MUSC Health
Medical University of South Carolina
Changing What's Possible

Genetic Testing and Screening Part 2- Carrier Screening

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Objectives

1. Identify characteristics of an effective carrier screen.
2. Calculate the risk for an affected pregnancy based on carrier frequencies.
3. Describe basic clinical features of the most common conditions included in screening: CF, hemoglobinopathies, SMA, and Fragile-X syndrome.
4. Recognize current ACOG and ACMG recommendations regarding carrier screening.
5. Identify capabilities and limitations of expanded carrier screening.

Carrier Screening Overview

- Purpose: To identify couples at risk to have an affected pregnancy (“Carrier couples”)
- Rationale: Everyone carries at least 2-3 autosomal recessive disorders.
- 80% of children with a genetic disorder are born to parents with no family history or symptoms of the disorder
- Benefits: Enables early treatment, higher quality of life, informed family planning.
- Limitations: Not every carrier will be detected (residual risk).

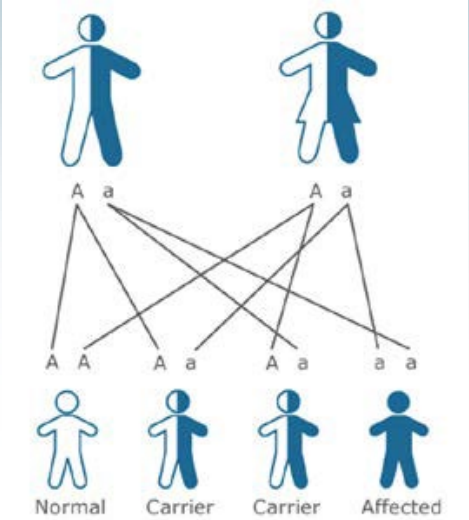
Carrier Screening Overview

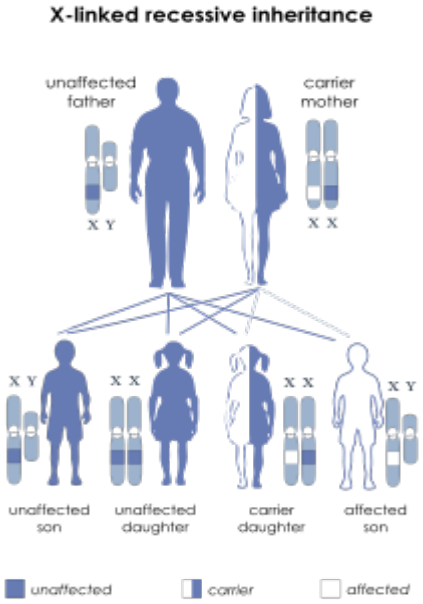
- Prevalence:
  - Mendelian recessive or X-linked conditions account for ~20% of infant mortality and 10% of pediatric hospitalizations
- Carrier screening can reduce incidence of devastating conditions
  - Tay-sachs incidence has decreased by 90% in 40 years due to awareness in Ashkenazi Jewish communities and widespread preconception screening.
  - Most children born with Tay-sachs today are non AJ.

Inheritance Patterns

- Autosomal recessive inheritance
  - If both parents are carriers, each pregnancy has 1 in 4 chance to be affected.

- X-linked recessive
  - Typically females are carriers and 50% risk for sons to be affected.





Carrier Screening Counseling

- **Pretest** education should include:
  - Carrier screening is voluntary
  - Results are confidential and protected in health insurance and employment by GINA (2008)
  - Review the disorder or nature of disorders on the screen
  - Patient's risk to be a carrier and risk for affected child
  - Possible results (positive, negative, unexpected finding)
  - Limitations: residual risk
  - Next steps: testing for partner for AR conditions
  - Availability of prenatal diagnosis if risk is confirmed

Carrier Screening Guidelines

- Current recommendations from ACOG is based on ancestry and family history
  - Screening is targeted for most common disorders in patient's ethnic group
  - Or affected family member

ACOG Recommendations


The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 691 • March 2017
(Reaffirmed 2020)

(Replaces Committee Opinion Number 318, October 2005; Committee Opinion Number 432, May 2009; Committee Opinion Number 442, October 2009; Committee Opinion Number 469, October 2010; Committee Opinion Number 486, April 2011)

- Every pregnant woman is ***offered*** screening; they may decline
- Ideally ***before*** pregnancy
- Step-wise or concurrent screening
- Review prenatal dx & IVF + preimplantation testing
- If positive, patient encouraged to share with family members
- Obtain a family history – genetic conditions, ethnic background & any known consanguinity
- Only to be repeated in select situations
- Prenatal carrier screening ≠ newborn screening
- Consider cost
- **CF + SMA for everyone +/- others based on ethnicity**

Ethnicity	Condition	Carrier Frequency
Caucasian (N. European)	Cystic Fibrosis	1 in 25
African American	Sickle Cell disease Beta-Thalassemia Alpha-Thalassemia Cystic Fibrosis	1 in 10 1 in 75 1 in 30 1 in 65
Asian	Alpha-Thalassemia Beta-Thalassemia	1 in 20 1 in 50
Hispanic	Cystic Fibrosis Beta-Thalassemia	1 in 45 1 in 30 – 1 in 50
Mediterranean	Beta-Thalassemia Cystic Fibrosis Sickle Cell	1 in 25 1 in 30 1 in 40
Ashkenazi Jewish	Tay-Sachs disease Gaucher disease Cystic Fibrosis Familial Dysautonomia Canavan* Others	1 in 30 1 in 15 1 in 25 1 in 32 1 in 40
French Canadian/Cajun	Tay-Sachs disease	1 in 30

Cystic Fibrosis (CF)

- Cystic fibrosis is an autosomal recessive condition due to a defect in chloride channels within cell membranes.
- Multisystem disease which leads multiple clinical symptoms including pulmonary disease (the major cause of morbidity and mortality in CF) and pancreatic insufficiency with malabsorption.
- More than 95% of males with CF are infertile due to congenital bilateral absence of the vas deferens (CBAVD)
- Incidence: 1 in 2500 in Caucasian and Ashkenazi Jewish Populations
  - 1 in 25 carrier frequency in these populations
  - Occurs in other populations with lower frequency

CF Carrier Screening

- Carrier screening involves DNA for select mutations or CFTR sequencing
  - Many genetics labs now use next-generation sequencing
  - Many labs screen for additional mutations (e.g. 106 mutations at Mayo)
  - Previously, ACMG recommended at least 23 of the most common mutations should be included – no longer the case!

- Complete CFTR gene sequencing and deletion/duplication analysis is available
  - This provides a higher detection rate and is recommended when:
    - An individual has been identified as a carrier or affected and their partner is pursuing screening
    - ~~Disease-causing mutations cannot be detected by first-tier tests for an affected individual~~

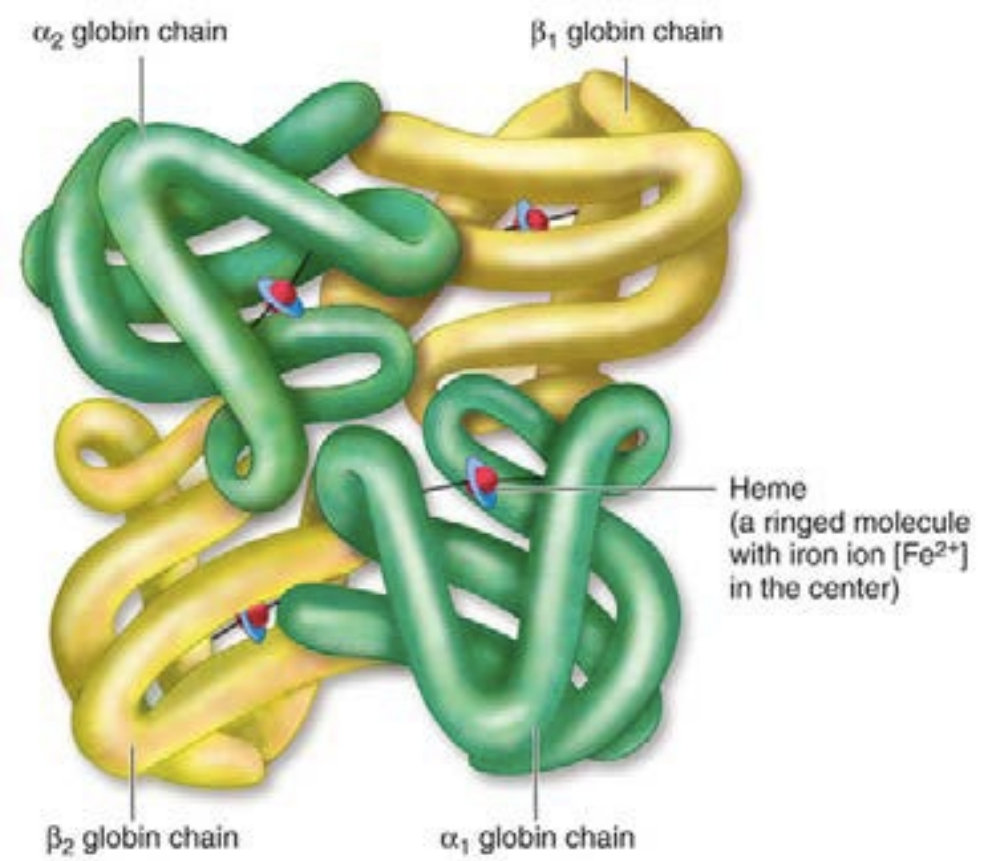
Cystic Fibrosis Screening (basic panel; 23 mutations)

Ethnicity	Carrier Freq.	Detection	Residual carrier risk
Northern European Caucasian	1 in 25	~90%	~ 1 in 250
Ashkenazi Jewish	1 in 25	97%	~1 in 930
Southern European Caucasian	1 in 30	70-80%	~1 in 97 to 1 in 140
Hispanic	1 in 45	57%	~1 in 105
African American	1 in 65	72%	~1 in 230
Asian	1 in 90	30%	

CF Screening Considerations

- CF represents a spectrum of clinical severity with a high degree of variable symptoms.
- The prognosis cannot be fully predicted based on disease-causing mutations.
  - Pancreatic function correlates with genotype
  - Genotype-specific therapies (modulators) now available
- It is possible to detect “affected” individuals through screening
  - Patient is asymptomatic or has mild symptoms, yet is homozygous for CF mutations
- ACOG recommends offering CF screening to **all** patients who are pregnant or considering pregnancy.

Hemoglobinopathy Carrier Screening

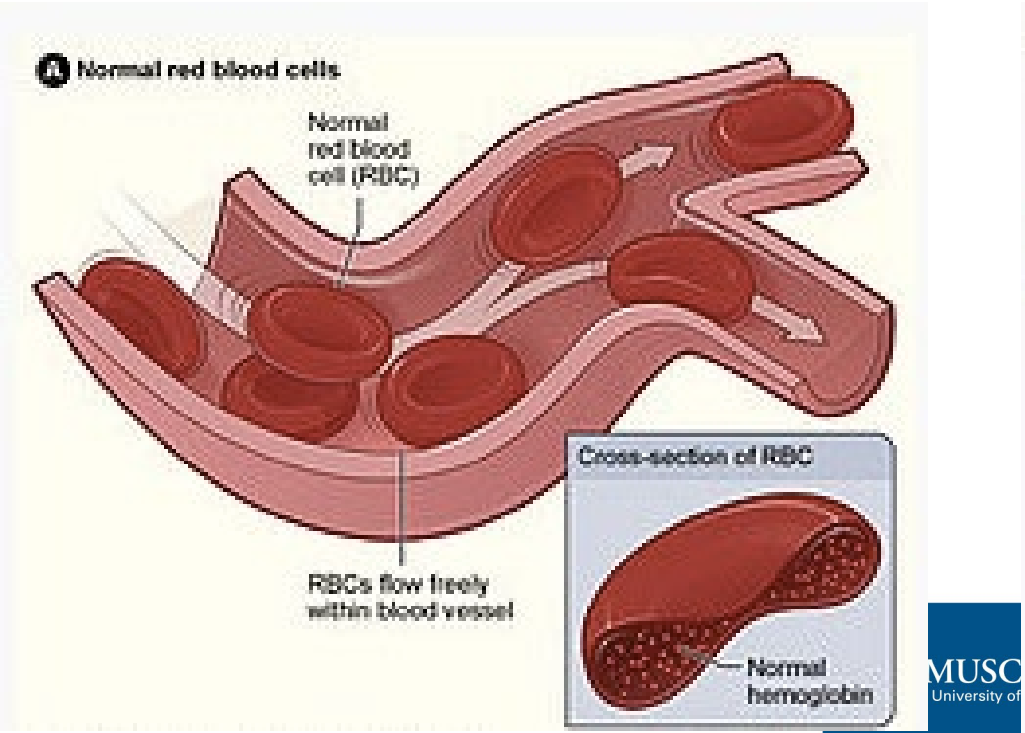


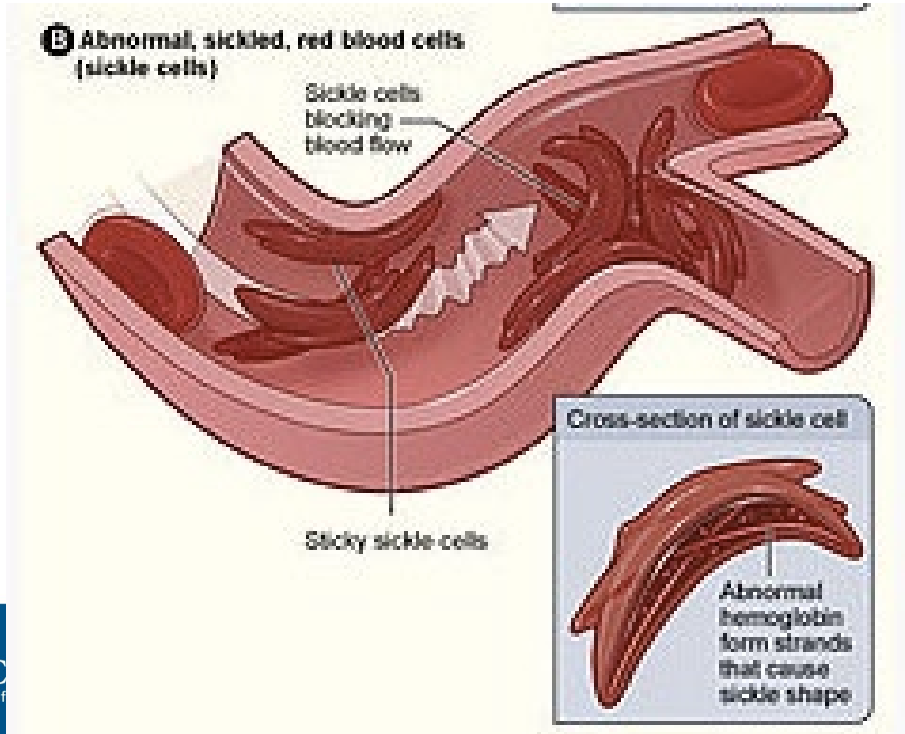
Hemoglobin

- Composed of 4 subunits, called globins or globin chains, and four oxygen-binding heme groups, which are attached to each globin.
- The two main types of globins are the α-globins and the β-globins, which are made in about equal amount in precursors of RBCs.
- Normal adult Hb (Hb A) has two α-globins and two β-globins (α2β2).
- Genes on chromosomes 16 and 11 encode the α-like globins and β-like globins, respectively.

Hemoglobinopathies

- Hemoglobin Variants:
  - Hb S, Hb C, etc (some variants have no clinical impact)
- Sickle cell disease is caused by abnormal hemoglobin due to homozygous mutations in the beta globin gene (HBB)





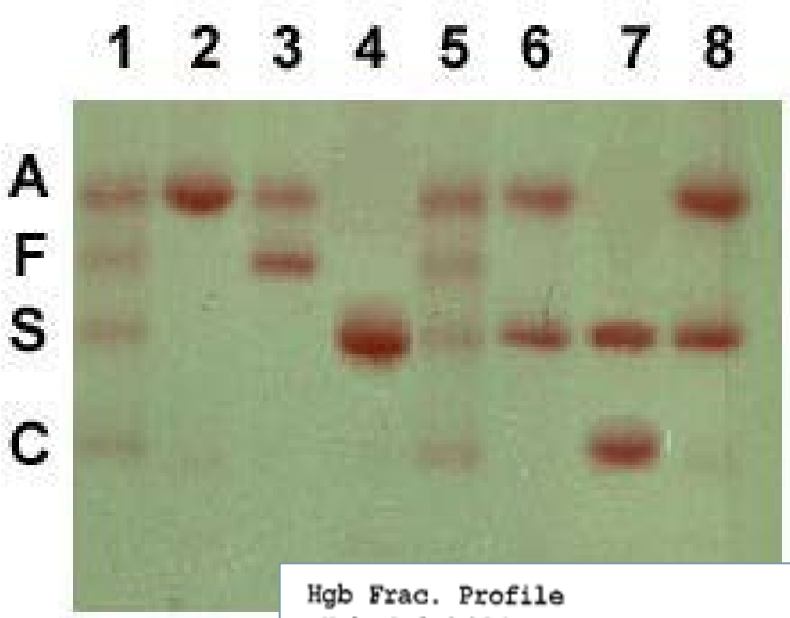
Sickle Cell Disease

- Sickle cell disease (SCD) is an autosomal recessive condition characterized by intermittent vaso-occlusive events and chronic hemolytic anemia.
- Vaso-occlusive events result in tissue ischemia leading to acute and chronic pain as well as organ damage that can affect any organ in the body.
- The spleen is particularly subject to infarction and the majority of individuals with SCD are functionally asplenic in early childhood, increasing risk for certain bacterial infections.
- Chronic hemolysis can result in varying degrees of anemia, jaundice, cholelithiasis, and delayed growth and sexual maturation.

Sickle Cell Disease

- 1 in 10 African Americans are carriers of an abnormal hemoglobin type
  - Hb S (sickle cell trait) is the most common
- ACOG recommends hemoglobinopathy carrier screening include **CBC and hemoglobin electrophoresis** (or equivalent)
  - Serum ferritin may be warranted to rule out iron deficiency vs. inherited anemia

Hemoglobin Electrophoresis



Hgb Frac. Profile

Hgb Solubility	Negative		Negative
Hgb A	97.8	%	94.0-98.0
Hgb S	0.0	%	0.0
Hgb C	0.0	%	0.0
Hgb A2	2.2	%	0.7-3.1
Hgb F	0.0	%	0.0-2.0

Interpretation

Normal adult hemoglobin present.

NOT the same as a hemoglobin solubility test!

Hemoglobin electrophoresis result example

Normal (adult)
-Hb A: 95-98%
-Hb A2: 2-3%
-Hb F: 0.8-2%
-Hb S: 0%
-Hb C: 0%

Sickle cell trait
-Hb A: 50-65%
-Hb A2: 1.5-4%
-Hb F: 0.8-2%
-Hb S: 35-45%
-Hb C: 0%

Sickle cell disease
-Hb A: 0%
-Hb A2: 2-4%
-Hb F: up to 10%
-Hb S: 80% +
-Hb C: 0%

Thalassemias

- Thalassemia is characterized by reduced production of specific globin chain (alpha or beta)

Alpha Thalassemia

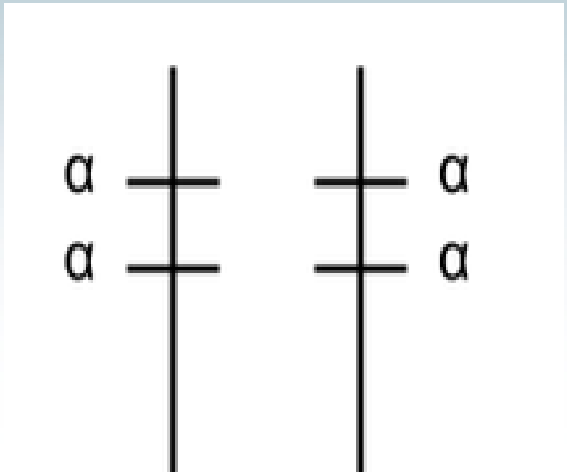
- Most common in people of African, Asian, Central American, Mediterranean and Middle Eastern descent
- Alpha-thalassemia (α-thal) has two clinically significant forms:
  - hemoglobin Bart hydrops fetalis (HbBart)
  - hemoglobin H (HbH) disease
- HbBart, the more severe form, is characterized by fetal onset of generalized edema, pleural and pericardial effusions, and severe hypochromic anemia.
  - Clinical features include: hepatosplenomegaly, extramedullary erythropoiesis, hydrocephaly, and cardiac and urogenital defects. Death usually occurs in the neonatal period.
- HbH disease is characterized by microcytic hypochromic hemolytic anemia, hepatosplenomegaly, mild jaundice, and sometimes thalassemia-like bone changes.

Alpha Thalassemia

- Hemoglobinopathy characterized by reduced synthesis of alpha globin chains
- Caused by deletions of the alpha globin genes: HBA1 and HBA2 located in alpha globin gene cluster on chromosome 16
  - Rare point mutations

One deletion	Two deletions α thalassemia minor	Three deletions Hb H Disease	Four deletions Hb Barts
Silent carrier; Asymptomatic, typically no anemia	Asymptomatic but typically have microcytic anemia by lab exam	Symptomatic microcytic anemia, extravascular hemolysis, splenomegaly, transfusion dependent later in life	Not compatible with life; causes hydrops fetalis

Alpha Thalassemia



$\alpha\alpha/\alpha\alpha$ = normal

$\alpha\alpha/\alpha$- = silent carrier

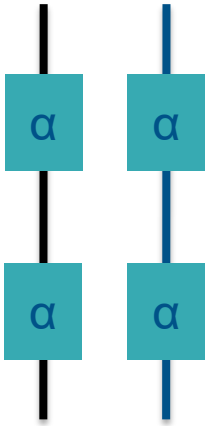
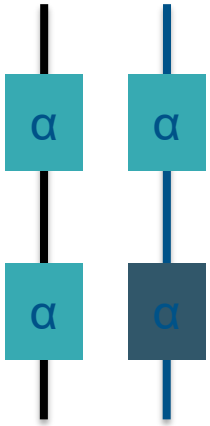
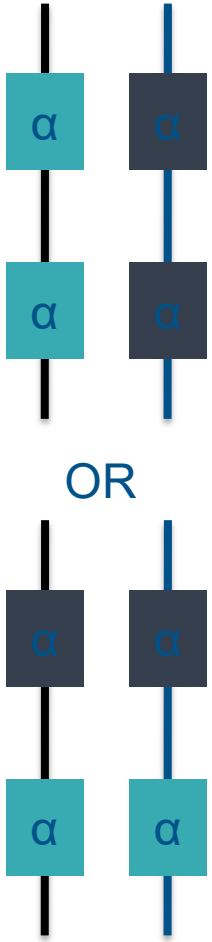
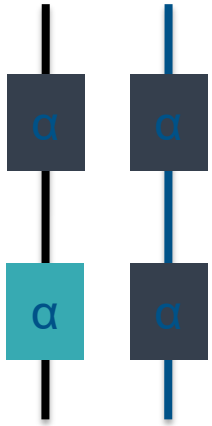
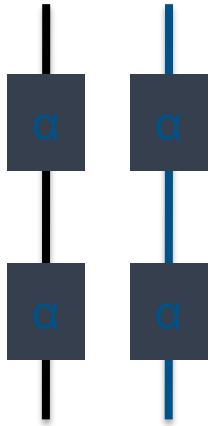
$\alpha-/\alpha-$ = carrier (trans) – common in Africans

$\alpha\alpha/--$ = carrier (cis) – common in Asians

$\alpha-/--$ = hemoglobin H disease (HbH)

--/-- = hemoglobin Bart disease or hydrops fetalis (Hb Bart)

Alpha Thalassemia

Normal	Silent Carrier	Alpha Thal Minor	Hb H Disease	Hydrops Fetalis
				

Alpha Thalassemia

- Risk depends on parental carrier status and configuration
- Carriers of 2 deletions (Alpha Thal Minor)
  - Cis (on same chromosome) is most common in Asian populations
  - Trans (opposite chromosomes) is most common in African and Mediterranean populations

  - Genetic testing: multiplex ligation-dependent probe amplification (MLPA) to detect deletions, sequencing for less common point mutations

Beta Thalassemia

- Beta-thalassemia (β-thal) is an autosomal recessive condition characterized by microcytic hypochromic anemia, an abnormal peripheral blood smear with nucleated red blood cells, and reduced amounts of hemoglobin A (HbA) on hemoglobin analysis.

- Individuals with thalassemia major have severe anemia and hepatosplenomegaly
  - Without treatment, affected children have severe failure to thrive and shortened life expectancy.

- Individuals with thalassemia intermedia present later and have milder anemia that only rarely requires transfusion.
  - These individuals are at risk for iron overload secondary to increased intestinal absorption of iron as a result of ineffective erythropoiesis.

Beta Thalassemia

- Populations more commonly affected:
  - Mediterranean (Italian, Greek, etc)
    - 1 in 25 carrier frequency
  - African Americans
    - 1 in 75 carrier frequency

- Beta Thalassemia mutations:
  - β= no mutations, normal beta globin production
  - β+= beta globin mutation which allows some beta chains to be formed but at reduced amounts
  - β^0 = beta globin mutation which prevents beta chain formations

Beta Thalassemia

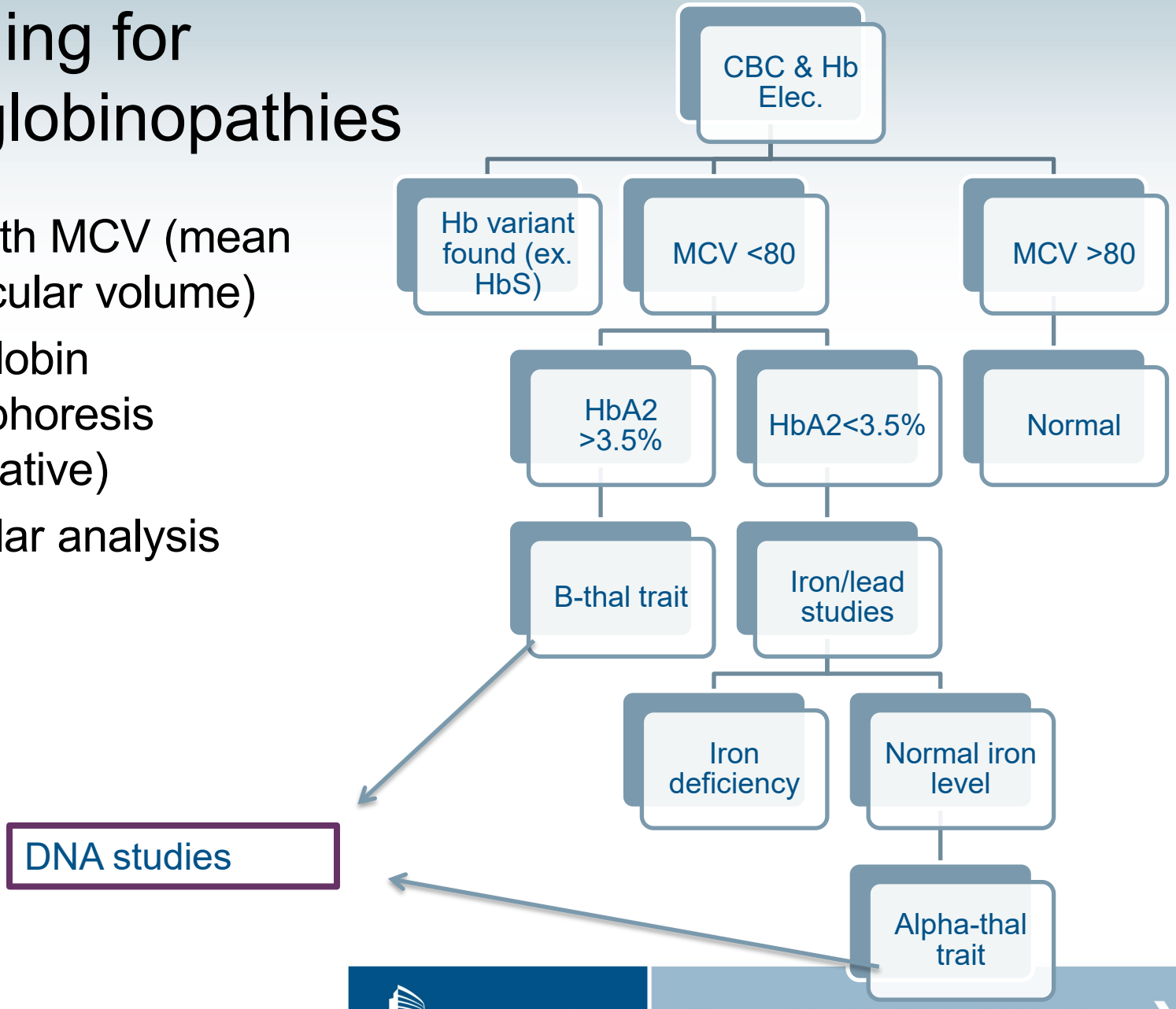
Thalassemia Minor	Thalassemia Intermedia	Thalassemia Major
Carrier (β^0/β) or (β^+/β) Generally asymptomatic but with microcytic anemia	Symptoms between minor and major (β^0/β) or (β^+/β^+) May be generally asymptomatic with mild anemia. Affected individuals may need occasional blood transfusions (illness, pregnancy, etc)	Homozygous affected (β^+/β^+) or (β^+/β^0) or (β^0/β^0) Severe microcytic anemia, splenomegaly, bone deformities, blood transfusions needed for treatment.

Screening for Thalassemias

- Routine CBC & hemoglobin electrophoresis is first step
  - CBC done routinely at the beginning of a pregnancy
  - Thalassemia carriers will typically have microcytic anemia
    - Low MCV- less than 80
  - Beta: hemoglobin electrophoresis findings:
    - Elevated HgbA2 and HgbF
- Reflex to serum ferritin to help determine alpha thalassemia versus iron deficiency
  - Alpha: normal hemoglobin electrophoresis, normal serum ferritin
- DNA analysis available for alpha and beta thalassemias

Screening for Hemoglobinopathies

- CBC with MCV (mean corpuscular volume)
- Hemoglobin electrophoresis (quantitative)
- Molecular analysis



Ashkenazi Jewish Screening

- Applies to Ashkenazi Jewish Populations
  - Trace origins back to France, Germany, and Eastern Europe
  - Sephardic Jews trace their origins back to Jews of Spain, Portugal, North Africa, and Middle East
  - 90%+ of Jews in North America are Ashkenazi Jewish

- High frequency of specific disorders likely due to founder effect, genetic drift, non-random mating, etc.

Ashkenazi Jewish Screening

ACOG

- Screen for cystic fibrosis, Canavan syndrome, familial dysautonomia and Tay-Sachs disease
- *Consider* screening for Fanconi anemia, Niemann-Pick, Bloom syndrome, familial hyperinsulinism, mucolipidosis IV, glycogen storage disease type I, Joubert disease, maple syrup urine disease, Usher syndrome, and Gaucher disease

Disease	Incidence AJ	General (Caucasian)	Carrier AJ	Carrier non-AJ
Cystic Fibrosis	1:2500	1:2500	1:25	1:25
Tay-Sachs	1:3000	1:313,600	1:30	1:280
Canavan	1:6400	Rare	1 in 38	1:400
Familial Dysautonomia	1:3700	Rare	1 in 30	<1:150
Gaucher	1:855	Unknown	1 in 18	~1:150
Niemann-Pick A	1:32,000	1:313,800 (both A &B)	1 in 90	~1:890
Fanconi Anemia C	1:32,000	1:100,000 (type A-N)	1 in 89	~1:900; (any type 1:300)
Bloom Syndrome	1:40,000	Rare	1 in 100	~1:1000
Mucolipidosis IV	1:62,500	Rare	Rare	Rare

Ashkenazi Jewish Screening

Many laboratories offer extended panels

Tay Sachs
Canavan
Familial dysautonomia
CF
Fanconi anemia type C
Gaucher disease I
Mucolipidosis IV
Niemann-Pick A/C
Bloom syndrome

Glycogen storage disease 1a
MSUD
Nemaline myopathy
Usher syndrome
Dihydrolipoamide dehydrogenase deficiency
Familial hyperinsulinism

AJ Screening Considerations

- Confusion between Jewish ancestry versus Jewish religion.
- Having one grandparent of Ashkenazi Jewish descent warrants offering carrier testing (1/4th ancestry)
- There is no special testing for other (e.g. Sephardic) Jewish populations

French Canadian/Cajun

- Increased incidence of Tay-Sachs disease
- Carrier frequency similar to that of Ashkenazi Jewish population
- 1 in 30 carrier frequency

- Per ACOG, carrier screening for Tay Sachs can be performed using molecular analysis OR enzyme analysis of hexosaminidase enzymatic activity in serum or leukocytes
  - During pregnancy, or in women taking oral contraceptives, testing of Hex A enzyme must be done on leukocytes.

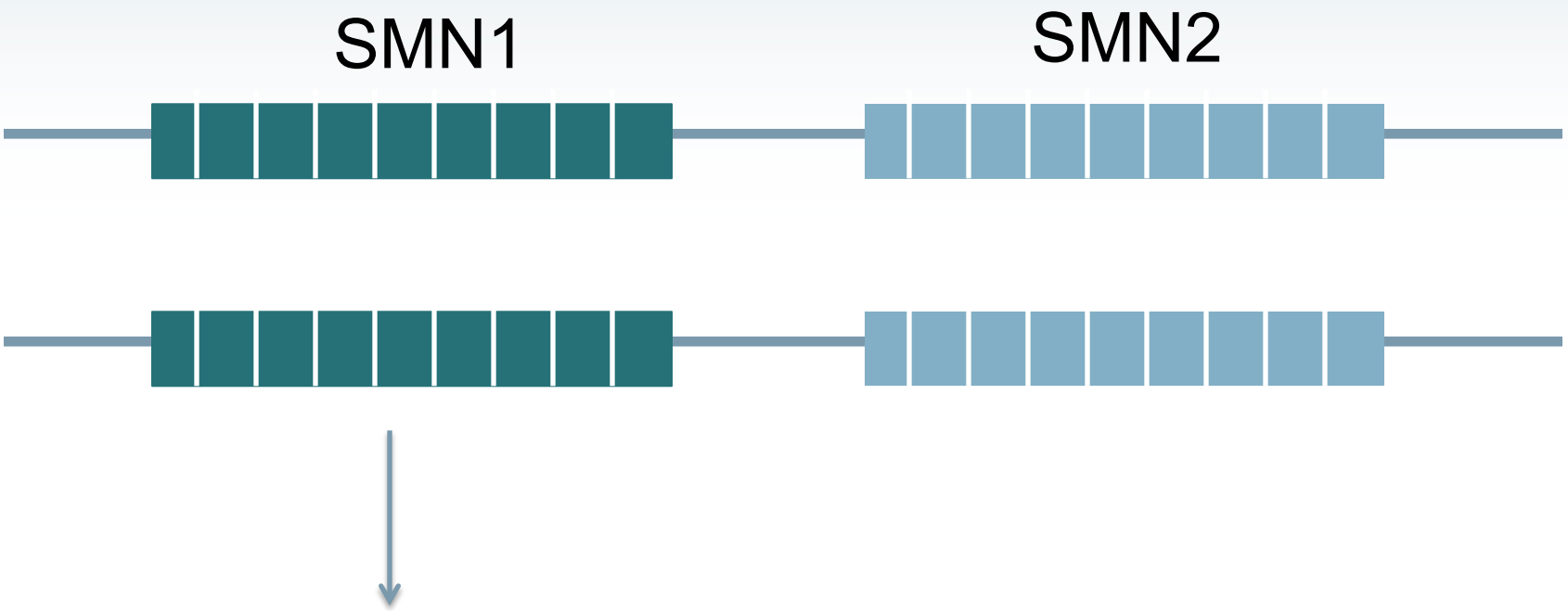
Spinal Muscular Atrophy (SMA)

- Spinal Muscular Atrophy is an autosomal recessive condition characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells (i.e., lower motor neurons) in the spinal cord and the brain stem nuclei.
- 2nd most common fatal AR disorder after cystic fibrosis
- Onset ranges from before birth to adolescence or young adulthood.
  - SMA subtype classification by age of onset and maximum function achieved is useful for prognosis and management.
- *SMN1* is the gene associated with SMA and typical individuals will have 2 or 3 copies of this gene.
  - Carriers have a single copy
  - *SMN2 gene* copy number has been shown to impact clinical course

SMA

- “SMA is present in all populations and therefore carrier screening should be offered to all couples regardless of race or ethnicity”
- Carrier frequencies:
  - Caucasian - 1 in 35
  - Ashkenazi Jewish - 1 in 41
  - Asian - 1 in 53
  - African American - 1 in 66
  - Hispanic - 1 in 117

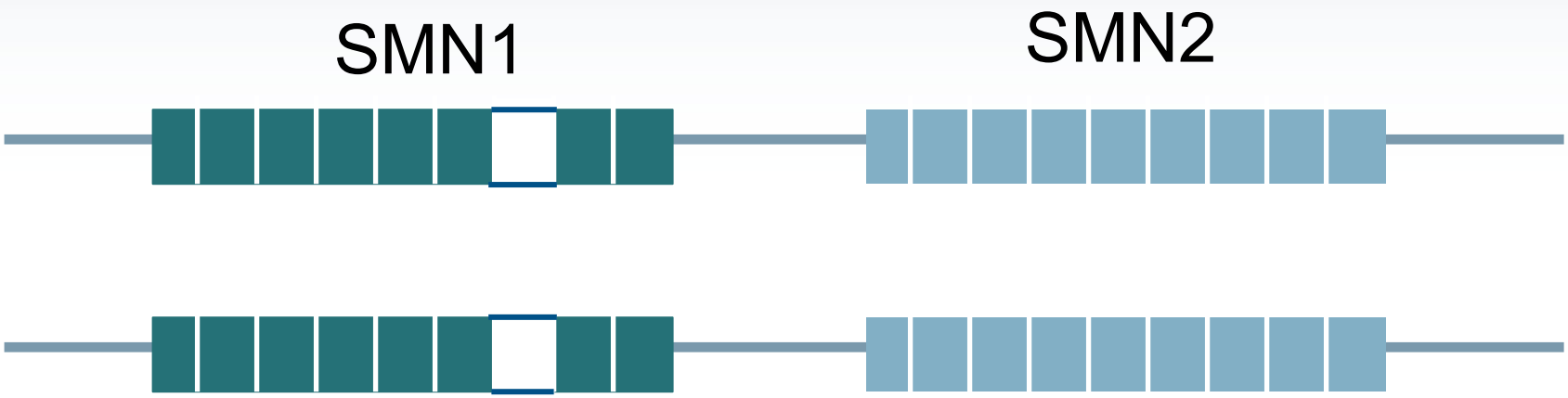
SMA: Molecular Genetics



Functional protein

Majority of transcripts are alternatively spliced to remove exon 7→non-functional protein

SMA: Molecular Genetics



95-98% of cases: homozygous deletion of exon 7 in SMN1

- SMN2 copy number modulates the phenotype, increased copy number of SMN2→milder phenotype
  Not a guarantee

SMA Screening Methodology

- Dosage test
- Determines how many copies of SMN1 and SMN2 does an individual have
- Possible results:
  - 2 copies SMN1 - normal
  - 3 copies SMN1 (or more) - normal
  - 1 copy SMN1 – CARRIER
- Can not determine point mutations

SMA advances

- Zolgensma – AAV vector delivers normal copy of SMN1 gene to target motor neurons
  - Zolgensma was approved by the FDA, under a priority review, on May 24, 2019, as a one-time IV treatment for people with any type of SMA up to age 2. It is not yet approved for use in other countries.
  - Its U.S. list price is $2.125 million for a single treatment, and Novartis allows for installment payments of $425,000 over five years.
- Nusinersen (Spinraza)
  - Nusinersen modulates alternative splicing of the *SMN2* gene, functionally converting it into *SMN1* gene, thus increasing the level of SMN protein in the CNS.
  - Approved in 2016
  - Injections every 4 months, ~$375000 annually

Fragile X: ACOG Recommendations

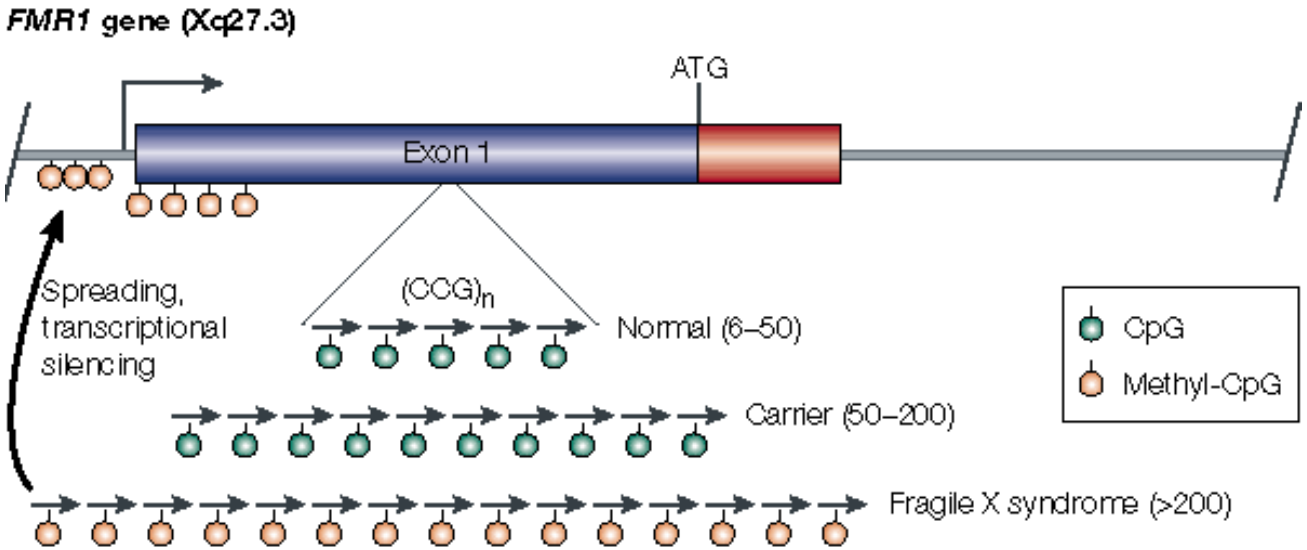
- Women with:
  - a family history of fragile X syndrome
  - a family history of unexplained mental retardation, developmental delay or autism
- Woman with ovarian insufficiency or failure or an elevated follicle stimulating hormone (FSH) levels before age 40 without a known cause
- Men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin

Fragile X

- Fragile-X syndrome is a X-linked condition associated with a trinucleotide repeat expansion in the *FMR1* gene.
- General population carrier rate = 1 in 259
- It is nearly always characterized by moderate intellectual disability in affected males and mild to moderate intellectual disability in affected females.
- Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes after puberty.
- Behavioral abnormalities and autism spectrum disorder are common.

Fragile X: Molecular Genetics

- X-linked inheritance
- Expansion of a triplet repeat (CGG) in FMR-1 gene promoter
- Expansion triggers hyper-methylation which silences gene
- Lack of gene expression causes phenotype



Fragile X Molecular Genetics

Mutation in the FMR-1 gene

Status of Individual	Number of repeats (CGG)
Unaffected	<45
Intermediate (grey zone)	45-54
Premutation	55-200
Full mutation	>200

Full mutation expansion from maternal premutation

Maternal Repeat Size	Full Mutation Expansion (%)
55-59	4
60-69	5
70-79	31
80-89	58
90-99	80
100-200	98

- Risk of expansion into a full mutation during female transmission
  - Risk correlates with repeat size
- Premutation alleles do not expand during male transmission
- Premutation carriers at risk for fragile-X associated tremor and ataxia (FXTAS) and females for premature ovarian failure (FXPOI)

Expanded Carrier Screening

- Expanded carrier screening uses panels of typically 100+ genetic conditions, most of which are rare.
- All individuals, regardless of ancestry, are offered screening for the same set of conditions. Addresses population admixture, ancestral uncertainty
- Majority of conditions included are autosomal recessive, some may be X-linked.
- Limitations: Low detection rate for some conditions, which may not meaningfully lower patient's carrier risk
- 40-60% screen positive rate if sequencing methodology
  - Requires considerable counseling resources
- About 1% of couples are a "carrier couple"

ACMG – 2021 Updated Recommendations

Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG PRACTICE RESOURCE

Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)

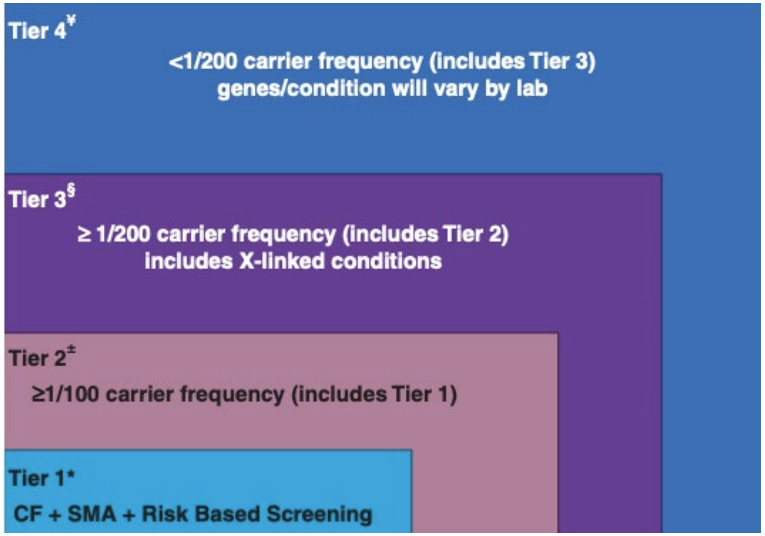
Anthony R. Gregg[1], Mahmoud Aarabi[2,3], Susan Klugman[4], Natalia T. Leach[5], Michael T. Bashford[6], Tamar Goldwaser[7,8], Emily Chen[9], Teresa N. Sparks[10,11], Honey V. Reddi[12,13], Aleksandar Rajkovic[10,11,14], Jeffrey S. Dungan[15] and ACMG Professional Practice and Guidelines Committee[16]*

ACMG Recommendations

- "Carrier screening paradigms should be ethnic and population *neutral* and more *inclusive* of diverse populations to promote equity and inclusion"

- All pregnant women should be offered tier 3 screening
  - 97 autosomal recessive diseases
  - 16 X-linked diseases

- Does NOT recommend offering tier 1 or tier 2 screening because these do not provide *equitable* evaluation of all racial/ethnic groups.



Rationale

- Self-reported ethnicity is commonly incorrect + increased population intermixing
- Better technology, faster turnaround times, lower costs
- Clinical utility: 60% took some action in response to being identified as an at-risk couple (Johansen et al)
  - Up to 77% when identified through preconception screening
- Individually rare but collectively common
  - Single gene disorders account for ~10% of all pediatric admissions and 20% of infant mortality
  - 1/280 births are affected with a Mendelian disorder with a cost of 100k-1M per child
  - Carrier screening for the whole population may cost less than treating affected children

Johansen Taber, K. A., Beauchamp, K. A., Lazarin, G. A., Muzzey, D., Arjunan, A. & Goldberg, J. D. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet. Med. 21, 1041–1048 (2019).

Curated list of genes

- Frequency of 1/200 in at least 6 subpopulations in the US
- **Profound:** shortened lifespan during infancy or childhood, intellectual disability
- **Severe:** death in early adulthood, impaired mobility or a [disabling] malformation involving an internal organ
- **Moderate:** neurosensory impairment, immune deficiency or cancer, mental illness, dysmorphic features
- Mild: not meeting one of those described

Example expanded carrier tests:

natera®

- Horizon 4
- Horizon 14
- Horizon 27
- Horizon 106
- Horizon 274
- Horizon 421
- Horizon Basic
- Horizon 445 - Custom
- Horizon 569 - Custom
- Horizon 574 - Custom
- Horizon 613 - Custom

Up to 787 with more coming every year!

fulgent®

Beacon 787-Expanded Carrier Screening Panel (With X-linked Disorders)

Calculating Risk

- An Ashkenazi Jewish couple wants to know their chance of having a child affected with Tay Sachs disease?
- Both have a “negative family history”

- Her carrier risk x his carrier risk x inheritance pattern risk

- 1/30 x 1/30 x ¼
- = 1 in 3,600 risk for affected child

- Carrier screening better defines personal risk for couples.

Questions?

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Practice Questions from Parts 1 & 2
(answers on last slide)

1.

A patient is referred to genetics due to a “screen positive” result from first trimester screening. Her results are as follows:

hCG: 2.35 MoM;

PAPP-A: 0.48 MoM;

NT: 3.3mm

What condition(s) is “screen positive” for?

- A) Down syndrome
- B) Trisomy 13
- C) Trisomy 18
- D) open neural tube defect

2.

A patient is referred to genetics due to a “screen positive” result from second trimester quad screening. Her results are as follows:

AFP: 0.35

hCG: 0.42

uE3: 0.29

DIA: 1.31

What condition is she “screen positive” for:

- A) Down syndrome
- B) Open neural tube defect
- C) Trisomy 13
- D) Trisomy 18

3.

A patient is referred to genetics for an abnormal AFP screening. Her AFP is 4.3 MoM. On detailed ultrasound, the spine and skull appear to be intact and normal in appearance (suggesting no open neural tube defects). What other birth defect should the sonographer examine the fetus for?

- A) heart defects
- B) facial clefting (cleft lip/cleft palate)
- C) abdominal wall defects
- D) duodenal atresia

4.

A patient is referred early in pregnancy for prenatal diagnosis because she and her husband are carriers for a genetic disorder. She would like to have invasive prenatal testing as soon as possible. What is the correct time frame for performing CVS?

- A) 6-8 weeks gestation
- B) 10-14 weeks gestation
- C) 15-22 weeks gestation
- D) 20-24 weeks gestation

5.

A patient is undergoing amniocentesis, what is an appropriate estimate to give her regarding her risk of complication (including miscarriage)?

- A) 0.25-0.5%
- B) 1%
- C) 1.5-2%
- D) 2.5%

6.

A patient has a “screen positive” result for Trisomy 18 (1 in 72) from second trimester quad screening. All are appropriate options to offer her except:

- A) cell free fetal DNA (NIPT)
- B) detailed ultrasound
- C) amniocentesis
- D) the option to repeat the test

7.

A 40 year old patient is referred to you prenatal genetic counseling. During the course of the session, you learn that she is of Greek decent (Mediterranean). What disorder would you be concerned about her being a carrier for?

- A) cystic fibrosis
- B) sickle cell anemia
- C) beta thalassemia
- E) spinal muscular atrophy

8.

You are seeing a couple who is interested in conceiving in the near future. She is of Ashkenazi Jewish descent and her husband has no known AJ ancestry. She is concerned about their risk of having a child with Tay Sachs disease. You know that the carrier frequency of Tay Sachs disease in the Ashkenazi Jewish population is 1 in 30 while the carrier frequency in the general population is 1 in 280. What do you tell them about their risk of having an affected child?

- A) 1 in 280
- B) 1 in 8,400
- C) 1 in 16,800
- D) 1 in 33,600

9.

In a CVS, what tissue is used for chromosome analysis?

- A) fetal serum
- B) placental tissue
- C) amniotic fluid for fetal skin cells
- D) amniotic fluid for fetal GI tract cells

10.

Which of the following IS NOT a characteristic of prenatal diagnostic tests

- A) cost effective
- B) invasive
- C) provides definitive answer
- D) risk involved

11.

Which of the following IS NOT a characteristic of screening tests

- A) cost effective
- B) easy to perform
- C) definitive answer
- D) defines at risk population

12.

Which correctly lists the 3 components of first trimester screening

- A) CRL measurement, hCG, PAPP-A
- B) NT measurement, hCG, AFP
- C) CRL measurement, uE3, PAPP-A
- D) NT measurement, hCG, PAPP-A
- E) NT measurement, uE3, AFP

13.

Results from first trimester screening are reported as

- A) The baby's karyotype (46,XX; 46,XY; etc.)
- B) a picture of the baby's chromosomes with "normal" or "abnormal"
- C) a fraction or odds ratio
- D) "affected" or "unaffected"

14.

All of the following are examples of screening tests, except

- A) quad/second trimester
- B) ultrasound
- C) CVS
- D) noninvasive prenatal testing (cffDNA)
- E) 1st trimester combined screen

15.

The following are examples of ultrasound “soft markers”, except:

- A) choroid plexus cysts
- B) thickened nuchal fold
- C) echogenic bowel
- D) ventriculomegaly
- E) gastroschisis

16.

All of the following are accepted criteria for widespread carrier screening except

- A) disorder is clinically severe
- B) Identification of the disorder prenatally would impact prenatal care
- C) high frequency of carriers in the screened population
- D) available screening test is reliable
- E) availability of prenatal diagnosis

17.

Counseling about the option of carrier screening for any disorder should include all of the following EXCEPT

- A) the purpose of screening
- B) disease features
- C) the patient's individual risk to be a carrier
- D) whether or not the patient would alter their pregnancy plans (eg. termination) in the event of an affected fetus
- E) carrier screening is optional

18.

The most common recessive condition in the French Canadian population is

- A) cystic fibrosis
- B) sickle cell anemia
- C) beta thalassemia
- D) Tay-sachs disease

Answers

1. A
2. D
3. C
4. B
5. A
6. D
7. C
8. D
9. B
10. A
11. C
12. D
13. C
14. C
15. E
16. B
17. D
18. D