CLINICAL GENETICS

Novels in Prenatal Genetic Screening
Genetics in Today Medicine:

• The Human Genome Project has brought inherited health factors to the forefront

• Genetic risk assessment, screening and testing is becoming part of primary medical care

• Clinical genetics and primary care need to work together to offer appropriate services
We Are Working Together

• Risk assessment for common genetic conditions
  • likely to be performed in the primary care/prenatal setting

• Screening and testing for genetic conditions
  • increasingly performed in primary care/prenatal care

• Patients with rare or more complex genetic conditions, risks, or family histories
  • likely continue to be served by genetics specialists
Family History

• Screens for reproductive genetic risks

• Appropriate for patients considering pregnancy or already pregnant

• Contains referral guidelines for genetic services
Assessment Areas

• Maternal age

• Family medical history (both sides)

• Current pregnancy/pre-pregnancy history

• Ethnic background (both sides)
Maternal Age

• Maternal age 35 or older at time of delivery: increased risk for chromosome abnormalities

• Options for prenatal testing/screening:
  • CVS
  • Amniocentesis
  • Multiple marker screening
    • 1st or 2nd trimester, or combined
  • Ultrasound
Family Medical History

• For a family history of a diagnosed genetic condition or birth defect and a patient who is currently pregnant, referral to a Prenatal Diagnosis Clinic is appropriate.

• Examples:
  – Nephew with Duchenne Muscular Dystrophy
  – Brother with Fragile X syndrome
  – Previous child with spina bifida, etc.
Family Medical History

• For a non-specific, but concerning history, referral to a Medical Genetics Clinic (e.g. OHSU) is appropriate.

• Examples:
  – Close family member with mental retardation, etiology unknown
  – Multiple family members with ‘kidney disease’
  – Previous child with seizure disorder and developmental delay
Pregnancy History

• During pregnancy, any reported exposures or maternal conditions would be reasonable to refer to a genetics service – especially those known to be teratogens
  • E.g. accutane, seizure medications, lithium, coumadin, “street drugs”, high fevers, viral infections, maternal diabetes, etc.

• Preconception counseling should always include a discussion of folic acid
  • Thought to decrease the risk of neural tube defects by 50-70%
    • 0.4 mg is recommend for all women
    • 4.0 mg is recommended for women at increased risk
Ethnicity-Based Genetic Carrier Screening

- Purpose: To detect couples at risk for prenatally diagnosable genetic diseases
- Tests offered based on ethnic background
- Should be offered to patients:
  - Seeking preconception counseling, OR
  - Seeking infertility care, OR
  - During the first or early second trimester of pregnancy
## Carrier Frequencies based on Ethnic Origin

<table>
<thead>
<tr>
<th>Population</th>
<th>Condition</th>
<th>Carrier Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>Sickle Cell</td>
<td>1 in 10</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 65</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 75</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>Gaucher disease</td>
<td>1 in 15</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 26 – 1 in 29</td>
</tr>
<tr>
<td></td>
<td>Tay-Sachs disease</td>
<td>1 in 30</td>
</tr>
<tr>
<td></td>
<td>Dysautonomia</td>
<td>1 in 32</td>
</tr>
<tr>
<td></td>
<td>Canavan disease</td>
<td>1 in 40</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>Alpha-Thalassemia</td>
<td>1 in 20</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European American</td>
<td>Cystic Fibrosis</td>
<td>1 in 25 - 1 in 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Canadian, Cajun</td>
<td>Tay Sachs disease</td>
<td>1 in 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>Cystic Fibrosis</td>
<td>1 in 46</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 30 - 1 in 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean</td>
<td>Beta-Thalassemia</td>
<td>1 in 25</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 29</td>
</tr>
<tr>
<td></td>
<td>Sickle Cell</td>
<td>1 in 40</td>
</tr>
</tbody>
</table>
Principles of Carrier Screening

• Counseling before screening should include:
  • Purpose, voluntary nature of screening
  • Range of symptoms and severity of each disease
  • Risk of carrier status and affected offspring
  • Meaning of positive and negative results
  • Factors to consider in decision-making
  • Further testing would be necessary for prenatal diagnosis
Informed Consent

• Utilize patient resources materials
  • Patient brochures about CF and other ethnicity-based genetic screening available from multiple sources
  • Carrier screening videos can be shown in office settings

• Document informed consent discussion and patient decision
Important Points

• Carrier screening is **optional**
  • Patient education/informed decision-making is crucial

• Testing can be done sequentially or concurrently
  • If >12 weeks gestation, discuss concurrent testing

• Insurance coverage for carrier screening???
  • Varies by insurer (*not covered by OHP and some other major insurers*)

• Genetic counseling is available to carriers and strongly advised for carrier/carrier couples
Caucasian Patients:

**ACMG guidelines, Oct. 2001**

- Offer cystic fibrosis carrier screening to:
  - Individuals with a family history of CF
  - Reproductive partners of carriers/persons with CF
  - Couples where one or both partners are Caucasian & are planning a pregnancy or seeking prenatal care

- “Make CF screening available” to couples in other racial or ethnic groups at lower risk
CF Carrier Screening

• 1/25 to 1/29 carrier rate in general Caucasian population and Ashkenazi Jewish population

• Carrier screening by DNA mutation analysis
  • ACMG suggests panel of 25 most common mutations
  • Some labs do additional mutations but at higher cost

• www.genetests.org

• Mutations differ in severity – contact genetics to discuss particular carrier results
## Carrier Rates: Cystic Fibrosis

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Carrier Frequency</th>
<th>Detection Rate</th>
<th>Carrier risk after negative test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern European Caucasian</td>
<td>1/25 – 1/29</td>
<td>85-90%</td>
<td>~1 in 250</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>1/26 - 1/29</td>
<td>97%</td>
<td>~1 in 930</td>
</tr>
<tr>
<td>Southern European Caucasian</td>
<td>1/29</td>
<td>70-80%</td>
<td>~1 in 97 to 1 in 140</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/46</td>
<td>57%</td>
<td>~1 in 105</td>
</tr>
<tr>
<td>African American</td>
<td>1/65</td>
<td>72%</td>
<td>~1 in 232</td>
</tr>
<tr>
<td>Asian</td>
<td>~1/90 (?)</td>
<td>~30% (?)</td>
<td>Not available</td>
</tr>
</tbody>
</table>
Asian Patients

• Standard to review MCV
  • If <80, screen for thalassemia w/quantitative hemoglobin electrophoresis
  • Alpha-thalassemia carrier rates up to 1/20
  • Beta-thalassemia carrier rates 1/30 to 1/50

• Cystic fibrosis carrier rate 1/90 or less
  • Detection rate is very low (~ 30%)
  • Not standard to do CF screening
  • Make available upon patient request
Hispanic/Latino Patients

- No standard protocol for carrier testing
  - Cystic Fibrosis: carrier rate 1/46
  - Beta-thalassemia: carrier rate 1/30 to 1/50
  - Sickle cell or other hemoglobin trait: Carrier rate 1/30 (Caribbean) to 1/200
- Could review MCV as a general screen
African-American Patients

• Standard to offer Sickle Cell screening
  • Sickle cell carrier rate is 1/10 to 1/12
  • Use Hb electrophoresis (NOT sickle dex)
• Standard to review MCV
  • Beta-thalassemia carrier rate about 1/75
  • If MCV low, offer thalassemia screen w/quantitative Hb electrophoresis
• CF carrier rate 1/65
  • no standards re: offering CF carrier screening
Ashkenazi Jewish Patients

• Standard of care to offer carrier screening for:
  • Tay-Sachs disease
  • Cystic Fibrosis
  • Canavan disease
  • Familial Dysautonomia

• All autosomal recessive conditions

• Carrier testing for other disorders also available (high anxiety/family history?)
Maternal Serum Screening

- Tests maternal serum markers to detect increased risk of fetal trisomy 21, trisomy 18 and/or neural tube defects
  - 2nd trimester maternal serum screening
  - 1st trimester maternal serum screening (with or without nuchal translucency measurement)
  - Integrated maternal serum screening
  - Other variations combining 1st and 2nd trimester screening results
Maternal Serum Screening

• **Patient education points:**
  • ‘This is only a screening test’
  • ‘The test is optional’
  • ‘A negative result does not guarantee a healthy baby’
  • ‘A positive result does not mean that the baby has a problem, **BUT** further testing (ultrasound & CVS or amniocentesis) would be offered’
  • Offered to all patients regardless of age – ‘there is a small risk in every pregnancy for these conditions’
2\textsuperscript{nd} Trimester Serum Screening

- **Timing:** 15 to 20 weeks gestation
- **Choices:**
  - Triple screen
  - Quad screen
- **Cost** $\sim$200
  - Insurance coverage varies
  - Triple covered by most, Quad by some
Triple Screen

• Analytes used (with maternal age):
  • Alpha-fetoprotein (AFP)
  • Unconjugated estriol (uE3)
  • Beta-Human Chorionic Gonadotropin (b-HCG)

• Detection rates/screen-positive rates vary by lab

• Detection rates with a 5% screen-positive rate
  • Down syndrome: 60-70%
  • Trisomy 18: 60%
  • NTD: 75-80%
Quad Screen

• Analytes used (with maternal age):
  • adds dimeric inhibin-A (DIA) to AFP, uE3 and beta-HCG
• Detection rates with 5% screen positive rate
  • Down syndrome: 75-80%
  • Trisomy 18: 60%
  • NTD: 75-80%
• Use quad screen over triple when available and when covered by insurance
2nd Trimester screening tips

- Use ultrasound dating if available
  - Even when LMP still used for due date
  - U/S dating gives more accurate results

- Cons of 2nd trimester screening
  - Later gestation - limits prenatal diagnosis options
  - Not as accurate for multiple gestation
  - Some labs do not offer calculations for twin gestations

- Pros:
  - Includes screening for NTDs via AFP analysis
  - Often covered by insurance
1st Trimester Maternal Serum Screening

• Timing:
  • 24-84 mm CRL (9 to 13+6 weeks gestation)

• Analytes used (with maternal age):
  • free Beta HCG
  • PAPP-A

• Detection rates with 5% screen positive rate:
  • Down syndrome: 68%
  • Trisomy 18: 90%

• Costs:
  • $100-200 for serum
  • $200 plus for NT U/S
1\textsuperscript{st} Tri Serum + NT

• Serum results combined with nuchal translucency (NT) measurement *
  • *Measured by an NT-certified ultrasonographer
  • Best visualized at CRL = 45 – 84 mm (11-14 wks gestation)
  • Increased NT = increased risk for Down syndrome / other disorders

• Detection rates with 5% screen positive rate:
  • Down syndrome – 90%,
  • Trisomy 18 – >90%

Increased NT

- Increased NT measurement (>3.5mm) associated with increased risk for:
  - Chromosome abnormalities
  - Major structural cardiac defects
  - NTDs, other structural anomalies, and specific genetic syndromes
  - SAB, IUFA, SGA and stillbirth
- If normal chromosomes and >NT, can offer:
  - 2nd trimester MSAFP screen
  - Fetal anomaly scan between 18-22 weeks
  - Fetal echocardiogram between 20-22 weeks
Pros: 1\textsuperscript{st} Trimester Serum + NT screen

- Fingerstick dried blood sample easy to collect and send via prepaid FedEx envelope
- Draw blood <11 wks if possible (more sensitive)
- Results take about 1 week
- Results available at earlier gestation
- Allows choice of CVS or amnio
- Higher detection rate than 2\textsuperscript{nd} trimester screen
- More accurate for multiple gestations
- Separate ultrasound/NT results on each fetus
Cons: 1st Trimester Serum + NT screen

• Requires NT measurement performed at a certified center
  • Often only available at perinatal centers
  • Often necessitates patient travel

• Does not screen for NTDs
  • Need to discuss 2nd trimester AFP screening with patients who have had 1st trimester screening

• May not be covered by insurance
Integrated Serum Testing

• Combined 1\textsuperscript{st} and 2\textsuperscript{nd} trimester biochemical screening
  • 1\textsuperscript{st} trimester dried blood sample
  • 2\textsuperscript{nd} trimester venipuncture

• Increased detection rate; decreased false positive rate

• Combined results given in 2\textsuperscript{nd} trimester after 2\textsuperscript{nd} screen

• Good for:
  • Communities without NT capabilities and/or CVS
  • Patients who are not highly anxious
  • Patients who cannot afford 1\textsuperscript{st} trimester US/NT screening
Ultrasound

• Nuchal translucency (NT) and nasal bone (NB)
  • Accompanies 1st trimester serum screening for Down syndrome.
  • Performed by NT and NB certified sonographers

• Fetal anatomy – 18-20 weeks
  • Offered for significant family history of detectable structural defects or genetic syndrome(s), for f/u of positive serum screens, for prenatal history of known teratogens, etc.

• Fetal echocardiogram - 20-22 weeks
  • Often useful for significant family history of structural cardiac lesions, certain genetic syndromes, certain teratogen exposures,

• Not perfect - a normal ultrasound does not mean a healthy baby
Fetal Ultrasound

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Fetal Ultrasound

• Fetal echocardiogram - 20-22 weeks
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• Patient counseling:
  – Fetal ultrasound is not perfect - a normal ultrasound does not mean a healthy baby
Ultrasound
Who to Refer – Ethnic Background

- Individuals with a family history of cystic fibrosis or other autosomal recessive disease
- Couples where both members are known carriers for an autosomal recessive disease
- Couples where one member is a carrier and has additional questions
- Pregnant carriers who do not have results on the father of baby
Who To Refer –
Positive Family History

• If patient or partner indicates family history of birth defects, inherited condition(s) or history of pregnancy exposure:
  • Assess level of concern and desire for more information about risks to pregnancy
  • Refer for genetic counseling with patient consent
Who To Refer –
Prenatal Genetic Services

• Advanced maternal age
• Request for 1st trimester marker screening with NT
• Abnormal serum marker screening results
• Fetal abnormalities on prenatal ultrasound
• Personal or family history of a known or suspected genetic disorder, birth defect, or chromosome abnormality
• Family history of mental retardation of unknown etiology
• Patient with a medical condition known or suspected to affect fetal development
Who to refer (cont)

- Exposure to a known or suspected teratogen
- Either parent or family member with a chromosome rearrangement
- Parent a known carrier or has a family history of a disorder for which prenatal testing is available
- Unexplained infertility or multiple pregnancy losses or previous stillbirths
- Absence of the vas deferens
- Premature ovarian failure
THANK YOU FOR YOUR ATTENTION!
ANY QUESTION?