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Corporate Medical Policy

Prenatal Screening (Genetic) AHS – M2179 **"Notification"**

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Description of Procedure or Service

Prenatal screening encompasses any testing done to determine the health status of the pregnant individual and/or fetus. Genetic prenatal screening encompasses screening to determine risk of fetal abnormalities, including genetic and developmental abnormalities. Any individual undergoing screening tests, especially genetic carrier screenings, must realize the limitations of screening tests and the difference between screening and diagnostic testing. Screening refers to testing of asymptomatic or healthy individuals to search for a condition that may affect the pregnancy or individual, whereas diagnostic testing is used to either confirm or refute true abnormalities in an individual (Grant & Mohide, 1982; Lockwood & Magriples, 2023).

This policy addresses broad prenatal genetic screening, as well as screening for conditions not addressed in condition-specific policies. For situations in which prenatal and preconception screening may be discussed in further detail, please see the "Related Policies" section of this policy document.

- Terms such as male and female are used when necessary to refer to sex assigned at birth.

Related Policies:
Prenatal Screening (Nongenetic) AHS-G2035
Prenatal Screening for Fetal Aneuploidy AHS-G2055
Genetic Testing for *FMR1* Mutations AHS-M2028
Chromosomal Microarray and Low-pass Whole Genome Sequencing AHS-M2033
Pre-Implantation Genetic Testing AHS-M2039
Genetic Testing for Hereditary Hearing Loss AHS-G2148
Genetic Testing for Cystic Fibrosis AHS-M2017
Genetic Testing for Polyposis Syndromes AHS-M2024
Genetic Testing for Fanconi Anemia AHS-M2077
Genetic Testing for Neurodegenerative Disorders AHS-M2167
Red Blood Cell Molecular Testing AHS-M2170

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for prenatal screening (genetic) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Prenatal Screening (Genetic) is covered

1. For individuals who are pregnant **or** who are capable of becoming pregnant and seeking pre-conception care, single gene or multi-gene panel screening of the individual for conditions classified through ACMG as a Tier 1, Tier 2, or Tier 3 condition (see Note 1) is considered medically necessary.

2. For pregnant individuals and those capable of becoming pregnant who come from a family with a genetic disorder for which a properly validated test is available, the following testing is considered medically necessary:
    a. Testing restricted to the known mutation.
    b. Comprehensive genetic testing, including multi-gene panel testing specific to the familial genetic disorder, when the specific familial mutation is unknown.

3. For individuals who are planning a pregnancy with a reproductive partner who is known or found to be a carrier of a recessively inherited disorder, genetic testing specific to the genes for which the reproductive partner is a carrier is considered medically necessary.

4. For RHD negative pregnant individuals, fetal RHD genotyping using maternal plasma is considered medically necessary.

5. For fetuses with a high risk for a genetic disorder, prenatal genetic testing using cells obtained for diagnostic cytogenetic testing (i.e., amniocentesis or chorionic villus sampling [CVS]) is considered medically necessary

Note 1: Please see the "Guidelines and Recommendations" section of this policy for ACMG's tiered system based on carrier frequency (Tables 1-6).

Note 2: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

When Prenatal Screening (Genetic) is not covered

Carrier screening for the same gene more than once per lifetime is considered not medically necessary.

Reimbursement is not allowed for the use of non-invasive prenatal screening (NIPS) to screen for single-gene mutations (i.e., autosomal recessive, autosomal dominant, X-linked) in the fetus.

For all other inherited medical disorders not meeting the above criteria, pre-conceptional or prenatal genetic testing considered investigational.

Policy Guidelines

Prenatal screening is a part of overall prenatal care to promote optimal care of both mother and baby. Prenatal screening allows for assessment and monitoring of the fetus for the presence of congenital defects or disease. Various professional medical organizations provide guidelines for prenatal screening. "Screening is an offer on the initiative of the health system or society, rather than a medical intervention in answer to a patient's

complaint or health problem. Screening aims at obtaining population health gains through early detection that enables prevention or treatment" (de Jong et al., 2015).

Genetic screening tests, including carrier screening for genetic mutations and fetal testing for chromosomal aneuploidy, can be a part of prenatal screening. Aneuploidy screening may be performed on cell-free DNA in maternal circulation or by examining maternal serum levels of specific biochemical markers for trisomy (Lockwood & Magriples, 2023). These non-invasive prenatal testing (NIPT) can possibly decrease the number of more invasive procedures and the risks of unwanted side effects. A chromosomal microarray (CMA) can screen all chromosomes in a single test and "can detect many very small variants that cannot be detected by traditional karyotyping" (de Jong et al., 2015). The American College of Obstetricians and Gynecologists (ACOG) recommends CMA for instances where the ultrasound of a fetus shows a major structural abnormality (ACOG, 2016a). CMA in this situation should be performed on DNA from amniotic fluid, chorionic villus cells, or cord blood, rather than on maternal serum cell-free DNA since the process does not include an amplification step and the maternal DNA signal would be many times higher than the fetal DNA (Miller, 2023).

Several companies, such as LabCorp, have developed panels to test for potential genetic mutations in pregnant individuals, or in individuals planning to become pregnant. This includes the Inheritest® Carrier Screening which encompasses six different panels to identify potential genetic mutations. These six panels include the Inheritest® 500 PLUS Panel (which screens 525 genes for several clinically relevant genetic disorders), the Inheritest® Comprehensive Panel (which screens for more than 110 disorders), the Inheritest® Ashkenazi Jewish Panel (which screens for more than 40 Ashkenazi Jewish related disorders), the Inheritest® Society-Guided Panel (which screens for more than 13 disorders highlighted in the American College of Medical Genetics and Genomics and the American Congress of Obstetricians and Gynecologists guidelines), the Inheritest® Core Panel (which screens for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy), and the Inheritest® CF/SMA (spinal muscular atrophy) Panel (which screens only for cystic fibrosis and spinal muscular atrophy) (LabCorp, 2023).

Additionally, the company BillionToOne has created a noninvasive prenatal screening test. UNITY Complete® uses cell-free DNA from a maternal blood draw and assesses for seven aneuploidies (trisomy 21, trisomy 18, trisomy 13, monosomy X, XXX, XXY, and XYY), and five recessive conditions (cystic fibrosis, spinal muscular atrophy, sickle cell disease, alpha thalassemia, and beta thalassemia). This screen functions in a sequential manner. First, the screen uses NGS of genomic DNA to assesses maternal carrier status for genes associated with the most common single-gene recessive disorders. If the pregnant individual is identified as a carrier for a pathogenic variant in one or more of these genes, the sample is then reflexed to single-gene noninvasive prenatal screening (sgNIPS). In sgNIPS, NGS is performed on cfDNA extracted from the original blood sample, from which fetal risk is calculated. Fetal risk assessment is summarized as low risk (fetal risk 1/500), high risk (fetal risk >1/4), increased risk or decreased risk (fetal risk between 1/500 and 1/4), or no result (BillionToOne, 2023; Hoskovec et al., 2023).

Red blood cell antigen discrepancy between a mother and fetus may also occur during pregnancy. This is known as hemolytic disease of the fetus and newborn (HDFN), and causes maternal antibodies to destroy the red blood cells of the neonate or fetus (Calhoun, 2023). Alloimmunization is the immune response which occurs in the mother due to foreign antigens after exposure to genetically foreign cells, occurring almost exclusively in mothers with type O blood. However, while ABO blood type incompatibility is identified in almost 15% of pregnancies, HDFN is only identified in approximately 4% of pregnancies (Calhoun, 2023). Another important inherited antigen sometimes found on the surface of red blood cells is known as the Rhesus (Rh)D antigen. During pregnancy and delivery, individuals who are RhD negative may be exposed to RhD positive fetal cells, which can lead to the development of anti-RhD antibodies. This exposure typically happens during delivery and affects subsequent pregnancies; infants with RhD incompatibility tend to experience a more severe form of HDFN than those with ABO incompatibility. The clinical presentation of HDFN may be mild (such as hyperbilirubinemia with mild to moderate anemia) to severe and life-threatening anemia (such as hydrops fetalis). Less severely affected infants may develop hyperbilirubinemia within the first day of life; infants with RhD HDFN may also present with symptomatic anemia requiring a blood

transfusion. In more severe cases, infants with severe life-threatening anemia, such as hydrops fetalis, may exhibit shock at delivery requiring an emergent blood transfusion (Calhoun, 2023).

The administration of anti-D immune globulin has been able to dramatically reduce, but not eliminate, the number of RhD alloimmunization cases. "Anti-D immune globulin is manufactured from pooled plasma selected for high titers of IgG antibodies to D-positive erythrocytes" (Moise, 2024). Before the development of this anti-D immune globulin, it has been reported that 16% of pregnant RhD-negative individuals with two deliveries of RhD-positive ABO-compatible infants became alloimmunized. However, this rate falls to 1-2% with routine postpartum administration of a single dose of anti-D immune globulin. An additional administration in the third trimester of pregnancy further reduces the incidents of alloimmunization to 0.1-0.3% (Moise, 2024).

Fetal RhD genotyping using cell-free fetal DNA from maternal plasma can be performed to identify fetal blood type most accurately after 11 weeks of gestation. While the United States has not implemented fetal RhD genotyping for routine prophylaxis and fetal monitoring protocols, several European countries, such as Denmark, the Netherlands, England, Sweden, France and Finland, do utilize fetal RhD determination so that the administration of anti-D immune globulin can be avoided when an RhD-negative fetus is identified (Moise, 2024). Daniels et al. (2007) report that approximately 40% of RhD-negative pregnant individuals are carrying a RhD-negative fetus; genotypic screening would, therefore, be very valuable in preventing these individuals from receiving unnecessary anti-D immune globulin. Kent et al. (2014) suggest that the administration of anti-D immune globulin to the one third of pregnant individuals who do not require this administration is unethical, and that the availability of RhD genotyping to all RhD-negative pregnant individuals would assist in more informed choices being made regarding anti-D immune globulin administration. Finning et al. (2008) agree with the previous statements, declaring that "high throughput RHD genotyping of fetuses in all RhD negative [individuals] is feasible and would substantially reduce unnecessary administration of anti-RhD immunoglobulin to RhD negative pregnant [individuals] with an RhD negative fetus."

Analytical Validity

A prospective cohort study by de Haas et al. (2016) completed a nationwide program in the Netherlands to determine the sensitivity of fetal RhD screening for the safe guidance of targeted anti-immune globulin prophylaxis. A total of 25,789 RhD-negative pregnant individuals participated in this study. Fetal testing for the *RHD* gene was assessed in the 27th week of pregnancy. Fetal *RHD* test results were compared to serological cord blood results after birth. "Sensitivity for detection of fetal *RHD* was 99.94% (95% confidence interval 99.89% to 99.97%) and specificity was 97.74% (97.43% to 98.02%). Nine false-negative results for fetal RHD testing were registered (0.03%, 95% confidence interval 0.01% to 0.06%)" (de Haas et al., 2016). They conclude that fetal RhD testing is a highly reliable testing method.

Manfroi et al. (2018) completed fetal *RhD* genotyping with real-time polymerase chain reaction (qPCR) using cell-free fetal DNA extracted from maternal plasma. A commercial multiple-exon assay was used to determine fetal *RHD* genotypic accuracy. A total of 367 plasma samples obtained between the 24th and 28th weeks of pregnancy were used for this study. Neonatal results were available for 284 of the pregnancies. The sensitivity was reported at 100% and specificity at 97.5%. The diagnostic accuracy was 96.1% with the inclusion of 9/284 inconclusive results (Manfroi et al., 2018). The authors conclude that this is therefore an accurate and reliable tool for targeted prenatal immunoprophylaxis.

Clinical Utility and Validity

Education and counseling are a key factor in prenatal screening and diagnostic tests. Yesilcinar and Guvenc (2021) found that a proactive intervention approach decreased anxiety and decisional conflict in the pregnant individual and increased attitudes towards the tests, having a positive effect on the pregnant individual's knowledge level and decision satisfaction. This allowed the individual to make more informed decisions, such as opting to have screening and diagnostic testing performed. Decreasing anxiety during pregnancy is beneficial to the fetus and individuals receiving educational intervention showed decreased anxiety when receiving genetic screening results as compared to individuals not receiving the same intervention (Yesilcinar

& Guvenc, 2021). Migliorini et al. (2020) have also reported that the use of cell free DNA (cfDNA) screening, combined with a detailed ultrasound examination, as a first-trimester risk assessment is associated with improved maternal reassurance and satisfaction and decreased anxiety, as compared to individuals who received standard first-trimester combined screening with nuchal translucency (NT) and biochemistry (Migliorini et al., 2020).

Biro et al. (2020) report on a noninvasive prenatal testing method for congenital heart disease, utilizing the measurement of cell-free nucleic acid and protein biomarkers in maternal blood. Congenital heart disease is considered the most common fetal malformation. While prenatal ultrasonography is currently used to diagnose congenital heart disease, it is not the most accurate method. After a large review completed with PubMed and Web of Sciences databases, the authors conclude that most fetal congenital heart disease related disorders can be diagnosed by noninvasive prenatal testing (NIPT) techniques. Further, cell-free RNAs and circulating proteins are potential biomarkers for fetal congenital heart disease and may be able to improve the detection rate in early pregnancies (Biro et al., 2020).

A study by Persico et al. (2016) investigated the clinical implication of cfDNA testing in high-risk pregnancies. In their cohort of 259 singleton pregnancies, cfDNA testing provided results in 249 (96.1%). Further, cfDNA testing identified 97.2% (35/36) of trisomy 21, 100% (13/13) of trisomy 18, 100% of trisomy 13 (5/5), and 75% of sex chromosome aneuploidies (3/4). The authors conclude that "a policy of performing an invasive test in [individuals] with a combined risk of ≥1 in 10 or NT ≥4 mm and offering cfDNA testing to the remaining cases would detect all cases of trisomy 21, 18 or 13, 80% of sex aneuploidies and 62.5% of other defects and would avoid an invasive procedure in 82.4% of euploid fetuses" (Persico et al., 2016). These data support the earlier meta-analysis that reported NIPT sensitivity of trisomy 21, trisomy 18, and trisomy 13 of 99%, 96.8%, and 92.1%, respectively and specificities of 99.92%, 99.85%, and 99.80%, respectively, for trisomies 21, 18, and 13 (Dondorp et al., 2015; Gil et al., 2014).

A multi-year study of more than 5000 patients in public hospitals in Spain examined the effect of NIPT on the number of invasive procedures performed, showing that the introduction of NIPT drastically reduced the incidences of invasive procedures. The data shows that despite a 60.5% reduction occurred in invasive procedures, the chromosomopathy detection rate was unaffected; moreover, the ratio of positive invasive procedures was improved to 50%, indicating that unwarranted invasive procedures had been avoided (Martinez-Payo et al., 2018). The authors of the study concluded, "NIPT introduction has caused a significant reduction of 60.5% of IP [invasive procedures] in high chromosomopathy risk patients after combined screening without modifying detection rate" (Martinez-Payo et al., 2018).

A meta-analysis was completed by Mackie et al. (2017), researching the accuracy of cell-free fetal DNA NIPT testing in singleton pregnancies. A total of 117 studies were included, analyzing 18 different conditions. For RHD testing, a sensitivity of 0.993 and specificity of 0.984 was identified and for fetal sex identification, a sensitivity of 0.989 and a specificity of 0.996 was calculated (Mackie et al., 2017). With such high sensitivity and specificity calculations, NIPT testing for fetal sex and RHD status may be considered accurate diagnostic tools.

Clausen et al. (2014) completed a two-year evaluation of nationwide prenatal RhD screening in Denmark. A total of 12,668 pregnancies were analyzed, with blood samples drawn in week 25 of pregnancy. DNA was extracted from these blood samples and was analyzed for the *RHD* gene. Results were later compared to the serological typing of the newborns after birth. "The sensitivity for the detection of fetal *RHD* was 99.9% (95% CI: 99.7-99.9%). Unnecessary recommendation of prenatal RhD prophylaxis was avoided in 97.3% of the [individuals] carrying an RhD-negative fetus. Fetuses that were seropositive for RhD were not detected in 11 pregnancies (0.087%)" (Clausen et al., 2014). This study shows high sensitivity of fetal *RHD* genotyping, results which were recently supported by another large-scale meta-analysis completed by Yang et al. (2019), focusing on NIPT testing for fetal RhD status. A total of 3921 results confirmed that "High-throughput NIPT is sufficiently accurate to detect fetal RhD status in RhD-negative [individuals] and would considerably reduce unnecessary treatment with routine anti-D immunoglobulin" (Yang et al., 2019).

Darlington et al. (2018) completed an analysis of 11 French Obstetric Departments with a total of 949 patients to determine the effectiveness of RhD genotyping. The patients were separated into two groups (genotyping

group: n=515, and control group: n=335). The authors concluded that "Early knowledge of the RHD status of the fetus using non-invasive fetal *RHD* genotyping significantly improved the management of *RHD* negative pregnancies with a small increase in cost" (Darlington et al., 2018).

Runkel et al. (2020) completed a systematic review to determine the benefit of NIPT for fetal RhD status in RhD-negative pregnant individuals because "All non-sensitized Rhesus D (RhD)-negative pregnant [individuals] in Germany receive antenatal anti-D prophylaxis without knowledge of fetal RhD status." The meta-analysis included data from 60,000 participants, with the focus of the research on the impact of fetal and maternal morbidity. The researchers concluded that "NIPT for fetal RhD status is equivalent to conventional serologic testing using the newborn's blood. Studies investigating patient-relevant outcomes are still lacking" (Runkel et al., 2020).

Hoskovec et al. (2023) evaluated the "clinical performance of carrier screening for cystic fibrosis, hemoglobinopathies, and spinal muscular atrophy with reflex single-gene noninvasive prenatal screening (sgNIPS)." In the study, 9151 pregnant individuals were screened for carrier status. As a result, 1669 (18.2%) of the sampled individuals were found to carry one or more harmful genetic variations and were subsequently tested using sgNIPS. The results of sgNIPS were then compared to the outcomes of 201 pregnancies, which were obtained from surveys completed by parents or reports from healthcare providers. In conclusion, carrier screening using sgNIPS during pregnancy presents an alternative approach that circumvents the need for a paternal sample. It offers accurate assessment of fetal risk promptly, facilitating prenatal counseling and pregnancy management.

Westin et al. (2022) conducted a retrospective study which aimed to "validate the sgNIPT in clinical samples and identify high-risk SCD fetuses in a cohort of at-risk pregnancies." This retrospective clinical investigation gathered 77 maternal blood samples from pregnant patients at either Baylor College of Medicine or the University of Alabama at Birmingham. These patients were identified as having at least one harmful HBB allele. The results of this study highlighted that sgNIPT screening promotes "efficient and accurate fetal risk assessment for SCD in pregnant patients" (Westin et al., 2022).

It is notable that the field continues to evolve, with potential shifts from one testing method to another in pursuit of optimality and comprehensiveness. A multicenter retrospective study of singleton high-risk pregnancies for chromosomal abnormalities was conducted by Zhu et al. (2020) to evaluate the utility of expanded noninvasive prenatal screening as compared with chromosomal microarray analysis (CMA). The analysis enrolled subjects who underwent expanded NIPS and CMA sequentially during pregnancy from 2015 through 2019. The study demonstrated that of the 943 high-risk pregnancies, 550 (58.3%) cases had positive NIPS results, while positive CMA results were detected in 308 (32.7%) cases, and the agreement rates between NIPS and CMA were 82.3%, 59.6% and 25.0% for trisomy 21, 18 and 13, respectively. Regarding rare aneuploidies and segmental imbalances, NIPS and CMA results were concordant in 7.5% and 33.3% of cases. However, copy number variants were better detected with CMA than with NIPS and additional genetic aberrations were detected by CMA in one of 17 high-risk pregnancies that were otherwise passed over when processed with NIPS. The researchers contend that CMA should be offered for high-risk pregnancies to provide comprehensive detection of chromosomal abnormalities in these pregnancies (Zhu et al., 2020).

This policy focuses on genetic testing performed during pre-conception and/or prenatal periods as part of a comprehensive prenatal care program.

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG)

In 2021, ACMG released an updated guideline for screening for autosomal recessive and X-linked conditions during pregnancy and preconception. Their practice resource reviews aim to recommend "a consistent and equitable approach for offering carrier screening to all individuals during pregnancy and preconception" and

replaces any earlier ACMG position statements on prenatal/preconception expanded carrier screening and provide the following recommendations:

- "Analytical validity of carrier screening is to be established by a laboratory in compliance with CLIA/CAP regulations and adhering to ACMG Laboratory Standards and Guidelines."
- "As evidence evolves, ClinVar and ClinGen continually update pathogenicity of variants and the association between genes and conditions, respectively."
- "Carrier screening enables those screened to consider their reproductive risks, reproductive options, and to make informed decisions."
- "Published evidence supports clinical utility for carrier screening of multiple conditions simultaneously."
- "The phrase "expanded carrier screening" be replaced by "carrier screening."
- "Adopting a more precise tiered system based on carrier frequency:
  - Tier 4: <1/200 carrier frequency (includes Tier 3) genes/condition will vary by lab
  - Tier 3: ≥ 1/200 carrier frequency (includes Tier 2) includes X-linked conditions
  - Tier 2: ≥1/100 carrier frequency (includes Tier 1)
  - Tier 1: *CF* [Cystic Fibrosis] + *SMA* [spinal muscular atrophy] + Risk Based Screening
    - "Tier 1 screening conveys the recommendations previously adopted by ACMG and ACOG" and "adopts an ethnic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy. Beyond these two conditions, additional carrier screening is determined after risk assessment, which incorporates personal medical and family history as well as laboratory and imaging information where appropriate."
    - "Tier 2 carrier screening stems from an ACOG recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100." However, "data demonstrate that carrier screening for two common conditions using a carrier frequency threshold of 1/100 may not be equitable across diverse populations. Others have shown that limiting the carrier frequency to ≥1/100 creates missed opportunities to identify couples at risk for serious conditions."
    - "We define Tier 3 screening as carrier screening for conditions with a carrier frequency ≥1/200 . . . Tier 2 and Tier 3 screening prioritize carrier frequency as a way to think about conditions most appropriate for screening in the general population. However, when ACOG proposed this level, they did not specify whether it was thinking about carrier frequency in terms of the global population or subpopulations. We use "carrier frequency" to mean in any ethnic group with reasonable representation in the United States."
    - "Tier 4 includes genes less common than those in Tier 3 and can identify additional at-risk couples. Tier 4 has no lower limit carrier screening frequency and can greatly extend the number of conditions screened . . . the clinical validity at this level of carrier screening may be less compelling, therefore we suggest reserving this level of screening for consanguineous pregnancies (second cousins or closer) and in couples where family or medical history suggests Tier 4 screening might be beneficial . . . Importantly, patients should understand that their chance of being a carrier for one or more conditions increases as the number of conditions screened is increased."
- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.
- Tier 4 screening should be considered:
  - When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer);
  - When a family or personal medical history warrants.
- ACMG does NOT recommend:
  - Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups.
  - Routine offering of Tier 4 panels.
- "Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion."
- "All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive (Tables 1–5) and X-linked (Table 6) conditions."

- "Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions (Tables 1–5) when carrier screening is performed simultaneously with their partner."
- "All XX patients should be offered screening for only those X-linked genes listed in Table 6 as part of Tier 3 screening."
- "When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered" (Gregg et al., 2021).

Table 1. Autosomal recessive genes for screening with carrier frequency ≥1/50.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
141900	*HBB*	0.119837	603903	Sickle cell anemia β-thalassemia
			613985	
613208	*XPC*	0.050885	278720	Xeroderma pigmentosum
606933	*TYR*	0.049337	203100	Oculocutaneous albinism type 1A and 1B
			606952	
613815	*CYP21A2*	0.048459	201910	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
612349	*PAH*	0.046068	261600	Phenylketonuria
602421	*CFTR*	0.040972	219700	Cystic fibrosis
600985	*TNXB*	0.035134	606408	Ehlers–Danlos-like syndrome due to tenascin-X deficiency
606869	*HEXA*	0.033146	272800	Tay–Sachs disease
121011	*GJB2*	0.026200	220290	Nonsyndromic hearing loss recessive 1A
			601544	Nonsyndromic hearing loss dominant 3A
602858	*DHCR7*	0.023709	270400	Smith–Lemli–Opitz syndrome
277900	*ATP7B*	0.021983	606882	Wilson disease
608034	*ASPA*	0.019856	271900	Canavan disease
607008	*ACADM*	0.016583	201450	Medium-chain acyl-coenzyme A dehydrogenase deficiency
602716	*NPHS1*	0.015994	256300	Finnish congenital nephrotic syndrome
601785	*PMM2*	0.015877	212065	Carbohydrate-deficient glycoprotein syndrome type Ia
607440	*FKTN*	0.015660	611615	Cardiomyopathy, dilated, 1X
			253800	Walker–Warburg congenital muscular dystrophy
605646	*SLC26A4*	0.015422	600791	Deafness autosomal recessive 4
			274600	Pendred syndrome
126340	*ERCC2*	0.015255	610756	Cerebrooculofacioskeletal syndrome 2
			601675	Trichothiodystrophy 1, photosensitive
603297	*DYNC2H1*	0.014817	613091	Short-rib thoracic dysplasia 3 with or without polydactyly

OMIM Online Mendelian Inheritance in Man.[55]
[a]Values round to ≥ 0.02 (two decimal places).

Table 2. Autosomal recessive genes for screening with carrier frequency <1/50 to ≥1/100.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
610142	*CEP290*	0.014422	610188	Joubert syndrome 5
			611755	Leber congenital amaurosis 10
607839	*GBE1*	0.013799	232500	Glycogen storage disease, type IV
			263570	GBE1-related disorders
606800	*GAA*	0.013565	232300	Glycogen storage disease, type II (Pompe disease)
100725	*CHRNE*	0.013526	100725	Myasthenic syndrome, congenital, 4A, slow-channel
				Myasthenic syndrome, congenital, 4B, fast-channel
613742	*G6PC*	0.013401	232200	Glycogen storage disease type IA
611409	*OCA2*	0.013113	203200	Oculocutaneous albinism brown and type II
120120	*COL7A1*	0.012995	226600	Recessive dystrophic epidermolysis bullosa
600509	*ABCC8*	0.012242	618857	Diabetes mellitus, permanent neonatal 3
612724	*ALDOB*	0.012119	229600	Hereditary fructosuria
613899	*FANCC*	0.011992	227645	Fanconi anemia, complementation group C
604597	*GRIP1*	0.011989	617667	Fraser syndrome
248611	*BCKDHB*	0.011760	245600	Maple syrup urine disease
613726	*ANO10*	0.010781	613728	Spinocerebellar ataxia 10
104170	*NAGA*	0.010637	609241	Schindler disease, type 1
				Schindler disease, type 3
607608	*SMPD1*	0.010259	257200	Niemann–Pick disease, type A
			607616	Niemann–Pick disease, type B
608400	*USH2A*	0.010203	276901	Usher syndrome, type 2A
609058	*MMUT*	0.009999	251000	Methylmalonic aciduria–methylmalonyl–CoA mutase deficiency
600650	*CPT2*	0.009742	600649	Carnitine palmitoyltransferase II deficiency, infantile
			608836	Carnitine palmitoyltransferase II deficiency, lethal neonatal
608894	*AHI1*	0.009740	608629	Joubert syndrome 3

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.02 and ≥ 0.01 (two decimal places).

Table 3. Autosomal recessive genes for screening with carrier frequency <1/100 to ≥1/150.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
608172	*DHDDS*	0.009340	613861	Congenital disorder of glycosylation type 1
				Retinitis pigmentosa 59
606152	*SLC19A3*	0.009163	607483	Basal ganglia disease, biotin-responsive
606999	*GALT*	0.009132	230400	Galactosemia
118485	*CYP11A1*	0.008771	613743	Adrenal insufficiency, congenital, with 46, XY sex reversal, partial or complete
190000	*TF*	0.008615	209300	Atransferrinemia
609831	*MMACHC*	0.008610	277400	Methylmalonic aciduria with homocystinuria cblC type
601615	*ABCA3*	0.008587	610921	Surfactant metabolism dysfunction, pulmonary 3
606463	*GBA*	0.008572	230800	Gaucher disease, type I
			230900	Gaucher disease, type II
605248	*MCOLN1*	0.008531	252650	Mucolipidosis type IV
607840	*GNPTAB*	0.008454	252500	Mucolipidosis type II alpha/beta
			252600	Mucolipidosis type III alpha/beta
613228	*AGA*	0.008364	208400	Aspartylglucosaminuria
605514	*PCDH15*	0.008330	609533	Deafness, autosomal recessive 23
			602083	Usher syndrome, type 1F
613871	*FAH*	0.007716	276700	Tyrosinemia type I
607358	*AIRE*	0.007664	240300	Autoimmune polyendocrinopathy syndrome type I
606151	*BBS2*	0.007501	615981	Bardet–Biedl syndrome 2
			616562	Retinitis pigmentosa 74
606530	*CYP27A1*	0.007399	213700	Cerebrotendinous xanthomatosis
611204	*CCDC88C*	0.007282	236600	Congenital hydrocephalus 1
136132	*FMO3*	0.007190	602079	Trimethylaminuria
613277	*TMEM216*	0.007107	608091	Joubert syndrome 2
			603194	Meckel syndrome 2
605080	*CNGB3*	0.006849	262300	Achromatopsia 3
607117	*MCPH1*	0.006822	651200	Primary microcephaly 1, recessive
602671	*SLC37A4*	0.006748	232220	Glycogen storage disease Ib
			232240	Glycogen storage disease Ic
170280	*PRF1*	0.006734	603553	Hemophagocytic lymphohistiocytosis, familial, 2
604272	*SCO2*	0.006671	604377	Mitochondrial complex IV deficiency, nuclear type 2
604285	*AGXT*	0.006648	259900	Hyperoxaluria, primary type I

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.01 and ≥ 0.007 (two decimal places).

Table 4. Autosomal recessive genes for screening with carrier frequency <1/150 to ≥1/200.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
609575	*ACADVL*	0.006419	201475	Very long chain acyl-CoA dehydrogenase deficiency
608310	*ASL*	0.006190	207900	Argininosuccinate aciduria
607261	*EVC2*	0.006083	225500	Chondroectodermal dysplasia
607574	*ARSA*	0.005986	250100	Metachromatic leukodystrophy
251170	*MVK*	0.005966	260920	Hyper-IgD syndrome
			610377	Mevalonic aciduria
606702	*PKHD1*	0.005960	263200	Autosomal recessive polycystic kidney disease
609019	*BTD*	0.005953	253260	Biotinidase deficiency
171760	*ALPL*	0.005719	146300	Hypophosphatasia, adult
			241510	Hypophosphatasia, childhood and infantile
209901	*BBS1*	0.005713	209900	Bardet–Biedl syndrome 1
118425	*CLCN1*	0.005688	255700	Congenital myotonia, autosomal recessive form
609506	*CYP27B1*	0.005512	264700	Vitamin D–dependent rickets, type 1
174763	*POLG*	0.005330	203700	Mitochondrial DNA depletion syndrome 4A
			613662	Mitochondrial DNA depletion syndrome 4B
609014	*MCCC2*	0.005184	210210	3-methylcrotonyl CoA carboxylase 2 deficiency
605908	*MLC1*	0.005058	604004	Megalencephalic leukoencephalopathy with subcortical cysts
607809	*ACAT1*	0.005000	203750	α-Methylacetoacetic aciduria
612013	*CC2D2A*	0.004969	612285	Joubert syndrome 9
			612284	Meckel syndrome 6
606718	*SLC26A2*	0.004715	226900	Epiphyseal dysplasia, multiple, 4
			600972	Achondrogenesis Ib
236200	*CBS*	0.004676	236200	Homocystinuria, B6 responsive and nonresponsive
600073	*LRP2*	0.004676	222448	Donnai–Barrow syndrome
252800	*IDUA*	0.004675	607014	Mucopolysaccharidosis, Ih (Hurler S)
			607015	Mucopolysaccharidosis, Ih/s (Hurler–Scheie S)
606596	*FKRP*	0.004668	613153	Muscular dystrophy–dystroglycanopathy, type A, 5
			606612	Muscular dystrophy–dystroglycanopathy, type B, 5
610326	*RNASEH2B*	0.004609	610181	Aicardi Goutieres syndrome 2
611524	*RARS2*	0.004592	611523	Pontocerebellar hypoplasia type 6

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.007 and ≥ 0.005 (two decimal places).

Table 5. Genes that were ascertained for screening outside of the gnomAD criteria[a].

OMIM gene	OMIM gene name	Published carrier frequency[b]	Rationale for inclusion	Ethnic group	OMIM phenotype	Conditions
141800	*HBA1*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
141850	*HBA2*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
600354	*SMN1*	1/60[18]	ACOG/ACMG and carrier frequency	US panethnic	253300	
					253550	Spinal muscular
					253400	atrophy types: I, II, III, IV
					271150	
604982	*HPS1*	1/59[56–58]	Carrier frequency	PR	203300	Hermansky Pudlak S. 1
606118	*HPS3*	1/59[56]	Carrier frequency	PR	614072	Hermansky Pudlak S. 3
603722	*ELP1*	1/32[59]	ACOG/ACMG and carrier frequency	AJ	223900	Familial dysautonomia
606829	*FXN*	1/60–1/100[60]	Carrier frequency	Caucasians[d]	229300	Friedreich ataxia
238331	*DLD*	~1/100[59,61]	Carrier frequency	AJ	246900	Dihydrolipoamide dehydrogenase deficiency
161650	*NEB*	1/168[59]	Carrier frequency	AJ	256030	Nemaline myopathy 2
606397	*CLRN1*	1/120[59]	Carrier frequency	AJ	276902	Usher syndrome 3a
604610	*BLM*	1/100[59]	ACMG and carrier frequency	AJ	210900	Bloom syndrome

ACMG American College of Medical Genetics and Genomics, *ACOG* American College of Obstetricians and Gynecologists, *AJ* Ashkenazi Jewish (≥2% of the US population), *OMIM* Online Mendelian Inheritance in Man,[55] *PR* Puerto Rican, *SEA* South East Asian.
[a]Carrier frequency of a sequence variant is <1/200, if reported in gnomAD.[50]
[b]Diagnostic laboratory data was not used for carrier frequency data.
[c]Specific data for general US population not available; however, recognized as common among many US immigrant populations.[62]
[d]This term is no longer used by the journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognize it does not accurately describe the ancestry of the populations originally studied.[46]

Table 6. X-linked genes recommended for carrier screening.

OMIM gene	OMIM gene name	OMIM phenotype	Phenotype
300371	*ABCD1*	300100	Adrenoleukodystrophy (ALD)
300806	*AFF2*	309548	Mental retardation, X-linked, associated with fragile site FRAXE
300382	*ARX*	308350	Developmental and epileptic encephalopathy 1 (DEE1)
300377	*DMD*	300376	Muscular dystrophy, Becker type (BMD)
		310200	Muscular dystrophy, Duchenne type (DMD)
306700	*F8*	300841	Hemophilia A (HEMA)
300746	*F9*	306900	Hemophilia B (HEMB)
309550	*FMR1*	300624	Fragile X syndrome (FXS)
300644	*GLA*	301500	Fabry disease
308840	*L1CAM*	307000	Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)
300552	*MID1*	300000	Opitz GBBB syndrome, type I (GBBB1)
300473	*NR0B1*	300200	Adrenal hypoplasia, congenital (AHC)
300461	*OTC*	311250	Ornithine transcarbamylase deficiency
300401	*PLP1*	312920	Spastic paraplegia 2, X-linked (SPG2)
312610	*RPGR*	300029	Retinitis pigmentosa 3 (RP3; RP)
		300455	Retinitis pigmentosa, X-linked, and sinorespiratory
		300834	Infections, with or without deafness
			Macular degeneration, X-linked atrophic
300839	*RS1*	312700	Retinoschisis 1, X-linked, juvenile (RS1)
300036	*SLC6A8*	300352	Cerebral creatine deficiency syndrome 1 (CCDS1)

OMIM Online Mendelian Inheritance in Man.[55]

Tables 1-6 from (Gregg et al., 2021)

CFTR Variant Testing

In 2020, the ACMG provided a technical standard for CFTR variant testing. These standards state the following as it pertains to pregnancy:

"During pregnancy, simultaneous testing may be desired depending on gestational age, family and personal history, ethnicity, or patient preferences. Carrier testing may be offered to individuals with a positive family history of CF, in partners of individuals with a positive family history, in partners of CAVD males, to

reproductive age women, and to gamete donors. CFTR variant testing can also be performed for prenatal diagnosis using cells obtained for diagnostic cytogenetic testing (i.e., amniocentesis or chorionic villus sampling [CVS])" (Deignan et al., 2020).

"As a way to ensure that CFTR variant testing for carrier screening and diagnostic testing purposes remains inclusive, the ACMG recommends either a classification-based reporting approach or a classification-based (targeted) testing approach (which has historically been used for CFTR carrier screening). For those laboratories who wish to continue using a targeted testing approach, the ACMG-23 variant panel remains as the minimum list of CFTR variants that should be included. Laboratories may want to consider adding additional variants to their panel depending on the ethnic composition of their expected test population. However, the minimum list of CFTR variants recommended for pan-ethnic carrier screening has not been increased at this time" (Deignan et al., 2020).

In 2023, the ACMG provided updated recommendations for CFTR carrier screening which includes a new minimum CFTR variant set (increased from 23 to 100 variants). The updated ACMG position statement states the following:

"This new set now supersedes the previous set of 23 CFTR variants recommended by the ACMG. These revised recommendations apply only to carrier screening. They do not apply to CFTR variant testing for diagnosis or newborn screening. All other aspects of the updated 2020 ACMG CFTR technical standards still apply" (Deignan et al., 2020; Deignan et al., 2023).

American College of Obstetricians and Gynecologists (ACOG)

ACOG has several practice guidelines related to prenatal care as well as both pre-conception and prenatal testing. ACOG recommendations and guidelines include the following:

Genetic Testing and Genetic Counseling: Concerning genetic testing and genetic counseling, ACOG recommends:

- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is **not** recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published" (ACOG, 2016a). This was reaffirmed in 2023.
- Chromosomal microarray analysis (CMA) is recommended for patients with a fetus with at least one major structure abnormality identified via ultrasound. CMA can be considered for all pregnant individuals who undergo prenatal diagnostic testing; however, "In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed. Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities" (ACOG, 2016a). This was reaffirmed in 2023.
- "All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is recommended for [individuals] with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or [individuals] with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity" (ACOG, 2017a). This was reaffirmed in 2023.
- "The American College of Obstetricians and Gynecologists discourages direct-to-consumer genetic testing without appropriate counseling. . . Patients may present after direct-to-consumer testing already has been performed, and clinicians should be prepared to review these results or refer to a health care professional with the appropriate knowledge, training, and experience in interpreting test results. . . Given the insufficient data to support the use of single nucleotide polymorphisms (SNP) testing for medical purposes, SNP testing to provide individual risk assessment for a variety of diseases or to tailor drug therapy outside of an institutional review board-approved research protocol

is not recommended. The American College of Obstetricians and Gynecologists recommends that the use of these technologies be viewed as investigational at this time" (ACOG, 2021).
- ACOG notes that "Cascade testing has been shown to be cost effective in part because testing for specific mutations (e.g., those identified in the affected relative) is less expensive than whole-gene sequencing" (ACOG, 2018). This was reaffirmed in 2022.

Prenatal Diagnostic Testing for Genetic Disorders: Concerning prenatal diagnostic testing for genetic disorders, ACOG has published the following recommendations:

- "An abnormal FISH result should not be considered diagnostic. Therefore, clinical decision making based on information from FISH should include at least one of the following additional results: confirmatory traditional metaphase chromosome analysis or chromosomal microarray, or consistent clinical information (such as abnormal ultrasonographic findings or a positive screening test result for Down syndrome or trisomy 18)."
- "All pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors."
- "Prenatal genetic testing cannot identify all abnormalities or problems in a fetus, and any testing should be focused on the individual patient's risks, reproductive goals and preferences."
- "Genetic testing should be discussed as early as possible in pregnancy, ideally at the first obstetric visit, so that first-trimester options are available" (ACOG, 2016b).

Prevention of Rh D Alloimmunization: Concerning the prevention of Rh D alloimmunization, ACOG has published the guidelines supporting the administration of anti-D immune globulin to individuals in various scenarios. However, these guidelines do not mention the use of cell-free fetal DNA for fetal RHD testing to determine if anti-D immune globulin is needed (ACOG, 2017c).

Genetic Carrier Screening: Concerning genetic carrier screening, including testing for specific conditions, ACOG recommends [(ACOG, 2017a, 2017b) reaffirmed 2023]:

- "Carrier screening and counseling ideally should be performed before pregnancy."
- "If an individual is found to be a carrier for a specific condition, the individual's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes. Concurrent screening of the patient and her partner is suggested if there are time constraints for decisions about prenatal diagnostic evaluation."
- "Carrier screening for a particular condition generally should be performed only once in a person's lifetime, and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations."
- "Prenatal carrier screening does not replace newborn screening, nor does newborn screening replace the potential value of prenatal carrier screening."
- "The cost of carrier screening for an individual condition may be higher than the cost of testing through commercially available expanded carrier screening panels. When selecting a carrier screening approach, the cost of each option to the patient and the health care system should be considered."
- "Screening for spinal muscular atrophy should be offered to all [individuals] who are considering pregnancy or are currently pregnant. In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible, before testing. If the reports are not available, *SMN1* deletion testing should be recommended for the low-risk partner."
- "Cystic fibrosis carrier screening should be offered to all [individuals] who are considering pregnancy or are currently pregnant. Complete analysis of the *CFTR* gene by DNA sequencing is not appropriate for routine carrier screening."
- "A complete blood count with red blood cell indices should be performed in all [individuals] who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of a hemoglobinopathy. Ideally, this testing also should be offered to [individuals] before pregnancy. A

hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent). If red blood cell indices indicate a low mean corpuscular hemoglobin or mean corpuscular volume, hemoglobin electrophoresis also should be performed."

- "Fragile X premutation carrier screening is recommended for [individuals] with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant."
- "If a [individual] has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an *FMR1* premutation."
- "All identified individuals with intermediate results and carriers of a fragile X premutation or full mutation should be provided follow-up genetic counseling to discuss the risk to their offspring of inheriting an expanded full-mutation fragile X allele and to discuss fragile X-associated disorders (premature ovarian insufficiency and fragile X tremor/ataxia syndrome)."
- "Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation."
- "DNA-based molecular analysis (e.g., Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining *FMR1* triplet repeat number (e.g., premutations). In rare cases, the size of the triplet repeat and the methylation status do not correlate, which makes it difficult to predict the clinical phenotype. In cases of this discordance, the patient should be referred to a genetics professional."
- "When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay–Sachs disease and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder."
- "Screening for Tay–Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with Tay–Sachs disease also should be offered screening. When one member of a couple is at high risk (i.e., of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with Tay–Sachs disease) but the other partner is not, the high-risk partner should be offered screening. If the high-risk partner is found to be a carrier, the other partner also should be offered screening. Enzyme testing in pregnant [individuals] and [individuals] taking oral contraceptives should be performed using leukocyte testing because serum testing is associated with an increased false-positive rate in these populations. If Tay–Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay–Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel" (ACOG, 2017b).
- Regarding expanded carrier screening panels, ACOG recommends that "the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life." ACOG further states that "screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth" (ACOG, 2017a).

Carrier Screening in the Age of Genomic Medicine: Concerning carrier screening in the age of genomic medicine, the ACOG has published the following guidelines (ACOG, 2017a):

- "Ethnic-specific, pan-ethnic and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening
- If a patient requests a screening strategy other than the one used by the obstetrician-gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives

- All patients who are considering pregnancy or already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. Fragile X premutation carrier screening is also recommended for [individuals] with a family history of fragile x-related disorders or intellectual disability suggestive of fragile X syndrome, or [individuals] with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity
- If a [individual] is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child. Additional genetic counseling should be provided to discuss the specific condition, residual risk, and options for prenatal testing.
- Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening. Knowledge of the specific familial mutation may allow for more specific and rapid prenatal diagnosis.
- Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.
- Carrier screening panels should not include conditions primarily associated with a disease of adult onset" (ACOG, 2017a). This guideline was reaffirmed in 2023.

International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF)

The ISPD, SMFM and PQF published the following guidelines on the use of genome-wide sequencing for fetal diagnosis:

- The use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis (CMA), has already been performed and is uninformative, is offered concurrently according to accepted practice guidelines, or for whom expert genetic opinion determines that standard genetic testing is less optimal than sequencing for the presenting fetal phenotype.
- The routine use of prenatal sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls (ISPD, 2018).

In addition to the joint position statement released in 2018, the IPSD released a guideline in 2020 on the use of cfDNA screening for trisomies in multiple pregnancies:

- "The use of first trimester cfDNA screening for the common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence showing high detection and low false positive rates with high predictive values. **Moderate."**
- "It is preferable for laboratories performing cfDNA testing in multi-fetal pregnancies to take evidence of zygosity into consideration (eg, chorionicity, sex of the fetuses, embryo transfer history) for the interpretation of both test results and fetal fractions. **Moderate."**
- "Screening options for triplet pregnancies are lacking and cfDNA may be a potential option. However, diagnostic testing should always be offered and the limitations of screening tests stressed. **Low"** (Palomaki et al., 2021).

College of American Pathologists (CAP) Transfusion Medicine Resource Committee (TMRC) Work Group

The following recommendations were given by the CAP TMRC Work Group:

- The Work Group recommends that *RHD* genotyping be performed whenever a discordant RhD typing result and/or a serological weak D phenotype is detected in patients, including pregnant individuals, newborns, and potential transfusion recipients. It is anticipated that the immediate benefit will be fewer unnecessary injections of RhIG and increased availability of RhD-negative RBCs for transfusion.
- Other than RHD genotypes weak D type 1, 2, or 3, the Work Group recommends that individuals with a serological weak D phenotype receive conventional prophylaxis with RhIG, including postpartum RhIG if the newborn is RhD-positive or has a serological weak D phenotype (Sandler et al., 2015).

State and Federal Regulations, as applicable

The FDA has approved many tests for conditions that can be included in a prenatal screening, such as HSV, chlamydia, gonorrhea, syphilis, and diabetes. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81171, 81172, 81200, 81209, 81241, 81242, 81243, 81244, 81251, 81255, 81257,81260, 81290, 81329, 81330, 81400, 81401, 81403, 81404, 81405, 81406, 81412, 81443, 81479, 81599, S3845, S3846, S3849, 0400U, and 0449U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

9/13/22 New policy developed. BCBSNC will provide coverage for Prenatal Screening (genetic) when the medical criteria and guidelines outlined in the policy are met. Medical Director review 7/2022. **Notification give 9/13/2022 for effective date 10/18/2022.** (tt)

11/1/22 Policy title updated to include "AHS-M2179" to align with Avalon. (tt)

6/30/23 Added CPT code 0400U to Billing/Coding section, effective 7/1/2023. (tt)

8/15/23 Reviewed with Avalon Q2 CAB 2023. Updated description, policy guidelines, and references. Coverage of carrier screening expanded to include all of Tier 1/2/3 screening as recommended by ACMG. Medical Director review 7/2023. (tt)

9/4/24 Reviewed with Avalon Q2 CAB 2024. Updated description, related policies, policy guidelines, and references. When covered #3 updated for clarification that screening in the reproductive partner is restricted to the genes for which their partner tested positive by carrier screening, not broad screening for themselves. When covered #5 updated for clarification that fetal testing must be a form of testing, not a form of screening (e.g., cfDNA screening), from an amnio or CVS sample. Added "**Note 2:** For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy" under when covered section. Added the following statement to when not covered: "Reimbursement is not allowed for the use of non-invasive prenatal screening (NIPS) to screen for single-gene mutations (i.e., autosomal recessive, autosomal dominant, X-linked) in the fetus." Added 0449U, 81479, 81599 to Billing/Coding section. Medical Director review 7/2024. **Notification given 9/4/2024 for effective date 11/13/2024.** (tt)