PRENATAL GENETIC TESTING

What midwives and clients need to know
Objectives

- Discuss prenatal genetic testing options
  - Differentiate between screening and diagnostic testing
  - Review strengths and limitations
  - Address misleading advertising claims
- List indications for referring to genetic counseling
- Describe the clinical utility of genetic information for pregnancy planning and improving birth outcomes
- Describe approaches for accessing information about cost and insurance coverage of testing and counseling
- List and discuss key themes that emerged from a qualitative study on genetic counseling and CPMs
Types of Screening Tests

• First trimester screening
  • MSS (maternal serum screening)
  • MSS + NT (nuchal translucency u/s)
• Second trimester screening
  • MSS
    • Triple screen
    • Quad screen
    • Fetal anatomic survey
• NIPT (1st or 2nd trimester)
• Carrier screening for parents
Conditions Screened

- Common Aneuploidies (extra or missing chromosomes)
  - Trisomy 21 (Down Syndrome)
  - Trisomy 18 (Edward syndrome)
  - Trisomy 13 (Patau syndrome)
  - Monosomy X (Turner syndrome)
  - Other
First Trimester Screening: MSS

• Blood test
• Usually done betw. ~10w3d - 13w6d (most accurate betw. 11-12 wks)
• Provides risk assessment for T21 and T18
  • Reported as risk of 1 in X or 1:X
• PAPP-A
  • Pregnancy associated plasma protein-A
  • Produced by placenta
  • Significantly decreased in Tri21
  • Somewhat decreased in Tri18
• b-hCG (or hCG)
  • Elevated (doubled) in T21
  • Decreased in T18
Nuchal Translucency (NT)

- Measurement of the fluid filled space at the back of the neck between the soft tissue and the skin
- Needs to be measured by an NT-certified sonographer
- Increased NT differential includes:
  - Aneuploidy
    - Down syndrome
    - Turner syndrome
    - Others
  - Structural heart defect
    - Fetal echocardiogram is recommended
  - Genetic syndromes
    - Noonan syndrome, etc
    - There is no way to test for all of these during a pregnancy
  - Adverse outcome
NT continued
Second Trimester MSS

- Blood test
- Usually done betw. ~14-22 wks (most accurate betw. 15-18 wks)
- Various combinations w/1st trimester screen: sequential, integrated, contingency can increase sensitivity and specificity
- Quad screen: 4 analytes screened
  - AFP
  - hCG
  - uE3
  - Inhibin A
- Provides risk assessment for open neural tube defects (ONTD), abdominal wall defects, T21, T18
  - 80% detection rate (w/ 5% FPR)*
- First trimester screen does not screen for ONTDs, so may get an AFP in addition to FTS
  - Potentially actionable
  - Should be delivered with neurosurgeon ready to close the opening → reduces likelihood of paralysis and incontinence
## Background about the analytes

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Description</th>
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| **Alpha-Fetoprotein (AFP)**   | • Synthesized in the liver, then excreted by the kidneys  
                                • Levels peak in the 3rd trimester  
                                • Can detect at ~80% of spina bifida and ~95% of anencephaly |
| **Human Chorionic Gonadotropin (hCG)** | • Produced by placenta  
                                • Levels peak at 8 wks, decrease steadily until 20 wks, then plateau |
| **Unconjugated Estriol (uE3)** | • Produced by the placenta  
                                • Involved in the beginning of the cholesterol pathway  
                                • Increases steadily throughout pregnancy |
| **Dimeric Inhibin-A**          | • Produced mostly by placenta  
                                • Remains constant between 10-25 wks gestation |
Analyte levels

Typical levels over time

Levels w/ ONTD, Tri21, T18

<table>
<thead>
<tr>
<th>Level of Analytes</th>
<th>AFP</th>
<th>hCG</th>
<th>uE3</th>
<th>Inhibin-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTD</td>
<td>↑↑</td>
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</tr>
<tr>
<td>Tri 21</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Tri 18</td>
<td>↓</td>
<td>↓</td>
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</tr>
</tbody>
</table>
### MSS results can reveal other information

<table>
<thead>
<tr>
<th>Condition</th>
<th>Biological Changes</th>
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</thead>
<tbody>
<tr>
<td>Twins</td>
<td>2x for all</td>
</tr>
<tr>
<td>Fetal demise:</td>
<td>↓ hCG, ↓ uE3</td>
</tr>
<tr>
<td>Recent</td>
<td>↑ AFP</td>
</tr>
<tr>
<td>Older</td>
<td>↓ AFP</td>
</tr>
<tr>
<td>Triploidy (3 of each chromosome → 69 total)</td>
<td></td>
</tr>
<tr>
<td>Diandry (single oocyte fertilized by diploid sperm)</td>
<td>↑ AFP, ↑ uE3</td>
</tr>
<tr>
<td>Digyny (diploid oocyte fertilized by single sperm)</td>
<td>↑↑ hCG, ↑↑ hCG</td>
</tr>
<tr>
<td>Smith Lemli Opitz</td>
<td>↓↓↓ uE3</td>
</tr>
<tr>
<td>X-linked Ichthyosis</td>
<td>↓↓↓ uE3</td>
</tr>
<tr>
<td>Congenital Finnish Nephrosis</td>
<td>↑↑↑ AFP</td>
</tr>
</tbody>
</table>
cfDNA/NIPT/NIPS

• What’s in a name?
  • cfDNA
  • NIPT vs NIPS

• Blood test
  • Usually after 10 wks
  • Screens for common aneuploidies (T21, T18, T13)
  • Sex of the baby
  • Some labs offer other conditions: sex chromosome aneuploidies (e.g. Turner syndrome, Klinefelter syndrome), microdeletions (e.g. DiGeorge syndrome (22q11), Prader Willi syndrome, Angelman syndrome)

• Whole genome?
  • TAT: 8-10 days, varies by lab
cfDNA technology

• Different companies use different technologies and algorithms
  • Massively parallel sequencing (MPS)
  • Targeted sequencing
  • Single nucleotide polymorphisms (SNPs)
• Important to understand that…
  • All approaches look at both maternal and fetal DNA fragments
    • Abnormal result could be maternal or fetal in origin
  • “Fetal” DNA comes primarily from the placenta (trophoblast cells)
Limitations of cfDNA screening

- Does not test for every condition
  - Not a test for all or even most anomalies
  - Does not screen for ONTDs
- No call results (~1-8%)
  - Due to low fetal fraction (percentage of fetal DNA in maternal blood stream)
- Possible causes:
  - Fetal aneuploidy
  - High maternal weight
  - Early gestational age
  - Maternal condition (e.g. lupus)
  - Pharmaceutical agents (e.g. low molecular weight heparin)
- Repeating test may not (40-50% of the time) yield a result
- Twins
  - Increased no call rate and false negative rate
Limitations continued

• Screening vs diagnostic
  • False positives and false negatives
  • Should not be used as the basis for decisions to terminate pregnancy w/o confirmation by diagnostic test (CVS or amniocentesis)

• Confusing/misleading descriptions of accuracy
  • Companies often report tests as >99% accurate, with a <.1% false positive rate
  • Sounds almost diagnostic, but what does this really mean?
Notice that:

- It’s a screening test but says “Positive for Trisomy 21”
- Some company reports say “Screen Positive” or give a risk as “1 in x”
- Performance measures reported are sensitivity and specificity
  - Both very high (>99%) for Tri21
- Sensitivity: true positives/ all actual positives
  - 99% sensitivity means that for every 100 cases, 99 tested positive and 1 tested negative (but shouldn’t have)
  - 99.9% specificity means that for every 1000 who do not have the condition, 999 tested negative and 1 tested positive (but shouldn’t have)
Is it sufficient to report only sensitivity and specificity?

• What questions are not answered with these statistical measures?
  1. If my pregnancy tested positive for trisomy 18, what is the chance the fetus is affected with trisomy 18? (Positive Predictive Value)
     • PPV: true positive/all positive tests (true + and false +)
  2. If my pregnancy tested negative for trisomy 18, what is the chance the fetus is truly unaffected? (Negative Predictive Value)
     • NPV: true negative/ all negative tests (true – and false – )

• Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are population dependent statistical measures
  • To answer questions 1 and 2 above, we need to know the chance that a pregnancy is affected in the first place
    • Chance for aneuploidy goes up with age of mother
      • PPV for a 25 year old woman w/ positive screen for Tri18: 13 %
      • PPV for a 40-year-old woman w/ positive screen for Tri18: 68%
Population-dependence of PPV and NPV

Fig. 1. The importance of population prevalence on the predictive value for a screening test: an illustration with cell-free DNA.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
Measures of Test Validity

1. **Sensitivity**: probability that a woman carrying an abnormal pregnancy will **test** + (i.e. true positive)

2. **Specificity**: probability that a woman carrying a normal pregnancy will **test** – (i.e. true negative)

3. **Positive Predictive Value (PPV)**: if someone has a + test, what is the probability that their pregnancy actually has the abnormality? (opposite of false positive rate)

4. **Negative Predictive Value (NPV)**: if someone has a - test, what is the probability that their pregnancy does **not** have the abnormality? (opposite of false negative rate)
More on False Positives

• False positives due to other biological explanations
  • Positive for a different condition
  • Maternal malignancy (e.g. maternal tumor w/ increased chromosome 13)
  • Vanishing twin (up to 8 wks post demise)
• Mosaicism
  • Confined placental mosaicism
  • Low level fetal mosaicism
  • Maternal mosaicism
Cost and Insurance coverage for cfDNA

- Cost varies by insurance company but increasingly covered for women of all ages
  - Changing rapidly, so check back often
- Many labs will offer lower rates for those without coverage
  - Often <$200
- Call the company to find out details
Types of Diagnostic Testing

• Diagnostic Testing Types
  • Chorionic villus sampling (CVS)
  • Amniocentesis

• Karyotype

• Other technologies zoom in to show missing or extra genetic material
  • FISH (rapid interphase fluorescence in situ hybridization)
    • Screening (must be confirmed)
    • 2-3 days (cultured or uncultured cells)
    • Aneuploidy, microdeletions, microduplications
  • Microarray
  • Other molecular testing
Diagnostic Testing Indications

• Indications
  • f/u after high risk screening result or abn. u/s
  • Parents known carriers of a condition, e.g. sickle cell, cystic fibrosis
  • Parent known translocation carrier
  • Previous pregnancy w/aneuploidy
  • Woman prefers diagnostic test to screening tests

• Turn around time:
  • Karyotype: 7-14 days (requires cultures cells)
  • FISH: 2-3 days (does not require cultured cells, but is considered a screening test and requires confirmation)
  • Chromosomal microarray: 3-7 days (can be done on uncultured cells)
CVS

- Timing: 10-13w6d
- Method: Transcervical or transabdominal aspiration of chorionic villi from developing placenta
- Accuracy: 98-99%
- Detects:
  - Chromosomes
  - Sex
  - Extra or missing chromosomes
  - Missing or extra pieces of chromosomes, rearrangements (part of one chromosome stuck to another)
CVS Risks/Limitations

• Miscarriage
  • Historically quoted as 1% above background rate of 3-5%
  • Loss rate has decreased over time
    • 2015 meta-analysis: .22% (1 in 455)

• Limb-reduction defects
  • Early studies showed risk
  • Later studies suggest risk is related to CVS before 10 wks
  • World Health Organization: rate of limb-reduction defects after CVS not significantly greater than in general population

• Other complications
  • Vaginal spotting or bleeding
  • culture failure, amniotic fluid leakage, infection: <.5%
  • Reasons for incorrect results: maternal cell contamination (analyzing mom’s cells); mosaicism (<1% of the time) → f/u w/amnio
Amniocentesis

• Timing: after 15 weeks
• Method: u/s guided insertion of a needle through mother’s uterus into the amniotic space to remove fluid
  • Karyotype, FISH, microarray
  • to detect extra or missing chromosomes or extra or missing pieces of genetic material
• Accuracy: 99.8-99.9%
• Non-genetic indications: in addition to those listed earlier, (high risk screening, known condition, etc.): ONTDs, fetal lung maturity, intrauterine infections (cytomegalovirus, toxoplasmosis), injection of fluid in case of severe oligohydramnios
Amnio: Risks and Limitations

• Miscarriage
  • Historically quoted at .5% (1 in 200)
  • Currently estimated at .1-.3 % (1 in 1000 to 1 in 300) in experienced centers

• Other complications
  • Vaginal spotting or amniotic fluid leakage (1-2% of cases)
  • Needle injuries to fetus have been reported but are rare when performed under continuous u/s guidance
  • Amniotic fluid cell culture failure (.1% of samples)
Clinical Utility

• Is there more than just the question of continuing the pregnancy when aneuploidy or an anomaly has been detected?
  • Abdominal wall defects
  • Neural tube defects
  • Cardiac defects
  • Antepartum testing
  • Emotional preparedness
  • Support services/advocacy organizations
  • Place of birth
Reasons for Referral to Genetic Counseling

- Want to better understand the strengths and limitations of prenatal testing and screening options/want help weighing pros and cons
- Increased chance of aneuploidy
  - Chance increases with mother’s age
- Prenatal screening showed increase risk of genetic condition or congenital anomaly
- Diagnostic testing showed chromosome or genetic condition
- Parents have a health concern or genetic condition and want to know chances that child has the same condition
- 3+ unexplained miscarriages
- Stillbirth or baby who died shortly after birth
- Exposure during pregnancy (medication, drug, alcohol, infection, radiation) and want to understand risks
- Parents want to discuss chance of genetic conditions based on ancestry and possibly have carrier testing
- Partners are blood relatives and want to discuss chance of recessive condition
Who are Genetic Counselors?

- Master’s level professionals trained in genetics and counseling
- Emphasis on explaining complex genetic information in simple, clear ways
- Trained to be “non-directive”
  - Present information and let client choose without influence
- Connect family with resources, such as advocacy organizations
  - E.g. Down Syndrome Congress has “First Call” services, where mothers to be can talk to parents with children who have DS
- Session commonly includes:
  - Comprehensive 3-generation family history
  - Discussion of testing options includes
    - Strengths and limitations of tests
    - Client’s priorities and values
Family history

• Known or suspected genetic condition
  • Certain combinations of congenital anomalies may indicate genetic condition
    • e.g. cleft palate with Tetralogy of Fallot (TOF) could indicate DiGeorge syndrome

• Multiple family members with the same or related condition
  • Conditions may manifest differently and at different ages in different family members

• Stillbirth or baby who died shortly after birth

• Intellectual disability (ID)
  • Boy w/ID and/or autism + mom or female relative with premature ovarian insufficiency + older male relative w/ ataxia (loss of movement control) with could indicate Fragile X syndrome
  • Down syndrome may be sporadic or may indicate parent with a balanced translocation

• Dx an earlier age than expected
  • E.g. breast cancer <50
Family history

• Helpful for identifying referrals
• What to ask
  • 3 generations
  • Any known or suspected genetic conditions?
    • Similar health conditions in the family?
  • Multiple miscarriages (esp. 3+)
  • Intellectual disability
  • Congenital anomalies (e.g. cleft palate, hole in the heart)
  • Women who went through menopause < 40 yrs (screening for Fragile X carrier)
  • Stillbirth or baby who died shortly after birth
  • Cancers before age 50
  • Ancestry
  • Chance that parents are blood relatives (consanguinity)
Carrier Screening

- Members of certain groups are more likely to be carriers of certain recessive conditions
  - Ancestry-based screening?
  - Expanded carrier screening panels
  - May not be a family history of these conditions
- Sensitivity of genetic tests is dependent on often dependent on ancestry; they will not pick up 100% of carriers
  - Cystic fibrosis: Caucasian and Eastern European Jewish ancestry
  - Tay Sachs: Eastern European Jewish, French Canadian, Cajun ancestry
  - Spinal Muscular Atrophy: all groups
  - Fragile X: all groups
  - Sickle cell anemia and thalasemias: African, Asian, Mediterranean, Middle Eastern
    - Low MCV and no iron deficiency
Family history tools

• http://www.talkhealthhistory.org/
• https://familyhistory.hhs.gov/fhh-web/home.action
• http://www.marchofdimes.com/Your_family_health_historypreconceptionprenatal.pdf
• http://www.geneticalliance.org/ksc_assets/tools/book1ga_ll022309.pdf
PERCEPTIONS AND ATTITUDES TOWARD GENETIC COUNSELORS AND GENETIC TESTING AMONG CERTIFIED PROFESSIONAL MIDWIVES IN VERMONT: A QUALITATIVE STUDY

For submission to *Journal of Midwifery and Women’s Health*
Jazmine Gabriel, Melissa Cheyney and Paul Burcher
Study Purpose

- The purpose of this study was to use open-ended, semi-structured interviews to examine the perspectives of Certified Professional Midwives toward genetic counselors and genetic counseling services.
Methodology

• Qualitative methodology
  • Sampling: targeted, state-specific, voluntary, theoretical
    • N=10
    • Contextualize findings within specific politico-legal and cultural setting

• Modified-grounded theory
  • Consensus coding of dominant themes
  • Concept saturation: no new themes emerge with subsequent interviews
### Results

<table>
<thead>
<tr>
<th>Analysis Level</th>
<th>Theme</th>
<th>Subthemes</th>
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<tbody>
<tr>
<td><strong>Systems Level</strong></td>
<td>Access to genetic testing</td>
<td>Confusion about cost, insurance, and referral</td>
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<tr>
<td><strong>Practice-level</strong></td>
<td>How information about genetic testing is presented</td>
<td>Nondirective counseling with respect to genetic testing</td>
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<tr>
<td></td>
<td></td>
<td>CPM awareness of limits of their own knowledge</td>
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<tr>
<td></td>
<td></td>
<td>Desire for more information</td>
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<tr>
<td><strong>Client-level</strong></td>
<td>Concerns about genetic testing: Is it worth it?</td>
<td>Fear of Cost</td>
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<td>Fear of false positives</td>
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<td></td>
<td></td>
<td>Fear of undermining women’s confidence with negative language</td>
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Theme 1: Access to genetic testing:
Confusion about cost, insurance, referral process

• “I’ve been working in this community for 23 years and still, whenever I call up the UVM [University of Vermont Medical Center] to find out the fees, how much it will cost a client, I can’t find that out.”

• “[U]p at UVM, whatever lab they use will cap it at $200, which basically means it would not be prohibitive for most of my clients. And then they also do have forgiveness—if someone were uninsured, they could go to UVM to get assistance. So I feel like financially there’s not really a barrier.”
It’s frustrating. If there were health clinics where they could go—Maybe there is something out there, but I just don’t know where it would be. I mean, genetic counseling—what do they do out there? Blood work? And amniocentesis? Who knows. I mean who’s going to do that for free? Nobody.

**Theme 1: Confusion about cost, insurance, referral process**

- Insider-outsider dimension
  - Clients can’t afford it
  - Must go through OB to get to GC
"...the fact that I can order stuff, the fact that I know I can call him, the fact that he sends me a report, that I can get the lab results straight from him—all those things make him feel very approachable and like it is collaborative care and makes me want to reach out to him.

**Theme 1: Confusion about Cost, Insurance, Referral Process**

- Overcoming home-hospital divide
  - Vermont as model of collaborative/integrative care
Theme 2: Practice-level patterns: Non-directive counseling and the need for more information

- Subthemes:
  - A) Nondirective counseling
    - Know your options even if plan to decline
    - Insider-outside dimension
  - B) Awareness of knowledge limitations
    - Comfort with limits
    - Frustrated
  - C) Desire for more information
Non-directiveness

Responses to client skepticism:

• “A lot of clients don’t know—I don’t think they know—how to think about genetic counseling when they come into care. They just say, ‘I wouldn’t terminate my pregnancy, so I’m not doing any.’ And I say, ‘Well, it’s not just about that.’”

• “Sometimes it’s not always easy, but I can sense if someone is leaning towards wanting to know about this stuff, it’s going to come out, and I’m going to know it and we’re going to talk about it…. people who choose homebirth are generally not the kind of people who are going to go down that road, at least in my opinion, of genetic testing.”
Awareness of knowledge limitations and the need for more information

• “I feel like it’s really valuable to refer out for genetic counseling. I’m not a genetic counselor. It’s not my specialty. It’s someone else’s.”
  • Comfort with limitations of her knowledge

• “I don’t know all that’s being offered these days in the hospital setting. I don’t work in that setting at all. So—how can I educate somebody about things I don’t know about?”
  • Frustrated with her lack of knowledge/powerlessness to address it

• “I’m sure you know more about genetics than I will ever know, but I am working with folks daily who need to use that information.”
  • Frustrated that information is not crossing the home-hospital divide
Theme 3: Midwives’ client-level concerns about the value of genetic testing

- Subthemes:
  - A) Fear of costs
  - B) Fear of false positives
  - C) Concerns about undermining women’s confidence
Fear of false positives

- My only reservation is that testing is not 100%. There are small percentages where it can do more damage either way—false positives or false negatives, false hope and false fear, are the main issue. And what can you really do with this information? Knowing you have a problem with your baby often does not lead to a solution or a cure.

- A lot of my clients definitely don’t want to do the first and second trimester screens. If they were the option, they would say, “No, I’m not doing any.’ But it’s this new screening that people get all fired up about.”

- Again now, most of my clients still aren’t doing it, and I don’t try to push anybody, but I am pretty- It’s just to me it’s a totally different world. A different world. I feel like I can (pause) not recommend it—but I can explain it and support it in a way I couldn’t with previous testing methods.
Concerns about language

• “I often hesitate to give them something that defines them as problematic simply because of their age…Depending on the situation, I will give them information about the risks of being a first time mom, an elderly prima, they call them, but the more I do births, the less and less I want to burden them with that because sometimes I think it undermines their confidence in themselves.”

• “And you know, it carries all the way to through the labor itself, and then into parenting even. But to lose confidence in the ability of their body to do this function that they were designed to do…and then to have all these people always doubting, or you know, planting the seeds of doubt because of their age. I just find it frustrating.”

• “Even if someone is high risk—and this isn’t just genetic counseling—but you know ‘advanced maternal age’ is a term that’s not very body positive and friendly.”
Discussion

• Home-hospital divide has impacts on collaborative care of all kinds, but also specifically on access to genetics services
  • Many clients plan to decline all testing, but many were excited about cfDNA
  • Important not to make assumptions about all choices based on the choice to have a home birth
• Education and knowledge-level of CPMs
  • Variable knowledge levels
  • Self-awareness: All wanted more information
• Concerns about genetic testing and lessons for other providers
  • Information not necessarily neutral
  • Concerns about impact on wellbeing and confidence of the pregnant person
Resources

• PPV Calculator: https://www.perinatalquality.org/vendors/nsgc/nipt/
• https://prenatalinformation.org/resources/
• https://ghr.nlm.nih.gov/

Questions?
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