Case Presentation

• 36 year old female G1 P0
  – Referred to High Risk OB / MFM @ 11 5/7 wks
  – Advanced maternal age

• Family history
  – Non-contributory

• Risks for Trisomy 21 (Down) and Trisomy 18
  – Trisomy 21  1/120
  – Trisomy 18  1/440

• First screen
  – Nuchal translucency and blood work
Amnion

Nuchal Translucency

Dist = 0.083cm

Amnion

Nuchal Translucency

Dist = 0.56cm
Early (1st Trimester) Screening In Preg (ESP)

- Started January 2006
- Provides non-invasive testing in 1st trimester
- No risk of loss with good detection
- Age + Nuchal translucency + maternal blood sample
- 45 minute time clinic slot
  - Genetic counseling
- Re-assess risk

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**SequentialScreen**™ First Trimester
Dawn Syndrome, Trisomy 18

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Referring Physician:</th>
<th>Client #:</th>
<th>904056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-assessment</td>
<td>Genetic counseling:</td>
<td>Genetic</td>
<td>Age: 39.3 yrs</td>
</tr>
<tr>
<td>NT: 1.5 mm</td>
<td>Gev. Age: 13.3 wks</td>
<td>Nuchal</td>
<td>Term: 38.9</td>
</tr>
<tr>
<td>CRL: 72.7 mm</td>
<td>Race: White</td>
<td>Transluc</td>
<td>IDDM: No</td>
</tr>
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<td>Gest. Age: 13.3 wks</td>
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</table>

**INTERPRETATION:** Final result pending second trimester sample
Optimal draw dates: 12/31/2006 - 01/14/2007

<table>
<thead>
<tr>
<th>Screening Risk</th>
<th>Age Related Risk</th>
<th>Risk Cutoff</th>
</tr>
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<tr>
<td>&quot;1:10,000&quot;</td>
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<td>1:95</td>
</tr>
<tr>
<td>&quot;1:10,000&quot;</td>
<td>1:260</td>
<td>1:100</td>
</tr>
</tbody>
</table>

The second trimester specimen may be collected between 15 and 21 weeks GA. This patient's maternal age is noted above. This test does not reliably detect other chromosomal abnormalities.

Risk assessment for open neural tube defects (ONTD) is available in the first trimester.

Maternal serum screening is as some level of imperfect but negative and false positive results and is not a substitute for diagnostic testing. It remains standard of care to offer prenatal diagnosis to women age 35 or older in term.

Please check the patient information used in this risk assessment and call with any questions.
SequentialScreen™ First Trimester
Down Syndrome, Trisomy 18

Patient Name:
Referring Physicians: Elliot H. Phillips, M.D.
Specimen #: 1162455002
Client #: 602025
DOB: 01/02/1971
SSN: 842-88-0292
Date Collected: 12/18/2005
Date Received: 12/20/2005
Lab ID: M264168
Specimen Type: Serum

Pregnancy Information used in risk calculations:
US Date: 12/18/2005
NT: 17 mm
CRL: 57.7 mm
Gest. Age: 12.1 wks

Sonographer:
Elliot Phillips
# of Fectuses: 1
Weight: 145 lbs
Race: White
Age at Term: 25.9
Active: No
CS Fam. Hist: No

Results:
Nuchal Translucency: 11.33 mm
PAPP-A: 1.30 MoM
hCG: 1.04 MoM

INTERPRETATION: Screen Positive - Increased risk of Down Syndrome

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</tr>
</thead>
<tbody>
<tr>
<td>Down Syndrome</td>
<td>1:33</td>
<td>1:50</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1:969</td>
<td>1:100</td>
</tr>
</tbody>
</table>

Genetic counseling, high resolution ultrasound, and/or consideration of a diagnostic procedure are recommended.
Second trimester serum screening for Down syndrome is NOT indicated.
NOTE: The NT measurement, 17 mm, is unusually high. Please call with the correct measurement if this is incorrect.

Risk assessment for open neural tube defects (ONTD) is not available in the first trimester.
Maternal serum screening has some level of inherent false negative and false positive results and is not a substitute for diagnostic testing. It remains standard of care to offer prenatal diagnosis to women age 35 or older at birth.
Please check the patient information used in this risk assessment and call with any corrections.

Cleveland Clinic

Chromosome Analysis

Patient Name:
Referring Physicians: Elliot H. Phillips, M.D.
Specimen #: 1162455002
Client #: 602025
DOB: 01/02/1971
SSN: 842-88-0292
Date Collected: 12/20/2005
Date Received: 12/20/2005
Lab ID: M264168
Specimen Type: AMNIO

Indication: Advanced maternal age

Metaphases Counts: 10
Colony Counts: 15
Rounding Technique: GTW
Metaphases Analyzed: 9
Number of Cultures: 3
Starting Resolution: 400
Metaphases Karyotyped: 3
Substructure: N
Dept. Section: A1
RESULT: 48,XY
Male karyotype

INTERPRETATION:
This analysis shows no evidence of clinically significant numerical or structural chromosome abnormalities.
The standard cytogenetic methodologies utilized in this analysis do not reliably detect small rearrangements and may miss mosaicism, and exclude detect microdeletions.

Cleveland Clinic
**SequentialScreen™ First Trimester**

Down Syndrome, Trisomy 18

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**Patient Information**

- **Patient Name:**
- **Referring Physician:** Elliot H. Phillips, M.D.
- **Specimen #:** 11064354
- **Client #:** 6029296
- **DOB:** Date Collected: 01/11/2007
- **SSN:** Date Received: 01/13/2007
- **Lab ID:** M89493
- **Specimen Type:** Serum

**Pregnancy Information used in risk calculations:**

- **US Date:** 01/11/2007
- **NT:** 4.1 mm
- **CRL:** 5.3 mm
- **Gest. Age:** 11.9 wks
- **Sonographer:** Elliot Phillips
  - # of Fetuses: 1
  - Weight: 147 LB6
  - Age At Term: 43.7
  - IOCM: No
  - Race: White
  - DS Fam. Hx: No

**Results:**

- **Nuchal Translucency:**
  - PAPP-A: 2.93 mMoM
  - hCG: 0.45 mMoM

**INTERPRETATION:** Screen Positive - Increased risk of Down Syndrome and Trisomy 18

**Screening Risk**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Down Syndrome</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:5</td>
<td>1.24</td>
<td>1.50</td>
</tr>
<tr>
<td>1:9</td>
<td>1.97</td>
<td>1.100</td>
</tr>
</tbody>
</table>

Genetic counseling, high resolution ultrasound, and/or consideration of a diagnostic procedure are recommended.

**Risks:**

- **Second trimester serum screening for Down Syndrome is NOT indicated.**
- **Maternal serum screening has some level of inherent false negatives and false-positives.**
- **It is a substitute for diagnostic testing.**

Please check the patient information used in this risk assessment and consult any corrections.

---

**InSight Analy**

**Patient Name:**

- **Referring Physician:** Elliot H. Phillips, M.D.
- **Specimen #:** 11064374
- **Client #:** 6029296
- **DOB:** Date Collected: 01/16/2007
- **SSN:** Date Received: 01/17/2007
- **Lab ID:** 146252
- **Hospital ID:** 17F9026
- **Specimen Type:** CVS

**Indication:** Advanced maternal age

**Results:**

- **Chromosomes 13, 18, 21, X, Y:**
  - Chromosomes 13: 2
  - Chromosomes 18: 2
  - Chromosomes 21: 3
  - Chromosomes X: 1
  - Chromosomes Y: 1

**RESULTS:**

- PATTERN CONSISTENT WITH TRISOMY 21 (DOWN SYNDROME)

**Sex:** Male

**INTERPRETATION:**

**ABNORMAL INSIGHT RESULT**

Interphase fluorescence in situ hybridization showed three chromosome 21 signals, consistent with trisomy 21 (Down syndrome).

**ISCN Nomenclature:**

- 21G1.2 (D11Z3) (11q14-ter) (D11Z3) (11q14-ter)
- 21G1.2 (D11Z3) (11q14-ter) (D11Z3) (11q14-ter)
- 21G1.2 (D11Z3) (11q14-ter) (D11Z3) (11q14-ter)

**RECOMMENDATIONS:**

- Genetic counseling is recommended.
- It is standard of care that no irreversible therapeutic action be initiated on the basis of this abnormal screening result alone. Standard cytogenetic analysis is recommended. If cytogenetic analysis has been ordered from Genzyme Genetics, that result is pending.

**COMMENTS:**

- Detection of all prenatal chromosome abnormalities cannot be detected by InSight, including structural abnormalities, mosaicism, and numerical abnormalities of other chromosomes. This result should be considered preliminary.

**Data:**

- Data from chromosome 21nd prenatal blood samples are limited: however, in over 40,000 informative aortic aneuploidy. Ruff specimens using the Amniotic Fluid probe set shows that 1.5% of results are false positives, false negatives, and incorrect sex determinations have occurred. The presence of maternal blood in the specimen or the presence of oligohydramnios increases the risk of incorrect results due to maternal cell contamination.

- The result is 99.4% sensitive and the negative predictive value of a normal InSight result is 99.9% for the detectable aneuploidies.

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(C) Cleveland Clinic 2012
Nuchal Translucency (NT)

- Is mine normal??
  - Less than 3 mm.
- Can NOT be obtained (7%)  
- Don’t guess at it!!  
- What to Do?  
  - Be patient - 20 minutes!!  
  - Offer serum integrated screening  
  - Proceed to QUAD screen  
  - Re-calculate risk  
- Or bring the patient back !!!

Other Benefits of 1ST Trimester

- Early and accurate dating  
- Early recognition of multiples  
- Can identify increased risk of cardiac anomalies  
- Early recognition of some abnormalities  
- Other?
Cystic Hygroma

- Disorder of lymphatic drainage in the fetus
- 50% normal karyotype
- 46 XO Turner’s Syndrome is common
- Septated cystic hygroma
  - Worse prognosis
- Of all cases, long term prognosis is “normal” in 17%
ACOG Advocates Down’s Screening In All Pregnancies

Multiple studies have shown combined testing with nuchal translucency, free β-human chorionic gonadotropin (free β-HCG), and pregnancy-associated plasma protein A (PAPP-A) is more effective than nuchal translucency alone. The ACOG guidelines also recommend that women found to have increased risk of aneuploidy based on this screening should be offered genetic counseling and the option of chorionic villus sampling (CVS) or second-trimester amniocentesis.

The bulletin will be significant because it will focus obstetricians to pay attention to what has actually been going on for Down’s Screening page 4.

NEW CPT CODE!

Effective January 1st 2007

Beginning January 1, 2007 there will be two new CPT codes available for billing Nuchal Translucency ultrasound measurements:

76813 - Ultrasound, pregnant uterus, real-time with image documentation, first trimester nuchal translucency measurement, transabdominal or transvaginal approach, single or first gestation

76814 - Each additional gestation (to be used in conjunction with 76813 for multiple gestations)
Genetic Counseling

• Non-judgemental, provide accurate data
• Understandable language
• Provide choices
• STILL, can’t do enough!!!
  – Brochure, web site
  – DVD (12 min) with script
  – Group counseling

Never Enough

What About the Neural Tube?

• Ultrasound at 18 - 20 weeks
• Triple test or AFP3
• Quad screen or AFP4
  – 2nd part of Screening

• Alternative
  – ONLY AFP (15 weeks)
  – If combined first screen risk is LOW
  – ie 1/3000-4000
2nd Trimester Screening

- Combined with the first screen (NT + Blood)
  - Sequential screening
    - Results from 1st screen in 4 - 5 days
    - At 15 weeks, quad screen
    - Result again in 4 - 5 days
    - Sensitivity 85%
  - Integrated screening
    - No results from 1st screen
    - At 15 weeks, quad screen
    - Single result at 16 weeks!
    - Higher sensitivity

Patient Satisfaction

- In Cleveland, patients do not want to wait until 15 weeks
  - Want to know immediately
  - They choose the sequential

- Even with higher detection or efficiency
  - Rare to accept integrated screening

- Very Important
- Part of Cleveland Clinic Annual Professional Review
- Private Practice
  - Don’t offer, lose patients
- Give patients a choice
Rural and Remote OB Screen (MFM for RROB)

- Cleveland Clinic Family Health Center in Wooster, OH
  - 65 miles south of Cleveland
  - Monthly onsite
  - Same day telephonic, Virtual Visit

- MFM consult
  - Face to face or remote
  - Contact with patient and local OB provider
  - Ultrasounds, blood work and risk assessment
    - Transmitted to MFM via EMR, reviewed, reported
  - If abnormal, need to be seen at MFM
    - During monthly on site visit or at MFM office
    - Further counseling and testing as appropriate
  - DVD, CCF website and brochures

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Estimates of the First Trimester Risk for Down Syndrome Based on Maternal Age

<table>
<thead>
<tr>
<th>Maternal Age at Delivery</th>
<th>Down Syndrome Age Related Risk</th>
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<tbody>
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<td>16</td>
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<tr>
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<tr>
<td>45</td>
<td>1: 3500</td>
</tr>
</tbody>
</table>

Risk estimates are based on actual maternal age listed in the columns.

Reference: “Revised estimates of the maternal age specific live birth prevalence of Down’s syndrome.”
J. H. Morant, D. S. M. Motion, E. Abberan
Journal of Medical Screening 2002; 9:2-6
Invasive Genetic Testing

- **Chorionic Villus Sampling (CVs)**
  - 10 - 13 weeks
  - Transvaginal or transabdominal
  - Risk of loss 1 / 200-300
  - Results in 3 days with FISH

- **Amniocentesis**
  - 15 - 20 weeks, later
  - Transabdominal
  - Risk of loss 1 / 330-400 ?
  - Results in 3 days with FISH
  - Less mosaicism

- **What’s new?**
  - Maternal blood sampling for fetal cells
  - Fetal chromosome analysis with linear array probes
    - Not very accurate, costly ($1,900)
Prenatal Diagnosis

- Non-judgemental
- Provide accurate data
- Understandable language
- Provide choices
- Still, can’t do enough
- Genetic counseling

Pre Natal Screening

- Enterprise wide standard based on guidelines
  - Fetal sonographic examinations

- Do it early
  - 1st trimester, 10 4/7 – 13 6/7 weeks

  OR

- Do it late
  - 2nd trimester, 18 - 20 weeks

- Both not necessary for the low risk pregnancy
From ACOG Practice Bulletin 88, 2009 with permission
Nuchal Translucency Certifications

- Certification is important
- Society for Maternal Fetal Medicine
  - www.SMFM.org
- The Fetal Medicine Foundation
  - www.fetalmedicine.com
- The Fetal Medicine Foundation US
  - www.fetalmedicineUSA.com