Objectives

• Discuss the role of genetic consultation in obstetrics
• Understand the difference between screening and testing
• Describe various screening and diagnostic options for prenatal diagnosis
• Review the role of ultrasound in prenatal diagnosis
• Review key statistics to assist in the interpretations of genetic tests

General Introduction

• Importance of prenatal genetic screening
  – Reassurance
  – Majority of patients undergo screening or diagnostic testing for this reason
  – Prepare for a child with special needs
  – Therapeutic alteration of outcome (rare)
  – Terminate pregnancy

Elements of Genetic Counseling

• Time
• Sometimes requires a known diagnosis
• Communication
  – Information gathering
  – Patient/family education
• Non-directive counseling
  – An objective discussion
  – Probably unrealistic
• Important to know limitations of knowledge and refer appropriately

Groups With Increased Genetic Risk

• Pregnant women
• Advanced maternal age
• Certain ethnic groups
  – Ashkenazi Jews
  – French Canadians
  – Cajun
• Previous affected fetus
• Fetus with a major sonographic anomaly
• Men/Women carrying chromosomal abnormalities
  – Translocation
  – Inversion
  – Aneuploidy

Factors Affecting Genetic Risk

• Environment
• Genetics
• Socioeconomic status
• Maternal diabetes
• Maternal weight
• Maternal alcohol use
• Family History of NTD
• Medication exposures
Baseline Genetic Risk

- 3-5% of live births will have a major birth defect
- 10% of live births will have a minor congenital abnormality
- Down Syndrome (Trisomy 21)
  - Most common trisomy of live births
  - 1/800 live births

Ethnic Genetic Disorders

Definitions

A Diagnostic Test
- Offered to a large, low-risk group
- Identifies smaller group who may benefit from further testing
- Inexpensive
- Low risk to the patient
- Easy

A Screening Test
- Offered to a high-risk group
- Provides a definitive result
- Expensive
- Higher risk to the patient
- More difficult to perform

Effectiveness of a Screening Test

- Detection rate
  - How many affected pregnancies will be identified by the test
- False positive rate
  - Number of unaffected pregnancies that screen positive by the test
- Odds of being affected given a positive result
  - Combines detection rate, false positive rate and the disease prevalence into one ratio
  - Allows comparison of the number of diagnostic procedures required to identify one affected pregnancy using each screening test

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- Prenatal screening
  - Assessment of risk fetus affected by a genetic disorder
- Prenatal genetic diagnostic testing
  - Determines with as much certainty as possible whether a specific genetic disorder is present
  - Chromosomes evaluated for presence/absence of abnormalities in number, deletions, and duplications, or DNA evaluated for specific genetic disorders
- No one screening test is superior to another
  - Screening should be an informed patient choice that fits the clinical circumstances, values, interests, and goals
- Chromosomal abnormalities occur in 1 in 150 live births
  - Prevalence greater earlier in gestation as aneuploidy accounts for a significant number of early pregnancy loss
  - Factors which increase risk of fetal aneuploidy
    - Increasing maternal age
    - History of a prior aneuploid fetus
    - Presence of fetal anomalies
ACOG Practice Bulletin
May 2016 Number 163

- Autosomal trisomies most common aneuploidy
  - Down syndrome (trisomy 21) most common
  - 1 in 800 live births
  - Most common form of inherited intellectual disability
  - 95% of cases of Down syndrome result from nondisjunction involving chromosome 21
- Most common sex chromosome aneuploidy
  - Klinefelter syndrome (47,XXY)
  - 1 in 500 males
  - Only viable monosomy is Turner syndrome (45,X)

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- Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy
- Choice to undergo prenatal diagnosis depends on woman’s goals, values, and desire for informational accuracy
- Screening identifies two groups
  - Positive screen/increased risk of fetus with aneuploidy
    - Offered counseling and diagnostic testing
  - Negative screen/lowest posttest probability of evaluated aneuploidy
    - Counseled regarding an adjusted lower risk
    - Should not be offered additional screening tests - increased risk of false positives
    - May be offered diagnostic test if additional findings identified

ACOG Practice Bulletin
May 2016 Number 163

- Intent of counseling
  - To inform the pregnant woman about chromosomal disorders, provide information regarding her specific risks
  - Discussion of the adjusted likelihood of carrying a fetus with the evaluated aneuploidies
  - Potential for fetus to be affected by genetic disorders not evaluated by the screening/diagnostic test
  - Prenatal diagnosis of fetal aneuploidy
- Expectant management
  - Education for preparedness and expectations
  - Delivery at a tertiary care center
  - Potential need for hospice
- Terminations of pregnancy

ACOG Committee Opinion
October 2015 Number 643

- Identification and referral of maternal genetic conditions
  - Management of genetic conditions is complex and may require a multidisciplinary approach
  - Patients with genetic conditions or at risk of a genetic condition, should have a preconception evaluation with their obstetrician-gynecologists, genetics specialists, maternal-fetal medicine specialists, or other appropriate subspecialists
  - Patients with established causative mutations for a genetic condition, and who desire prenatal genetic testing, should be offered preimplantation genetic testing with in vitro fertilization
  - Once pregnant, patient with a genetic condition should have initial prenatal examination early in 1st trimester for coordination of prenatal screening/testing and evaluation

Common Cytogenetic Abnormalities

- Trisomy 21
  - 1 in 800 live births
- Trisomy 18
  - 1 in 8000 live births
- Trisomy 13
  - 1 in 20000 live births
- 45,X
  - 1 in 10000 live births
- 47,XXX; 47,XXY; 47,YYY
- Del(5p)
  - 1 in 20000 live births
Methods of Genetic Screening

- Maternal serum screening
- Ultrasound
- Combinations of the above
- Cell Free DNA analysis
  - MaterniT21 plus (Sequenom)
  - Harmony (Ariosa Diagnostics)
  - Verifi (Progenity)
  - Panorama (Natera)
- Expanded carrier screening panels

Biochemical Markers and Genetic Screening

Maternal Serum Screening

- Geared to the detection of Down syndrome
  - Most common chromosomal abnormality in live births
    - 1 in 800 live births
  - 95% trisomy 21
  - 3% translocations
  - 2% mosaic
  - Phenotype variable
- Trisomy 18
- Open Neural tube defects
- Smith-Lemli-Opitz

Trisomy 21

Maternal Serum Screening

- Trisomy 18
  - Low AFP, Estriol, and HCG
- Smith-Lemli-Opitz
  - Abnormality of cholesterol synthesis resulting in increased levels of 7-dehydrocholesterol
  - Due to absence of 7-dehydrocholesterol reductase

Alpha-Fetoprotein (AFP)

- Produced in the fetal liver and GI tract
- Excreted in the fetal urine
- Rises throughout pregnancy
- First protein routinely measured in the maternal blood
- High levels originally used to identify fetuses at risk for neural tube defects
- 1984 correlation of low AFP levels with fetuses with Down syndrome
Serum Alpha-Fetoprotein (MSAFP)

- **High**
  - Normal variant
  - Open neural tube defects
  - Abdominal wall defects
  - Bleeding
  - Fetal demise
  - Kidney disorders
  - Oligohydramnios
  - Multifetal gestation
  - Under estimated fetal age
  - Increase in 3rd trimester complications

- **Low**
  - Normal variant
  - Chromosomal trisomies
  - Gestational trophoblastic disease
  - Fetal death
  - Over estimated fetal age

Serum Proteins

- **Human Chorionic Gonadotropin (HCG)**
  - Placental glycoprotein
  - Peaks at 10 weeks' and then gradually declined
  - High levels associated with increased risk for Down syndrome
  - HCG and free beta HCG
    - Able to be utilized in both second and first trimesters

- **Estriol**
  - Produced from interaction of the placenta, fetus, and mother
  - Increases throughout pregnancy
  - Low levels associated with increased risk for Down syndrome
  - Addition to AFP and HCG resulted in the “triple test”
    - Detection rate of about 65% for a 5% false positive rate
    - Addition showed only a small incremental
    - Very low levels less than 0.5 MOM have also been associated with adverse pregnancy outcomes

- **Inhibin A**
  - Produced by the placenta
  - Addition to the “triple screen” resulted in the “quad screen”
    - Can detect 70-75% of cases of fetal Down syndrome
    - Unexplained elevation – greater than 2.0 MOM associated with increased risk of adverse pregnancy outcome

Quad Screen - Summary

- **Alpha-fetoprotein (AFP)**
  - Protein produced by the fetus' liver
  - Decreased in trisomy 21

- **Unconjugated Estriol (UE)**
  - Produced in the placenta, fetus liver, and input from maternal liver
  - Decreased in trisomy 21

- **Human Chorionic Gonadotrophin (hCG)**
  - Produced by the placenta
    - Elevated in trisomy 21

- **Inhibin-A**
  - Hormone produced by the placenta
    - Elevated in trisomy 21
Quad Screen – Adjustment Factors

- Gestational age
- Maternal weight
- Maternal race
- Maternal insulin-dependant diabetes
- Multiple fetal pregnancy
- Family history of Down syndrome

Maternal Serum Screening

- Limitations to 2nd trimester screening
  - Earliest can be performed - 15 weeks'
  - 25% of Down syndrome cases not identified
  - 60 amnios need to be done for single case of Down syndrome
  - 1 normal fetus lost for every three DS fetuses identified
- Interest in earlier screening methods

Prenatal Genetic Screening

- Maternal serum screening
  - 1st trimester
  - 2nd trimester
  - Combinations
  - Cell free fetal DNA analysis
  - Expanded carrier panels
- Prenatal sonography
  - 1st trimester
    - Nuchal translucency
    - Nasal bone
  - 2nd trimester
    - Nuchal fold
    - Minor markers
    - Cardiac defects

Methods of Screening

- First Trimester Serum Screening
  - Combination of free βhCG, PAPP-A, maternal age
  - PAPP-A
    - Pregnancy Associated Plasma Protein-A
    - Produced by the placental trophoblast
  - Detection rate - 60% with 5% false positive rate
    - Independent of other markers
    - Allows addition of other markers to alter the calculated risk
    - Down syndrome detection rates - 73% to 84% (FPR of 5%)

Nuchal Fluid Accumulation

- Potential Etiologies
  - Aortic isthmic narrowing
  - Other fetal cardiovascular defects
  - Abnormalities in the extracellular matrix
  - Abnormal or delayed development of the lymphatic system
  - Specific etiology may vary with the underlying condition
The Nuchal Translucency

• 11 – 13 6/7 weeks’ gestation
• Crown-rump length 45 and 84 mm
• Sagittal view of the fetus in a horizontal position with profile visible
• Neck in a neutral position
• Image fills 75% of the screen
• Widest part of translucency measured
• Measurement taken with inner border of horizontal line of calipers placed on line that defines nuchal translucency

Example


• Nuchal translucency greater than or equal to 3.0 mm considered screen positive
  – NT measurement of 3.0 mm or greater has minimal benefit in waiting for serum screening results
  – NO benefit for NT of 4.0 mm or greater
• Serum screening is not necessary
• Genetic consultation should be offered
• Fetal echocardiogram ordered to assess fetal cardiac anatomy

Nuchal Translucency and Congenital Heart Abnormalities

• Thicker the nuchal translucency, greater the risk
  – 10 weeks’ gestation

Thick Nuchal Translucency

• Greater the nuchal translucency – greater risk of adverse pregnancy outcome
• Normal karyotype
  – 2nd trimester detailed fetal anatomic survey
  – Fetal echocardiogram
  – Further counseling regarding potential for genetic syndromes

Types of Screening

• Integrated screening
  – First- and second-trimester combined test
  – Patient receiving a single risk assessment after second test
  – Can be performed with or without nuchal translucency
  – High rates of non-adherence (25% without nuchal reminder)
  – Highest detection rate
• Independent sequential screening
  – Obtain 2 individual results from 1st trimester then 2nd trimester testing without incorporating information from 1st trimester test
  – Has unacceptably high false-positive rate
  – NOT RECOMMENDED
Types of Screening

• Step-wise sequential screening
  – First-trimester screen and prenatal diagnosis if calculated risk above a specific cutoff
  – If patient screens below risk cutoff, she is offered second-trimester screening and receives a combined result

• Contingent screening
  – Groups women into a high, low, or intermediate risk categories after first-trimester screen with management dependent on first-trimester risk assessment
  – Most cost effective

Other Clinical Implications

• First trimester
  – PAPP A less than 0.4 MOM (5th percentile) and/or low HCG (less than 0.5 MOM) in first trimester
  • Spontaneous fetal and neonatal loss
  • Fetal growth restriction
  • Preeclampsia
  • Placental abruption
  • Preterm delivery

• Second trimester
  – Elevated hCG, AFP, dimeric inhibin A
  – Fetal death
  – Fetal growth restriction
  – Preeclampsia
  – Decreased MSAFP (less than 0.25 MOM) or estriol (less than 0.5 MOM)
  – Fetal death
  – Fetal growth restriction
  – Preeclampsia
  – Estriol less than 0.3 MOM
  – Genetic consultation for Smith Lemli Optiz

Other Clinical Implications

• Combination of a placenta previa and elevated MSAFP in the second or third trimester has been associated with placenta accreta

• Likelihood of adverse pregnancy outcome increases with the increasing number of minor markers
Noninvasive Prenatal Screening

- Noninvasive prenatal testing uses cell free short fragments of DNA isolated from plasma of pregnant women
- Testing should be an informed patient choice after pretest counseling - should not be part of routine prenatal laboratory assessment
- Should not be offered to low-risk women or women with multiple gestations because not been sufficiently evaluated
- Negative test result does not ensure an unaffected pregnancy
- Patient with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis
- Does not replace accuracy and diagnostic precision of CVS or amniocentesis

Committee Opinion Number 545, December 2012

Circulating Cell Free DNA (cfDNA)

- cfDNA originates from placental cells undergoing apoptosis releasing fetal cells into maternal circulation
- Circulating fetal DNA in maternal plasma greater than 10%
- Positive predictive value lower in the general population versus high risk patients
  - Lower prevalence of aneuploidy in a low risk population
- Cell free DNA assessment for microdeletions not validated and not recommended

Committee Opinion Number 545, December 2012

Natera

Panorama uses a proprietary, patented algorithm, called Natera's NATiUE, to take into account the actual DNA of the mother, and create the test results. This way, the test is based on statistical analysis of test results and the risk is calculated for each patient. The test result is a report that provides a personalized risk score. The test can be used earlier in the pregnancy than other NIPS. The NATiUE algorithm incorporates over 1000 SNP per chromosome evaluated, allowing Panorama to select SNPs that are not impacted by ethnicity.
ACOG Practice Bulletin
May 2016 Number 163

• Cell-free DNA is a screening test
  – Should not be used as a substitute for diagnostic test
  – Capabilities
    • Screen for a variety of fetal conditions
    • Determine fetal gender
    • Identify presence of Rh-positive fetus
    • Detect some paternal autosomal dominant conditions
  – Positive predictive value
    • 93% for Down syndrome,
    • 64% for trisomy 18
    • 44% for trisomy 13
    • 39% for sex chromosome aneuploidy
  – Positive screen may be placental mosaicism, resorbing twin, maternal malignancy or maternal aneuploidy

ACOG Practice Bulletin
May 2016 Number 163

• Cell-free DNA as a screening test
  – More effective with higher fetal fractions
  – Low fetal fraction
    • Sampling before 10 weeks’ gestation
    • High maternal body mass index
    • Fetal aneuploidy
      – 8% failed to obtain a result, and 22% of those were aneuploid
      – A non-reportable should be offered additional consultation and invasive diagnostic testing

Cell free DNA (cfDNA) Screening and Role of Ultrasound

• Society for Maternal-Fetal Medicine Consult Series recommendations (March 2017)
  – Sonogram for nuchal translucency in a patient with negative cfDNA screen not recommended
  – Diagnostic testing not recommended with only an isolated soft marker and a negative cfDNA screen
  – Isolated soft marker and negative 1st or 2nd trimester screen should be described as a variation of normal
  – Sonographic finding of a fetus with a structural abnormality should be offered diagnostic testing with chromosomal microarray
  – Routine screening for microdeletions with cfDNA not recommended

Cell free DNA (cfDNA) Screening and Role of Ultrasound

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In women who have already received a negative cfDNA screening result, ultrasound at 11+0 to 13+6 weeks’ gestation (or at the lowest risk for the specific fetal condition) is not recommended.</td>
<td>B</td>
</tr>
<tr>
<td>Diagnostic testing should not be recommended to patients solely for the indication of an isolated single-marker finding in the setting of a negative cfDNA screen.</td>
<td>B</td>
</tr>
<tr>
<td>In women with an isolated soft marker who has no other clinical explanations. Ultrasound should be offered for additional fetal examination, including maternal history, pregnancy ultrasound, alpha-fetoprotein, and the results of a specific test.</td>
<td>B</td>
</tr>
<tr>
<td>In women with an isolated soft marker who has no other clinical explanations, if second-trimester screening levels are recommended, the finding should not be listed as a normal finding.</td>
<td>C</td>
</tr>
<tr>
<td>The recommendation of amniocentesis or chorionic villus sampling is not based on ultrasound and should not be offered.</td>
<td>C</td>
</tr>
</tbody>
</table>

Routine screening for microdeletions with cfDNA is not recommended.

Society for Maternal-Fetal Medicine Consult Series Recommendations (March 2017)
NIPT – Standard of Care?? (NEJM 2014)

- DNA Sequencing versus Standard Prenatal Aneuploidy Screening
- Objective: Assess NIPT accuracy in low-risk patients
- Methods
  - Performed massively parallel sequencing in a blinded fashion
  - Comparison of false positive rates of detection of trisomies 21 and 18 with use of standard screening and cfDNA testing
  - Both outcomes or karyotypes were reference standard
- Results
  - False positive rates with cfDNA significantly lower than standard screening (0.3% vs. 3.6% for trisomy 21, and 0.2% vs. 0.6% for trisomy 18, P = 0.03)
  - cfDNA testing detected all cases of aneuploidy
  - Positive predictive values for cfDNA testing versus standard screening were 48.1% versus 4.2% for trisomy 21 and 45.0% versus 8.5% for trisomy 18
- Conclusions
  - In a general obstetrical population, prenatal testing with cfDNA test significantly lower false positive rates and higher positive predictive values for detection of trisomies 21 and 18 than standard screening

Screening for Open Neural Tube Defects

- Women undergoing 1st trimester screening should be offered 2nd trimester assessment for open fetal defects
  - MSAFP
    - Drawn as a single order
    - Not part of a Quad screen
  - Ultrasound
  - Both

ACOG Recommendations (LEVEL A)

- Cell-free DNA is a screening test and should not be used as a substitute for diagnostic testing
- All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action
- Women whose cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy
- Women with a positive screening test result for fetal aneuploidy should be offered further detailed counseling and testing
ACOG Recommendations (LEVEL C)

• Screening for aneuploidy should be an informed choice, that fits patient’s clinical circumstances, values, interests, and goals.
• Aneuploidy screening or diagnostic testing should be discussed and offered early in pregnancy, ideally at the first prenatal visit.
• All women should be offered option of aneuploidy screening or diagnostic testing regardless of age.
• If an isolated ultrasonographic marker for aneuploidy is detected, the patient should be offered aneuploidy screening if not yet performed.

ACOG Recommendations (LEVEL C)

• Women with a positive traditional screening result may prefer to have cell-free DNA screening rather than definitive testing.
  – May delay definitive diagnosis and fail to identify some fetuses with aneuploidy
• Parallel or simultaneous testing with multiple screening methodologies not cost-effective and should not be performed
• In multifetal gestations, if fetal demise or an anomaly is identified in one fetus, serum-based aneuploidy screening should be discouraged.

Current Screening Tests

<table>
<thead>
<tr>
<th>Screening Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2B</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>NT</td>
<td>98%</td>
<td>70%</td>
</tr>
<tr>
<td>Cell-free DNA</td>
<td>60%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Summary of Screening Modalities

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second trimester</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>First trimester</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Antenatal</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Maternal-fetal DNA</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Screening in Multifetal Gestations

• Affected by number of fetuses and zygosity
• No method of aneuploidy screening is as accurate as in singleton gestation
• Nuchal translucency measurements allow each fetus to be screened independently
• Single enlarged nuchal translucency in monozygotic twins may be early sign of twin to twin transfusion syndrome
• Cell-free DNA not recommended in twin gestation
• Serum based screening not recommended if there is a fetal demise or fetal anomaly in one twin due to risk of inaccurate results

Screening in Multiple Gestations

• Natera’s Panorama Non-Invasive Prenatal Test
  – Oct. 2, 2017
• Validated to screen twin pregnancies for zygosity and chromosomal abnormalities
  – Identifies monozygotic twins with >99% sensitivity/specificity
  • 67% of monozygotic twins are monochorionic
ACOG Committee Opinion 690 (March 2017)

Expanded Carrier Screening

- Acceptable strategy for pre-pregnancy and prenatal carrier screening
- If patient requests a screening strategy, test should be made available following counseling
- Criteria for disorders carrier screening panel
  - Carrier frequency of 1 in 100 or greater
  - Well-defined phenotype
  - Detrimental effect on quality of life
  - Cause cognitive or physical impairment
  - Require surgical or medical intervention
  - Have an onset early in life
  - Able to be diagnosed prenatally and afford opportunities for antenatal intervention to improve perinatal outcomes
- Carrier screening panels should not include conditions associated with a disease of adult onset

ACOG Committee Opinion 691 (March 2017)

- Spinal Muscular Atrophy (SMA-1 and SMA-2)
  - Screening for SMA should be offered
  - If no family history - SMN1 deletion recommended for low-risk partner
- Cystic Fibrosis
  - Screening should be offered
  - Complete analysis of CFTR gene by DNA sequencing not appropriate for routine carrier screening
- Hemoglobinopathies
  - CBC with red blood cell indices should be completed
  - Hemoglobin electrophoresis should be completed
  - Risk based on ethnicity (African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent)
  - Low mean corpuscular hemoglobin or low MCV

Microarray

Methods of Genetic Screening

- Microarray
  - Identifies chromosomal abnormalities including submicroscopic abnormalities too small to be detected by conventional karyotyping
  - Fetal DNA obtained from chorionic villus sampling or amniocentesis
  - Potential for complex results and clinically uncertain findings
  - Can result in substantial patient anxiety

Examples
Methods of Genetic Screening

**Microarray**
- Fetus with major structural abnormalities
  - Chromosomal microarray analysis – replaces fetal karyotype
- Structurally normal fetus undergoing invasive prenatal testing
  - Either fetal karyotype or chromosomal microarray
- Should not be restricted to women aged 35 years and older
- Intrauterine fetal demise when cytogenetic analysis desired
  - Chromosomal microarray analysis on fetal tissue
- Not recommended for evaluation of 1st or 2nd losses
- Comprehensive patient pretest and posttest genetic counseling from a genetic counselor or geneticist essential
- Should not be ordered without informed consent

ACOG Committee Opinion Number 581, December 2013

Diagnostic Methods

- **Preimplantation genetics (PID)**
  - Implies IVF
  - 8 cell stage
    - Blastomere day 3
  - Set apart 1-2 cells (embryobiopsy)
  - Tested by FISH
  - Implant embryos with favorable test results
  - Should still be offered aneuploidy screening/diagnosis during pregnancy

Ethics of Prenatal Screening

ACOG Committees on Ethics and Genetics Recommendations

- Identify patients who are candidates for genetic testing and maintain competence in advances in genetics
- Recognize geneticists and genetic counselors are important part of health care team
- Discuss with patients importance of genetic information
  - Recommend information be shared with potentially affected family members as appropriate
- Be aware that genetic information has potential to lead to discrimination in workplace and affect insurability
  - Physicians have an obligation that includes a mandate to prevent discrimination
  - Advocacy for legislation to ban genetic discrimination

Miscellaneous

- Genetic diagnosis for fetal demise
  - Conventional karyotype
    - Can only be obtained with living tissue
    - Higher culture failure rate
  - Microarray
    - Does not require viable cells
    - Preferred test
    - Cannot be contaminated with maternal tissue or blood

Ethics of Prenatal Screening

ACOG Committees on Ethics and Genetics Recommendations

- Genetic testing of the fetus offers opportunities and ethical challenges
- Preconception and prenatal genetic screening and testing recommended for a limited number of severe child-onset diseases
  - Allow for ART to avoid conception of an affected child
  - To detect and treat a fetus with a condition in utero
  - To consider termination of a pregnancy
  - To prepare for the birth of a child with special needs
  - Testing fetus for adult-onset disorders with no known therapeutic or preventive treatment (save prevention by pregnancy termination) should raise caution
  - Consideration should be given to interest individuals may have in terminating a pregnancy that may result in a life that they feel morally obliged or prefer not to bring into the world
  - Referral to support networks, counselors, social workers, or clergy
Summary

• Couples presenting for preconception consultation or obstetrical care require an individualized consultation for prenatal diagnosis
• Controversies continue regarding which option(s) should be offered to low risk patients
• All options should be offered and the patient’s decision should be honored
• More recommendations are likely – need to keep updated

Statistics Review

Describing Data

- **Mean**
  - Average value
- **Median**
  - 50th percentile or quartile
  - Data point “in the middle”
  - ½ observations below, ½ observations above
- **Mode**
  - Most common value/result

P value

- Decision to reject or accept null hypothesis based on the “p” value
- Relative likelihood that observed exposure-disease relationship due to chance alone
- P< 0.05
  - Less than a 5% likelihood that the observed results is due to chance alone
  - Less than a 5% chance that the decision to reject the null hypothesis is an error
  - Probability that a test statistic would be as extreme or more extreme than observed if the null hypothesis were true

Confidence Intervals

- Indication of the variability of a point estimate
  - Can refer to RR or OR
  - 95% often used
- If the 95% confidence limits do not cross one, then the results are statistically significant

Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Screening Test Results</th>
<th>Disease Present</th>
<th>Disease Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>a+c</strong></td>
<td><strong>b+d</strong></td>
<td>a+b+c</td>
</tr>
</tbody>
</table>
Sensitivity and Specificity

- Sensitivity - \( a/a+c \)
  - Proportion of truly diseased persons in the screened population who are identified as diseased by the screening test
- Specificity - \( d/b+d \)
  - Proportion of truly nondiseased persons who are identified as nondiseased by the test

Predictive Value

- Positive predictive value - \( a/a+b \)
  - Probability that a person with a positive test has the condition which the test detects
  - Dependent upon prevalence of disease as well as sensitivity and specificity

- Negative predictive value = \( d/c+d \)
  - Probability that the patient will not have the disease when restricted to all patients who test negative
  - \( \text{NPV} = \frac{TN}{TN + FN} \)
  - Denominator for negative predictive value is number of patients who test negative
  - Positive Predictive Value = True Positives/All Positives
  - Negative Predictive Value = True Negatives/All Negatives

Remember

- The sensitivity and specificity do not depend on the prevalence or pre-test probability of disease
- The predictive value varies with the pre-test probability of disease

Receiver Operator Curve

- Graphs tradeoff between sensitivity and specificity
  - Any increase in sensitivity results in a decrease in specificity
  - Closer curve follows the left-hand border and then the top border of the ROC space, the more accurate the test
  - Closer curve comes to the 45-degree diagonal, the less accurate the test

Statistics - Summary

- Sensitivity - true positives
  - How well test identifies outcome of interest
- Specificity - true negatives
  - How well test identifies those without the outcome
- Positive Predictive Value
  - Chance that a positive test will result in the outcome
- Negative Predictive Value
  - Chance that a negative test will not result in the outcome

- Likelihood Ratio (positive)
  - How much more likely a finding will result in disease than one without the finding
  - \( \frac{TP}{TP+FN} \)
  - \( \text{sensitivity} \)
- Likelihood Ratio (negative)
  - How much more likely absence of finding will result in absence of disease than presence of finding
  - \( \frac{FN}{FP+TN} \)
  - \( \text{false negative rate} \)
  - \( \text{true negative rate} \)
**Introduction**

- Least effective primary screening for trisomy 21
  - Detects 50 to 60 percent of affected fetuses
  - Should not be used in isolation to confirm or exclude trisomy 21

**Introduction**

- Rate of aneuploidy directly related to number of anomalies identified
- Specific anomaly may provide clues to the underlying aneuploidy
- Major structural anomalies vs minor markers
  - Minor marker
    - Structural change that may be transient and when in isolation is thought to have little pathologic significance
    - May be seen more frequently in chromosomally abnormal fetuses
  - Examples

**Major Ultrasound Findings and Associated Risks**

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Aneuploidy Risk</th>
<th>Associated Aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Hygroma</td>
<td>60 to 75 %</td>
<td>45X, 21, 18, XXY</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3-8%</td>
<td>13, 21, Triplody</td>
</tr>
<tr>
<td>Cardiac Defects</td>
<td>5-30%</td>
<td>21,18,13,22,8,9,</td>
</tr>
<tr>
<td>Complete AVSD</td>
<td>40-70%</td>
<td>21</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>30-40%</td>
<td>13,18</td>
</tr>
<tr>
<td>Hydrops</td>
<td>30-80%</td>
<td>13,21,18,45X</td>
</tr>
</tbody>
</table>

**Cystic Hygroma**
Cystic Hygroma

Turner Syndrome
- Cardiac defects
- Cystic hygroma
- Hydrops
- Renal anomalies
- Shortened femur

Hydrops

Hydrocephalus
Hydrocephalus