Prenatal Screening & Diagnosis

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Outline

- Definition
- Context
- Prenatal screening & diagnosis for chromosome abnormalities
- Carrier screening
- Family history
Definitions

Screening Tests

identify common or important fetal disorder
high detection rate and low FPR
reliable and reproducible
+ early enough in gestation
to permit safe and legal options for TABS

Risk Assessment
Definitions

Screening Tests

- Prevalence
- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
Definitions

Diagnostic Tests
invasive procedure to determine fetal karyotype

risk of loss with procedure
CVS
Amniocentesis

Diagnosis Confirmed
Context

WHEN

ideal time = prior to conception.

first prenatal visit approximately 9 weeks
WHAT

- What conditions should you offer screening for?
- What do you need to know about screening?
Screening for Aneuploidy
WHO

- ACOG 2007: Screening and Invasive Diagnostic Testing available to ALL WOMEN prior to 20 weeks gestation
  - Differences between screening and invasive testing should be explained

- Traditionally, women of “advanced maternal age” are offered genetic counseling
Goals

- Screening tests with high detection rates and low false positive rates.
- Diagnostic testing option if the screening test is positive.
- Provide Ob/Gyns with some suggested screening strategies they can choose to offer in their practice.
- Discuss the advantages and disadvantages of each screening test and some of the factors that determine which screening test should be offered.
Ideally, patients seen early and offered screening that combines first and second trimester testing.

Screening test depends on availability of NT certification and CVS availability.

Women found to be at an increased risk should be offered genetic counseling and invasive prenatal diagnosis.
Counseling Adequacy

- Length of discussion with women under 35 was 2.5 minutes
- Length of discussion with women over 35 was 6.9 minutes
- Obstetricians more likely to make recommendations than nurse midwives
- Obstetricians less likely to indicate it was voluntary than nurse midwives

Conclusion: information provided during the first prenatal visit is inadequate to allow for proper decision-making
What are Genetic Counselors?

- Genetic counselors: specialized in medical genetics and counseling
- Liaison between patients and the medical genetics "community"
What do Genetic Counselors do?

- Perform risk assessments
- Review screening and testing options
- Explain medical facts and the contributions of genetics
- Explain diseases and management options
- Assist patients develop the best plan for their family goals, values, and religious beliefs
- Assist patients and families adjust to the diagnosis
1984: msAFP
1988: uE3 and hCG added for “triple screen”
Mid–1990s: Inhibin A added for “quadruple screen”
2000: First trimester screening
2005: Combined first & second trimester screening
2008: h–hCG added for “penta screen”
Nuchal Translucency (NT)

- Fluid accumulation
- Measured between 11.1–13.9 weeks
- Increased NT is an indication: aneuploidy, genetic syndromes, or congenital malformations
Nuchal Translucency (NT)
Nuchal Translucency

- Fetus in midsagittal plane
- Fetal neck in neutral position
- Fetal image should be 75% of screen
- Amnion should be distinguished from fetal skin
- Calipers placed on the inner borders of the nuchal fold
Nuchal Translucency

- NT > 95% for GA by CRL
  Detection rate of 70%, FPR 9.0%

- Incidence of aneuploidy changes with NT width
  95%–3.4mm: 7%
  3.5mm–4.4mm: 20%
  4.5mm–5.4mm: 45%
  5.5mm–6.4mm: 50%
  >8.5mm: 75%

# Increased NT: Normal Karyotype

<table>
<thead>
<tr>
<th>NT</th>
<th>Fetal Death</th>
<th>Anomalies</th>
<th>Alive &amp; Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95%</td>
<td>1.3%</td>
<td>1.6%</td>
<td>97%</td>
</tr>
<tr>
<td>95–99%</td>
<td>1.3%</td>
<td>2.5%</td>
<td>93%</td>
</tr>
<tr>
<td>3.5–4.4mm</td>
<td>2.7%</td>
<td>10.0%</td>
<td>70%</td>
</tr>
<tr>
<td>4.5–5.4mm</td>
<td>3.4%</td>
<td>18.5%</td>
<td>50%</td>
</tr>
<tr>
<td>5.5–6.4mm</td>
<td>10.1%</td>
<td>24.2%</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;6.5mm</td>
<td>19.0%</td>
<td>46.2%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Souka, AP et al Am J Obstet Gynecol 2005
Increased NT: Normal Karyotype

- Major cardiac defects: NT > 99%
  - detection rate 31%, FPR 4.9%

- The greater the NT the greater the incidence
  - NT 2.5–3.4mm - 1%
  - NT > 6.5mm - 20%

- Recommendation: detailed anatomic survey and fetal echocardiogram when NT > 95th%

Souka, AP et al Am J Obstet Gynecol 2005
<table>
<thead>
<tr>
<th>Test Name:</th>
<th>First–trimester only</th>
<th>Serum Integrated Screen (w/o NT)</th>
<th>Integrated Screen (with NT)</th>
<th>Sequential Screen (with NT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>11w0d–13w6d</td>
<td>10w0d–13w6d and 15w0d–22w6d</td>
<td>11w0d–13w6d and 15w0d–20w6d</td>
<td>11w0d–13w6d and 15w0d–20w6d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results reported in 2nd trimester</td>
<td>Results reported in 2nd trimester</td>
<td>Results reported in 1st AND 2nd trimesters</td>
</tr>
<tr>
<td>What’s measured?</td>
<td>NT + serum β–hCG and PAPP–A</td>
<td>PAPP–A and AFP, uE3, β–hCG, inhibin A</td>
<td>NT + serum β–hCG and PAPP–A and AFP, uE3, β–hCG, inhibin A</td>
<td>NT + serum β–hCG and PAPP–A and AFP, uE3, β–hCG, inhibin A</td>
</tr>
<tr>
<td>Down syndrome detection &amp; FPR</td>
<td>80–85% 5–6%</td>
<td>85% 3–4%</td>
<td>87% 1%</td>
<td>86–90% overall 1.6–3.7%</td>
</tr>
<tr>
<td>Trisomy 18 detection &amp; FPR</td>
<td>80%</td>
<td>90% 0.1%</td>
<td>90% 0.1%</td>
<td>90% overall 0.1%</td>
</tr>
<tr>
<td>Open spina bifida detection &amp; FPR</td>
<td>N/A</td>
<td>80% 1–3%</td>
<td>80% 1–3%</td>
<td>80% 1–3%</td>
</tr>
<tr>
<td>Test Name:</td>
<td>Triple Screen</td>
<td>Quadruple screen</td>
<td>Penta Screen</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>14w0d–22w6d (optimum 16–18wks)</td>
<td>14w0d–22w6d (optimum 16–18wks)</td>
<td>14w0d–22w6d (optimum 16–18wks)</td>
<td></td>
</tr>
<tr>
<td>What’s measured?</td>
<td>AFP, uE3, β–hCG</td>
<td>AFP, uE3, β–hCG, inhibin A</td>
<td>AFP, uE3, β–hCG, h–hCG and inhibin A</td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td>55–80%</td>
<td>70–80%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>detection &amp; FPR</td>
<td>5–6%</td>
<td>4–5%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>~60%</td>
<td>~60%</td>
<td>~60%</td>
<td></td>
</tr>
<tr>
<td>detection &amp; FPR</td>
<td>&lt;0.2%</td>
<td>&lt;0.2%</td>
<td>&lt;0.2%</td>
<td></td>
</tr>
<tr>
<td>Open spina bifida</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>detection &amp; FPR</td>
<td>1–3%</td>
<td>1–3%</td>
<td>1–3%</td>
<td></td>
</tr>
<tr>
<td>Test Name:</td>
<td>Serum Integrated Screen (w/o NT)</td>
<td>Quadruple screen</td>
<td>Penta Screen</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------</td>
<td>------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>10w0d–13w6d and 15w0d–22w6d Results reported in 2(^{nd}) trimester</td>
<td>14w0d–22w6d (optimum 16–18wks)</td>
<td>14w0d–22w6d (optimum 16–18wks)</td>
<td></td>
</tr>
<tr>
<td>What’s measured?</td>
<td>PAPP–A and AFP, uE3, β–hCG, inhibin A</td>
<td>AFP, uE3, β–hCG, inhibin A</td>
<td>AFP, uE3, β–hCG, h–hCG and inhibin A</td>
<td></td>
</tr>
<tr>
<td>Down syndrome detection &amp; FPR</td>
<td>85% 3–4%</td>
<td>81% 4–5%</td>
<td>83% 5%</td>
<td></td>
</tr>
<tr>
<td>Trisomy 18 detection &amp; FPR</td>
<td>90% 0.1%</td>
<td>~60% &lt;0.2%</td>
<td>~60% &lt;0.2%</td>
<td></td>
</tr>
<tr>
<td>Open spina bifida detection &amp; FPR</td>
<td>80% 1–3%</td>
<td>80% 1–3%</td>
<td>80% 1–3%</td>
<td></td>
</tr>
</tbody>
</table>
What’s not recommended

- First trimester NT (no serum) + second trimester Quadruple marker screen: 93% detection, 9.9% false positive

- First Trimester Screen + second trimester Quadruple marker screen: 95% detection, 9.2% false positive
Fetal Anatomic Survey

- Structural anomalies
  Guidelines by ACOG and AIUM

- Minor markers
  Nuchal fold
  Choriod Plexus Cyst
  Echogenic intracardiac focus
  Echogenic bowel
  Renal pyelectasis
  Short femur/humerus
  Clenched hands
  Clinodactyly
  2-vessel umbilical cord
Ultrasound Detection Rates

- **Down syndrome**
  - Overall: 53% detection, 14.2% false positive\(^1\)
  - Structural anomaly: 23.7% detection, 2.9% false positive
  - Nuchal fold only: 11.8% detection, 0.9% false positive
  - Minor marker only: 17.6% detection, 10.4% false positive

- **Trisomy 18:**
  - GA <17.5 weeks: 52% detection\(^2\)
  - GA >17.5 weeks: 67% detection

- **Open spina bifida:**
  - ONTD: ~98% detection\(^3\)
  - Anencephaly: 100% detection

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\(^1\) Smith–Bindman et al, 2007 *Prenatal Diagnosis*
\(^2\) Bahado–Singh et al, 2003 *Obstetrics & Gynecology*
\(^3\) Dashe et al, 2006 *AJOG*
Prenatally & Postnatally Diagnosed Conditions Act (S. 1810)
a.k.a. Brownback–Kennedy Bill

“A bill to amend the Public Health Service Act to increase the provision of scientifically sound information and support services to patients receiving a positive test diagnosis for Down syndrome or other prenatally and postnatally diagnosed conditions.”

Became Federal Law in October 2008

http://www.govtrack.us/congress/bill.xpd?bill=s110-1810
What is Down syndrome?

- >95% “true” trisomy 21 (47 chromosomes)
- <5% translocation, mosaic
- Increased incidence of pregnancy loss
- 30–60% CHD (VSD, ASD most common) usually correctable by surgery
- ~10% gastrointestinal defects, usually correctable by surgery
- ~15% psych or neurobehavioral disorder (ADHD or autism–like)
- Average adult IQ 50–70 (“mild developmental/cognitive disability”)
- Increased incidence: Type 1 diabetes, hypothyroidism, hearing loss, orthodontic conditions, obstructive airway disease, AML, immune issues, congenital cataracts
- Average life span
What is trisomy 18?

- >99% “true” trisomy 18 (47 chromosomes)
- <1% “partial” trisomy 18 (translocations or mosaic)
- >90% conceptions miscarried, IUFD, stillborn
- Of those live born: ~50% pass away by one week of life, ~90% by six months of life
- <10% survive past one year of age, survival into adulthood is possible, not universally “lethal”
- 70–90% will have congenital anomalies and other “features” identified on ultrasound
What is open spina bifida?

- A type of Neural Tube Defect (NTD)
- Includes anencephaly, meningocele, and myelomeningocele
- 1/1,000 live births
- ~95% have no family history
- Most at risk—Hispanic, Caucasian
- Lowest risk—Black, Asian/Pac Isl.
- Preconceptual folic acid (0.4mg vs. 4.0mg), continued through first trimester, can reduce risk up to 70%
- Wide range of cognitive and physical abilities
- Treatment for hydrocephalus, urinary tract dysfunction, behavioral/mental health concerns (ADHD, depression), obesity
## What else can we learn?

<table>
<thead>
<tr>
<th>Low PAPP–A</th>
<th>High msAFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR</td>
<td>Placental anomaly/bleed</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>Abruption</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>IUGR</td>
</tr>
<tr>
<td>PTL/PTD</td>
<td>Uteroplacental insufficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elevated hCG</th>
<th>Elevated Inhibin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR, LBW</td>
<td>IUGR</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>PTL/PTD</td>
<td>PTL/PTD</td>
</tr>
<tr>
<td>Abruption</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low uE3</th>
<th>Other Aneuploidies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>78% detection, 6% false positive</td>
</tr>
<tr>
<td>Steroid Sulfatase Deficiency</td>
<td>Trisomy 13</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>45,X</td>
</tr>
<tr>
<td></td>
<td>Triploidy</td>
</tr>
</tbody>
</table>
Prenatal Diagnostic Testing
Amniocentesis

- Invasive diagnostic procedure
- Routinely done from 15–22 weeks

Amniotic Fluid
  - AFP/acetylcholinesterase
    (80% detection of closed NTDs, >99% detection for open NTDs)

Fetal Cells
  - Chromosomal analysis (karyotype)
  - Single gene/DNA testing
Chorionic Villus Sampling (CVS)

- Invasive diagnostic procedure
- Routinely done from 10–14 weeks
- Obtains chorionic villi for:
  - Chromosome analysis (karyotype)
  - Single gene/DNA testing
  - Biochemical studies on fetal cells
Options for Prenatal Diagnosis of chromosome abnormalities:

<table>
<thead>
<tr>
<th>Diagnostic test:</th>
<th>Chorionic villus sampling (CVS)</th>
<th>Amniocentesis (Amnio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method:</td>
<td>Analysis of placental tissue</td>
<td>Analysis of amniocytes</td>
</tr>
<tr>
<td>Gestational age:</td>
<td>10w0d–13w6d</td>
<td>15w0d and on</td>
</tr>
<tr>
<td>Accuracy:</td>
<td>99.9%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Miscarriage rate***:</td>
<td>1%</td>
<td>0.3–0.5%</td>
</tr>
</tbody>
</table>
Pre-implantation Genetic Diagnosis (PGD)

- IVF with genetic testing
- Can reduce the likelihood of implantation of an affected conception
- Sample one cell at the six to ten cell stage (day 3) to test for genetic condition at increased risk for:
  - Chromosomal abnormalities (FISH)
  - Some single gene disorders (PCR)
- Embryo transferred back on day 4 or 5
New Directions

- First trimester ultrasound for:
  - Nasal bone
  - Ductus Venosus
  - Tricuspid Regurgitation

- Non-invasive prenatal diagnosis (NIPD):
  isolation of fetal DNA in maternal serum
NIPD

- Available from Sequenom© in fall 2009.
- Extracts free-floating fetal DNA & RNA from maternal serum beginning as early as 10 weeks gestation.
- Uses mass spectroscopy to test for markers of trisomy 21.
- Eventually will test for trisomy 13 and trisomy 18. Could also test for X and Y chromosomes.
- Has the potential to test for single gene disorders.
Ethnicity-based Carrier Screening
What should patients know about ethnicity-based carrier screening?

- Screening is optional.
- If a patient is found to be a carrier it is recommended that the other biological parent is also screened.
- Screening does not detect 100% of carriers.
Cystic Fibrosis carrier screening: ACOG Committee Opinion

- Information should be made available to all couples.
- It is reasonable to offer screening to all couples, regardless of race or ethnicity.
- Screening should be offered before conception or early in pregnancy when both partners are Caucasian, European, or Ashkenazi Jewish.
- Genetic counseling is beneficial for individuals with a family history of CF.
- Genetic Counseling is recommended when both partners are carriers.
- Genetic Counseling is beneficial if screening identifies two CF mutations (i.e. the patient is actually affected with CF).
# CF Incidence Carrier Frequencies & Detection Rate by Ethnicity

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence of CF 1 in</th>
<th>Carrier freq. 1 in</th>
<th>% of mutations identified (25 mutation panel)</th>
<th>Prenatal detection rate (%)</th>
<th>Residual Risk after negative test in one parent ~1 in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>2,500</td>
<td>25</td>
<td>88</td>
<td>78</td>
<td>21,000</td>
</tr>
<tr>
<td>Ash. Jewish</td>
<td>2,300</td>
<td>24</td>
<td>94</td>
<td>89</td>
<td>83,000</td>
</tr>
<tr>
<td>African American</td>
<td>15,100</td>
<td>61</td>
<td>65</td>
<td>42</td>
<td>54,000</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13,500</td>
<td>58</td>
<td>72</td>
<td>52</td>
<td>18,000</td>
</tr>
<tr>
<td>Asian American</td>
<td>35,100</td>
<td>94</td>
<td>49</td>
<td>24</td>
<td>75,000</td>
</tr>
</tbody>
</table>
Factors to consider:

- What if CF carrier screening was done in a previous pregnancy?
- Implications now that CF is part of the Oregon NBS panel.
- What happens if your patient is found to be affected?
- Will this be covered by insurance?
Ashkenazi Jewish Carrier Screening

- Conditions recommended by ACOG:
  - Cystic Fibrosis
  - Tay Sachs disease
  - Canavan disease
  - Familial Dysautonomia
# Ashkenazi Jewish carrier screening

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
<th>Jewish carrier frequency</th>
<th>Detection rate</th>
<th>Non–Jewish carrier freq.</th>
<th>Non–Jewish detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay Sachs</td>
<td>1/3,000</td>
<td>1/30</td>
<td>94% DNA, 98% enzyme*</td>
<td>1/30 Fr. Canadian, Cajun</td>
<td>98% enzyme**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/50–1/150 Irish</td>
<td></td>
</tr>
<tr>
<td>Canavan</td>
<td>1/6,400</td>
<td>1/40</td>
<td>98%</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Familial Dysautonomia</td>
<td>1/3,600</td>
<td>1/32</td>
<td>99%</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1/2,500</td>
<td>1/26–1/29</td>
<td>97%</td>
<td>see previous table</td>
<td>see previous table</td>
</tr>
</tbody>
</table>

* = testing for pregnant women must be on leukocytes  
** = Pseudoallele common in some populations (Irish)
Additional conditions recommended by American College of Medical Genetics:

Bloom syndrome (1/104)
Fanconi Anemia group C (1/89)
Mucolipidosis type IV (1/100)
Niemann–Pick type A (1/90)
Gaucher disease (1/15)
Additional conditions that should be “made available”:

GSD type 1a (1/71)
MSUD (1/81)
DFNB1 (a.k.a. Connexin 26) (1/21)
Nonclassic 21–OHD CAH (1/27 affected)
Torsion Dystonia (~1/50)
Factor XI deficiency (1/12 affected)
Usher syndrome I (1/165)
Usher syndrome III (1/95)
Nemaline Myopathy (1/120)
Lipoamide dehydrogenase deficiency (E3) (1/100)
Familial Hyperinsulinism (1/100)
Carrier screening for CF, TSD, CD, and FD should be before conception or early in pregnancy.

Carrier screening for other disorders may be requested and patient education materials should be made available.

When only 1 partner is of AJ descent, test them first. The couple should be informed of the carrier frequency and detection rate for screening in the non-Jewish population.

Offer carrier screening if there is a family history. The patient may benefit from genetic counseling.

When both partners are carriers, they should be referred for genetic counseling.
Factors to consider:

- What if the patient’s partner is not Jewish?
- Will this be covered by insurance and is screening for more necessarily better?
- Tay Sachs Disease screening:
  - in other ethnic groups
  - Pseudodeficiency
  - in pregnant women and women on oral contraceptives
Individuals of African, Southeast Asian, and Mediterranean ancestry are at higher risk for being carriers of hemoglobinopathies and should be offered carrier screening.

If both parents are determined to be carriers, genetic counseling is recommended.

To ensure accurate hemoglobin identification, a CBC with determination of MCV is the appropriate initial laboratory test for individuals of non-African descent.

Individuals with low MCV should have hemoglobin electrophoresis. Iron-deficiency anemia should be excluded.

Individuals of African descent should have a CBC and hemoglobin electrophoresis. Solubility testing such as the Sickledex is inadequate for screening.
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>β–thal trait</th>
<th>α–thal trait</th>
<th>Sickle cell trait</th>
<th>Hb C trait</th>
<th>Other Hb variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean</td>
<td>1/20–1/30</td>
<td>1/30–1/50 (trans)</td>
<td>1/30–1/50</td>
<td>Rare</td>
<td>D, G, Lepore</td>
</tr>
<tr>
<td>African American</td>
<td>1/75</td>
<td>1/30 (trans)</td>
<td>1/10–1/12</td>
<td>1/50</td>
<td>O,D</td>
</tr>
<tr>
<td>Hispanic Mexican, Central America</td>
<td>1/30–1/50</td>
<td>Variable</td>
<td>1/30–1/200</td>
<td>Rare</td>
<td>J, E</td>
</tr>
<tr>
<td>Asian</td>
<td>1/50</td>
<td>1/20 (cis)</td>
<td>Rare</td>
<td>Rare</td>
<td>E</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>1/30</td>
<td>&gt;1/20 (cis)</td>
<td>Rare</td>
<td>Rare</td>
<td>E</td>
</tr>
<tr>
<td>India, Pakistan</td>
<td>1/30–1/50</td>
<td>Variable</td>
<td>1/50–1/100</td>
<td>Rare</td>
<td>D,O,E</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>1/50</td>
<td>Variable</td>
<td>1/50–1/100</td>
<td>Rare</td>
<td>D,O,E,J</td>
</tr>
<tr>
<td>West African</td>
<td>1/50</td>
<td>1/30 (trans)</td>
<td>1/6</td>
<td>1/20–1/30</td>
<td>O,D</td>
</tr>
</tbody>
</table>
Factors to consider:

- Are prenatal labs (CBC with MCV) considered screening for hereditary hemoglobinopathies?
- Oregon’s Newborn Screening program screens all babies for abnormal hemoglobin regardless of ethnicity.
The American College of Medical Genetics (ACMG) has recently recommended that all couples, regardless of ethnicity, be offered carrier screening for SMA.

ACOG has not issued a statement or practice bulletin yet.
Spinal Muscular Atrophy (SMA)

- Autosomal recessive inheritance
- Progressive muscle weakness resulting from degeneration & loss of anterior horn cells (i.e., lower motor neurons) in spinal cord and brain stem nuclei
- Carrier frequency: 1/40
- Incidence: ~1/6,000 across all ethnicities
- Classified based on age of onset and severity (3 different types)
SMA Carrier Screening

- Carrier screening, in an experienced lab, has ~90% detection rate
- Performed using “dosage analysis”
- Does not provide genotype/phenotype information

Genetic counseling should be made available to individuals requesting carrier screening due to the complexity of the screening and possibility of false-negative results.

–ACMG, 2008
Family History
Family History: What should we ask about?

- Congenital anomalies/Birth defects
- Developmental Disabilities/”MR”
- Known genetic conditions
- Still births/Neonatal Death/SIDS
- Recurrent pregnancy loss
- Consanguinity (related as second cousins or greater)
- Ethnicity

In first, second, and third (sort-of) degree relatives to the fetus
In Summary

- All patients, regardless of age, should be offered prenatal screening or diagnosis for chromosome abnormalities but the type of test offered depends upon resources available in the area.
- Women of advanced maternal age should still be offered genetic counseling and invasive diagnostic testing.
- Individuals should be offered screening based on ethnicity and family history.
- Prenatal screening is optional and patients should be informed of the risks, benefits, and limitations before screening is performed.