Prenatal Screening in Ontario: Past, Present and Future
Using Data to Inform Policy

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• We have no conflicts of interest to declare
Objectives

• To review:
  – The “landscape” of Canadian/Ontario healthcare that influences policy
  – Prenatal screening in Ontario (past and present)
  – Considerations to inform evolution of prenatal screening in Ontario
  – NIPT: the “disruptive” technology
  – BORN data to inform directions in screening
The UK: Holy Grail of Screening
In a public health context

Population: 64.1 million (2013)
Area: 243,610 km²

Sam Jordison
No “Canadian” Health Care System

Population: 35.16 million (2013)
Area: 9,985,000 km²
Canadian Health Care Considerations

- Access to ‘standardized’ care an issue for rural populations
- Guidelines need to consider geography/access/equity
Past and Present of Prenatal Screening in Ontario - 2010

PCMCH/BORN Committee Structure
Review of Prenatal Screening

• Review of Ontario paradigm of screening
  – Down syndrome (Trisomy 18/13)
  – Open Neural Tube Defects
  – funded since 1990’s

• Objective: to review and provide recommendations for evolution of prenatal screening

• Identified several gaps in “system”
Guiding Principles for Change

- Equality of access for all women in Ontario
- Prenatal screening services should be embedded into a system of care
- Flexibility to evolve as technologies and targets evolve

PCMCH 2015/16

- Task force convened to suggest provincial strategy for screening

- Developed a set of recommendations that is with MOHLTC
CONSIDERATIONS TO GUIDE PRENATAL SCREENING IN ONTARIO

- Cell-free (cfDNA) are short DNA fragments
- cfDNA in maternal blood comes from both mother and fetus
- In trisomy 21 the amount of cfDNA for chromosome 21 is higher than in normal pregnancies
Considerations for Prenatal Screening in Ontario

- Prenatal screening historically for Down syndrome
- Evaluation of screening test based on certain measurable parameters
  - Detection Rate
  - False Positive Rate
- Other jurisdictions have broadened scope
- Maternal Child Screening Committee considers other “targets”
Clinically in 2017:

Prenatal screening ≠ Screening for Down syndrome

- Clinical value of combined screening (with NT scan) for DS allows for screen for fetal health
  - Early fetal structure
  - Multiples
  - NT
- Most guidelines recommend 11 to 14 week scan regardless of NIPT

SOGC 2017 Updated Guideline
Ultrasound Obstet Gynecol. 2014
NIPT: The Disruptive Technology

- Method to analyze cell-free DNA from trophoblast of placenta
- Studies to date:
  - 99% DR for DS
  - 98% DR for T18
  - 99% DR for T13
  - 0.13% FPR

Jurisdictions with some funded NIPT:
BC, Manitoba, Ontario, Nova Scotia, PEI, Yukon and Nunavut

Jurisdictions with a request into government for funding:
Alberta, Saskatchewan, Nfld & Labrador, NWT

Non-Invasive Prenatal Testing, NIPT Canadian Environmental Scan 2016. Shannon Ryan CCGC.
RYAN Policy Research Consulting
Where does NIPT fit into the prenatal screening pathway?

- Standard screening differs by province/territory
- Differing access to NT scan
- Many provinces/territories have current first/second trimester screens
- Should NIPT be primary screen for areas with challenging access to NT scan?
Considerations for incorporation of NIPT into prenatal screening?

- Most international jurisdictions recommend “contingent” model
  - NIPT follows positive standard test (in lieu of amniocentesis)
  - Best value
- Ontario data supports contingent screening

Prenatal Diagnosis 2015, 35, 959–967
Prenatal Diagnosis 2015, 35, 1347–1352
Costs of NIPT implementation

- **Primary** NIPT shown to increase costs of prenatal screening programs significantly
  

- In Ontario, would **quadruple** cost of testing system

In Ontario

• Recent shift from a test done over two trimesters to an improved first trimester system

• Enhanced FTS
  – PAPP-A
  – Free BHCG
  – AFP
  – PIGF

All with NT scan
EFTS vs Integrated Prenatal Screen

Slightly higher FPR
Earlier results → better pregnancy care
Offer of alternative NIPT or diagnostic test
EFTS for T21 with contingent CffDNA: A Comparative Performance and Cost Analysis

• Compared several scenarios of current screening, EFTS with contingent cffDNA and primary cffDNA for performance and cost

• Even with cost of NIPT of $200, contingent screening is cheaper and almost as effective primary NIPT
  – Advantage of incorporating first trimester scan

Huang et al: in press JOGC
2012-2016

THE ONTARIO EXPERIENCE
BORN and Prenatal Screening

• Quality Assurance Reporting

• Data available for analysis:
  – Multiple marker screening (lab)
  – Amniotic fluid AFP screening (lab)
  – Prenatal screening follow-up (clinical)

• Additional data sources
  – NIPT (pre-patriation)
  – Cytogenetics
What can we assess?

- Utilization rates:
  - Multiple marker screening, amniocentesis and NIPT
- Descriptive of NIPT specific data:
  - Pre-patriation only
- Multiple marker screening performance
Multiple Marker Screening (MMS) Uptake by LHIN

Data source: BORN Ontario, EDD April 2012 - Nov 2016
Notes: Numerator: Singleton pregnancies that have a multiple marker screening test for Down syndrome
Denominator: Total singleton pregnancies
Utilization of MMS, NIPT and amniocentesis (by EDD)

Data source: BORN Ontario, EDD April 2012-Nov 2016
Notes: Numerator: Pregnancies that have a multiple marker screening test for Down syndrome, a NIPT or an amniocentesis
Denominator: Number of total pregnancies
Utilization of NIPT and amniocentesis among MMS positive (by EDD)

Data source: BORN Ontario, EDD April 2012-June 2017

Notes: Numerator: Pregnancies that have a NIPT or an amniocentesis
Denominator: Number of pregnancies that have a positive multiple marker screening test for T21 or T18
NIPT uptake characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>15w4d</td>
<td>14w4d</td>
</tr>
<tr>
<td>Maternal age</td>
<td>36.3y</td>
<td>37y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal age of women who had NIPT (final test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (at EDD)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>&lt;20</td>
</tr>
<tr>
<td>20-24</td>
</tr>
<tr>
<td>25-29</td>
</tr>
<tr>
<td>30-34</td>
</tr>
<tr>
<td>35-39</td>
</tr>
<tr>
<td>&gt;=40</td>
</tr>
</tbody>
</table>

Data source: BORN Ontario, Fiscal Year 2012-2015
Notes: All test: Number of all NIPT tests
       Final test: Final test from a pregnancy from the same NIPT laboratory
What about performance?

- Currently available information, literature-based:

<table>
<thead>
<tr>
<th>Test</th>
<th>Markers</th>
<th>Trim</th>
<th>Term Risk Cut-off</th>
<th>DR (%)</th>
<th>FPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS</td>
<td>NT, PAPP-A, f-BHCG, MA</td>
<td>1</td>
<td>1/350</td>
<td>78-85</td>
<td>3-9%</td>
</tr>
<tr>
<td>IPS</td>
<td>NT, PAPP-A, AFP, uE3, total hCG, MA</td>
<td>1 &amp; 2</td>
<td>1/200</td>
<td>85-90</td>
<td>2-4%</td>
</tr>
</tbody>
</table>

Prenatalscreeningontario.ca/for-health-care-providers/screening-options 2017; Excellence and Leadership in Prenatal Screening in Ontario: The Road Forward 2013
MMS Performance – T21

<table>
<thead>
<tr>
<th>Screen modality &amp; risk cut-off</th>
<th>Number screened</th>
<th>Number screen positive</th>
<th>PR (%)</th>
<th>Number of T21 by cyto (true cases)</th>
<th>Number of T21 screen positive</th>
<th>DR (%)</th>
<th>Observed # cases per 1000 screened pregnancies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS</td>
<td>74,672</td>
<td>5,662</td>
<td>7.6%</td>
<td>194</td>
<td>189</td>
<td>97.4%</td>
<td>2.60</td>
</tr>
<tr>
<td>IPS</td>
<td>358,824</td>
<td>8,481</td>
<td>2.4%</td>
<td>158</td>
<td>139</td>
<td>88.0%</td>
<td>0.44</td>
</tr>
<tr>
<td>Total (all types)</td>
<td>485,462</td>
<td>16,340</td>
<td>3.4%</td>
<td>374</td>
<td>348</td>
<td>93.0%</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data source: BORN Ontario, Fiscal Year 2013-2015

Notes:
- **PR**: Positive rate, The proportion of screened pregnancies with a positive test result
- **DR**: Detection rate, The proportion of affected pregnancies with a positive test result
- *Observed # of cases is lower than the true incidence, as not all cytogenetics records were available for analysis*
## MMS Performance – T18

### Multiple marker screening performance for trisomy 18 by screen modality

(Ontario, Singleton, ascertained by cytogenetics result)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Number screened</th>
<th>Number screen positive</th>
<th>PR (%)</th>
<th>Number of T18 by cyto (true cases)</th>
<th>Number of T18 screen positive</th>
<th>DR (%)</th>
<th>Observed # cases per 1000 screened pregnancies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTS</td>
<td>74,608</td>
<td>480</td>
<td>0.6%</td>
<td>48</td>
<td>35</td>
<td>72.9%</td>
<td>0.64</td>
</tr>
<tr>
<td>IPS</td>
<td>358,813</td>
<td>973</td>
<td>0.3%</td>
<td>25</td>
<td>21</td>
<td>84.0%</td>
<td>0.07</td>
</tr>
<tr>
<td>Total (all types)</td>
<td>485,385</td>
<td>1,697</td>
<td>0.3%</td>
<td>81</td>
<td>63</td>
<td>77.8%</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Data source: BORN Ontario, Fiscal Year 2013-2015

Notes:

- **PR:** Positive rate, The proportion of screened pregnancies with a positive test result
- **DR:** Detection rate, The proportion of affected pregnancies with a positive test result
- *Observed # cases is lower than the true incidence, as not all cytogenetics records were available for analysis*
Next steps: data informing policy

• More outcomes data = Better understanding of comparative performance:
  – MMMS, NIPT
• Determine optimum screening pathways and educational initiatives

• Evaluating screening performance for other perinatal outcomes
Acknowledgements

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Ann Sprague
Mari Teitelbaum

Laboratories:
• Prenatal Serum Screening
• NIPT
• Cytogenetics
MMS utilization by EDD

NIPT fully patriated in January 2016, approx. EDD of July 2016

Data source: BORN Ontario, EDD April 2012 - Nov 2016
Notes: Numerator: Singleton pregnancies that have a multiple marker screening test for Down syndrome
Denominator: Total singleton pregnancies

Uptake rate (%)

EDD

FTS  IPS  QUAD  SIPS  Other  All screen