**Understanding Your Genetic Screening Questionnaire**

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**Genetic Diseases are Not as Rare as we Think!**

2-3% of newborns have a congenital disease or malformation

These result in:
- More than 20% of infant mortality
- 30% of ICN admissions

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**Effectiveness of Genetic Screening**

- N=158 women referred for genetic counseling
- Pedigree vs Questionnaire vs Both
- Add’l genetic risks found in:  
  - Questionnaire 20%  
  - Pedigree 34%  
  - Both 50%  

_Cohn et al, Obstet Gynecol, 1996_
Family History

First Degree Relatives: siblings, parents and children

Second & Third Degree Relatives: Aunts, Uncles, Nieces, Nephews and Cousins

Second & Third Degree Relatives: Parent, Aunt, Cousins
Will You Be 35 or Older on Your Due Date?

- Risk of Down syndrome (and other chromosome problems) increased after one affected pregnancy
- Risk is about 1%, or 0.5% above age risk, whichever is higher
- Recurrence may be higher or lower with history of other chromosome problems

Have you, or the baby’s father, had a pregnancy or a child diagnosed with Down syndrome?
Have you, or the baby’s father, had a pregnancy or a child diagnosed with Down syndrome?

- Risk is NOT increased with other affected relatives (eg sibling) unless due to a translocation

Translocation Down Syndrome

- Translocations cause <5% of Down syndrome
- Suspect translocation with multiple affected relatives or history of multiple miscarriages
- Chance of translocation also higher if mother was young when DS affected pregnancy occurred
  ➢ Ideally, confirm with a karyotype

Have you, the baby’s father, or any relative had a neural tube defect?

(or heart defect, cleft lip or palate, clubbed feet, etc)
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Multifactorial Disorders

- CL/CP, NTD, clubfoot, congenital heart defects
- Combination of genetic and environmental factors
- Recurrence depends on # of affected relatives
- Some are part of genetic syndromes, so with SEVERAL affected relatives, or other birth defects too, risk may be much higher

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Multifactorial Disorders

- First degree relative 3-4%
- Second degree relative 0.6%
- Third degree relative 0.3%
- Two first degree relatives 10%
Are you OR the baby’s father from any of these ethnic backgrounds:
• Italian
• Greek
• Middle Eastern
• Spanish
• Southern Chinese
• Asian Indian
• Taiwanese
• Filipino
• Southeast Asian

If YES, have you or the baby’s father been tested to see if you are a carrier of thalassemia or another hemoglobinopathy?

Hemoglobinopathies
• Most common genetic diseases worldwide
• 7% of world’s population are carriers
• Most prevalent in equatorial areas

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Distribution of Malaria and Sickle Cell Disease
Thalassemias: Alpha and Beta

- Caused by decreased production of either the alpha or beta chain of hemoglobin
- Both are autosomal recessive
- Both are associated with a low MCV
- Differences in alpha and beta thalassemia (both diagnostic evaluation and clinical picture) due to hemoglobin protein structure and ratio of alpha and beta chains

<table>
<thead>
<tr>
<th># globin genes</th>
<th>Genotype</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>aa/aa</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>a-/aa</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>a-/a-</td>
<td>Mild anemia, low MCV, At risk of fetal hydrops (SE Asian genotype)</td>
</tr>
<tr>
<td>1</td>
<td>a-/--</td>
<td>Hb H disease</td>
</tr>
<tr>
<td>0</td>
<td>--/--</td>
<td>Hb Bart’s, hydrops fetalis</td>
</tr>
</tbody>
</table>

Structure of hemoglobin

Alpha Thalassemia

- Common in SE Asian populations
- Also occurs in some Mediterranean populations (Greek)
- Causes fetal hydrops and stillbirth
- Associated with low MCV but normal Hb electrophoresis
Beta Thalassemia

- Common in Mediterranean, SE Asian, African, some Middle Eastern populations
- No fetal implications (does not cause hydrops)
- Symptomatic at 18 months of age; Hb F converts to adult Hb A
- Hemolytic anemia, splenomegaly, iron overload, bony/skeletal changes
- Association with low MCV and increased Hb A₂

Are you, or the baby’s father, of African American or African descent?

- If yes, have you or the baby’s father ever been tested to see if you are a carrier of sickle cell anemia?

Thalassemias

<table>
<thead>
<tr>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV</td>
<td>Low</td>
</tr>
<tr>
<td>Hb elect.</td>
<td>Normal</td>
</tr>
<tr>
<td>Symptoms</td>
<td>In utero</td>
</tr>
<tr>
<td>Other beta chain mutations (S,C,E)</td>
<td>No disease</td>
</tr>
</tbody>
</table>

Sickle Cell Anemia

- Caused by point mutations in the beta chain of hemoglobin
- In deoxygenated blood, Hb S is not as soluble as normal hemoglobin
- Molecules aggregate and distort RBCs, leading to vasoocclusion and local hypoxia
Sickle Cell Disease

- Hb S mutation in beta globin gene
- Very common in African American population (~1/12 is a carrier)
- If patient is a carrier, and her partner is not available, but is AA, risk of affected offspring is: 
  \[1 \times \frac{1}{12} \times \frac{1}{4} = \frac{1}{48}\]
- Combination of sickle cell + beta thal mutations causes sickle cell like condition

Who to Screen, and How?

Is patient at risk for sickle cell disease?
- African Americans primarily, also some other groups
- Need MCV AND hemoglobin electrophoresis regardless of MCV results
  - Hb S carriers are NOT microcytic
  - Sickle prep is not adequate screening

Who to Screen, and How?

Is patient at risk for thalassemia?
- SE Asian, Mediterranean, African American
- Measure MCV. If low:
  - Check hemoglobin electrophoresis
  - Iron deficiency?
- If Hb electrophoresis normal->alpha thal carrier
- If elevated Hb A2->beta thal carrier

Sickle cell anemia

African Americans:
- 1/12 are carriers
- 1/300 affected

Other groups at risk:
- Greeks
- Italians
- Turks
- Arabs
- S Iranians
- Asian Indians
- Some Brazilian, Caribbean, Central American groups
Thalassemia Screening

Low MCV/normal Hb electrophoresis:
- Alpha thal carrier
  - Check partner MCV and Hb electrophoresis
  - If low->DNA studies for alpha thal

Low MCV/high Hb A2
- Beta thal carrier
  - Check partner MCV and Hb electrophoresis

Are you, or the baby’s father, of Ashkenazi Jewish background?

- If yes, have you or the baby’s father been tested for Tay Sachs disease, cystic fibrosis, Canavan disease, or Familial dysautonomia?

Tay Sachs Disease

- TSD is a lysosomal storage disease caused by hexosaminidase A (hex A) deficiency
- Resultant accumulation of GM2 gangliosides results in progressive neuro-degeneration
- Death in early childhood
- There is no treatment or cure

Hex A Activity in Tay Sachs Disease

- Hex A Activity in Tay Sachs Disease
  - Normal individuals
  - Homozygotes
  - Adult Tay–Sachs disease
  - Juvenile Tay–Sachs disease
  - Severe Tay–Sachs disease
Even Tay Sachs screening gets complicated, however…

Enzyme assay vs DNA?
- Initially screening involved enzyme assay for Hexosaminidase A activity
- More recently, a DNA test was developed
- DNA testing sensitive in Ashkenazi Jewish patients but NOT in others
  - *Enzyme testing preferable in most cases*
- In complex cases, a combination of tests may be required

Who to Screen?

Groups at increased risk:
- Ashkenazi Jewish 1/27
- Louisiana Cajun 1/27
- French Canadian 1/27-73
- Irish Americans 1/50
- Pennsylvania Dutch ??

Groups not at risk
- Non-Jewish, Sephardic 1/250

Ashkenazi Jewish Screening
- ACOG recommends screening for TSD, Canavan disease, cystic fibrosis, familial dysautonomia
  - Testing also available for Bloom syndrome, Fanconi anemia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease
- Most severe, untreatable and relatively rare
- 1/5 Ashkenazi Jews carries one of these nine disorders
  - *Availability of tests raises ethical, medico-legal, and practical difficulties*
Do you, the baby’s father, or anyone in your families have cystic fibrosis?

Cystic Fibrosis transmembrane conductance regulator gene (CFTR)

- Defective chloride transport->high sweat chloride levels
- Tenacious mucous in lungs and pancreas-> severe pulmonary disease, pancreatic insufficiency, malabsorption
- Wide range of severity, although most die of pulmonary disease at mean age of 37 (2006)

Cystic Fibrosis

- Most common autosomal recessive disorder among Caucasians (1/3300)
- ~1/25 Caucasians with no family history is a carrier of CF
- 80% of children with CF are born to parents with no prior history of the disease

ACMG/ACOG recommendations for CF screening (2001)

**CF testing should be offered to:**
- Individuals with a family history of CF
- Partners of persons with CF
- Couples in whom *one or both* partners are Caucasian and who are currently planning a pregnancy or seeking prenatal care
- Testing should be *made available* to couples who are of other ethnicities
Testing for CF by genetic mutation analysis

- Over 1400 gene mutations identified
- Standard recommendation is a 23 mutation panel
  - Detects 94% Ashkenazi, 88% other Caucasian carriers
- Adding additional mutations is of limited benefit, as each new mutation typically rare
- Rare mutations are often of uncertain clinical significance

CF Detection Rates and Carrier Risks*

<table>
<thead>
<tr>
<th>Group</th>
<th>Carrier risk</th>
<th>Detection rate</th>
<th>Carrier risk w/neg test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi</td>
<td>1/24</td>
<td>94%</td>
<td>1/400</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1/25</td>
<td>88%</td>
<td>1/208</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1/46</td>
<td>72%</td>
<td>1/164</td>
</tr>
<tr>
<td>African-Am</td>
<td>1/65</td>
<td>65%</td>
<td>1/186</td>
</tr>
<tr>
<td>Asian-Am</td>
<td>1/94</td>
<td>49%</td>
<td>1/184</td>
</tr>
</tbody>
</table>

*Risks only apply with NEGATIVE family history!

CF Screening Recommendations (ACOG 2005)

- Information about CF should be made available to all couples
- It is reasonable to offer CF to all pregnant patients or test selectively (Caucasian, Ashkenazi Jewish, European)
- Negative results must be interpreted based on patient’s ethnicity
- Sequential or concurrent testing reasonable, depending on GA of patient

Ethnicity Based Screening

- Ashkenazi Jews: Tay Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia
- Louisiana Cajun, Fr Canadian: Tay Sachs disease
- Caucasians: Cystic fibrosis
- Africans, African Americans: Sickle cell anemia, beta thalassemia
- Southeast Asians: Alpha thalassemia
- Mediterraneans: Beta thalassemia
Do you, the baby’s father, or anyone in your families have hemophilia or another bleeding disorder?

Do you, the baby’s father, or anyone in your family have a neuromuscular disease or muscular dystrophy?

Muscular Dystrophies

X-Linked Disorders
Queen Victoria’s Family Tree

Spinal Muscular Atrophy

- Severe hereditary neuromuscular disorder
- Degeneration of alpha motor neurons in spinal cord, resulting in proximal muscle weakness and paralysis
- Several types of varying severity
- Type I is most severe; usually results in death by age 2 from respiratory failure

SMA Carrier Testing
American College of Medical Genetics

- Ffits criteria for screening (severe, high frequency, availability of test and prenatal dx, access to GC)
- Carrier testing is offered for disorders with a similar carrier frequency
- SMA carrier testing should be offered to all couples regardless of race/ethnicity

Prior et al, Genet in Med, 2008

- Autosomal recessive
- Second most common fatal AR disorder after cystic fibrosis
- ~1/10,000 live births, 1/40-60 carrier frequency
- Occurs in all ethnic groups
Complexities of Carrier Testing for SMA

- Negative screen reduces but does not eliminate risk (detects ~90%)
- Carrier testing does not predict type
  - 70% of cases are severe phenotype
  - 30% are less severe

ACOG Committee on Genetics (2009)

- “Laboratories and advocacy organizations are promoting widespread screening”
- “...prenatal screening for SMA is not recommended in the general population at this time.”
- GC and screening should be offered to:
  - Persons with a family history
  - Those who request it

Do you, the baby’s father, or anyone in your families have autism, mental retardation, or Fragile X syndrome?
Fragile X Syndrome

- Most common inherited form of mental retardation
  - MR, joint laxity, tall stature, large jaw, characteristic faces, hyperactive behavior
- Most common single gene defect associated with autism
- 1/4000 males and 1/8000 females affected
- Carrier frequency 1/157
  
  Berkenstadt et al, 2007

Fragile X Syndrome: Other features

Associated with a broad spectrum of clinical features:
- Late onset tremor/ataxia syndrome
- Premature ovarian failure
- Female infertility
- Psychiatric disease
- Autism

Fragile X Syndrome

- At present, population screening is not recommended
  - Partly because the genetic counseling is so complex
  - Outcome in females is unpredictable, from typical fragile X syndrome to a normal outcome

Testing for Fragile X recommended for:
- Infertile women, esp with elevated FSH
- Egg and sperm donors
- Patients with a personal or family history of MR or developmental disabilities
- Patients with a personal or family history of autism

McConkie-Rosell et al, 2007
Who Needs a GC Referral?

• Previous affected child with most anything
• More remote family history of mental retardation
• Family history of X-linked disorder (Fragile X, hemophilia, muscular dystrophy) on MOTHER’s side of the family
• History of common autosomal recessive disorder in 3d degree or closer relative
  – Cystic Fibrosis, Tay Sachs, Spinal Muscular Atrophy

Summary and Take Home Message

• Low threshold to provide testing on patient request (when test is available)
• Consider referral to genetic counselor for such requests

Summary and Take Home Message

• Be familiar with ACOG guidelines for screening
• Be aware of any screenable genetic disorders that occur in high frequency in ethnic groups in your community
• Offer Fragile X screening for any maternal history of elevated FSH, infertility, autism, as well as undiagnosed mental retardation

Thank You!