New advances and updates in genetic counseling: Prenatal diagnosis of Down syndrome

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Conflicts of Interest

• I have no conflicts of interest nor any financial relationships with commercial interests to disclose
Goals

• Recognize the role of the genetic counselor when screening for Down syndrome
What is a genetic counselor?

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.
SCREENING & DIAGNOSTIC TESTING OPTIONS
# Screening vs diagnostic

## Screens
- Separates into “low-risk” and “high-risk”
- Offered to all in target population
- Simple, accessible, affordable
- Ideally has low false-negative results (leads to increased false positives)
- Low-risk/no-risk

## Tests
- Establishes diagnosis
- Offered to those at “high-risk” in target population
- Complex, invasive, expensive
- Ideally has no false-positive or false-negative results
- Potential risks
Screening and Diagnostic Testing options for Down syndrome in Pregnancy

**SCREENS**
- First Trimester Screen
- Second Trimester Screen (Triple Screen, Quad Screen, Penta Screen)
- Combined, Integrated, Sequential, (Stepwise, contingent) screens
- Non-Invasive Prenatal Testing (NIPT)/Cell free fetal-DNA
- Ultrasound

**DIAGNOSTIC TESTS**
- CVS (chorionic villus sampling)
- Amniocentesis
Screening
FIRST TRIMESTER SCREEN

• Methodist sends samples to NTD Labs (also done through Genzyme, ARUP, LabCorp, Quest, etc)
  • Valid between 11+1 and 13+6 weeks
  • 2-part test
    • Blood sample
    • Ultrasound (Nasal bone, Nuchal translucency)
  • Assesses chance of baby having Down syndrome, T18/T13
  • Potential incidental findings

<table>
<thead>
<tr>
<th>Screen</th>
<th>Detection</th>
<th>FPR</th>
<th>FPR for 35+</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS w/ NB</td>
<td>96%</td>
<td>2%</td>
<td>No data, but likely around 11%</td>
</tr>
</tbody>
</table>
FIRST TRIMESTER SCREEN

• Typical DS pattern

- AFP
- PAPP-A
- \( \beta hCG \)
- NT

Absent NB
SECOND TRIMESTER SCREEN (QUAD SCREEN)

- Methodist sends quad screens to ARUP
  (also done at Genzyme, NTD Labs, LabCorp, Quest, etc)
- Performed between 14+0 and 24+6
- Measures 4 analytes: AFP, uE3, hCG, DIA
- Assesses chance of baby having Down syndrome, trisomy 18 or open neural tube/ventral wall defect
- Incidental findings

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>DETECTION RATE</th>
<th>FALSE POSITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>60%</td>
<td>3.45%</td>
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<tr>
<td>25</td>
<td>62.2%</td>
<td>3.99%</td>
</tr>
<tr>
<td>30</td>
<td>69.9%</td>
<td>6.21%</td>
</tr>
<tr>
<td>35</td>
<td>82.9%</td>
<td>14.07%</td>
</tr>
<tr>
<td>40</td>
<td>94.1%</td>
<td>32.95%</td>
</tr>
<tr>
<td>45</td>
<td>98.8%</td>
<td>60.04%</td>
</tr>
<tr>
<td>49</td>
<td>99.7%</td>
<td>78.48%</td>
</tr>
</tbody>
</table>

Average detection rate quoted as 81%
Average false positive rate quoted as 4-5%

*Adapted from Benn et al, 2001*
QUAD SCREEN

• Typical DS pattern

AFP
uE3
hCG
DIA
Other Integrated, sequential, (stepwise vs contingent)

- Integrated: FTS + STS THEN results
- Stepwise Sequential: FTS THEN results
  - Positive: Diagnostic test offered
  - Negative: STS, then combined results
- Stepwise Contingent: FTS THEN results
  - Positive: Diagnostic test offered
  - Negative: No further screening
  - Intermediate: STS THEN combine results
NIPT (Non-Invasive Prenatal Testing)

- Also known as cell-free fetal DNA testing
  - High sensitivity and specificity, but **NOT DIAGNOSTIC**
  - Assesses amount of cell-free DNA from mother and baby found in maternal serum
  - Different labs assess different conditions, but ALL assess Down syndrome
    - Most tests ordered through Methodist are Sequenom’s MaterniT21 Plus (or sometimes MaterniTGenome)
    - Natera’s Panorama
    - Progenity’s Verifi
    - Ariosa’s Harmony
    - Counsyl’s Informed Pregnancy Screen
    - LabCorp’s InformaSeq
  - Incidental findings
NIPT

- The cell-free DNA from the pregnancy is largely derived from the placenta, with only a small amount likely from the fetus
  - About 10% of circulating DNA in maternal plasma is from plametal/fetal cells
  - Sometimes, the chromosome make-up of the placenta DIFFERS from the baby’s chromosome make-up
  - cffDNA quickly leaves a woman’s system after delivery

Photo: courtesy of Sequenom
MPGS (massively parallel genomic sequencing) does not differentiate which fragments come from the mother and which from the fetus.

The quantitative over-representation of Trisomy 21 fragments in an affected pregnancy is significant and can be measured with high precision.

Unaffected Fetus

Fetus with Trisomy 21
NIPT

• Insurance companies used to only cover the cost of the test for high risk patients, but this is changing. “High risk” is defined as:
  • Advanced Maternal Age (>35)
  • Family history (previous child with a trisomy)
  • Ultrasound findings
  • Parent with a balanced translocation involving 21
  • Abnormal blood screen (first trimester screen, quad screen, etc.)

• Professional societies now moving toward recommending NIPT be offered to all pregnant patients (NSGC, ACMG) or making all patients aware of the test (ACOG, SMFM)

• Performance: Positive & Negative Predictive Value

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Prevalence</th>
<th>PPV for DS</th>
<th>NPV for DS</th>
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<tbody>
<tr>
<td>20</td>
<td>0.00084</td>
<td>48%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>25</td>
<td>0.00096</td>
<td>51%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>30</td>
<td>0.0014</td>
<td>61%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>35</td>
<td>0.0034</td>
<td>79%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>40</td>
<td>0.0116</td>
<td>93%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>45</td>
<td>0.0454</td>
<td>98%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>49</td>
<td>0.1667</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

*Data derived from NIPT/Cell Free DNA Screening Predictive Value Calculator (created by the National Society of Genetic Counselors and the Perinatal Quality Foundation)
ULTRASOUND

• “Genetic sonogram, anatomy scan, etc.” performed between 18 and 22 weeks
  • May identify markers or birth defects that commonly occur in Down syndrome or other genetic conditions
    • “False positives” occur on 2nd trimester ultrasound, too
      • Heart defect – up to 0.7% of babies
      • Echogenic bowel – up to 1.7% of babies
      • Hydronephrosis – 2-3%
      • Absent nasal bone – varies by ethnicity, 2-9%
      • Short long bones – 6-7% of babies
      • Intracardiac echogenic focus – up to 20% of babies

• LIMITATIONS
  • Quality of images may be poor (ie: baby’s position or gestational age, maternal scar tissue or body habitus, etc)
  • Baby may not have birth defects or markers – depending on the source, 25-50% of babies with Down syndrome are MISSED on ultrasound
Diagnostic Testing
DIAGNOSTIC TESTING

• CVS (chorionic villus sampling)
  • Rarely done (especially locally)
  • Performed around 12 weeks (as early as 10)
  • FISH/chromosome studies on chorionic villi, not directly on the baby
    • Chance of false positive - confined placental mosaicism (1-5% of the time, depending on the study)
    • Risk of miscarriage usually quoted as 1-2%

• Amniocentesis
  • Usually after 15 weeks
  • FISH/chromosome studies done on baby’s cells in the amniotic fluid
    • Over 99% accurate
    • Risk of miscarriage varies by study: historically quoted as about 0.5%
Genetic Counseling for a Diagnosis of Down syndrome
Genetic Counseling for a diagnosis of Down syndrome

• Giving a diagnosis
  • Management for the remainder of pregnancy
  • Discussion of postnatal health and developmental implications of the diagnosis

• Discussing options
• Discussing impact on future reproduction
GIVING A DIAGNOSIS

- Who gives the diagnosis?
- Importance of language
  - Avoid “I’m sorry” or “Bad news”
- No personal opinions
- Match patient’s language

Setting
- Most prefer ASAP
- Dx given to both parents
- In person or arranged call

Information given
- Unbiased, up-to-date and accurate information at the time of diagnosis
GIVING A DIAGNOSIS

• Recent effort to standardize information given to families receiving a diagnosis across the country
  • This booklet is in English (front) and Spanish (back)
GIVING A DIAGNOSIS

• The Nebraska legislature passed LB891 in 2016 to help standardize information given to families in our state.
  • If you give a patient a Down syndrome diagnosis or a “likely” diagnosis, you are **legally required** to give them this information sheet.
  • It can be found on the DHHS website: [http://dhhs.ne.gov/publichealth/Pages/DownSyndrome.aspx](http://dhhs.ne.gov/publichealth/Pages/DownSyndrome.aspx)
  • They have sheets in both English and Spanish
Down Syndrome Information for New and Expectant Parents

This information with web links is available at www.dshs.ne.gov/DownSyndrome

Overview of Down Syndrome
Down syndrome is a genetic condition and developmental disability that is usually caused by an extra copy of the twenty-first chromosome. According to current data about 250,000 people in the United States have Down syndrome. Studies show that about 1 in 800 babies are born with Down syndrome, and the chance of having a baby with the genetic condition increases with the age of the expectant mother. Down syndrome does not typically run in families and is not caused by anything either parent did or did not do.

Advances in medical care and research over the years have given people with Down syndrome better overall health. The traits, medical conditions, and abilities of people with Down syndrome vary widely and cannot be predicted before they are born. They generally have mild to moderate cognitive delays, low muscle tone, and higher chances for a variety of other health issues over their lifespan. Because of advances in health care, education, and public attitudes, common perceptions and future opportunities for people with Down syndrome have improved significantly over the past few decades.

Understanding Down Syndrome
- Children with Down syndrome are more similar to other children than they are different.
- Individuals with Down syndrome have a variable range of intellectual disability from mild to moderate (not typically severe).
- Babies with Down syndrome usually have developmental delays and benefit from early intervention, including physical, occupational, and speech therapy, to help them meet their milestones.
- 80% of babies with this condition have hypotonia or low muscle tone at birth. This usually improves with time, and physical therapy can help.
- 50% of babies with Down syndrome will have one or more health issues: 40–60% of babies with Down syndrome have a heart condition and 12% have a gastrointestinal condition, which may require surgery. The outcomes of these surgical repairs are very good. Referrals to specialists are appropriate for identified complications.
DISCUSSING OPTIONS

• From the “Genetic Counselors’ Scope of Practice” statement:
  • Promote client-specific decision making in an unbiased non-coercive manner that respects the client’s culture, language, traditions, lifestyle, religious beliefs and values.
  • Non-directive / person-centered counseling (based upon Carl Rogers’ theory)

• When a prenatal diagnosis is made:
  • Continue the pregnancy and parent the child
  • Terminate the pregnancy
  • Continue the pregnancy and place the child for adoption
DISCUSSING OPTIONS

• Continue the pregnancy and parent
  • Discuss likely pregnancy prognosis
    • Increased risk of stillbirth, regardless of birth defects
    • Personalize discussion based on what we know about baby
  • Discuss possible health considerations in the newborn period
    • Newborn Screen
    • Hypotonia & feeding problems
• Address family’s questions about health and development over their child’s life
DISCUSSING OPTIONS

• Terminating the pregnancy
  • Not performed locally in a hospital setting
  • Refer to a few different locations, depending upon patient preference/situation
    • Dr. Carhart’s office in Bellevue
    • Planned Parenthood in Omaha or Lincoln
    • Out of state for selective reduction of multiples pregnancy if one affected
    • Out of state for late-term (after 22 weeks)
DISCUSSING OPTIONS

• Adoption
  • Within family
  • Down syndrome specific adoption agencies
DISCUSSING REPRODUCTIVE CONSIDERATIONS

• Different “types” of Down syndrome
  • “Non-hereditary” Trisomy 21
  • Robertsonian Translocation
  • Mosaic Down syndrome
“Non-hereditary” Trisomy 21
Robertsonian translocation between 14 and 21
Goals revisited

- Recognize the role of the genetic counselor when screening for Down syndrome
Questions?

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