

Expanded Carrier Screening in Reproductive Medicine—Points to Consider

A Joint Statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine

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The Perinatal Quality Foundation and the American College of Medical Genetics and Genomics, in association with the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the National Society of Genetic Counselors, have collaborated to provide education for clinicians and laboratories regarding the use of expanded genetic

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carrier screening in reproductive medicine. This statement does not replace current screening guidelines, which are published by individual organizations to direct the practice of their constituents. As organizations develop practice guidelines for expanded carrier screening, further direction is likely. The current statement demonstrates an approach for health care providers and laboratories who wish to or who are currently offering expanded carrier screening to their patients.

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Carrier screening for inherited genetic conditions is an important component of preconception and prenatal care. The purpose of carrier screening is to identify couples at risk for passing on genetic conditions to their offspring. Condition-directed carrier screening has focused most often on the assessment of ancestry and on individual conditions. Limitations to this approach include inaccurate knowledge of ancestry in our increasingly multiethnic society, recognition that genetic conditions do not occur solely in specific ethnic groups, and that screening for individual conditions limits the amount of accessible genetic information for participants.

Today, high-throughput genotyping and sequencing approaches allow for efficient screening of a large number of conditions simultaneously. Use of this technology provides information regarding many more conditions than the currently recommended



screening guidelines and is referred to as expanded carrier screening. Although expanded carrier screening provides more comprehensive screening, this method also presents challenges in patient management. Traditional methods of carrier screening generally have focused on conditions that significantly affect quality of life as a result of cognitive or physical disabilities or a requirement for lifelong medical therapies and have a fetal, neonatal, or early childhood onset and well-defined phenotype. In contrast, current expanded panels include additional conditions that have significant variation in their presentation, including variable age of onset. Although some genetic variants on expanded panels have a relatively consistent phenotype, others are less clearly defined (Appendix 1). Expanded carrier screening panels often include conditions for which carrier screening of the general population is not recommended by current practice guidelines (eg, fragile X syndrome, hemochromatosis, and factor V Leiden).¹⁻³ Finally, expanded carrier screening panels may include rare conditions; for such disorders, the precise carrier frequency as well as the proportion of condition-causing variants that can be detected may be unknown. Therefore, calculation of residual risk after a negative screening test may not be possible for all conditions. Whether the practitioner follows current professional society recommendations or uses expanded carrier screening, the goal of preconception and prenatal carrier screening is to provide couples with information to optimize pregnancy outcomes based on their personal values and preferences. Carrier identification allows for preconception planning as well as the option of prenatal diagnosis for the couple at risk. Early identification of affected pregnancies allows condition-specific counseling and care.

PROFESSIONAL ORGANIZATION SCREENING GUIDELINES

Professional practice guidelines currently recommend offering carrier screening for individual conditions based on condition severity, race or ethnicity, prevalence, carrier frequency, detection rates, and residual risk. At present, the American College of Obstetricians and Gynecologists, American College of Medical Genetics and Genomics, and National Society of Genetic Counselors recommend panethnic screening for cystic fibrosis, and the American College of Medical Genetics and Genomics recommends panethnic screening for spinal muscular atrophy. Screening recommendations for other conditions are race- or ethnicity-based. Current guidelines are summarized in Table 1.

THE EXPANDED SCREENING PARADIGM

Expanded carrier screening incorporates the following concepts:

1. All individuals, regardless of race or ethnicity, are offered screening for the same set of conditions.
2. Expanded carrier screening panels can include more than 100 genetic conditions, most of which are rare. Before testing, it is not practical or necessary to fully explain all of the clinical and test characteristics of each condition.
3. Pretest education and consent should broadly describe the types of conditions being screened for and their common features as well as the limitations of screening. Educating patients before testing may be done verbally or by using other informational approaches such as pamphlets, videos, or online resources. General concepts to be included in pretest counseling should include:
 - a. Some conditions screened have less well-defined phenotypes.
 - b. Because many conditions being screened are rare, disease prevalence, mutation frequencies, and detection rates may be imprecise and residual risk estimations may not be reliable.
 - c. Screen-negative results reduce the likelihood of the carrier state for the conditions, but a residual risk of being a carrier always remains.
 - d. Screening panels may change over time, and there may be differences in the conditions screened between laboratories. Despite this, carrier rescreening typically is not offered or recommended.
4. The majority of conditions on current expanded panels are autosomal-recessive. However, some may be X-linked or autosomal-dominant single-gene conditions.
5. Expanded screening panels include most of the conditions recommended in current guidelines. However, the molecular methods used in expanded carrier screening are not as accurate as methods recommended in current guidelines for the following conditions:
 - a. Screening for hemoglobinopathies requires use of mean corpuscular volume and hemoglobin electrophoresis.



Table 1. Current Carrier Screening Guidelines

Condition	The College	ACMG	NSGC	Screening Approach	Comment
Hemoglobinopathies	African ancestry: hemoglobin electrophoresis	No current guideline	No current guideline	Ancestry-based	Sickledex and other solubility tests do not identify variant hemoglobins other than hemoglobin S
College Practice Bulletin No. 78, 2007 ⁴	Mediterranean ancestry: if anemia and MCV less than 80 fL, evaluate for iron deficiency; if iron study results are normal, perform hemoglobin electrophoresis Southeast Asian ancestry: if anemia and MCV less than 80 fL, evaluate for iron deficiency; if iron study results are normal, perform hemoglobin electrophoresis; if hemoglobin electrophoresis result is normal, molecular testing for α thalassemia is indicated (*silent carriers [1/4 gene copies deleted] have normal hemoglobin and MCV)			African Americans, southeast Asians, Mediterranean	
Conditions prevalent among Ashkenazi Jewish population	Offer screening for Tay-Sachs disease, cystic fibrosis, Canavan disease, and familial dysautonomia to those with Ashkenazi Jewish ancestry; educational materials and genetic counseling as requested for additional conditions	Offer screening for Tay-Sachs disease, cystic fibrosis, Canavan disease, and familial dysautonomia (same as the College) to those with Ashkenazi Jewish ancestry and in addition offer screening for Niemann-Pick (type A), Bloom syndrome, Fanconi anemia group C, Mucopolidosis IV, and Gaucher disease	No current guideline	Ancestry-based	Biochemical screening of hexosaminidase; an enzyme is the most sensitive screening test for Tay-Sachs disease in all populations

(continued)



Table 1. Current Carrier Screening Guidelines (continued)

Condition	The College	ACMG	NSGC	Screening Approach	Comment
ACMG 2008, reaffirmed 2013 ⁵	Tay-Sachs in individuals who are Cajun and French Canadian			ACMG: Ashkenazi Jewish	
College Committee Opinion No. 442, 2009 ⁶				The College: offer Tay-Sachs screening to those of Ashkenazi Jewish, French Canadian, and Cajun ancestry	
Cystic fibrosis	Offer CF carrier screening to all women of reproductive age; complete sequencing of the CF gene is not appropriate for carrier screening	Offer population screening using a panel of 23-pathogenic variants in the <i>CFTR</i> gene associated with classic CF and present in at least 0.1% of patients with CF	Carrier testing for CF should be offered to all women of reproductive age, regardless of ancestry, preferably before pregnancy	Panethnic	
ACMG 2004, ⁷ reaffirmed 2013				The College and ACMG: women who are pregnant or who are planning pregnancy	
College Committee Opinion No. 486, 2011 ⁸					
NSGC, 2014 ⁹					
Spinal muscular atrophy	Testing recommended only when a family history of spinal muscular atrophy is present	Offer screening regardless of ancestry or family history	No current guideline	Targeted	ACMG emphasizes need for genetic counseling
ACMG, 2008 ¹⁰				The College recommends only for positive family history	
College Committee Opinion No. 432, 2009 ¹¹				Panethnic	
				ACMG	

(continued)



Table 1. Current Carrier Screening Guidelines (continued)

Condition	The College	ACMG	NSGC	Screening Approach	Comment
Fragile X syndrome	Screening should be limited to individuals with family history of intellectual disability suggestive of fragile X syndrome, unexplained intellectual disability, or developmental delay, autism, or primary ovarian insufficiency	Screening should be limited to individuals with family history of intellectual disability suggestive of fragile X syndrome	Screening should be limited to individuals with family history of intellectual disability suggestive of fragile X syndrome	Targeted	The College, ACMG, and NSGC do not recommend population carrier screening
	ACMG, 2005 ¹¹			The College, ACMG, and NSGC	
	College Committee Opinion No. 469, 2010 ¹²				
	NSGC, 2012 ¹³				

The College, American College of Obstetricians and Gynecologists; ACMG, American College of Medical Genetics and Genomics; NSGC, National Society of Genetic Counselors; MCV, mean corpuscular volume; CF, cystic fibrosis.

- b. Tay-Sachs disease carrier testing has a low detection rate in non-Ashkenazi populations using molecular testing for the three common Ashkenazi mutations. Currently, hexosaminidase A enzyme analysis on blood is the best method to identify carriers in all ethnicities.

OFFERING EXPANDED CARRIER SCREENING

When offering expanded carrier screening, the following are appropriate considerations: women of reproductive age should ideally be offered carrier screening before conception. Gamete donors should undergo carrier screening before their use as part of all screening programs. Preconception screening may be offered sequentially; one partner can be screened and, if they screen positive for any condition, the other partner would be offered screening for that condition. Preconception concurrent screening of the couple may also be offered.

In pregnancy, decisions regarding sequential compared with concurrent screening may depend on gestational age, availability of the partner, local program structure, and patient preferences. Concurrent screening optimizes time to consider diagnostic testing and reproductive options.

For patients with a positive family history of a genetic condition, genetic counseling is indicated for accurate risk assessment, to review familial variants (if known), and to ensure the most specific

carrier test is offered to address the familial risk. Expanded carrier screening does not replace genetic counseling or assessment of familial risk. For couples identified with a risk of an inherited condition, diagnostic testing may be indicated.

Patients and health care providers may be confused regarding the differences between newborn screening and expanded carrier screening. Patients should be aware that newborn screening is mandated by all states and can identify some genetic conditions in the newborn. However, newborn screening may include a different panel of conditions than expanded carrier screening. Newborn screening does not usually detect children who are carriers for the conditions being screened so will not necessarily identify carrier parents at increased risk. Conversely, expanded carrier screening in the preconception or prenatal period is not a substitute for newborn screening and should not be used as a rationale for refusing or not offering newborn screening.

COMPONENTS OF CONSENT FOR EXPANDED CARRIER SCREENING

Individuals offered expanded carrier screening should be provided counseling leading to informed consent or the option to decline and either should be documented in the medical record. Components of consent should include:



1. Carrier screening of any nature is voluntary, and it is reasonable to accept or decline.
2. Results of genetic testing are confidential and protected in health insurance and employment by the Genetic Information Non-Discrimination Act of 2008.¹⁴
3. Conditions included on expanded carrier screening panels vary in severity. Many are associated with significant adverse outcomes such as cognitive impairment, decreased life expectancy, and need for medical or surgical intervention.
4. Pregnancy risk assessment depends on accurate knowledge of paternity. If the biologic father is not available for carrier screening, accurate risk assessment for recessive conditions is not possible.
5. A negative screen does not eliminate risk to offspring.
6. Because expanded carrier screening includes a large number of disorders, it is common to identify carriers for one or more conditions. In most cases, being a carrier of an autosomal-recessive condition has no clinical consequences for the individual carrier. If each partner is identified as a carrier of a different autosomal-recessive condition, offspring are not likely to be affected.
7. In some instances, an individual may learn that they have two pathogenic variants for a condition (homozygous or compound heterozygous) and thus learn through carrier screening that they have an autosomal-recessive condition that could affect their personal health. Some expanded screening panels screen for selected autosomal-dominant and X-linked conditions, and likewise an individual may learn that they have one of these conditions that might affect their health. Referral to an appropriate specialist for medical management and genetic counseling is indicated in such circumstances to review the inheritance patterns, recurrence risks, and clinical features.

POSTTEST COUNSELING

Health care providers who use expanded carrier screening should have a plan to provide accurate information to patients identified as carriers of a condition. When a pregnant patient is found to be a carrier of an autosomal-recessive condition, the biologic father of the fetus should be offered screening for that condition as soon as possible if concurrent screening was not performed. If one partner is found to be a carrier of an autosomal-recessive condition and the other has a negative screening result for that condition,

the chance that the couple will have an affected pregnancy is significantly reduced and no further testing of the partner should be offered; prenatal diagnosis is not indicated. Counseling should include that the partner is unlikely to have a mutation for the same disorder, but a residual risk persists for the couple to have an affected child. An exception is Tay-Sachs disease: if one partner is a carrier and their non-Ashkenazi partner is a noncarrier by only molecular testing, further screening through enzyme analysis is strongly recommended.

Further risk reduction through sequencing of the gene in question is possible, but this is not routinely recommended and is used only with caution. Uncertainties may be encountered such as a variant of uncertain significance or a novel or less well-described mutation, both of which preclude prediction of the phenotype in compound heterozygotes.

If both partners are identified as carriers of the same autosomal-recessive condition, they have a 25% risk of having an affected child with each pregnancy. Genetic counseling by a certified genetics professional is indicated and for pregnant patients, prenatal diagnosis should be offered.

If an affected fetus is identified, all reproductive options should be discussed including: prenatal management, delivery planning and coordination of care for the child as well as pregnancy termination or adoption planning. In the preconception period, counseling should also review preimplantation genetic diagnosis and use of noncarrier donor gametes as additional options.

Carrier screening results should be available to the patient, and counseling should include an explanation of the condition and its inheritance. Posttest counseling should also include the significance of this information for other family members who may also be carriers (eg, parents or siblings). Written information for the patient to share with relatives about the availability of carrier screening should be available.

CONDITIONS INCLUDED ON PRECONCEPTION AND PRENATAL EXPANDED CARRIER SCREENING PANELS

Expanded panels screen for conditions with a wide range of severity and age of onset and frequently have carrier frequencies that are not known for all populations. The following considerations should be addressed when health care providers select a preconception or prenatal carrier panel for use in practice and as laboratories consider inclusion and exclusion of conditions:



1. The condition being screened for should be a health problem that encompasses one or more of the following:
 - a. Cognitive disability.
 - b. Need for surgical or medical intervention.
 - c. Effect on quality of life.
 - d. Conditions for which a prenatal diagnosis may result in:
 - i. Prenatal intervention to improve perinatal outcome and immediate care of the neonate.
 - ii. Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care.
 - iii. Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth.
2. Health care providers may choose not to screen for some conditions on expanded carrier screening panels (see Appendix 2). It may be preferable to exclude conditions in which:
 - a. The disorder is associated most often with an adult-onset phenotype and molecular testing cannot distinguish between childhood or adult onset (eg, α 1 antitrypsin deficiency).
 - b. Variants have high allele frequencies and low penetrance of a phenotype (eg, MTHFR).
 - c. The most appropriate approach to screening is something other than molecular testing, often because of low penetrance when molecular variants are identified (eg, hereditary hemochromatosis).

INTERPRETATION OF MOLECULAR FINDINGS

Expanded carrier screening can be performed by genotyping or by DNA sequencing. Genotyping searches for known pathogenic and likely pathogenic variants. Sequencing analyzes the entire coding region of the gene and identifies alterations from the expected normal sequence. Although genotyping includes only selected variants, sequencing has the potential to identify not only pathogenic and likely pathogenic variants, but also benign and likely benign variants. Sequencing also can identify variants of uncertain significance, which have an uncertain effect on gene function and thus an uncertain relationship to clinical phenotype. Health care providers should also be aware that multiple genes can cause a specific condition and that expanded carrier screening may therefore investigate more than one gene implicated in the pathogenesis of a condition. Also, within any gene, a large number of variants may be investigated.

Given these complexities, it is recommended that laboratories include genetic conditions in their testing panels that meet the criteria subsequently. Health care

providers are cautioned against routinely offering tests that do not meet these criteria:

1. The genes and variants included should have a well-understood relationship with a phenotype. Case reports should not be accepted as the only form of evidence. Phenotype–genotype correlation should at a minimum include multiple families that provide a minimum level of unbiased ascertainment. Laboratories should be able to provide information about the phenotype for any conditions included on a panel.
2. When the carrier frequency and detection rate are both known, residual risk estimation should be provided in laboratory reports. Where this information is not available or reliable, the limitations of interpretation of negative screening should be clearly communicated in laboratory reports.
3. Because all individuals have numerous variants within their genes, restricting the variants that are included in screening to those with the highest likelihood of being pathogenic will decrease the number of people who require follow-up. This can be accomplished by limiting the variants on a genotyping panel. Variants of uncertain significance detected by sequencing should not be reported.
4. The laboratory performing screening should report all variants that are pathogenic or likely pathogenic. Guidance for defining pathogenicity in molecular analysis is provided by the American College of Medical Genetics and Genomics.¹⁵

FUTURE DATA COLLECTION AND RESEARCH NEEDS IN EXPANDED CARRIER SCREENING

Currently, there is little evidence that addresses reproductive outcomes when expanded carrier screening is used. As expanded carrier screening is introduced into practice, there is a unique opportunity to gather outcome data and information about the technical aspects and associated counseling surrounding this new paradigm. We suggest the following.

Development of a Curated Data Repository of Variants and Associated Phenotypes

As panethnic genotyping and sequencing is performed on the general population, previously unreported and relatively rare variants will be identified. To improve the predictive value of carrier testing, these variants and the full phenotypes of homozygotes and compound heterozygotes should be collected and available to clinicians, counselors, and investigators. Similarly, determining the frequency of variants in previously untested ethnic and racial groups is required because risks associated with gene variants



may vary with different genetic backgrounds and in different environmental situations. Laboratories share responsibility for collaborative analysis of expanded carrier screening to further our understanding of human mutation.

Education of Physicians and Other Health Care Providers

Obstetricians, reproductive endocrinologists, general practitioners, midwives, nurse practitioners, and other clinical providers will offer most carrier screening. Expanded carrier screening technology offers an opportunity to educate care providers regarding high-throughput genomic technologies, including the risks and benefits of the implementation of these technologies into clinical practice.

Education of Patients

Research is needed to identify best practices to educate individuals about the concept of expanded carrier screening and allow them to make informed decisions. Information needs regarding expanded carrier screening will vary between individuals. Minimum criteria for what information should be disclosed before screening should be developed and empirically tested to assess patient satisfaction.¹⁶

Educational Resources for Health Care Providers and Patients

Educational materials will need to be developed in print, video, or web-based formats that describe the nature and limitations of expanded carrier screening. These materials should be independent of commercial laboratories' marketing materials.

Evaluation of Patient and Health Care Provider Attitudes Toward Expanded Carrier Screening

There remain a number of unsettled issues concerning expanded carrier screening, including the range of severity of the conditions that should be included on panels and whether they should include adult-onset conditions. Specific guidance on these issues will require additional research about patient and health care provider attitudes.¹⁷

Cost of Expanded Carrier Screening

Future studies that explore the overall cost of implementation of expanded carrier screening are needed. The downstream costs of genetic counseling, partner testing, patient anxiety, and the potential need for prenatal diagnosis need to be considered.

SUMMARY

In this document, representatives from several professional organizations, each with an interest in the implementation of screening for heritable conditions, have collaborated to provide points to consider for clinical providers and laboratories. These are not meant to replace existing practice guidelines and policy statements. Rather, they offer an opportunity for health care providers to better understand expanded carrier screening. Many more conditions, genes, and variants are analyzed when expanded carrier screening is used compared with current screening approaches. As such, expanded carrier screening can provide information about carrier status beyond population estimates and eliminates the need for ethnicity-based screening. However, this approach introduces complexities that require special consideration. Health care providers are reminded that the focus of carrier screening is to identify the at-risk fetus. In some circumstances, molecular testing is not the optimal or currently recommended screening approach (eg, hemoglobinopathies, Tay-Sachs disease, hereditary hemochromatosis). Health care providers are urged to increase their knowledge of genetic screening terminology and remember that residual risk is always present, although not always quantifiable. There are unique research opportunities that are important to pursue to further our understanding of the full effect of expanded carrier screening on patients, health care providers, counselors, laboratories, and a health care system that has a vested interest in reproductive outcomes.

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Appendix 1: Glossary

Variants

Variant—a change in the normal nucleotide sequence of a gene.

Pathogenic variant—a nucleotide sequence that is known to result in an abnormal phenotype when inherited alone (dominant conditions) or with other similar variants (recessive conditions).

Likely pathogenic variant—a nucleotide sequence that has characteristics that are consistent with those that are known to cause an abnormal phenotype, but the level of evidence does not reach that which is seen for known pathogenic conditions.

Variant of uncertain significance—a nucleotide sequence with characteristics or a level of evidence that leaves uncertainty with respect to pathogenicity.

Benign variant—a nucleotide sequence that has characteristics or a level of evidence that is consistent with a normal phenotype.

Screening Metrics

Residual risk—as applied to an individual being screened:

1. A numeric measure of the chance of being a carrier after a negative screening test.
2. Mathematically: carrier frequency \times (1 – detection rate).

Residual risk—As applied to the fetus:

1. A numeric measure of the chance that a fetus will have a condition after one or both parents test negative for that condition.
2. Mathematically:
 - a. If both parents test negative: [carrier frequency \times (1 – detection rate)]² \times 0.25.
 - b. If one parent tests positive and one tests negative: [carrier frequency \times (1 – detection rate)] \times 1 \times 0.25.

Detection rate—the proportion of carriers that is identified by the screening test (ie, sensitivity).

Disease prevalence—the proportion of individuals in a population that has a condition.

Carrier frequency—the proportion of individuals in a population that has a pathogenic variant for a condition.

Populations

Ethnicity—originating from a large group that shares racial, language, national, or cultural characteristics.

Race—one of the groups into which the world's population can be divided on the basis of physical characteristics that result from genetic ancestry.

Ethnic screening—screening approach that is based on race, ethnicity, or both.

Panethnic screening—screening approach that is without regard to race or ethnicity.



Targeted screening—screening or testing approach that is based on specific characteristics or risk factors.

Conditions*

Common—we define this as a carrier frequency of one in 50 or greater.

Uncommon—we define this as a carrier frequency of between one in 50 and one in 100.

Rare—we define this as a carrier frequency of between one in 100 and one in 250.

*Note these definitions are expert opinion rather than evidence-based.

Genetic Information Nondiscrimination Act of 2008,

Pub. L. No. 110-233, 122 Stat. 881 (2008). Also known as GINA, this law protects genetic information from being used in health insurance decisions as well as employment decisions. This law does not apply to life insurance, disability insurance, or long-term care insurance. The U.S. military (or the TRICARE military health system), Veterans' health care administered by the Veterans' Administration, The Federal Employees Health Benefits Plan, and the Indian Health Service are not included in this protection.

Appendix 2: Conditions With Unclear Value on Preconception and Prenatal Screening Panels

Alpha 1 Antitrypsin (A1AT)

Alpha 1 antitrypsin deficiency is a genetic condition that is associated with lung and liver disease in adults. The risk of development of chronic obstructive pulmonary disease in an affected adult can be modified by avoiding inhalation of irritants including cigarette smoke. Approximately 10% of newborns with liver disease will be diagnosed with *A1AT* deficiency. Newborns may develop jaundice as part of inflammation of the liver associated with *A1AT* deficiency. Alpha-1 antitrypsin deficiency is the most common genetic cause of liver disease in children and is the most common genetic disease for which liver transplantation is done. Older children and teens can present with long-standing liver inflammation that has caused scarring (cirrhosis) to develop. In some cases, this may lead to liver cancer.¹⁸

Pros of Screening: Can identify those at risk for neonatal liver disease and avoid extensive workup and modify

care. Can avoid lung irritants and decrease the risk of adult lung disease.

Cons of Screening: Mostly associated with an adult disorder. Prenatal testing cannot differentiate childhood from adult phenotype.

Methylene Tetrahydrofolate Reductase (MTHFR)

Published literature linking *MTHFR* variants with clinical phenotypes is mixed. The *MTHFR* C677T allele is variably represented in populations but is reported to be present in 10–30% of individuals in the United States. Homozygosity has been shown to range from as high as 12% for blacks to 17% for whites. The A1298C allele is less well studied but is common also with reports suggesting an allele frequency of 9–10%.¹⁹ With these allele frequencies, it is easy to see how common phenotypes (eg, pregnancy loss) could be associated with *MTHFR* variants.

Pros of Screening: C677T homozygous patients may have a mildly increased risk of thromboembolism (odds ratio [OR] 1.27) and recurrent pregnancy loss (OR 2.7).²⁰

Cons of Screening: High frequency of carriers. Highly variable penetrance and variable expressivity. For the A1298C variant, there is no consensus regarding risk or defined phenotype.

Hereditary Hemochromatosis (HH)

HFE is the most common gene implicated in HH, but other genes are also etiologic.²¹ Screening for two common variants has been described (C282Y, H63D). Allele frequency is approximately 5% for C282Y and 13.5% for H63D in the U.S. population.²² Phenotypic expression of HH depends on the degree of iron accumulation, environmental factors (eg, alcohol exposure, viruses), and genetic factors other than *HFE* genotype.

Pros of Screening: Opportunity to control exposures that may result in expression of the phenotype.

Cons of Screening: Penetrance may be as low as 1–5%. Penetrance rates are not exclusively predicted by identification of molecular variants.²³

