

Prenatal Screening

Policy Number: AHS – G2035 – Prenatal Screening	Prior Policy Name and Number, as applicable:
Effective Date: 09/01/2022	

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I. Policy Description

Prenatal screening encompasses any testing done to determine the health status of the pregnant individual and/or fetus. Prenatal screening can range from screening for infectious diseases and conditions that may complicate the pregnancy all the way to testing 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, 2020).

II. Related Policies

Policy Number	Policy Title
AHS-G2009	Preventive Screening in Adults
AHS-G2042	Pediatric Preventive Services
AHS-G2045	Thyroid Disease Testing
AHS-G2055	Prenatal Screening for Fetal Aneuploidy
AHS-G2133	ZIKA Virus Risk Assessment

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage,

please visit their search website <http://www.cms.gov/medicare-coverage-database/overview-and-quicksearch.aspx?from2=search1.asp&> or the manual website.

Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

- 1) The following routine prenatal screening **MEETS COVERAGE CRITERIA** for all pregnant individuals:
 - a) Screening for HIV infection
 - b) Screening for *Chlamydia trachomatis* infection
 - c) Screening for *Neisseria gonorrhoea* infection
 - d) Screening for hepatitis B
 - e) Screening for syphilis
 - f) Screening for hepatitis C
 - g) Screening for bacteriuria
 - h) Screening for fetal aneuploidy in accordance with Avalon Policy AHS-G2055-Prenatal Screening for Fetal Aneuploidy
 - i) Screening for type 2 diabetes at the first prenatal visit
 - j) Screening for gestational diabetes during gestational weeks 24 – 28 and at the first prenatal visit if risk factors are present
 - k) Determination of blood type, Rh(D) status, and antibody status during the first prenatal visit, and repeated Rh (D) antibody testing for all unsensitized Rh (D)-negative individuals at 24 to 28 weeks' gestation, unless the biological father is known to be Rh (D)-negative
 - l) Screening for anemia meets coverage criteria with a CBC or hemoglobin and hematocrit with mean corpuscular volume
 - m) Screening for Group B strep once, recommended during gestational weeks 36 to 37 by American College of Obstetricians and Gynecologists (ACOG)
 - n) Urinalysis and urine culture
 - o) Rubella antibody testing
 - p) Testing for varicella immunity
 - q) Screening for tuberculosis in pregnant individuals deemed to be at high risk for TB (i.e. individuals with close contact with individuals with active pulmonary / respiratory tuberculosis or highly contagious active tuberculosis and individuals who are immunocompromised)
- 2) Third trimester re-screening of *Chlamydia trachomatis*, *Neisseria gonorrhoea*, syphilis, and/or HIV infections **MEETS COVERAGE CRITERIA** for pregnant individuals who meet ANY one of the following high-risk criteria:
 - a) Sexually active young individuals under 25 years
 - b) New or multiple sexual partners

- c) Past history of sexually transmitted diseases (Bacterial Vaginosis, Chancroid, Chlamydia, Gonorrhea, Genital Herpes, Hepatitis B, Hepatitis C, HIV/AIDS, Human Papillomavirus, Lymphogranuloma Venereum, Syphilis, Trichomoniasis)
 - d) Current sex workers
 - e) Past or current injection drug use
- 3) For pregnant individuals and those persons seeking pre-conception care, any of the following testing* (See Note 1 below) of carrier status **MEETS COVERAGE CRITERIA**:
- a) Carrier screening for Canavan disease, Tay-Sachs' disease, familial dysautonomia, Gaucher disease, Fanconi Anemia, Niemann-Pick type A, Bloom syndrome and mucopolidosis IV
 - b) Carrier screening for Fragile X syndrome
 - c) Carrier screening for spinal muscular atrophy
 - d) Carrier screening for hemoglobinopathies and/or thalassemia
 - e) Next generation sequencing (NGS) panel testing, as long as a single appropriate AMA genetic sequencing procedure test code is submitted
- 4) Carrier screening* (See Note 1 below) of the biological father **MEETS COVERAGE CRITERIA** when the biological mother is known or found to be a carrier of a recessively inherited disorder. Carrier testing limitations:
- a) Repeat carrier screening for the same disorder **does not meet coverage criteria**
- 5) Fetal Fibronectin (FFN) assays **MEET COVERAGE CRITERIA** for pregnant individuals who meet ALL the following criteria:
- a) Singleton or twin gestations,
 - b) Intact membranes,
 - c) Cervical dilation <3 cm, and
 - d) Patient experiencing symptoms suggestive of preterm labor between 24 and less than 35 weeks' gestation.
- 6) Testing pregnant individuals for thyroid dysfunction is covered in accordance with Avalon Policy AHS-G2045-Thyroid Disease Testing.
- 7) Screening for Zika virus testing is covered in accordance with Avalon Policy AHS-G2133-Zika Virus Testing.
- 8) Fetal RHD genotyping using maternal plasma **MEETS COVERAGE CRITERIA** in RHD negative pregnant individuals.
- 9) Pre-conception carrier screening in patients with a family history of a known inherited disorder and if positive, testing of the partner **MEETS COVERAGE CRITERIA**.
- 10) Carrier screening more than once per lifetime **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

- 11) All other applications of the FFN assay **DO NOT MEET COVERAGE CRITERIA**, including, but not limited to the following:
- As part of routine pregnancy monitoring in asymptomatic individuals with singleton gestation and no risk factors for preterm birth.
 - As part of clinical monitoring of asymptomatic individuals at high risk for preterm birth, including but not limited to those with multiple gestations, history of preterm birth, uterine malformation, cervical incompetence, or history of two or more spontaneous second trimester abortions.
 - As part of clinical monitoring in individuals with triplet or higher-order gestations, intact membranes, cervical dilation <3 cm, and who are experiencing symptoms suggestive of preterm labor.
 - As a test to identify individuals at term being considered for induction who are likely to deliver within 24–48 hours and therefore, do not require induction.
- 12) Serial monitoring of salivary estriol levels as a technique of risk assessment for preterm labor or delivery **DOES NOT MEET COVERAGE CRITERIA**.

Note 1: Carrier screening should be performed using the most appropriate carrier test (e.g. dosage/deletion for *SMN1* and NOT full gene sequencing; *DMD* del/dup testing and NOT full gene sequencing).

IV. Table of Terminology

Term	Definition
ACMG	American College of Medical Genetics and Genomics
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
cfDNA	Cell-free DNA
CMA	Chromosomal microarray
CNVs	Copy number variants
<i>DMD</i>	Dystrophin
EIA	Enzyme immunoassay
ELISA	Enzyme linked immunosorbent assay
FANCC	Fanconi anemia complementation group C
FFN	Fetal fibronectin
FIA	Fluorescence immunoassay
FRAXE	Fragile site, folic acid type, rare, Fra(X)(Q28) E
GBS	Group B streptococcal disease
GDM	Gestational diabetes mellitus
GJB6	Gap junction protein

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDFN	Hemolytic Disease of The Fetus and Newborn
HIV	Human immunodeficiency virus
HRSA	Health Resources & Services Administration
HSV	Herpes simplex virus
ISPD	International Society for Prenatal Diagnosis
MMS	Microdeletion/microduplication syndromes
NGS	Next generation sequencing
NIPS-Plus	Expanded non-invasive prenatal screening
NIPT	Non-invasive prenatal testing
NT	Nuchal translucency
PAH	Phenylalanine hydroxylase
PITC	Provider-initiated HIV testing and counselling
PPVs	Positive predictive values
PQF	Perinatal quality foundation
RBC	Red blood cells
RCOG	Royal College of Obstetricians and Gynaecologists
RHD	Rh blood group D antigen
SMA	Spinal muscular atrophy
SMFM	Society for Maternal Fetal Medicine
<i>SMN1</i>	Survival of Motor Neuron 1
SNP	Single nucleotide polymorphism
STI	Sexually transmitted infection
TB	Tuberculosis
TMRC	Transfusion Medicine Resource Committee
VA/DoD	Veterans Affairs/Department of Defense
WHO	World Health Organization

V. Scientific Background

Prenatal screening is a part of overall prenatal care to promote optimal care of both mother and baby 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).”

Routine prenatal screening may include several laboratory tests, such as hematocrit or hemoglobin testing to check for anemia and possible thalassemia, pending further diagnostic testing. Blood typing and antibody screening can be performed to prevent possible alloimmunization or hemolytic diseases and glucose testing can screen for possible gestational diabetes mellitus. Screening for asymptomatic bacteriuria and proteinuria is recommended as well as screening for infectious disorders, such as HIV, syphilis, chlamydia, and gonorrhea (Lockwood & Magriples, 2020).

Additionally, 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, 2020). 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). In fact, 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, however, 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, 2020).

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, 2020).

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, 2020). 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, 2020). 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 (Calhoun, 2020). 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) (Calhoun, 2020). 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, 2020).

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, 2020). 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, 2020).

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, 2020). 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 1/3 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.” (Gajic-Veljanoski et al., 2021)

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). This is therefore an accurate and reliable tool for targeted prenatal immunoprophylaxis.

Liang et al. (2019) used cell-free plasma DNA to assess the clinical utility of using an expanded noninvasive prenatal screening (“NIPS-Plus”) to detect aneuploidy and genome-wide microdeletion/microduplication syndromes (MMS). Of the 94,085 individuals with singleton pregnancies enrolled in the study, 1128 were suspected of having clinically significant fetal chromosomal abnormalities. Follow-up testing in the study reported the positive predictive values (PPVs) of 95%, 82%, 46%, 29%, and 47% for T21, T18, T13, rare trisomies, and sex chromosome aneuploidies, respectively. For known MMS (n=32), PPVs were 93% (DiGeorge), 68% (22q11.22 microduplication), 75% (Prader-Willi/Angelman), and 50% (Cri du Chat). Thus, the researchers conclude that “the data have potential significance in demonstrating the usefulness of cfDNA profiling” and that “NIPS-Plus can be used as a

first-tier pregnancy screening method to improve detection rates of clinically significant fetal chromosome abnormalities” (Liang et al., 2019).

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).

Implementation of prenatal screening tests can positively affect pregnancies and pregnancy outcomes. The Centers for Disease Control and Prevention (CDC) reports that implementation of the 1996 guidelines concerning Group B Streptococcus (GBS) had a profound effect. Prior to screening and widespread use of intrapartum antibiotics, invasive neonatal GBS occurred in 2 – 3 cases per 1,000 live births; however, after prenatal screening implementation, the rate declined to 0.5 cases per 1,000 live births in 1999 (Schrag et al., 2002). The CDC also reports from a multi-year study that screening for syphilis in all pregnant individuals at the first prenatal visit (and then rescreening in third trimester for individuals at risk) is very important in preventing congenital syphilis, which can cause spontaneous abortion, stillbirth, and early infant death. They show that 88.2% of cases of congenital syphilis was avoided when proper screening was applied; moreover, 30.9% of the cases of congenital syphilis that did occur happened when the mother did not receive proper prenatal care (≥ 45 days before delivery) (Slutsker et al., 2018).

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).

It is important to note 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 1 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 laboratory testing performed during pre-conception and/or prenatal periods as part of a comprehensive prenatal care program.

VI. Guidelines and Recommendations

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:

- **Vitamin D Screening:** Concerning vitamin D screening, “there is insufficient evidence to support a recommendation for screening all pregnant [individuals] for vitamin D deficiency. For pregnant [individuals] thought to be at increased risk of vitamin D deficiency, maternal serum 25-hydroxyvitamin D levels can be considered and should be interpreted in the context of the individual clinical circumstance [reaffirmed in 2021] (ACOG, 2011).”
- **Lead Screening:** Concerning lead screening, they recommend risk assessment at the earliest contact of the patient to lead exposure using blood lead testing if even one single risk factor is identified. This was reaffirmed in 2019 (ACOG, 2012).
- **Subclinical Hypothyroidism:** ACOG Committee Opinion on subclinical hypothyroidism in pregnancy does not recommend routine screening for subclinical hypothyroidism. It states that “thyroid testing in pregnancy should be performed on symptomatic [individuals] and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease (e.g., diabetes mellitus) (ACOG, 2015).”
- **Depression and Anxiety:** “All obstetrician-gynecologists and other obstetric care providers screen patients at least once during the perinatal period for depression and anxiety symptoms using a standardized, validated tool. [They should] complete a full assessment of mood and emotional well-being (including screening for postpartum depression and anxiety with a validated instrument) during the comprehensive postpartum visit for each patient (ACOG, 2018).”
- **Listeria monocytogenes:** Concerning testing for *Listeria monocytogenes* (ACOG, 2014), “No testing, including blood and stool cultures, or treatment is indicated for an asymptomatic pregnant [individual] who reports consumption of a product that was recalled or implicated during an outbreak of listeria contamination. An asymptomatic patient should be instructed to return if she develops symptoms of listeriosis within 2 months of eating the recalled or implicated product.” If an exposed pregnant individual shows signs and symptoms consistent with infection,

then blood culture testing is the standard of care. Stool culture testing is not recommended since it has not been validated as a screening tool. This position was reaffirmed in 2019.

- **HIV:** Concerning HIV, ACOG recommends that all individuals should be tested for HIV with the right to refuse testing. “Human immunodeficiency virus testing using the opt-out approach, which is currently permitted in every jurisdiction in the United States, should be a routine component of care for [individuals] during prepregnancy and as early in pregnancy as possible. Repeat HIV testing in the third trimester, preferably before 36 weeks of gestation, is recommended for pregnant [individuals] with initial negative HIV antibody tests who are known to be at high risk of acquiring HIV infection; who are receiving care in facilities that have an HIV incidence in pregnant [individuals] of at least 1 per 1,000 per year; who are incarcerated; who reside in jurisdictions with elevated HIV incidence; or who have signs and symptoms consistent with acute HIV infection (eg, fever, lymphadenopathy, skin rash, myalgias, arthralgias, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation). Rapid screening during labor and delivery or during the immediate postpartum period using the opt-out approach should be done for [individuals] who were not tested earlier in pregnancy or whose HIV status is otherwise unknown. Results should be available 24 hours a day and within 1 hour (Pollock et al., 2019).”
 - For pregnant individuals who test positive for HIV, “Additional laboratory work, including CD4⁺ count; HIV viral load; testing for antiretroviral resistance; hepatitis C virus antibody; hepatitis B surface antigen and viral load; and hepatitis A using antibody testing for immunoglobulin G for [individuals] who have hepatitis B virus infection and who have not already received the hepatitis A virus vaccine series; complete blood count with platelet count; and baseline chemistries with comprehensive metabolic testing, will be useful before prescribing antiretroviral therapy (Pollock et al., 2019).”
- **Genetic Testing and Genetic Counseling:** Concerning genetic testing and genetic counseling, ACOG recommends:
 - “A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician–gynecologists or other obstetric–gynecologic providers and should be updated regularly. . . . If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.” (ACOG, 2019a)
 - “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.” This was reaffirmed in 2020 (ACOG, 2016a).
 - 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 (ie, 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 2020.

- “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 (Romero et al., 2017).” This was reaffirmed in 2020 (ACOG, 2020a).
- “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. . . 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, 2021a)
- ACOG “recommends considering whole-exome sequencing when specific genetic tests available for a phenotype, including targeted sequencing tests, have failed to arrive at a diagnosis in a fetus with multiple congenital anomalies suggestive of a genetic disorder (Vora et al., 2018)”; however, they note that “Cascade testing has been shown to be cost effective in part because testing for specific mutations (eg, those identified in the affected relative) is less expensive than whole-gene sequencing.” Reaffirmed 2020 (Witkop & ACOG, 2018).
- **Prenatal Diagnostic Testing for Genetic Disorders:** Concerning prenatal diagnostic testing for genetic disorders, ACOG has published the following recommendations (ACOG, 2016b):
 - “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
 - 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).” This guideline was reaffirmed in 2021.
- **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, 2017b).
- **Genetic Carrier Screening:** Concerning genetic carrier screening, including testing for specific conditions, ACOG recommends [(Rink et al., 2017; Romero et al., 2017) reaffirmed 2020]:
 - “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 (eg, Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining *FMR1* triplet repeat number (eg, 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 (ie, 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 (Rink et al., 2017).”
- 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 (Romero et al., 2017).”
- **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, panethnic 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 2020
- **Group B Streptococcal (GBS) Disease:** “all pregnant [individuals] should undergo antepartum screening for GBS at 36 0/7–37 6/7 weeks of gestation, unless intrapartum antibiotic prophylaxis for GBS is indicated because of GBS bacteriuria during the pregnancy or because of a history of a previous GBS-infected newborn. This new recommended timing for screening provides a 5-week window for valid culture results that includes births that occur up to a gestational age of at least 41 0/7 weeks” (ACOG, 2020b)
- **Lab Tests:** ACOG lists the following lab tests to be performed early in pregnancy: complete blood count (CBC), blood type and Rh factor, urinalysis, urine culture, rubella, hepatitis B, hepatitis C, HIV, sexually transmitted infection (STI) testing, and tuberculosis (ACOG, 2021b). ACOG lists the following lab tests to be performed later in pregnancy: glucose screening test and Group B streptococcus (GBS) screening (ACOG, 2021b).
- **Zika Virus:** The April 2019 update concerning Zika, ACOG states the following (ACOG, 2019b):
 - “Although rates of Zika virus infection have decreased in the United States, obstetrician-gynecologists and other health care providers should continue to assess their patients for potential exposure based on travel or sexual history and test symptomatic patients with

possible exposure and pregnant [individuals] with ongoing exposure regardless of symptoms in accordance with the Centers for Disease Control and Prevention recommendations. . . . Testing recommendations for pregnant [individuals] with possible Zika virus exposure differ based on the presence or absence of symptoms of Zika virus infection and the circumstances of possible exposure. If obstetrician-gynecologists or other health care providers identify a patient who has possibly been exposed to the Zika virus and may require testing, they should contact their local or state health department for assistance. Consultation with a maternal-fetal medicine specialist or an infectious disease specialist with expertise in the management of infectious diseases in pregnancy may be useful for pregnant [individuals] with possible maternal Zika virus infection or concerning fetal findings. Zika virus identification and follow-up care of infants born to [individuals] with possible exposure to Zika virus during pregnancy are critical and can ensure that appropriate intervention services are available to affected infants.”(ACOG, 2019b)

United States Preventive Services Task Force (USPSTF)

The United States Preventive Services Task Force (USPSTF) recommends the following testing for pregnant individuals:

- Screening for gestational diabetes in asymptomatic pregnant individuals at ≥ 24 weeks of gestation (Grade B) (Pillay et al., 2021; USPSTF, 2021)
- Screening for hepatitis B virus (HBV) infection at the first prenatal visit (Grade A) (Owens, Davidson, Krist, Barry, Cabana, Caughey, Doubeni, Epling, Kemper, et al., 2019; USPSTF, 2009, 2019)
- Screening for asymptomatic bacteriuria with urine culture is recommended in pregnant persons (Grade B) (Owens, Davidson, Krist, Barry, Cabana, Caughey, Doubeni, Epling, Kubik, et al., 2019; USPSTF, 2008a)
- Screening for HIV is recommended in all pregnant persons, including those in labor or whose HIV status is unknown at delivery (Grade A) (Moyer & USPSTF, 2013b; Owens, Davidson, Krist, Barry, Cabana, Caughey, Curry, et al., 2019)
- Rh (D) blood typing and antibody testing during the first prenatal visit (Grade A) (USPSTF, 2005)
- Repeated Rh (D) antibody testing for all unsensitized Rh (D)-negative individuals at 24-28 weeks’ gestation, unless the biological father is known to be Rh (D)-negative (Grade B) (USPSTF, 2005)
- Screening early for syphilis infection in all pregnant individuals (Grade A) (USPSTF, 2018)

Additional recommendations from the USPSTF that may be relevant during pregnancy include:

- Screening for chlamydia in sexually active individuals aged 24 years or younger and in older individuals who are at increased risk for infection (Grade B) (LeFevre & USPSTF, 2014)
- Screening for gonorrhea in sexually active individuals aged 24 years or younger and in older individuals who are at increased risk for infection (Grade B) (LeFevre & USPSTF, 2014)
- Screening for depression in general population, including pregnant and post-partum individuals (Grade B) (Siu & USPSTF, 2016)

Screening for hepatitis C virus (HCV) infection is recommended in all adults aged 18 to 79 years (Grade B) (Chou et al., 2020; Moyer & USPSTF, 2013a)

Concerning screening adults for drug use, Krist et al. (2020) state that “the USPSTF recommends screening by asking questions about unhealthy drug use in adults age 18 years or older. Screening should be implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred. (Screening refers to asking questions about unhealthy drug use, not testing biological specimens.)” The USPSTF also states that “this new evidence supports the current recommendation that primary care clinicians offer screening to adults 18 years or older, including those who are pregnant or postpartum, when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred.”

However, the USPSTF recommends against the following tests during pregnancy:

- Screening for bacterial vaginosis in pregnant individuals who are not at risk for preterm delivery (grade D); further, current evidence is insufficient for screening pregnant persons who are at increased risk for preterm delivery (Owens et al., 2020; USPSTF, 2008b)
- Serological screening for herpes simplex virus (HSV) in asymptomatic pregnant individuals (USPSTF, 2016)
- Screening for elevated blood lead levels in asymptomatic pregnant individuals has been given an I recommendation as current evidence is insufficient to determine if this testing is beneficial or not (Curry et al., 2019; USPSTF, 2006)
- “The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in pregnant [individuals] to prevent adverse maternal health and birth outcomes (Siu, 2015).”

American Diabetes Association (ADA)

The American Diabetes Association in the 2021 *Standards of Medical Care in Diabetes* make the following recommendations (American Diabetes, 2021a, 2021b):

- “Starting at puberty and continuing in all [individuals] with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. [Grade] **A**
- Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C <6.5% (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. [Grade] **B**
- [individuals] with preexisting diabetes who are planning a pregnancy should ideally be managed beginning in preconception in a multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. [Grade] **B**
- [individuals] with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care provider. [Grade] **B**
- Test for undiagnosed prediabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. [Grade] **B**
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant [individuals] not previously found to have diabetes. [Grade] **A**

- Screen [individuals] with a recent history of gestational diabetes mellitus at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria [Grade] **B**
- [individuals] with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. [Grade] **B**
- [individuals] with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. [Grade] **A**
- [individuals] with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. [Grade] **E**”

Centers for Disease Control and Prevention (CDC)

The Centers for Disease Control and Prevention (CDC) recommends:

Disease	First Prenatal Visit	Third Trimester	At Delivery
Syphilis	All pregnant individuals	Certain groups of pregnant individuals ⁵ at 28-32 weeks	Certain groups of pregnant individuals ⁵ at delivery
HIV	All pregnant individuals ¹	Rescreen individuals at high risk for acquiring HIV infection	Pregnant individuals not screened during pregnancy
Hepatitis B (HBV)	All pregnant individuals ²	Test those not screened prenatally and whose who engage in behaviors that put them at a high risk ⁷ for infection	Pregnant individuals not screened during pregnancy ⁶ , who are at high risk ⁷ , or with signs or symptoms of hepatitis
Chlamydia	All pregnant individuals <25 years of age and older pregnant individuals at increased risk ³	Pregnant individuals <25 years of age or continued high risk ³	N/A
Gonorrhea	All pregnant individuals <25 years of age and older pregnant individuals at increased risk ⁴	Pregnant individuals at continued high risk ⁴	N/A
Hepatitis C (HCV)	All ⁸ pregnant individuals during each pregnancy	N/A	N/A

Endnotes:

1. To promote informed and timely therapeutic decisions, health care providers should test individuals for HIV as early as possible during each pregnancy.

2. All pregnant individuals should be tested for hepatitis B surface antigen (HbsAg) during an early prenatal visit (e.g., first trimester) in each pregnancy, even if they have been vaccinated or tested previously.
 3. “Increased risk” means new or multiple sex partners, sex partner with concurrent partners, sex partners who have a sexually transmitted infection (STI).
 4. “At increased risk” means living in a high-morbidity area, having a previous or coexisting STI, new or multiple sex partners, inconsistent condom use among persons not in mutually monogamous relationships, exchanging sex for money or drugs.
 5. “Certain groups” includes individuals who are at high risk for syphilis during pregnancy, who live in areas with high numbers or syphilis cases, and/or who were not previously tested or had a positive test in the first trimester.
 6. Individuals admitted for delivery at a health care facility without documentation of HbsAg test results should have blood drawn and tested as soon as possible after admission.
 7. Having had more than one sex partner during the previous 6 months, an HbsAg-positive sex partner, evaluation or treatment for a STD, or injection-drug use (IDU).
 8. All pregnant individuals except in a setting where the prevalence of HCV infection is (HCV RNA-positivity) <0.1%.” (CDC, 2021a)
- “A second test during the third trimester, preferably at <36 weeks’ gestation, should be considered and is recommended for [individuals] who are at high risk for acquiring HIV infection, [individuals] who receive health care in jurisdictions with high rates of HIV, and [individuals] examined in clinical settings in which HIV incidence is ≥ 1 per 1,000 [individuals] screened per year” (CDC, 2021f).
 - “Regardless of whether they have been previously tested or vaccinated, all pregnant [individuals] should be tested for HBsAg at the first prenatal visit and again at delivery if at high risk for HBV infection (see STI Detection Among Special Populations). Pregnant [individuals] at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination” (CDC, 2021d)
 - “[individuals] aged <25 years and those at increased risk for chlamydia (i.e., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) should be screened at the first prenatal visit and rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant” (CDC, 2021b).
 - “Annual screening for *N. gonorrhoeae* infection is recommended for all sexually active [individuals] aged <25 years and for older [individuals] at increased risk for infection (e.g., those aged ≥ 25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI . . . [All individuals] who have been treated for gonorrhea should be retested 3 months after treatment regardless of whether they believe their sex partners were treated” (CDC, 2021c).
 - “CDC recommends hepatitis C screening . . . all [individuals] during each pregnancy, except in settings where the prevalence of HCV infection is <0.1%” (CDC, 2021e)
 - Zika virus testing for asymptomatic individuals is not currently recommended. For symptomatic pregnant individuals:

- “For symptomatic pregnant [individuals] who had recent travel to areas with active dengue transmission and a risk of Zika, specimens should be collected as soon as possible after the onset of symptoms up to 12 weeks after symptom onset.
 - The following diagnostic testing should be performed at the same time:
 - Dengue and Zika virus NAAT testing on a serum specimen, and Zika virus NAAT on a urine specimen, and
 - IgM testing for dengue only.
 - Zika virus IgM testing is NOT recommended for symptomatic pregnant [individuals].
 - Zika IgM antibodies can persist for months to years following infection. Therefore, detecting Zika IgM antibodies might not indicate a recent infection.
 - There is notable cross-reactivity between dengue IgM and Zika IgM antibodies in serologic tests. Antibodies generated by a recent dengue virus infection can cause the Zika IgM to be falsely positive.
 - If the Zika NAAT is positive on a single specimen, the Zika NAAT should be repeated on newly extracted RNA from the same specimen to rule out false-positive NAAT results. If the dengue NAAT is positive, this provides adequate evidence of a dengue infection and no further testing is indicated.
 - If the IgM antibody test for dengue is positive, this is adequate evidence of a dengue infection and no further testing is indicated (CDC, 2019).”
- “Evidence does not support routine HSV-2 serologic testing among asymptomatic pregnant [individuals]” (CDC, 2021a)
- “Evidence does not support routine screening for BV in asymptomatic pregnant [individuals] at high or low risk for preterm delivery” (CDC, 2021a)

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (ACMG) recommends that the following (Gregg et al., 2016):

- “Allowing patients to select *diagnostic* or *screening* approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences.”
- “Informing all pregnant [individuals] that *diagnostic* testing (CVS or amniocentesis) is an option for the detection of chromosome abnormalities and clinically significant CNVs [copy-number variants].”
- “Informing all pregnant [individuals] that NIPS [non-invasive prenatal screening] is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes).”
- “Offering *diagnostic* testing when a positive screening test result is reported after NIPS.”
- The ACMG does NOT recommend “NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21.”
- “Offering *diagnostic* testing for a no-call NIPS result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age. A repeat blood draw is NOT appropriate.”
- “Offering aneuploidy screening other than NIPS in cases of significant obesity.”

- “Offering *diagnostic* testing when a positive screening test result is reported after screening for sex chromosome aneuploidies.”
- “Offering *diagnostic* testing (CVS or amniocentesis) with CMA when NIPS identifies a CNV.”
- ACMG does NOT recommend “NIPS to screen for *genome-wide* CNVs. If this level of information is desired, then diagnostic testing (e.g., chorionic villous sampling or amniocentesis) followed by CMA is recommended.”
- “Offering aneuploidy screening other than NIPS for patients with a history of bone marrow or organ transplantation from a male donor or donor of uncertain biologic sex.”

In 2014, the ACMG released guidelines concerning the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency. They recommend PAH testing be part of newborn screening and that quantitative blood amino acids testing should be performed for diagnostic testing following a positive newborn screen of PAH deficiency. “Additional testing is needed to define the cause of elevated PHE and should include analysis of pterin metabolism; PAH genotypic is indicated for improved therapy planning (Vockley et al., 2014).”

In 2021, ACMG released an updated guideline for screening for autosomal recessive and X-linked conditions during pregnancy and preconception. Their practice resource reviews aims 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 $\geq 1/200$. . . 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 $\geq 1/50$.

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

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

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

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

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^aAfter 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	<i>HBA1</i>	U ^c	Carrier frequency	SEA and others	604131	α-Thalassemia
141850	<i>HBA2</i>	U ^c	Carrier frequency	SEA and others	604131	α-Thalassemia
600354	<i>SMN1</i>	1/60 ¹⁸	ACOG/ACMG and carrier frequency	US panethnic	253300	Spinal muscular atrophy types: I, II, III, IV
					253550	
					253400	
					271150	
604982	<i>HPS1</i>	1/59 ⁵⁶⁻⁵⁸	Carrier frequency	PR	203300	Hermansky Pudlak S. 1
606118	<i>HPS3</i>	1/59 ⁵⁶	Carrier frequency	PR	614072	Hermansky Pudlak S. 3
603722	<i>ELP1</i>	1/32 ⁵⁹	ACOG/ACMG and carrier frequency	AJ	223900	Familial dysautonomia
606829	<i>FXN</i>	1/60–1/100 ⁶⁰	Carrier frequency	Caucasians ^d	229300	Friedreich ataxia
238331	<i>DLD</i>	~1/100 ^{59,61}	Carrier frequency	AJ	246900	Dihydroliipoamide dehydrogenase deficiency
161650	<i>NEB</i>	1/168 ⁵⁹	Carrier frequency	AJ	256030	Nemaline myopathy 2
606397	<i>CLRN1</i>	1/120 ⁵⁹	Carrier frequency	AJ	276902	Usher syndrome 3a
604610	<i>BLM</i>	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.

^aCarrier frequency of a sequence variant is <1/200, if reported in gnomAD.⁵⁰

^bDiagnostic laboratory data was not used for carrier frequency data.

^cSpecific data for general US population not available; however, recognized as common among many US immigrant populations.⁶²

^dThis 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	<i>ABCD1</i>	300100	Adrenoleukodystrophy (ALD)
300806	<i>AFF2</i>	309548	Mental retardation, X-linked, associated with fragile site FRAXE
300382	<i>ARX</i>	308350	Developmental and epileptic encephalopathy 1 (DEE1)
300377	<i>DMD</i>	300376	Muscular dystrophy, Becker type (BMD)
		310200	Muscular dystrophy, Duchenne type (DMD)
306700	<i>F8</i>	300841	Hemophilia A (HEMA)
300746	<i>F9</i>	306900	Hemophilia B (HEMB)
309550	<i>FMRI</i>	300624	Fragile X syndrome (FXS)
300644	<i>GLA</i>	301500	Fabry disease
308840	<i>L1CAM</i>	307000	Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)
300552	<i>MID1</i>	300000	Opitz GBBB syndrome, type I (GBBB1)
300473	<i>NROB1</i>	300200	Adrenal hypoplasia, congenital (AHC)
300461	<i>OTC</i>	311250	Ornithine transcarbamylase deficiency
300401	<i>PLP1</i>	312920	Spastic paraplegia 2, X-linked (SPG2)
312610	<i>RPGR</i>	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	<i>RS1</i>	312700	Retinoschisis 1, X-linked, juvenile (RS1)
300036	<i>SLC6A8</i>	300352	Cerebral creatine deficiency syndrome 1 (CCDS1)

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

World Health Organization (WHO)

In 2016, the WHO released their publication titled, *WHO recommendations on antenatal care for a positive pregnancy experience*, which had the following recommendations (WHO, 2016):

- Anemia (Context-specific recommendation)—"Full blood count testing is the recommended method for diagnosing anaemia in pregnancy."
- Asymptomatic bacteriuria (Context-specific recommendation)—"Midstream urine culture is the recommended method for diagnosing asymptomatic bacteriuria (ASB) in pregnancy. In settings where urine culture is not available, on-site midstream urine Gram-staining is recommended over the use of dipstick tests as the method for diagnosing ASB in pregnancy."
- Gestational diabetes mellitus (Recommended)—"Hyperglycaemia first detected at any time during pregnancy should be classified as either gestational diabetes mellitus (GDM) or diabetes mellitus in pregnancy, according to WHO criteria."
- HIV and syphilis (Recommended)—"In high-prevalence settings, provider-initiated HIV testing and counselling (PITC) for HIV should be considered a routine component of the package of care for pregnant [individuals] in all antenatal care settings. In low-prevalence settings, PITC can be considered for pregnant [individuals] in antenatal care settings as a key component of the effort to eliminate mother-to-child transmission of HIV, and to integrate HIV testing with syphilis, viral or other key tests, as relevant to the setting, and to strengthen the underlying maternal and child health systems."
- Tuberculosis (Context-specific recommendation)—"In settings where the tuberculosis (TB) prevalence in the general population is 100/100 000 population or higher, systematic screening for active TB should be considered for pregnant [individuals] as part of antenatal care (WHO, 2016)."

To help circumvent prenatal transmission, the CDC also "recommends that all pregnant [individuals] get tested for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis during each pregnancy" as "screening is necessary to access medical services for HCV and treatment to prevent transmission of HIV, HBV, and syphilis to the infant" (CDC, 2020).

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 auto-somal 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)

The Canadian National Rh Working Group and the Society of Obstetricians and Gynaecologists of Canada (SOGC) Genetics Committee

Guidelines were published by a consensus meeting of the Canadian National Rh Working Group in collaboration with the SOGC Genetics committee. The following recommendations were provided:

- The current optimal management of the D-negative pregnant individual is based on the prediction of the fetal D-blood group by cell-free DNA in maternal plasma with targeted antenatal anti-D prophylaxis. This approach should be adopted in Canada (II-2A).
- While various algorithms of implementation of fetal RHD genotyping have been described, a model positioned in the first trimester appears to be most in alignment with the existing Canadian antenatal anti-D prophylaxis program and should be endorsed (II-2A).
- While the risk of a false-negative result with RHD genotyping is very small and the benefits of knowing the fetal RHD status in terms of compliance with prophylaxis seem to outweigh the risks, the chance of immunization is not zero. Quality control at a laboratory and clinical level should be of utmost priority in program planning (II-3A) (Johnson et al., 2017).

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

The following recommendations were given by the CAP RMRC 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).

Department of Veterans Affairs/Department of Defense (VA/DoD)

In the 3rd edition of the VA/DoD *Clinical Practice Guideline for the Management of Pregnancy (VA & DOD, 2018)*, they list the following lab tests as routine for all pregnancies in the first prenatal visit: HIV, CBC, ABO Rh blood typing, Antibody screen, anemia/hemoglobinopathies screen, rapid plasma 29egain,

gonorrhea, chlamydia, hepatitis B surface antigen test, rubella IgG, Urinalysis and culture, and varicella IgG (if status is unknown). They also list the following among their recommendations (VA & DOD, 2018):

- “We recommend screening for use of tobacco, alcohol, illicit drugs, and unauthorized use of prescription medication because their use is common and can result in adverse outcomes. For [individuals] who screen positive, we recommend additional evaluation and treatment.” [Strong]
- “We recommend screening for depression using a standardized tool such as the Edinburgh Postnatal Depression Scale or the 9- item Patient Health Questionnaire periodically during pregnancy and postpartum.” [Strong]
- “We suggest making prenatal diagnostic testing for aneuploidy available to all pregnant [individuals].” [Weak]
- “We recommend offering prenatal screening for aneuploidy and the most common clinically significant genetic disorders to all pregnant [individuals]. When aneuploidy screening is desired, cellfree fetal DNA screening should be considered; however, screening test selection should be individualized and take into account the patient’s age, baseline aneuploidy risk, and test performance for a given condition.” [Strong]
- “We suggest the two-step process (one-hour oral glucose challenge test followed by three-hour oral glucose tolerance test) to screen for gestational diabetes mellitus at 24-28 weeks gestation for all pregnant [individuals].” [Weak]
- “We suggest that pregnant [individuals] with an unexplained elevation of maternal serum alpha-fetoprotein be evaluated and counseled by a qualified obstetric provider due to increased risk for adverse perinatal outcomes.” [Weak]
- “We recommend **against** routine screening for preterm delivery using the fetal fibronectin test in asymptomatic [individuals].” [Strong, against]
- “We recommend considering the use of fetal fibronectin testing as a part of the evaluation strategy in [individuals] between 24 and 34 6/7 weeks gestation with signs and symptoms of preterm labor, particularly in facilities where the result might affect management of delivery.” [Strong]
- “We suggest that [individuals] who have undergone bariatric surgery should be evaluated for nutritional deficiencies and need for nutritional supplementation where indicated (e.g., vitamin B12, folate, iron, calcium).” [Weak]

Health Resources & Services Administration (HRSA)

The HRSA-supported Women’s Preventive Services Initiative (HRSA, 2017) recommends the following:

- Screening pregnant individuals for gestational diabetes mellitus after 24 weeks of gestation (preferably between 24 and 28 weeks of gestation)
- Individuals with risk factors for diabetes mellitus be screened for preexisting diabetes before 24 weeks of gestation—ideally at the first prenatal visit

Royal College of Obstetricians and Gynaecologists (RCOG)

The RCOG have given the following recommendation for prenatal and fetal genotyping: “Non-invasive fetal genotyping using maternal blood is now possible for D, C, c, E, e and K antigens. This should be

performed in the first instance for the relevant antigen when maternal red cell antibodies are present” (C recommendation) (RCOG, 2014).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
80055	Obstetric panel This panel must include the following: Blood count, complete (CBC), automated and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)
80081	Obstetric panel (includes HIV testing) This panel must include the following: Blood count, complete (CBC), and automated differential WBC count (85025 or 85027 and 85004) OR Blood count, complete (CBC), automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) HIV-1 antigen(s), with HIV-1 and HIV-2 antibodies, single result (87389) Antibody, rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901)
81001	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, with microscopy

81002	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; non-automated, without microscopy
81003	Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these constituents; automated, without microscopy
81007	Urinalysis; bacteriuria screen, except by culture or dipstick
81015	Urinalysis; microscopic only
82677	Estriol
82731	Fetal fibronectin, cervicovaginal secretions, semi-quantitative
82947	Glucose; quantitative, blood (except reagent strip)
82950	Glucose; post glucose dose (includes glucose)
82951	Glucose; tolerance test (GTT), 3 specimens (includes glucose)
82962	Glucose, blood by glucose monitoring device(s) cleared by the FDA specifically for home use
83020	Hemoglobin fractionation and quantitation; electrophoresis (eg, A2, S, C, and/or F)
83021	Hemoglobin fractionation and quantitation; chromatography (eg, A2, S, C, and/or F)
83036	Hemoglobin; glycosylated (A1C)
85004	Blood count; automated differential WBC count
85007	Blood count; blood smear, microscopic examination with manual differential WBC count
85009	Blood count; manual differential WBC count, buffy coat
85014	Blood count; hematocrit (Hct)
85018	Blood count; hemoglobin (Hgb)
85025	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count) and automated differential WBC count
85027	Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC and platelet count)
85032	Blood count; manual cell count (erythrocyte, leukocyte, or platelet) each
85041	Blood count; red blood cell (RBC), automated
85048	Blood count; leukocyte (WBC), automated
86480	Tuberculosis test, cell mediated immunity antigen response measurement; gamma interferon
86580	Skin test; tuberculosis, intradermal
86592	Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART)
86593	Syphilis test, non-treponemal antibody; quantitative
86631	Antibody; Chlamydia
86632	Antibody; Chlamydia, IgM
86701	Antibody; HIV-1
86702	Antibody; HIV-2
86703	Antibody; HIV-1 and HIV-2, single result
86762	Antibody; rubella
86780	Antibody; Treponema pallidum
86787	Antibody; varicella-zoster
86803	Hepatitis C antibody
86804	Hepatitis C antibody; confirmatory test (eg, immunoblot)
86850	Antibody screen, RBC, each serum technique
86900	Blood typing, serologic; ABO
86901	Blood typing, serologic; Rh (D)

87077	Culture, bacterial; aerobic isolate, additional methods required for definitive identification, each isolate
87081	Culture, presumptive, pathogenic organisms, screening only;
87086	Culture, bacterial; quantitative colony count, urine
87088	Culture, bacterial; with isolation and presumptive identification of each isolate, urine
87110	Culture, chlamydia, any source
87270	Infectious agent antigen detection by immunofluorescent technique; Chlamydia trachomatis
87320	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Chlamydia trachomatis
87340	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; hepatitis B surface antigen (HBsAg)
87341	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; hepatitis B surface antigen (HBsAg) neutralization
87490	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique
87491	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
87590	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, direct probe technique
87591	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
87592	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, quantification
87653	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group B, amplified probe technique
87800	Infectious agent detection by nucleic acid (DNA or RNA), multiple organisms; direct probe(s) technique
87802	Infectious agent antigen detection by immunoassay with direct optical observation; Streptococcus, group B
87810	Infectious agent antigen detection by immunoassay with direct optical observation; Chlamydia trachomatis
87850	Infectious agent antigen detection by immunoassay with direct optical observation; Neisseria gonorrhoeae
G0306	Complete CBC, automated (Hgb, HCT, RBC, WBC, without platelet count) and automated WBC differential count
G0307	Complete (CBC), automated (Hgb, HCT, RBC, WBC; without platelet count)
G0432	Infectious agent antibody detection by enzyme immunoassay (EIA) technique, HIV-1 and/or HIV-2, screening
G0433	Infectious agent antibody detection by enzyme-linked immunosorbent assay (ELISA) technique, HIV-1 and/or HIV-2, screening
G0435	Infectious agent antibody detection by rapid antibody test, HIV-1 and/or HIV-2, screening
G0472	Hepatitis C antibody screening, for individual at high risk and other covered indication(s)

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X. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date

07/19/2022	<p>Updated background, guidelines, and evidence-based scientific references.</p> <p>Removed related policies d/t GTM: M2028, M2033, M2039. Added Related policy G2045</p> <p>Revised CC3, Revised CC3 b, d, e f, and I; removed CC4b, Revised CC5, Revised CC6, removed CC6 a, b, & c.</p> <p>Revised code disclaimer statement</p> <p>Removed GTM:</p> <p>CC 3 a, c, g, and h; CC10; CC 13</p> <p>CPT codes removed: 81171, 81172. 81200, 81209, 81220, 81241, 81242, 81243, 81244, 81251, 81252, 81253, 81254, 81255, 81257, 81260, 81290, 81329, 81330, 81336, 81337, 81400, 81401, 81403, 81404, 81405, 81406, 81412, 81420, 81430, 81431, 81443, 81479, 81507, 84443, 84999, S3652, S3844, S3845, S3846, S3849, and S3850.</p>
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