Carrier Testing Panels for Genetic Diseases (for Louisiana Only)

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➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

State-Specific Criteria

The coverage criteria for genetic counseling contained in this policy represents Louisiana Medicaid Managed Care Organization Manual (LA MCO) coverage policy and is set forth below in accordance with s~~S~~tate requirements.

Genetic Counseling

Genetic counseling before and after all genetic testing is required. Counseling must consist of at least all of the following and be documented in the medical record:

- Obtaining a structured family genetic history
- Genetic risk assessment; and
- Counseling of the enrollee and family about diagnosis, prognosis, and treatment

(LA MCO Genetic Counseling and Testing~~, page 112~~)

Additional Non State Criteria

Ashkenazi Jewish Carrier Screening

Ashkenazi Jewish Carrier Screening is proven and medically necessary for evaluating the following:

- Individuals who are seeking prenatal care or planning a pregnancy who have not previously had informative Ashkenazi Jewish Carrier Screening; and

- At least one of the following additional criteria is met:
  - At least one reproductive partner is Ashkenazi Jewish (this individual has at least one Ashkenazi Jewish grandparent); or
  - The reproductive partners have a previously affected child with one of the genetic diseases included in the Ashkenazi Jewish Carrier Screening test and the results of this test will inform a current or future pregnancy; or
  - One or both individuals have a ~~first~~**First**- or ~~second-degree relative~~**Second-Degree Relative** who is affected and the results of this test will inform a current or future pregnancy; or
  - One or both individuals have a ~~first-degree relative~~**First-Degree Relative** with an affected offspring and the results of this test will inform a current or future pregnancy; or
  - One of the reproductive partners is already known to be a carrier for one of the genetic diseases included in the Ashkenazi Jewish carrier screening test and the results of this test will inform a current or future pregnancy

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

- Carrier testing for any additional genetic diseases as part of Ashkenazi Jewish Carrier Screening
- Ashkenazi Jewish Carrier Screening for all other indications

Expanded Carrier Screening Panel Testing

Expanded Carrier Screening Panel testing is unproven and not medically necessary for all indications due to insufficient evidence of efficacy.

Definitions

Carrier Screening: Genetic testing that is performed on an individual who does not have any symptoms of a genetic disorder but may be at risk to have a genetic variant that could be passed to children (**American College of Obstetricians and Gynecologists [**ACOG**]**, 2017a, reaffirmed 202~~0~~**3**).

Expanded Carrier Panel (ECS) Screening: Multiple genetic disorders that are screened for in one test using a single sample without regard to ethnicity or family history (ACOG, 2017a, reaffirmed 202~~0~~**3**). For the purpose of this policy, Expanded Carrier Panels for non-Ashkenazi Jewish Carrier Screening analyze ~~5~~**6** or more genes.

First-Degree Relative: First-Degree Relatives include parents, siblings and offspring (National Comprehensive Cancer Network, 2023).

Panel: A group of laboratory tests that are performed together to assess a body function or disease (Medicare, 2019 and McGraw Hill, 2002).

Second-Degree Relative: Second-Degree Relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren and nieces/nephews affected on the same side of the family (National Comprehensive Cancer Network, 2023).

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 federal, state, or contractual requirements 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
*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

Codes labeled with an asterisk (*) are not on the state of Louisiana Fee Schedule and therefore not covered by the State of Louisiana Medicaid Program.

Description of Services

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

Carrier Screening may be available for autosomal recessive conditions, autosomal dominant less penetrant conditions, X-linked conditions, and certain chromosome abnormalities. In general, Carrier Screening may be performed for conditions that are found in the general population (pan-ethnic), for diseases that are more common in a particular population, or based on family history. **Current recommendations for general population (pan-ethnic) screening by ACOG include cystic fibrosis screening, SMA screening and hemoglobinopathy screening.** For individuals of Ashkenazi Jewish descent (~~Gross et al., 2008~~**Eastern and Central European**), certain autosomal recessive conditions are more prevalent~~ and many~~. **Some** of these disorders are lethal in childhood or **are** associated with ~~significant~~ **substantial** morbidity~~.~~ **(ACOG 2022, ACOG 2017b, reaffirmed 2023).**

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

Ashkenazi Jewish Carrier Screening

Carrier Screening for individuals of Ashkenazi Jewish descent is focused on identifying reproductive partners who are at risk of having a child with a disorder that has a higher

prevalence in this population. ~~For individuals of Ashkenazi Jewish descent, certain autosomal recessive conditions are more prevalent and many of these disorders are lethal in childhood or associated with significant morbidity. The disorders generally screened in this population are Tay-Sachs, Canavan, Cystic fibrosis, Familial Dysautonomia, Fanconi Anemia, Niemann-Pick type A,~~ **The majority of individuals of Jewish ancestry in North America are of Ashkenazi Jewish descent and therefore have an increased risk of having children with one of these disorders (ACOG, 2017b; reaffirmed 2023** ~~Bloom syndrome, Mucolipidosis IV, and Gaucher disease. Since Carrier Screening includes only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a carrier. If an individual has no mutations detected on a Carrier Screening test, the individual still has some remaining risk of being a carrier (Gross et al., 2008; ACOG, 2017b; reaffirmed 2020~~).

Ashkenazi Jewish Carrier Screening ~~should~~**may commonly** include testing for the genetic diseases ~~recommended~~**outlined** by ~~American College of Obstetricians and Gynecologists (~~ACOG~~) and/or the American College of Medical Genetics (ACMG):~~:

- Tay Sachs disease
- Canavan disease
- Cystic fibrosis
- Familial dysautonomia
- Bloom syndrome
- Fanconi anemia
- Niemann-Pick disease
- Gaucher disease
- Mucolipidosis IV
- Maple Syrup Urine Disease
- Joubert syndrome
- Glycogen storage disease 1A
- Familial hyperinsulinism
- Usher 1F and ~~111A~~**111**

Expanded Carrier Screening **(ECS)** Panels

For Carrier Screening, ~~new~~ technologies~~,~~ such as next generation sequencing technology or chromosomal microarray~~,~~ have created the ability to screen for genetic mutations using genetic Panels instead of single genes. For the purpose of this policy, Expanded Panels analyze ~~5~~**6** or more genes for non-Ashkenazi Jewish Carrier Screening**,** which is beyond what is recommended by ACOG for DNA~~-~~-based screening ~~(ACOG 2017a; reaffirmed 2020).~~**.** For Ashkenazi Jewish disorders, ~~Expanded Carrier Screening (~~ECS~~)~~ Panels are those that go beyond the diseases listed above**, hemoglobinopathy screening,** and spinal muscular atrophy screening ~~(ACOG 2017a and ACOG 2017b; reaffirmed 2020).~~**.** Expanded Panels are able to analyze many genes simultaneously, however there is a lack of evidence to establish the clinical utility of gene test panels that include genes that are not associated with a specific inherited disorder (ACOG~~, 2020a).~~ **2022, ACOG, 2017a, reaffirmed 2023).** Furthermore, there is a lack of standardization in the genetic Panel composition, thus Panels for similar conditions may evaluate different ~~set of genes. Currently, there are no existing professional guidelines to support the ordering and evaluation of Carrier Screening by expanded Panels (Grody et al., 2013).~~**sets of genes.**

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

Leung et al. (2021) developed a method of calculating disease prevalence, ethnic carrier frequency, detection rate (DR) and recurrence risks (RR) metrics across four autosomal recessive gene conditions (ABCC8, ASPA, GAA and MMUT) using cystic fibrosis (CF) as proof of concept. A step-by-step approach for calculating DR and RR was based on the sum of disease allele frequencies of pathogenic variants found in literature. Following CF

guidelines, 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 1 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 demonstrate a wide range of DR and RR. Possible explanations for this discrepancy include~~:~~ difference in calculation method for DR~~;~~, difference in definitions for DR or laboratories calculate DR that is more consistent with the definition of analytical sensitivity which may increase RR~~;~~, known technical challenges of NGS may limit detection of variants~~;~~, timing of publications may also lead to frequency reporting discrepancies. The authors emphasized that accurate DR 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 DR.

Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person. For information regarding noninvasive prenatal screening (NIPT) for fetal aneuploidy, refer to the Medical Policy titled Cell-Free Fetal DNA Testing (for Louisiana Only).

Clinical Evidence

Ashkenazi Jewish Carrier Screening

Shi et al. (2017) genotyped over 3,000 individuals of self-reported Ashkenazi Jewish (AJ) ancestry to analyze the carrier frequency of 29 recessive genetic diseases to determine if additional disorders should be considered as part of routine carrier screening. The team reviewed the literature and the internal database at their lab to identify the genes that should be screened, and utilized pre-existing, de-identified samples from research participants. There were ~~2252~~ **2,252** AJ individuals tested for 29 recessive disorders, and an additional ~~1390~~ **1,390** AJ and ~~6813~~ **6,813** non-AJ individuals were screened for a subset of 18 recessive disorders. The authors identified seven disorders with a carrier frequency of greater than 1 in 100, nine with a carrier frequency between 1 in 100 and 1 in 200, and four between 1 in 200 and 1 in 500. Nine conditions had a carrier frequency of less than 1 in 500 or were not found. Of the 20 diseases with a carrier frequency higher than 1 in 500, two were eye diseases that the authors felt were not appropriate to be included for reproductive related carrier screening. Of the remaining 18 disorders, the team calculated that the cumulative chance for an individual to be a carrier of one of the 18 diseases was 1 in 6. However, the chance that an AJ couple would be carriers of the same disease and be at risk for an affected pregnancy is 1 in 441.

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

~~Clinical Practice Guidelines~~

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

~~The ACMG practice guideline from 2008, reaffirmed in 2013 (Gross, et al., 2008) and the 2017 ACOG Committee Opinion No. 691, reaffirmed in 2020 both recommend carrier screening for Ashkenazi Jewish individuals for:~~

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

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

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

~~If only one member of the couple is Ashkenazi Jewish, ideally, that individual should be tested first. One Jewish grandparent is sufficient to offer testing. If the Jewish partner has a positive carrier test result, the other partner (regardless of ethnic background) should be tested for variants associated with that particular disorder. (Gross et al. 2008). ACOG similarly states that carrier screening for this disorder can be considered, as well as Usher syndrome, but notes that the prevalence of these disorders in non-Jewish populations is unknown and counseling prospective parents on residual risks when one partner is non-Jewish can be complicated.~~

~~National Tay-Sachs and Allied Diseases Association (NTSAD)~~

~~Screening for TS should be offered when considering pregnancy/during pregnancy if either member of the couple is Ashkenazi Jewish, French-Canadian, or of Cajun descent. The NTSAD 2019 Position Statement issued the following summary points of consideration:~~

- ~~Full-exon gene sequencing by NGS is a highly sensitive molecular test that detects coding sequence changes throughout the HEXA gene and has high carrier detection across all ethnic groups~~
- ~~Genotyping is less sensitive than full-exon sequencing by NGS and should not be the test of choice when screening for Tay-Sachs disease carrier status~~
- ~~Carrier testing by HEXA enzyme activity is sensitive for carrier detection. Subsequent molecular testing may be necessary in some cases and leukocyte testing instead of serum is recommended for women who are pregnant or using oral contraceptives~~
- ~~Data supports a shift toward routine use of full-exon HEXA NGS for Tay-Sachs carrier screening in individuals of all ethnic backgrounds, while continuing to regard HEXA enzyme testing as another reliable carrier screening method~~

Expanded Carrier Screening (ECS)

There is limited evidence to support the use of ECS testing for any indication. ~~Identified clinical practice~~ **Existing** guidelines ~~do not recommend its use as a primary testing choice. In addition, guidelines highlight~~ **note** the risks of ECS, including identifying variations of uncertain significance and inclusion of disorders that can be characterized by a wide range of phenotypical expression or incomplete penetrance (when not all carriers are symptomatic). ECS may also cause undo anxiety or stress in individuals undergoing testing, and a need for further follow up and counseling.

~~To address concerns regarding the impact of expanded carrier screening (ECS) on health care utilization, Kauffman et al. (2021) conducted a randomized controlled trial examining the effects of disclosing negative (normal) ECS on utilization compared with usual care (UC). The authors assessed differences between women randomized to ECS (n = 127) and UC (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 five years prior to and at any point following randomization with a documented pregnancy. The authors did not find any evidence of harms on 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 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 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 testing. Of the 304 participants that had data analyzed, there were only 2 cases noted in which ECS screening led to inappropriate health care utilization: 1 patient misunderstood the carrier result and sought treatment for hemochromatosis and 1 patient who attempted to refuse first trimester prenatal screening because she did not understand how it differed from ECS. Limitations for this study include the possibility of refusals of standard of care treatment that were not documented, lack of racial/ethnic and socioeconomic diversity, and exclusion of male partners. The authors note that future studies should continue to evaluate the possibility of harms of screening, specifically for non-White and low-income populations.~~ **In an effort to ascertain a carrier screening panel design which is consistent with existing carrier screening recommendations published by ACOG (2017b) and ACMG (2021), Johansen Tabor et al. (2022) 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. Individuals with family or personal history of disease or reported consanguinity were excluded, and 11 races/ethnicities were represented. Forty conditions had carrier frequencies of ≥1 in 100 and 75 conditions had carrier frequencies of ≥1 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 met conservative thresholds (including carrier frequency of ≥1 in 100) and 74 conditions met more liberal thresholds (including carrier frequency of ≥1 in 200). In a panel which tests for 37 conditions, all 7 conditions currently recommended by both ACOG and ACMG for screening in at least one race/ethnicity would be included; this panel would detect 63% of carriers and 84.6% of at-risk couples (ARCs) (as compared to 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 including 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. Noted limitations include the possibility that conditions beyond what was**

included in this study may meet ACOG or ACMG guideline criteria. In addition, although the researchers took steps to ensure accuracy of carrier frequency data, there is potential for over- or under-estimation. The development of transparent and consistent panel design which aligns with evidence-based guidelines is recommended.

Ramdaney et al ~~(2021~~**. (2022**) conducted a systematic evidence review to evaluate the client and provider experiences for ~~expanded carrier screening (ECS).~~**ECS.** The authors reviewed literature between January 1, 2003, and May 31, 2021**,** and found 36 articles that fit the inclusion criteria. Sixteen of the articles evaluated test outcomes, ten 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 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 cystic fibrosis (CF) and spinal muscular atrophy (SMA) would have missed at least 881 of 966 at-risk couples (ARCs). The authors noted that decision-making following actual carrier screening results varied largely **depending** on ~~if~~ **whether** the clients were preconception or already pregnant. With preconception, most clients elected to pursue or indicated interest in preimplantation genetic testing (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 that 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 and 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 were a concern for genetic counselors. Limitations included significant inconsistency in methodologies and patient population which limited the ability to assess the impact of ECS within the United States. There was a lack of studies documenting outcomes for minimal guideline-based carrier screening compared to ECS. Additionally, most of the studies included were observational and the majority were rated poor/very poor quality or a high risk of bias.

To address concerns regarding the impact of ECS on health care utilization, Kauffman et al. (2021) conducted a randomized controlled trial examining the effects of disclosing negative (normal) ECS on utilization compared with usual care (UC). The authors assessed differences between women randomized to ECS (v = 127) and UC (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 five years prior to and at any point following randomization with a documented pregnancy. The authors did not find any evidence of harms on 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 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 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

testing. Of the 304 participants that had data analyzed, there were only 2 cases noted in which ECS screening led to inappropriate health care utilization: 1 patient misunderstood the carrier result and sought treatment for hemochromatosis and 1 patient who attempted to refuse first trimester prenatal screening because she did not understand how it differed from ECS. Limitations for this study include the possibility of refusals of standard-of-care treatment that were not documented, lack of racial/ethnic and socioeconomic diversity, and exclusion of male partners. The authors note 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 with which ethnicity-based carrier screening captures disease risk for recessive conditions. A 96-gene ~~expanded carrier screen (~~ECS~~)~~ **panel** was performed on 93,419 individuals; correspondence was assessed among carrier status, self-reported ethnicity, and a dual component genetic ancestry calculated from sequencing data. The authors reported that 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 individuals 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, patients with intermediate genetic ancestry backgrounds- who did not self-report the associated ethnicity had significantly elevated carrier risk. For 7/16 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 utilized across laboratories when considering genes for ECS panel inclusion according to the authors.

Arjunan et al. (2020) utilized a published algorithm that stratifies diseases into four classes of severity (mild, moderate, severe and profound) for 176 genes screened by ~~expanded carrier screening (~~ECS~~),~~**;** objective severity classifications were then assigned. Previous reports from ACOG/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 the American College of Obstetricians and Gynecologists (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. 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. 170/176 genes (96.6%) met at least one of the four criteria, 129/176 (73.3%) met at least two, 73/176 (41.5%) met at least three, and 17/176 (9.7%) met all four. The authors note that the MD and GC reviewers who reviewed the conditions for this study may not be replicated in practice by clinicians with either similar or different expertise. In addition, the MD reviewers were not blinded to the GC final classifications, so it's possible they were influenced by the GC 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.

ACOG proposed that disorders included in ECS panels should have a carrier frequency of 1/100 or greater, detrimental impact on quality of life and a well-defined phenotype. Balzotti et al. (2020) utilized a ClinGen framework to determine clinical validity of gene-disease relationship for 208 autosomal recessive and X-linked conditions offered at commercially available ECS panels by Myriad Women's Health (Foresight) and Baylor Genetics (GeneAware). 100% of conditions met the evidence threshold for supporting a gene-disease association. 98% (203/208) reached the strongest (definitive) level of gene-

disease association; of the remaining 5, 4 were classified as moderate evidence and one was classified as having limited evidence. Twenty-one gene-disease pairs were curated independently by Myriad and Baylor to determine 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 (18 disorder subset of the pan-ethnic panel) for 2,398 individuals who self-identified as being of AJ descent with no personal or family history of a genetic disorder. The pan-ethnic panel assessed 434 targeted, pre-defined variants in 87 genes that cause 87 disorders was tested in 1,150 individuals and the AJ specific panel assessed a subset of 147 variants in 18 genes that cause 18 disorders was tested in 1,248 individuals. The pan-ethnic panel identified 431 individuals (37.5%) as carriers of at least one disorder and 87 of these (76%) were carriers of 2 or more disorders. For the AJ panel, 319 (25.6%) individuals were determined to be carriers of at least one disorder and 60 (4.8%) of these individuals are carriers for multiple disorders. The researchers also re-analyzed the pan-ethnic data for the 18 genes in the AJ specific panel for those individuals 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) and the researchers state that 151 individuals would have been missed for carrier detection. The researchers conclude that this data may contribute to further professional discussion on the clinical utility of expanded carrier screens.

Westemeyer et al. (2020) performed a retrospective analysis of data from a cohort (n = 381,014) receiving expanded carrier screening of up to 274 genes. The cohort included mostly women (339,739; 89.17%) and various ethnicities: 148,828 (39.06%) Caucasian, 62,626 (16.44%) Hispanic, 52,454 (13.77%) African American, and the remaining 117,106 (30.74%) were either of other races/ethnicities or did not provide information. The majority of individuals (374,911) were tested for CFTR and 14,229 (3.8%) were found to have a pathogenic or likely pathogenic variant yielding a 1/26 carrier frequency. For CF, 44.0% (~~6260~~ **6,260**/14,229) of carriers identified had a variant not on the standard genotyping panel. Similarly, 344,407 individuals were screened for SMA and 14,606 (4.24%, 1/24) were found to be carriers or at-risk silent carriers. Out of the 14,606 carriers for SMA, 8,763 (2.54%, 1/39) 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 individuals were tested and 38,300 (63.78%) were positive for at least one disorder. The researchers also observed the carrier rates for this large 274 gene panel compared to those in the literature. Of the 274 genes screened, 117 had a different than expected carrier rate. The researchers concluded that assuming random pairing across the study population, approximately 1/175 pregnancies would be affected by a disorder in the 274-gene screening panel.

For the majority of expanded carrier panels, there is no consensus on what genes should be included that would be relevant for multiple ethnic groups. 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, Ashkenazi Jewish, 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 (VCR) to then be able to estimate the gene carrier rates (GCR). Across the ancestries, the highest GCR for a single gene was determined to be for African/African American at 12% for HBB. The carrier rates declined for most ancestries as only 30 of the genes in the Ashkenazi Jewish group had a carrier rate > 1%. Likewise, in the Hispanic population on 6 of the genes had a GCR > 1%. Overall, the researchers found that 32.6% (East Asian) to 62.9% (Ashkenazi Jewish) of individuals are variant carriers, however, screening all 415 genes would only identify 0.17-2.52% of couples as at risk.

Johansen et al. (2019) reported on a survey of the females from ~~1701~~ **1,701** at risk couples (ARC) who participated in ~~expanded carrier screening (~~ECS~~)~~ of 176 genetic conditions. The cohort was identified from over 270,000 individuals who underwent screening via the laboratory's ECS from September 1, 2015, to December 31, 2017. Females 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 labs ECS, (2) were aged 18 years or older, (3) had consented to being contacted about participating in research at the lab, and (4) for those carrying pathogenic or likely pathogenic variants associated with autosomal recessive conditions, had reproductive partners meeting the same eligibility criteria and were confirmed by the lab as being carriers of a pathogenic variant in the same gene. Couples carrying only variants known to cause mild presentations of biotinidase deficiency (D444H), ~~NPHS2related~~**NPHS2-related** nephrotic syndrome (R229Q), and 21-OH deficient congenital adrenal hyperplasia (CAH) (CYP21A2 gene duplication) were excluded. The ~~1701~~**1,701** ARC were geographically dispersed and comprised 15 ethnicities and over 9 religions. The ARC reported being at risk for 53 different conditions, with 10% indicating they were at risk for 2 conditions and 1.8% being at risk for 3 conditions. The actions taken by the ARC were broken down into those receiving preconception ECS results and those receiving the results during the prenatal period. ECS was performed on 235 preconception ARC, 77% of which indicated they planned or ~~pursed~~ **pursued** pregnancy management options, of which 59% for in vitro fertilization (IVF) with preimplantation genetic diagnosis for monogenic/single gene disorders (PGT-M), 48% prenatal diagnosis, 18% donor gamete, 12% addition and 9~~-~~% no longer planning to get pregnant. Of the 154 ARCs who received the ECS results while pregnant, 37% ~~perused~~ **pursued** invasive prenatal testing (PNDx), of which 36% had affected pregnancies, and 40% of those resulted in termination. Of the 63% that did not have PNDx, 75% had given birth at the time of the survey and 44% of those planned or pursued postnatal diagnosis. In addition, 2.1% terminated the pregnancy without PNDx. The authors asked about actions in subsequent pregnancies. Of those who perused PNDx through Chorionic villus sampling ~~(~~(CVS~~)~~) or amniocentesis, 29% had affected fetuses, and 75% of those terminated their pregnancies. Limitations of the study included patient's recall 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 population such as cystic fibrosis. However, the authors tried to decrease these effects by analyzing results in aggregate and by condition severity. Overall, study represents largest cohort of ARCs to date and diverse couples screened for up to 176 conditions.

Peyser et al. (~~2018~~ **2019**) compared the efficiency of ~~expanded carrier screening (~~ECS~~)~~ to ethnic-based screening to identify carriers. A cohort of ~~4232~~ **4,232** patients seeking fertility treatment was studied. ECS was performed at one genetic testing laboratory for patients seen between June 2013 and July 2015. Ethnicity was self-reported. Carrier status based on ECS was calculated. Carrier rates were also determined for the ACOG recommended ECS panel (ACOG-based screening) and ethnic- based screening (ACOG and ACMG ethnicity panel recommendations). The ECS utilized was made up of 400 variants of 102 genes associated with 100 genetic conditions. Fragile X CGG repeat size and the number of

SMN1 exon 7 copy-number status to screen for spinal muscular atrophy were also included in the ECS. Carrier rates were calculated for the overall study population and for each ethnic subpopulation and then compared to determine differences between carrier identification rates by each panel. The ECS panel did not screen for α-thalassemia and maple syrup urine disease 1A (MSUD1A), 2 conditions included in the ACOG-based screening panel. Therefore, the carrier rate for the ACOG-based screening was calculated without including these two conditions. A total of ~~4232~~ **4,232** patients were tested ~~(2880~~**[2,880** females ~~[~~(68.1~~%]; 1352%); 1,352~~ males ~~[~~(31.9~~%])~~**%)]** for carrier status using ECS. Applying ethnic based screening recommendations would have resulted in 359 out of ~~4232~~ **4,232** (8.5%) patients identified as carriers. Upon applying the AGOC based screening guidelines, 659 out of ~~4232~~**4,232** (15.6%) would have been identified as carriers. With the ECS panel, ~~1243~~**1,243** (29.4%) of patients 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 3 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 Pacific Islander cohort. Further, looking at the overall population and five subpopulations, carrier rates were statistically different in all 3 comparisons: Mixed or Other Caucasian, Southern European, Northern European, ~~Unknow~~ **Unknown**/Not Reported, and Ashkenazi Jewish. In three subpopulations, ~~that is~~ **(**Hispanic, South Asian, and Middle Eastern~~,~~**),** significant differences were observed in ethnic-based screening versus ECS and ACOG-based ethnic screening versus ECS, but not the ethnic-base screening versus ACOG-based screening. Ethnic based screening versus ECS only provided statistical differences in the African or African American population. However, in ~~2~~ **two** subethnic populations, East Asian and Southeast Asian, the carrier numbers for each panel were not statistically significant. A total of ~~1206~~**1,206** couples were screened using the ESC panel, 15 (1.2%) of which were identified as carrier couples. In revealing the ethnicity of each partner, 8 of 15 (53%) would have been recognized through ethnic-based screening guidelines. In addition to carrier couples, 73 women were found be carriers of Fragile X, with variation in repeat numbers identified and thus variation in classification of the reproductive risk. In conclusion, the authors present data that ECS is greater to ethnic-based genetic screening at identifying genetic disease carriers and carrier couples. The authors argue that their study provides additional evidence that ECS provides a larger amount of preconception information for patients.

Shraga et al. (2018) reported on reliability self-reported ethnicity verses genetic ancestry for clinical decision-making in the context of genetic carrier screening. The ~~9138~~ **9,138** participants were referred by a variety of healthcare 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 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, Other. For the option "Other", ~~people~~ **individuals** could write in the self-identified ethnicity. All responses were mapped to appropriate categories when applicable, i.e., Caucasian/White mapped to European. The second self-report was obtained during the post-test appointment with a genetic counselor. During the family history portion of the consultation, individuals were asked to identify their race/ethnicity or where their family originated from. For situations where patients did not participate in counseling or were

unreachable, a "family history" ethnicity was not generated, and the patients 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 patient 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 removed them from the ultimate estimation. The authors also validated the genetic ancestry model by applying a set of ~~2504~~**2,504** samples with known origin from the 1000 Genomes project. This test showed the set of ~~1142~~**1,142** SNPs was able to correctly estimate continental ancestry in the included populations. The results also validate the approach of using pre-commuted 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 to that provided during the genetic counseling session. For each ethic group, counts were generated for: 1) each patient who selected it on the requisition form, 2) each patient who identified it during consults, and 3) each patient who did both. Patient 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 patients that selected East Asian on the requisition form identified as have East Asian during the genetic counseling session, while 99.2% of patients identified 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 were different. Another observed difference was between self-reported ethnicity on the requisition form and genetic ancestry in South Asians and Southeast Asians. 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, indicating that self-reporting of ethnicity cannot be relied upon. 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, in the carrier rate for cystic fibrosis varies from 1.6% to 3.67% in the Latin American population**,** depending on the percent 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 recurrence risk and providing appropriate testing, and impact decision making. Thus, the authors suggest in order to mitigate these risks and ensure serious genetic disorders are not missed; expanded carrier screening panels should be utilized. Despite the disadvantages of expanded carrier panels, given that self-reporting of ethnicity is unreliable and can lead to providing an uncomplete picture of risks to couples, the expanded carrier screens provide a comprehensive approach. The authors also concluded that genetic ancestry should be determined by appropriate clinical testing rather than self-report in order to provide accurate carrier rates, detection rates and residual risks based on self-reported ethnicity. 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 the ancestry model used is based on allele frequencies estimates from small sample size and assumes that assembling people by continent provides meaningful estimates of origin. Additional studies with 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 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 recommend the use of expanded pan-ethnic carrier screening panels. In addition, in order to accurately estimate carrier rates and residual risks, they recommend the use of a genetic ancestry model in clinical genetic testing.

Terhaar et al. (2018) retrospectively report on their experience as a commercial laboratory with reproductive carrier screening comparing three panels; 3 genes, 23 genes, or 218 genes. Data was assessed on 75,036 individuals referred by a healthcare provider in the United States. Three genes were assessed in 51,584 samples, and 7.2% had a positive result. The 23 gene panel was assessed for 19,550 samples, and 13.2% were positive. Finally, 3,902 samples were assessed for 218 genes, and 36% were positive. Overall, 127 conditions came up positive at least once in this group. The authors noted that those that seeking the 218 gene panel were more ethnically diverse when compared to the other groups. It was not reported in this study if any at risk couples were identified. In addition, it was noted that while receiving more genomic information can be beneficial to patients and providers who want a lot of information to inform medical management, this may also place a burden on clinical care. Most of the disorders identified were inherited in a recessive manner, requiring the clinicians to provide counseling and screening for a reproductive partner. Large panels may identify conditions with mild phenotypes. Common diseases like cystic fibrosis may be familiar to clinicians, but rare diseases may not. Educational resources for clinicians and patients are needed in order to ensure informed conversations and decision making.

Wilfond et al. (2018) reported on lessons learned from the NextGen study, a prospective study designed to explore the best approaches to genomic based reproductive carrier screening. The study randomized women who saw a genetic counselor in person who desired carrier screening and randomized them to those that received genomic sequencing (n = 133) and those who received usual care-meaning no additional screening (n = 180). If a woman was positive, her male partner was offered genome sequencing to determine the risk of having an affected pregnancy. In the genome sequencing arm, the team chose to report on 728 conditions, and categorized the conditions into five classes that participants could choose to learn about or not. The classes included diseases with a shortened life span, serious conditions, mild conditions, conditions with unpredictable outcomes, adult--onset conditions, and medically actionable conditions related to the individual's personal health (secondary to carrier screening.) Overall, 15 at risk couples were identified, and most were for adult--onset conditions. Eight were at risk for hereditary hemochromatosis, two for alpha-1-antitrypsin deficiency; one for non-syndromic hearing loss, one for Factor V Leiden homozygous offspring, and the remaining were for X-linked disorders. These included spondyloepiphyseal dysplasia, G6PD deficiency, and hemophilia A. Overall, however, 78% of participants had at least one finding. This leads to concerns about implementation of this approach into clinic workflows. The median time needed to prepare for a follow up visit for positive results disclosure by a genetic counselor was 64 minutes. In this study, 26% of women became pregnant before disclosure, adding additional time sensitivity to developing a genomic based screening program. The authors noted that their study design and size did not allow for a complete analysis of clinical utility, but they highlighted some anecdotal evidence that was collected. It was reported that women did not seek out more mental health or other services compared to those receiving usual care. They did not report more anxiety or depression. One participant declined amniocentesis for chromosome abnormalities because she believed the expanded carrier screening covered that, and this misconception was later corrected. The woman identified as a carrier of hemophilia A did undergo an amniocentesis, and the fetus was male and

found to carry the pathogenic variant. This altered the birth plan and allowed the neonatal team to intervene early. The baby did experience a rare subgaleal hemorrhage after birth, which was immediately treated. Finally, the authors noted that their study was small and on an older, more educated population. When asked about what they might pay out of pocket for genome sequencing, participants were willing to pay a little more than a copay, but the amount varied based on income. In conclusion, the authors noted that genomic sequencing as an approach to routine carrier screening could have significant impact on clinical workflow and resources, the optimal gene targets need to be identified, and may not be accessible to low-income patients. Additional research is needed to address these issues.

Ghiossi et al. (~~2017~~**2018**) studied the decision making of 537 couples who were identified to be carriers of the same genetic disease after undergoing expanded carrier screening for 110 genes through their commercial lab. These couples represented 1% of 51,775 couples screened between August 2014 and August 2015. The diseases included in the study were classified to be profound, severe, or moderate in terms of clinical impact. All couples were invited to participate in a survey about reproductive decision making, and 64 completed the survey. Of these, 45 couples had sought screening prior to pregnancy, and 62% reported that they planned to use preimplantation genetic diagnosis or prenatal diagnosis in a future pregnancy. Twenty-nine percent did not plan to alter reproductive decision making and the remaining four survey responses were unclear. Of the 19 pregnant couples, 10 elected to have prenatal diagnosis but two miscarried before testing could occur. Of those that had testing, five pregnancies were unaffected, and three were affected. Two affected pregnancies were terminated. The remaining couples did not think the condition they were at risk for was significant enough to undergo invasive testing. Perceived severity of the disorder appeared to impact decision making, as 76% of couples who were at risk for a profound or severe disorder reported altering reproductive decision making as a result, compared to only 22% of those at risk for moderate conditions. The authors also compared the choices made by the couples by diseases in professional society screening guidelines (20 couples) and diseases not currently in guidelines (22 couples~~),~~**)** and found no significant difference in decision making. The authors noted that limitations of the study included the low response rate, lack of random sampling, and possible response bias.

Haque et al. (2016) created a model of fetal risk based on a commercial laboratories experience with expanded carrier screening. From January 2012 to July 2015, the laboratory screened 346,790 individuals that were referred for testing by their healthcare provider. The expanded carrier screening test offered was for 110 genes, including 94 conditions categorized as severe or profound. Two platforms were utilized. The first was a targeted genotyping platform for 417 known pathogenic variants, and the second was next generation sequencing for all genes. Healthcare providers could select the testing platform and genes desired for their patient, so not all patients were screened for all conditions. Targeted genotyping was performed on 308,668 patients, and 47,590 carriers were identified, and 279 individuals were homozygous or compound heterozygotes. Next generation sequencing was completed on 38,122 individuals, and 11,088 people were carriers, and 124 were identified as homozygous or compound heterozygous. Results were reviewed in the context of the participant gender and self-reported race/ethnicity. The largest racial mix in the study was "mixed or other Caucasian." The smallest group included in the analysis was SE Asian, although Finnish was the smallest overall and excluded from the final analysis due to small numbers. The authors utilized the results of both platforms to estimate the carrier frequency by ethnic group, and then modeled the carrier frequency, carrier couple frequency for couples of the same ethnicity, and resulting fetal risk. Based on the model, the authors then compared the detection rate of potential at risk couples for diseases included in current professional

carrier screening guidelines against the detection rate of all profound and severe diseases in the expanded carrier screening panel. When hemoglobinopathy genes are excluded from analysis, African Americans were noted to have 18% of profound or severe recessive diseases covered by guidelines, and 82% were outside of guidelines, with a calculated cumulative risk of 1 in 1,741 to have a fetus affected by any profound/severe condition in the study. The Ashkenazi Jewish group had 45% within guidelines, and 55% outside of guidelines with a modeled fetal risk on 1 in 255. Mixed or other Caucasian had 32% within guidelines, and 68% outside of guidelines with a modeled fetal risk on 1 in 649. The authors conclude that current guidelines do not perform equally well between self-reported ethnic groups, and currently target diseases prevalent in European populations. Expanded carrier screening may identify couples at risk for other conditions that are important in a diverse population. Limitations identified for the study ~~includes~~ **include** the use of an artificial construct to calculate disease frequencies and fetal ~~resulting~~ **resulsi** from random mating within an ethnic group. Disease frequencies in the general population might vary when compared to the population referred for genetic testing by a healthcare provider. The model ~~doesn't~~ **does not** fully address the racial/ethnic admixture possible in the study population or in real world reproductive pairing. Prospective studies comparing current standard of care with expanded carrier screening are needed before expanded carrier screening is fully adopted.

Clinical Practice Guidelines

American College of Obstetricians and Gynecologists (ACOG)

In **a 2022 Practice Advisory, ACOG updated** their ~~2017~~**recommendations on hemoglobinopathies in pregnancy, noting that previously, 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 about 1 in 66 individuals in the United States have a trait related to hemoglobinopathy, ACOG recommends offering hemoglobinopathy 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 690 **(2017a**, reaffirmed ~~2020,~~**2023),** ACOG states that if an expanded carrier screening test is to be considered, **several of** the following consensus driven criteria should be ~~considered~~**met**:

- ~~Have~~**The disorder should have** a carrier frequency greater than 1 in 100
- The condition should have a well-defined phenotype, a detrimental effect on quality of life, cause physical or cognitive impairment, and have onset early in life
- ~~Can~~**Diagnosis can** be ~~diagnosed~~**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 testing.

In ACOG Committee Opinion No. 691 (2017b, reaffirmed in 2023), carrier screening for the four diseases below was recommended for individuals of Ashkenazi Jewish descent:

- **Canavan disease (1/6,400; 1/40)**
- **Cystic fibrosis (1/2,500-3,000; 1/29)**
- **Familial Dysautonomia (1/3,600; 1/32)**

- **Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30)**

The Committee Opinion points out that more comprehensive screening panels for individuals of Ashkenazi Jewish descent have been promoted by some experts, to include less-common diseases with carrier rates from 1/15 to 1/168. 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 Ashkenazi Jewish descent, that individual should be offered screening first, and if 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.

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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~~—~~– Cystic Fibrosis (CF) + Spinal Muscular Atrophy (SMA) + Risk Based Screening
- Tier 2~~—~~–– ≥ 1/100 carrier frequency (includes Tier 1)
- Tier 3~~—~~–– ≥ 1/200 carrier frequency (includes Tier 2) includes X-linked conditions
- Tier 4~~—~~–– < 1/200 carrier frequency (includes Tier 3)

~~The~~ **In addition, the** ACMG ~~Practice Resource~~ **resource** includes the following recommendations**:**

- **The term "carrier screening" should replace the term "expanded carrier screening"**
- **Promotion of paradigms** for **carrier** screening ~~autosomal recessive~~ **that are ethnic** and ~~X-linked conditions during pregnancy and preconception~~**:population neutral**
- Tier 3 carrier screening for autosomal recessive and X-linked conditions should be offered ~~for~~**to** all pregnant patients 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.**
- 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.**

An ACMG Position Statement states that although some commercial laboratories offer expanded carrier screening panels, there is little consensus on which disease genes and mutations to include in these panels (Grody et al., 2013; Edwards et al., 2015). Panels for that include multiple carrier screening tests may be useful if they include the diseases that are present with increased frequency in a specific population (i.e.,

Ashkenazi Jewish Carrier Screening), but do not have clinical utility when they include a larger number of genetic diseases for which the individual does not have an increased risk of being a carrier.

National Society of Genetic Counselors

The National Society of Genetic Counselors (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.

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 (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm.
(Accessed ~~April 20~~**June 14**, 202**3**~~2~~)

References

American College of Obstetricians and Gynecologists. Committee Opinion No. 690: Carrier screening in the age of genomic medicine. Obstet Gynecol. 2017a Mar;129(3):595-596. Reaffirmed ~~2020~~**2023**.

American College of Obstetrics and Gynecologists. Committee Opinion No. 691: Carrier screening for genetic conditions. Obstetrics and Gynecology. Mar 2017b;129(3):e41-e55. Reaffirmed ~~2020~~**2023**.

American College of Obstetricians and Gynecologists. Practice Advisory: Hemoglobinopathies in Pregnancy. August 2022. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/08/hemoglobinopathies-in-pregnancy. Accessed May 8, 2023.

Arjunan A, Litwack K, Collins N, Charrow J. Carrier screening in the era of expanding genetic technology. Genet Med. 2016 Dec;18(12):1214-1217.

Arjunan A, Bellerose H, Torres R, et al. Evaluation and classification of severity for 176 genes on an expanded carrier screening panel. Prenatal Diagnosis.2020 Sep;40(10):1246-1257.

Balzotti M, Meng L, Muzzey D, et al. Clinical validity of expanded carrier screening: Evaluating the gene-disease relationship in more than 200 conditions. Human Mutation. 2020 May; 41(8):1365-1371.

Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol 2015;125:653–62.

Ghiossi CE, Goldberg JD, Haque IS, et al. Clinical utility of expanded carrier screening: ~~reproductive~~**Reproductive** behaviors of at-risk couples. J Genet Couns. ~~2017 Sep~~ **2018 Jun;**27~~.~~

(3):616-625. Gregg AR, Aarabi M, Klugman S, et al; ACMG Professional Practice and Guidelines Committee. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Oct;23(10):1793-1806.

Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013 Jun;15(6):482-3.

~~Gross SJ, Pletcher BA, Monaghan KG, et al. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med. 2008 Jan;10(1):54-6, reaffirmed 2013.~~

Guo MH, Gregg AR. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. Genet Med. 2019;21(9):1940-1947.

Haque IS, Lazarin GA, Kang HP, et al. Modeled fetal risk of genetic diseases identified by expanded carrier screening. JAMA. 2016 Aug 16;316(7):734-42.

Johansen Taber KA, Beauchamp KA, Lazarin GA, et al. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. 2019 May;21(5):1041-1048.

Johansen Taber K, Ben-Shachar R, Torres R, et al. A guidelines-consistent carrier screening panel that supports equity across diverse populations. Genet Med. 2022 Jan;24(1):201-213.

Kaseniit K, Haque I, Goldberg J, et al. Genetic Ancestry analysis on > 93,000 individuals undergoing expanded carrier screening reveals limitations of ethnicity-based medical guidelines. Genet Med. 2020 Oct;22(10): 1694-1702.

Kauffman TL, Dickerson JF, Lynch FL, et al. Impact of expanded carrier screening on health care utilization. Am J Manag Care. 2021 Aug;27(8):316-321.

Louisiana Medicaid Managed Care Organization (MCO) Manual, Genetic Counseling and Testing. https://ldh.la.gov/assets/medicaid/Manuals/MCO_Manual.pdf, Accessed June 14, 2023.

Leung M, McAdoo S, Watson D, et al. A transparent approach to calculate detection rate and residual risk for carrier screening. J Molec Diagn. 2021 Jan;23(1):91-100.

McGraw-Hill Concise Dictionary of Modern Medicine. Test panel. (2002). Available at: https://medical-dictionary.thefreedictionary.com/~~testpanel~~**test+panel**. Accessed April ~~20, 2022~~**14, 2023**.

Medicare Claims Processing Manual Chapter 16 - Laboratory Services January 11, 2019.Available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c16.pdf. Accessed April ~~20, 2022~~ **14, 2023**.

Louisiana Medicaid Managed Care Organization (MCO) Manual, Genetic Counseling and Testing~~, page 112~~. **https://ldh.la.gov/assets/medicaid/Manuals/MCO_Manual.pdf** ~~https://ldh.la.gov/assets/medicaid/MCOManual_2021-09-27_published.pdf~~, Accessed ~~May 9, 2021.2022~~**June 14, 2023**.

~~National Tay-Sachs and Allied Diseases Association (NTSAD) Position Statement. 2019 Update. Standards for Tay-Sachs carrier screening. Available at: https://www.ntsad.org. Accessed: April 20, 2022.~~

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian and pancreatic. v3.2023.

Peyser A, Singer T, Mullin C, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med~~ 2018 Oct 16.~~**. 2019 Jun;21(6):1400-1406.**

Ramdaney A, Lichten L, Propst L, et al. Expanded carrier screening in the United States: A systematic evidence review exploring client and provider experiences. J Genet Couns. 2022 ~~Feb 25.~~**Aug;31(4):937-948.**

Rosenblum LS, Zhu H, et al. Comparison of pan-ethnic and ethnic-based carrier screening panels for individuals of Ashkenazi Jewish descent. J Genet Couns. 2020;29(1):56-66.

Sagaser KG, Malinowski J, Westerfield L, et al. Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors. J Genet Couns. 2023 Feb 9.

Shi L, Webb BD, Birch AH, et al. Comprehensive population screening in the Ashkenazi Jewish population for recurrent disease-causing variants. Clinical genetics. 2017;91(4):599-604.

Shraga R, Yarnall S, Elango S, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. BMC ~~Genetics. (~~**Genet.** 2017~~)~~ **Nov 28;**18~~:~~**(1):**99.

Terhaar C, Teed N, Allen R, et al. Clinical experience with multigene carrier panels in the reproductive setting. Prenat Diagn. 2018 Apr 23**;38(8):572-7**.

Westemeyer M, Saucier J, Wallace J, et al. Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach Genet Med. 2020 Aug;22(8):1320-1328.

Wilfond BS, Kauffman TL, Jarvik GP, et al. Lessons learned from a study of genomics-based carrier screening for reproductive decision making. Health Aff (Millwood). 2018 May;37(5):809-816.

Policy History/Revision Information

Date	Summary of Changes

TBD	**Title Change**
	• Previously titled *Carrier Testing for Genetic Diseases (for Louisiana Only)*
	Definitions
	• Added definition of:
	  ○ First-Degree Relative
	  • Second-Degree Relative
	• Updated definition of "Expanded Carrier Panel (ECS) Screening"
	Supporting Information
	• Updated *Description of Services, Clinical Evidence,* and *References* sections to reflect the most current information
	• Archived previous policy version CS151LA.F

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