmed 2025), ACOG states that all individuals who are pregnant or considering pregnancy should be offered carrier screening for CF, SMA, and complete blood count and screening for thalassemias and hemoglobinopathies. If ECS is to be considered, several of the following consensus-driven criteria should be met:

- The disorder should have a carrier frequency of greater than one in 100
- The condition should have a well-defined phenotype, have a detrimental effect on quality of life, cause physical or cognitive impairment, and have onset early in life
- Diagnosis can be made 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

ACOG advises that not all individuals who are at risk of the conditions screened will be identified through carrier screening and stresses the importance of genetic counseling for all individuals undergoing carrier screening.

In ACOG *Committee Opinion No. 691* (2017b; reaffirmed in 2025), carrier screening for the four diseases below was recommended for individuals of AJ descent:

- Canavan disease (carrier frequency one in 40)
- CF (carrier frequency one in 29)
- Familial dysautonomia (carrier frequency one in 32)
- Tay-Sachs disease (carrier frequency one in 30)

The committee opinion points out that more comprehensive screening panels for individuals of AJ descent have been promoted by some experts to include less common diseases with carrier rates from one in 15 to one in 168. These include:

- Bloom syndrome
- Familial hyperinsulinism
- Fanconi anemia
- Gaucher disease
- Glycogen storage disease
- Joubert syndrome
- Maple syrup urine disease
- Mucolipidosis type IV
- Niemann-Pick disease
- Usher syndrome

When only one partner is of AJ descent, that individual should be offered screening first; if the individual is found to be a carrier, the other partner should then be offered screening. Of note, carrier frequency and detection rate in non-Jewish individuals are unknown for the majority of disorders discussed above, so accuracy in predicting risk is likely reduced.

American College of Medical Genetics and Genomics (ACMG)

An ACMG practice resource (Gregg et al., 2021) identifies and recommends adoption of a tiered approach to carrier screening.

- Tier 1: CF plus SMA plus risk-based screening
- Tier 2: At least one in 100 carrier frequency (includes Tier 1)
- Tier 3: At least one in 200 carrier frequency (includes Tier 2 and X-linked conditions)
- Tier 4: Less than one in 200 carrier frequency (includes Tier 3)

In addition, the ACMG resource includes the following recommendations:

- The term “carrier screening” should replace the term “expanded carrier screening”
- Promotion of paradigms for carrier screening that are ethnic and population neutral
- Tier 3 carrier screening for autosomal recessive and X-linked conditions should be offered to all pregnant individuals and those planning a pregnancy
- Tier 3 carrier screening for autosomal recessive conditions may be offered to reproductive partners of pregnant individuals or those planning pregnancy when screening is performed simultaneously with their partner

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- Tier 4 screening should only be considered if a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer) or when a family or personal medical history warrants such testing

National Society of Genetic Counselors (NSGC)

The NSGC (Sagaser et al.) published an evidence-based practice guideline in 2023, recommending that ECS be offered to all individuals considering reproduction, pregnant individuals, and their partners and those who might otherwise contribute biologically to the pregnancy. They assert that the final decision regarding carrier screening should take place after shared decision-making, considering the specific features of individuals and their personal values and preferences. Use of ECS provides an alternative to ethnicity-based screening and would potentially identify more carriers of autosomal recessive and X-linked conditions, without dependence on race. The authors note that this recommendation is conditional and is "based on the balance of benefits and harms of ECS, and low and moderate certainty in the evidence. There are no specific clinical criteria or set of conditions associated with the conditional recommendation for ECS." Efforts to focus on addressing barriers to ECS, including insurance coverage, access to genetics professionals, and educational needs of impacted individuals, are recommended.

Royal College of Obstetricians and Gynaecologists (RCOG)

In a 2024 scientific impact paper (number 74), Elson et al. summarize the use of ECS in reproductive medicine, including discussion of clinical, technical, and ethical considerations as well as value and risk. The authors indicate that while targeted carrier screening before conception is appropriate for individuals who are at a high risk of carrying a gene that is known to cause severe disease, there is insufficient evidence to recommend testing all prospective parents routinely. They further point out that there is a lack of standardization among ECS panels currently on the market; providers are encouraged to gain a thorough understanding of the specific panel used before interpretation of results is performed. Interpretation should be performed only by clinicians with appropriate knowledge of clinical genetics. Lastly, the authors point out that further work to determine the appropriate genes for inclusion in ECS panels, considering population/ethnicity variation and the potential benefits to individuals and their offspring while minimizing unnecessary screening, is needed.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed February 16, 2026)

Refer to the following website for a list of nucleic acid–based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Heath: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed February 16, 2026)

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Policy History/Revision Information

Date	Summary of Changes
07/01/2026	**Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version 2026T0586S

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, 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, 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.

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