Prenatal and Postnatal Diagnoses of Down Syndrome:
Delivering Results in our New Age of Genetic Testing

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Disclosure Statement

• I volunteer in a non-paid capacity to non-profits: Massachusetts Down Syndrome Congress Band of Angels Foundation National Center for Prenatal and Postnatal Down Syndrome Diagnoses Resources
• I have a sister with Down syndrome

Activity Objectives

Describe the current prenatal testing on Down syndrome available and soon to be available to expectant parents.

Define the components of effective communication between healthcare providers and parents when receiving a prenatal or postnatal diagnosis of Down syndrome.

Identify the resources available to health care providers wanting to improve their communication skills in this arena.

Down Syndrome

• Trisomy, chromosome 21
• Translocation Down syndrome
• Mosaic Down syndrome
• ~ 1 / 792 liveborns
• About 210,000 families in U.S.
• About 5,000 children born / yr

Prenatal Testing for Down Syndrome

Prenatal Screening
- Triple Screen (βhCG, AFP, uE3)
- Quadruple Screen (βhCG, AFP, uE3, Inhibin-A)
- First-trimester Combined (Ultrasound, βhCG, PAPP-A)
- Integrative Screen
- Sequential Screen

Prenatal Diagnosis
- Chorionic Villus Sampling: ~99.9% (10-14 weeks, ≤ 1% spontaneous)
- Amniocentesis: ~99.9% (after 15th week, ≤ 0.25% spontaneous)

~2% (~72%)

References
- NEJM (2005), 353:2001-2011
- APLM (2013), 137:921-926
Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood

DNA sequencing of maternal plasma to detect Down syndrome: An international clinical validation study

Shotgun Sequencing: cfDNA

- **Risk**: A simple blood test, no risk to the fetus
- **Accuracy**: Varies per condition
- **Timing**: Performed as early as 10 weeks of gestation
- **Availability**: Now multiple companies in U.S. and world
- **Cost**: Dependent, in part, on insurance coverage
- **Turn-around time**: ~10 days
- **Advantages**: Will pick up trisomy 21, translocation Down syndrome, and high-level mosaic Down syndrome
- **Disadvantage**: Doesn’t distinguish types of Down syndrome
Other NIPS Limitations

- Unbalanced translocations from non-tested chromosomes, microduplications, microdeletions not validated
- Not able to distinguish specific forms of aneuploidy
- Does not screen for single-gene mutations
- Uninformative test results could lead to a delay in diagnosis or eliminate the availability of information for risk assessment
- Must keep timing of results in mind
- Does not screen for neural tube defects
- Does not replace the utility of first-trimester ultrasound
- Limited data on twins and higher-order pregnancies
- No role in predicting late-term pregnancy complications

Many Professional Position Statements

Prenatal Testing for Down Syndrome

Prenatal Screening

- Triple Screen: (βhCG, AFP, uE3)
- Quadruple Screen: (βhCG, AFP, uE3, inhibin-A)
- First-trimester Combined: (Ultrasound, βhCG, PAPP-A)
- Integrative Screen: Sequential Screen: Independent
- Sequential Contingent

Prenatal Diagnosis

- Chorionic Villus Sampling: ~99.9% (10-14 weeks, ≤ 1% spontaneous terminations)
- Amniocentesis: ~99.9% (after 15th week, ≤ 0.25% spontaneous terminations)
- NIPS: ~99% ~20%

“High-risk” Expectant Mothers

Box 1. Indications for Considering the Use of Cell-Free Fetal DNA
- Maternal age ≥ 35 years or older
- Fetal ultrasound findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test result for aneuploidy, including first-trimester, repeat, or integrated screen, or a quad screen
- Parental balanced Robertsonian translocation with increased risk of fetal trisomy T or trisomy D

Many Professional Position Statements

Prenatal Testing for Down Syndrome

Prenatal Screening

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Prenatal Diagnosis

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- NIPS: ~99% ~20%
No NIPS Lab Fully Adherent to ACMG

For the latest version of our analyses to adherence to ACMG recommendations:
https://prenatalinformation.org/table/

Termination Rates High After CVS or Amnio

U.S. with no selective terminations for DS
Regional Differences

<table>
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<tr>
<th>Region</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Northeast</td>
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</tr>
<tr>
<td>West</td>
<td>27%</td>
</tr>
<tr>
<td>Midwest</td>
<td>27%</td>
</tr>
<tr>
<td>South</td>
<td>23%</td>
</tr>
<tr>
<td>Hawaii</td>
<td>62%</td>
</tr>
</tbody>
</table>

Racial/Ethnic Differences

- Asian/Pacific Islanders: 61%
- Non-Hispanic whites: 39%
- Non-Hispanic blacks: 27%
- Hispanics: 18%
- American Indians: 16%

U.S. Reduction Percentages for Down Syndrome

Women Who Chose to Terminate

- In Netherlands, women recruited prospectively before or during hospital admission for termination ≤ 24 wks
- 4 months after termination: 71 women completed survey (77% response rate)
  - Mean age: 38 years, not religious (44%), Catholic (27%), college (47%)
- 97% of women described pregnancy as formerly wanted

Motivations for Termination

- 92%: I believed the child would never be able to function independently
- 90%: I considered the abnormality too severe
- 83%: I considered the burden for the child itself too heavy
- 82%: I worried about the care of the child after my/our death
- 78%: I considered the uncertainty about the consequences of the abnormality too high
- 73%: I considered the burden too heavy for my other children

Family Attitudes about Down Syndrome

Sent surveys to 4,924 families
- GA, MA, CO, NC, TX, and CA
- 2,044 parents/guardians from 1,407 households (29% response)
- 822 brothers/sisters, ages 9 – 62 (19% response)
- 284 people with Down syndrome, ages 12 – 52 (17% response)
- 3,150 TOTAL family members

Diversity among Hispanic origin and religion

Parents’ Attitudes about Down Syndrome

Sent surveys to 4,924 families
- 2,044 parents/guardians from 1,407 households (29% response)
- 99% love their son/daughter with Down syndrome
- 97% are proud of son/daughter with Down syndrome
- 79% felt outlook on life was more positive because of son/daughter
- 5% felt embarrassed, in general, by son/daughter with Down syndrome
- 4% regret having their son/daughter with Down syndrome
Siblings’ Attitudes about Down Syndrome

822 brothers/sisters, ages 9 – 62 (19% response)
- 97% ages 9-11, love their brother/sister with DS
- 94% ages >12, are proud of brothers/sister with Down syndrome
- 88% ages >12, felt they were better people because of sib
- 7% ages >12, felt embarrassed, in general, by sib with Down syndrome
- 4% ages >12, wish they could trade in sib with Down syndrome

Attitudes from People with Down Syndrome

284 people with Down syndrome, ages 12 – 52 (17% response)
- 99% happy with their lives
- 99% said that they love their families
- 97% liked who they are
- 96% liked how they look
- 86% indicated they could make friends easily
- 4% expressed sadness about their life

Expectant mothers making “informed decisions”?

- non-directive counseling
- accurate information
- up-to-date information
- balanced information

What Change is Needed?

1. Develop standardized practice guidelines on how to deliver prenatal diagnosis
2. Train healthcare professionals of today and tomorrow to deliver complete, consistent, nonjudgmental, noncoercive information.
3. Develop consistent, gold-standard information about prenatal testing
Prenatal Recommendations

1. Results of prenatal screening should be clearly explained as a risk assessment, not a "positive" or "negative" result.
2. Prior to CVS or amnio, discuss all reasons for prenatal diagnosis.
3. Healthcare professional(s) most knowledgeable about DS should deliver the news—most likely OB and genetic professional together.
4. If in-person visit not possible, news should be delivered over phone at pre-arranged time.
5. Answer: What is DS? What causes the condition?
7. Use non-directive language.
8. Offer up-to-date materials or bibliography.
9. Make follow-up appts, including specialists, as needed.

Postnatal Recommendations

1. OBs and pediatricians should coordinate their messaging. Ideally, they would meet together with parent(s) to deliver the news.
2. Inform parents of suspicion for DS immediately, even if diagnosis is not yet confirmed.
3. Deliver diagnosis in a private room.
4. Parents should be informed together.
5. The infant with DS should be present and referred to by name.
6. Begin conversation with positive words, such as congratulations on the birth of the child.
7. Provide accurate, up-to-date information.
8. Limit discussions to medical conditions that the infant has or might develop within 1 year of age.
9. Connect to local parent support groups and/or other families.
10. Follow-up appointments should be arranged, as desired and needed.

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Training Modules

• Brighter Tomorrows is an interactive online simulation that asks medical professionals to view virtual patient-doctor sessions and provide responses to questions and situations
• Developed in collaboration between physicians and parents
• In tests with 30 residents in OB/GYN and Pediatrics showed significant improvement in knowledge and level of comfort
• Access to online simulation: www.brighter-tomorrows.org.

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Pre-Test NIPS Pamphlet

Available in print, online, & in Spanish: http://www.lettercase.org/prenataltesting
Recognized by the National Society for Genetics Counselors for input by Genetic Counselors

Prenatal, Pre-Decision Info: Down syndrome

This booklet was prepared with assistance from the Down Syndrome Consensus Group which includes representatives of:
- The National Society of Genetic Counselors
- The American College of Medical Genetics and Genomics
- The American College of Obstetricians and Gynecologists
- American Academy of Pediatrics
- Association of University Centers on Disabilities
- Down Syndrome Education International
- The National Down Syndrome Society
- Down Syndrome Diagnosis Network

Prenatal, Pre-Decision Information

http://www.understandingdownsyndrome.org/

Prenatal, Post-Decision to Continue

www.downsyndromepregnancy.org
Prenatally and Postnatally Diagnosed Condition Awareness Act

Purpose: to ensure that more accurate, up-to-date information is given to mothers who have fetuses or children with Down syndrome

October 8, 2008: President Bush signed into law (Public Law 110-374)

Funding Opportunities: Once funds are available, hospital and departments could apply for competitive grants

State version of the law:
MA, MO, VA, KY, MD, DE, OH, PA, LA, FL, IL, MN, TX, IN

MA Dept. of Public Health

Massachusetts Down Syndrome Congress

Parents’ First Call Program is a group of trained mothers and fathers available 24/7 for new and expectant parents

• Can match per religious, race, or language preference
• Can talk by phone, e-mail, or in-person
• Confidential discussions
• Free information given, different for prenatal and postnatal consultations

www.mdsc.org

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