Medical Assistance Program Oversight Council (MAPOC)
Women and Children’s Health Committee

Improving Access to Non-Invasive Prenatal Screening for Connecticut Medicaid Beneficiaries

Monday, August 10, 2020
Presenters:

• Ashley Svenson, MS, CGC: Employee of Myriad Genetics Laboratories, Inc.

• Julie Pawelczyk: Coalition for Access to Prenatal Screening

• Amanda Vitale: Coalition for Access to Prenatal Screening
Choosing the Right Screening Test

Impact of false negative results:
• Missed diagnosis (unprepared for birth of baby with special medical needs)
• Missed opportunity for specialized care
• Provider: medical-legal risk

Impact of false positives results:
• Anxiety
• Wait to see specialist (discussion of results, diagnostic testing)
• Unnecessary invasive procedures (risk, cost)
• Provider: office resources (time counseling/procedures, cost to healthcare system)

Goal: Provide patients a screening option with a high sensitivity/specificity; ensure all patients have equal access, i.e. one standard of care for all.
Screening Through the Years

1970: Alpha-fetoprotein (AFP) for neural tube defect
1980: AFP for Trisomy 21
1990: Triple screen for Trisomy 18
2000: Imaging matures: NT Screening
2010: Integrated screen
2020: Guidelines recommend standard offering of NIPS for all pregnancies

ACOG: “All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders regardless of maternal age.”

Noninvasive prenatal screening (NIPS) first available; improves PPV for Trisomy 21 from <5% to 60%+

Inhibin for Trisomy 21 (quad screen)
# NIPS vs. Quad Screen

<table>
<thead>
<tr>
<th>NIPS</th>
<th>Quad Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal and <strong>placental cfDNA fragments are sequenced</strong> and counted (WGS method) or ratios are compared (SNP method)</td>
<td>In combination with maternal factors (age, weight, race, diabetes), <strong>four serum analytes (AFP, hCG, Inhibin A, and uE3) are measured</strong> and compared to median values for gestational age</td>
</tr>
<tr>
<td>Risk assessed for T21, T13, T18, and sex chromosome abnormalities (optional)</td>
<td>Risks assessed for T21, T18, and ONTD’s (may also indicate risk for adverse outcomes)</td>
</tr>
<tr>
<td>Can be done ≥ 10 weeks gestational age</td>
<td>Must be done 15-22 weeks, inaccurate dating leads to decreasing accuracy</td>
</tr>
<tr>
<td>&gt;99% detection rate for T21 with 0.5% FPR</td>
<td>81% detection rate for T21 with 5% FPR</td>
</tr>
</tbody>
</table>

“**Women who undergo cell free DNA screening should be offered assessment for open fetal defects by ultrasound, MS-AFP, or both**” – ACOG Practice Bulletin 163
Clinical Experience in Average Risk Population

NEXT Study (2015): Standard Screening vs. cfDNA Analysis by NGS for Trisomy 21

15,841 women undergo standard screening

- 884 positive
  - 30 had T21 (TP)
  - 854 did not (FP)

- 14,957 negative
  - 8 had T21 (FN)
  - 14,949 did not (TN)

15,841 women undergo cfDNA screening

- 47 high risk
- 15,794 low risk

- 38 had T21 (TP)
- 9 did not (FP)

- 0 had T21 (FN)
- 15,794 did not (TN)

The mean maternal age was 30.7 years

Clinical Experience in Average Risk Population

NEXT Study (2015): Standard Screening vs. cfDNA by NGS for Trisomies 13 & 18

<table>
<thead>
<tr>
<th>Trisomy</th>
<th>Test Metric</th>
<th>NIPS</th>
<th>Serum screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>PPV</td>
<td>80.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>False Positive Rate</td>
<td>0.06%</td>
<td>5.6%</td>
</tr>
<tr>
<td>18</td>
<td>PPV</td>
<td>90.0%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>False Positive Rate</td>
<td>0.01%</td>
<td>0.31%</td>
</tr>
<tr>
<td>13</td>
<td>PPV</td>
<td>50%</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>False Positive Rate</td>
<td>0.02%</td>
<td>0.25%</td>
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</table>

In low-risk population, sensitivities and specificities are similar to those in high-risk population.

In three large-scale studies, performance of cfDNA sequencing was compared to multiple-marker screening in the general obstetrical population. All three studies found:

- False positive rates associated with cfDNA screening less than 1/10th as high as with multiple-marker screening
- Significantly higher positive predictive values

NIPS Reduces Invasive Procedures

Trends in invasive procedures: example from US center with >15,000 pregnancies over observation period

Invasive testing rates have declined considerably (often by >50%) at many centers in the US and globally

2. Warsof SL et al. Overview of the impact of noninvasive prenatal testing on diagnostic procedures Prenatal Diagnosis 2015, 35, 1-8
## Clinical Evidence in the General Population

17 Publications with > **88,000** Average Risk Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Journal</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolaides et al.</td>
<td>Nov-2012</td>
<td>American Journal of Obstetrics and Gynecology</td>
<td>2,049</td>
</tr>
<tr>
<td>Dan et al.</td>
<td>9-Nov-2012</td>
<td>Prenatal Diagnosis</td>
<td>1,387</td>
</tr>
<tr>
<td>Fairbrother et al.</td>
<td>15-Mar-2013</td>
<td>Prenatal Diagnosis</td>
<td>289</td>
</tr>
<tr>
<td>Gil et al.</td>
<td>6-June-2013</td>
<td>Ultrasound Obstetrics &amp; Gynecology</td>
<td>1,111</td>
</tr>
<tr>
<td>Song et al.</td>
<td>17-Jun-2013</td>
<td>Prenatal Diagnosis</td>
<td>1,741</td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>20-Nov-2013</td>
<td>Fetal Diagnosis and Therapy</td>
<td>101</td>
</tr>
<tr>
<td>Lau et al.</td>
<td>10-Feb-2014</td>
<td>Ultrasound Obstetrics &amp; Gynecology</td>
<td>368</td>
</tr>
<tr>
<td>Bianchi et al.</td>
<td>27-Feb-2014</td>
<td>New England Journal of Medicine</td>
<td>1,914</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>4-Jul-2014</td>
<td>Prenatal Diagnosis</td>
<td>26</td>
</tr>
<tr>
<td>Pergament et al.</td>
<td>Aug-2014</td>
<td>Obstetrics &amp; Gynecology</td>
<td>518</td>
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</table>
**Clinical Evidence in the General Population**

Continued

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<th>Author</th>
<th>Date</th>
<th>Journal</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>Korostelev et al.</td>
<td>9-Sep-2014</td>
<td>Gynecological Endocrinology</td>
<td>190</td>
</tr>
<tr>
<td>Quezada et al.</td>
<td>20-Nov-2014</td>
<td>Ultrasound Obstetrics &amp; Gynecology</td>
<td>2,851</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>8-Apr-2015</td>
<td>Ultrasound in Obstetrics &amp; Gynecology</td>
<td>40,287</td>
</tr>
<tr>
<td>Palomaki et al.</td>
<td>12-Jan-2017</td>
<td>Genetics in Medicine</td>
<td>2691</td>
</tr>
<tr>
<td>Caldwell et all.</td>
<td>1-Feb-2017</td>
<td>SMFM Annual Meeting 2017</td>
<td>16,585</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td>88,227</td>
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</table>

cfDNA performance in the general obstetric population has been documented in at least 17 studies covering over 88,000 subjects
What does NIPS coverage look like across the country?
Map of State Medicaid Coverage of cfDNA-based Noninvasive Prenatal Screening

- **Covers NIPS for Average Risk Women**
- **Covers NIPS for Only High Risk Women**
- **Reviewing High Risk Policy, Average Risk Under Consideration**
- **Denies NIPS Completely**
- **Temporary Coverage due to COVID-19**
Examples of Recent Clinical Reviews of NIPS by Medicaid

Washington

Conducted year-long assessment of NIPS. On January 17, 2020, WA Health Technology Clinical Committee **voted 8-2-0 to cover NIPS for Medicaid enrollees.**

- 8 votes were “unconditional”, 2 votes for “with conditions” and zero votes for restricted coverage.

Health Technology Assessment (HTA) draft findings document states: “A *majority of committee members found the evidence sufficient to determine that use of cfDNA prenatal screening for chromosomal aneuploidies is safer, more effective or more cost-effective than comparators*.”

Iowa

October 2019: IA Medicaid Clinical Advisory Committee voted to “open testing to all pregnant women with singleton pregnancy, consistent with ACOG recommendation.”
Blue Cross Blue Shield TEC Assessment

- TEC Assessment 2013: Trisomy 21

Blue Cross Blue Shield Technology Evaluation Center Assessment: Sequencing-Based Tests to Determine Fetal Down Syndrome (Trisomy 21) from Maternal Plasma DNA

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 with confirmatory testing of positive results (as expected to be performed in a real-world clinical setting) in **both high-risk and average-risk women screened for trisomy 21** meets TEC criteria.

In decision model, sequencing-based maternal plasma fetal trisomy 21 testing:

- Reduced invasive confirmatory procedures needed and consequent associated miscarriages
- Improved detected cases of trisomy 21, compared to standard screening procedures in either high- or average-risk pregnant women
Connecticut’s Commercial Insurance
Coverage of NIPS

Covers NIPS for all pregnant women in Connecticut

*Coverage due to COVID19
As of July 2018, ACOG Committee Opinion 640 is not current

PB 163 is the current opinion: “All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age.”

Restated in CO 693
<table>
<thead>
<tr>
<th>Professional Society Positions</th>
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</table>
| **International Society for Prenatal Diagnosis**  
*April 2015* | “cfDNA screening as a primary test offered to all pregnant women [is currently considered an appropriate protocol option].”  
[1](#) |
| **American College of Obstetricians and Gynecologists (ACOG), jointly with the Society for Maternal Fetal Medicine (SMFM)**  
*May 2016* | “Aneuploidy screening or diagnostic testing should be discussed and offered to **all** women early in pregnancy, ideally at the first prenatal visit. All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age.”  
[2](#) |
| **American College of Medical Genetics and Genomics (ACMG)**  
*July 2016* | Recommends “Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)”  
[3](#) |
| **National Society of Genetic Counselors (NSGC)**  
*October 2016* | “The National Society of Genetic Counselors supports prenatal cell-free DNA (cfDNA) screening, also known as NIPT or NIPS, as an option for pregnant patients.”  
[4](#) |

One Standard of Care for All Patients

20% of pregnancies in the United States are to women considered high risk (>35, family history of affected pregnancy)
  • NIPS is a *widely available* screening and regularly utilized.

80% of pregnancies in the United States are to women considered low or average risk
  • NIPS access *can be sporadic*, often dependent on a patient’s location or health insurance plan -- creating two different standards of care.

Goal: Ensure all patients receive the best quality care and establish a single standard of care.