Prenatal Screening and Diagnosis in Ontario
Past, Present and Future

David Chitayat, MD
Head, The Prenatal Diagnosis and Medical Genetics Program
Mount Sinai Hospital
Staff, Division of Clinical and Metabolic Genetics
The Hospital for Sick Children
dchitayat@mtsini.ai.on.ca
DISCLOSURES

I have no conflict of interest and nothing to disclose.
Birth Defects
World Wide

- There are 139 million births/year
- 7.9 million babies are born with birth defects (6%)
- 3.3 Million die under age 5
- 3.2 Million are disabled for life

Ontario

- 140,000 births/year in Ontario
- Infant mortality rate 4.6/1000
- Number of babies born with Down syndrome/year ??
- BORN - Ontario's pregnancy, birth and childhood registry and network
Prenatal Diagnosis

- Prevention
- Diagnosis
- Treatment
Prenatal Diagnosis

Prevention

Diagnosis

• Treatment
Prenatal Diagnosis

Prevention

- Primary prevention
- Secondary “prevention”
“Only through the practice of preventive medicine will we keep the costs from becoming so excessive that the public will decide that Medicare is not in the best interests of the people of the country.”

*Tommy Douglas* (founding father of the Canadian Medicare)
Primary Prevention

Objective

To stop inherited and non-inherited congenital disorders from arising in the first place by identifying and avoiding causative factors.
Primary Prevention - Examples

- Prevention of Rhesus hemolytic disease of the newborn by injecting Rhesus negative mothers with anti-D immunoglobulin during pregnancy and after delivery.

- Immunization of young girls against rubella infection

- Folic acid supplementation to prevent neural tube defects, and cardiac and renal abnormalities
Autosomal Recessive Segregation, Both Parents Carriers

- Unaffected Individual
- Carrier
- Affected Individual

Unaffected: 25%
Carrier: 50%
Affected: 25%
Genetic Screening
Ethnic Background

- Screening of couples of Black, Asian and Mediterranean descent for hemoglobinopathies and thalassemia
Genetic Screening
for the most common mutations causing the following conditions in the Ashkenazi Jewish Population

- Bloom syndrome
- Canavan disease
- Familial dysautonomia
- Fanconi anemia, type C
- Mucolipidosis, type IV
- Niemann-Pick disease, type A and B
- Tay-Sachs disease
My Recommendation to the Government
Expanding the Prenatal/preconception Screen

<table>
<thead>
<tr>
<th>Condition</th>
<th>Carrier rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>1/25</td>
</tr>
<tr>
<td>SMA</td>
<td>1/38</td>
</tr>
<tr>
<td>Fragile X</td>
<td>1:260 female</td>
</tr>
</tbody>
</table>

- Provide free of charge PGD to couples who are carriers of an AR or X-linked conditions.
Prenatal Diagnosis

Prevention

- Primary prevention
- Secondary “prevention”
Secondary Screening “Prevention”

- Screening for Down syndrome and other fetal chromosome abnormalities

- Screening for Open Neural Tube Defects and Abdominal wall defect

- Screening for structural fetal abnormalities
Secondary “Prevention”

- Screening for Down syndrome and other fetal chromosome abnormalities
- Screening for Open Neural Tube Defects and Abdominal wall defect
- Screening for structural fetal abnormalities
History of Prenatal Screening and Biomarkers

**1960’s** - Maternal age associated with risk for having a baby with Down syndrome

**1972** - HIGH AFP = anencephaly [ONTD]  
(Brock, Lancet)

**1984** - LOW AFP = T18 + Down syndrome  
(Merkatz et al., AJOG)

**1990’s** - Multiple biomarkers (AFP, uE3, hCG, DIA…)
  - Ultrasound
  - NT
  - (NB, DV, TR, fronto-maxillary angle…)
Maternal age & Trisomy 21

Odds of affected pregnancy in women age ≥35 years:
One live birth per 155 pregnancies
Birth outcomes
Maternal ages 35-40 years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>96.5%</td>
</tr>
<tr>
<td>Non-chromosomal problem</td>
<td>2.5%</td>
</tr>
<tr>
<td>Chromosomal problem</td>
<td>0.5 - 1%</td>
</tr>
</tbody>
</table>
Maternal age, fertility and Spontaneous abortions

Figure. Fertility and Miscarriage Rates as a Function of Maternal Age.
Chromosome abnormalities

- Incidence of chromosome abnormalities in newborns - 0.6%
- 60% Down syndrome (Trisomy 21)
- 10% Trisomy 18 and Trisomy 13
- 25% Sex chromosome abnormalities [45,X;47,XXY; 47,XXX; 47,XYY]
- 5% Other (del, dup, transl)
Risk of Chromosome AbN = Risk of SA with amnio at 35YR

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>DS</th>
<th>Any Chromosome Abn</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1/1667</td>
<td>1/526</td>
</tr>
<tr>
<td>25</td>
<td>1/1200</td>
<td>1/476</td>
</tr>
<tr>
<td>30</td>
<td>1/952</td>
<td>1/385</td>
</tr>
<tr>
<td>35</td>
<td>1/378</td>
<td>1/192</td>
</tr>
<tr>
<td>40</td>
<td>1/106</td>
<td>1/66</td>
</tr>
<tr>
<td>45</td>
<td>1/30</td>
<td>1/21</td>
</tr>
</tbody>
</table>
Age as a screen for Chromosome abnormalities

≥35 years = screen positive

- A miscarriage and a birth of a baby with a chromosome abnormality do not have the same impact.

- Risk for a miscarriage associated with amniocentesis is < 0.5%

- Detection rate only 30% (depends on age of population)
Advanced paternal age

- Association with autosomal dominant conditions: Marfan syndrome, myositis ossificans, Apert syndrome, achondroplasia, thanatophoric dysplasia, OI, NF1 etc.
- Association with ASD: In comparison to paternal age (≤29y), risk of autism increased 2.18 times for children born from fathers in their thirties, 2.71 times for fathers in their forties, and 3.22 thereafter.
- Increased risk of total childhood leukemia and ALL
- Increased risk for both schizophrenia and OCD
- Association with rare de novo CNVs not flanked by segmental duplications
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - **HIGH** AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - **LOW** AFP = T18 + T21 (Merkatz et al., AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

- Ultrasound
  - NT
  - (NB, DV, TR, fronto-maxillary angle…)
Maternal Serum AFP Screening for ONTD & AWD

- Chance of ONTD & AWD increases with increased MS-AFP levels
- Positive screen = 2.2 MoM (~1/460)
- MS-AFP can detect 80% of the fetuses with ONTD and abdominal wall defect
- Diagnostic test - Offer detailed fetal ultrasound and amniocentesis (for AF-AFP ± AChE)
2D Ultrasound

“Banana” sign

Spinal lesion T12-S1

“Lemon” sign
Intracranial Translucency
1st trimester PND of NTD
Maternal Serum AFP Screening for ONTD & AWD

Time for a change

<table>
<thead>
<tr>
<th></th>
<th>Anencephaly</th>
<th>Spina bifida</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester TV</td>
<td>90%</td>
<td>44%</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>100%</td>
<td>92-95%</td>
</tr>
</tbody>
</table>

- Should we continue the MS-AFP screening for ONTD and AWD???
- ONTD and AWD are not different than the other fetal abnormalities and should be detected by a detailed fetal ultrasound.
Secondary Prevention - Time for a change

- Screening for Down syndrome and other fetal chromosome abnormalities
- Screening for Open Neural Tube Defects and Abdominal wall defect
- Screening for structural fetal abnormalities
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - HIGH AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - LOW AFP = T18 + T21 (Merkatz et al., AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

- Ultrasound
  - NT
  - (NB, DV, TR, fronto-maxillary angle…)

MOUNT SINAI HOSPITAL
MS-AFP

- Found to be elevated in cases of ONTD and AWD

- Subsequently found to be low in pregnancies with Down syndrome and Trisomy 18

- BUT age +AFP- still not a great screen (high false positive and poor detection – 60% for 5% FPR)
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - HIGH AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - LOW AFP = T18 + Down (Merkatz, AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

Ultrasound
- NT
- (NB, DV, TR, fronto-maxillary angle…)
4 Biochemical Markers

- Fetal
  - AFP
  - UE3

- Placental
  - hCG
  - Inhibin-A
Maternal Serum Triple Screen for Down syndrome (15w-20w5d)

- Maternal Age: age will ↑ chance
- AFP ↓ (fetoplacental)
- uE3 ↓ (fetoplacental)
- hCG ↑ (placenta)

Positive screen = 1/385 + chance for DS

Detection rate varies w/ age (~70% for 5% FPR)
Maternal Serum Quad Screen for Down syndrome (15w-20w5d)

- Maternal Age: age will $\uparrow$ chance
-AFP - $\downarrow$ (fetoplacental)
- uE3 - $\downarrow$ (fetoplacental)
-hCG - $\uparrow$ (placenta)
-Inhibin A - $\uparrow$ (Placenta)

Positive screen $\geq 1/385$

- Detection rate varies w/ age
  - <35 yrs: 76%
  - 35 – 39 yrs: 92%
  - $\geq$ 40 yrs: 97%
Maternal Serum Quad Screen for Trisomy 18

- Maternal Age: age will \(\uparrow\) chance
- AFP - \(\downarrow\) (fetoplacental)
- uE3 - \(\downarrow\) (fetoplacental)
- hCG - \(\downarrow\) (placental)
- Inhibin A - \(\downarrow\) (placental)
- measured 15w0d to 20w5d

Positive screen \(\geq 1/100\)

Detailed ultrasound is also a good screen for Trisomy 18
4 Biochemical Markers

- Fetal
  - AFP
  - UE3

- Placental
  - hCG
  - Inhibin-A
Suggested Management for Abnormal Maternal Serum Markers

- Offer screen for aneuploidy/ONTD
- Examine serum markers as well as overall risk in consideration of placental disorders
  - PAPP-A $< 0.4$ MoM
  - T2 AFP $> 2.5$ MoM
  - BHCG $> 3$ MoM
  - Inhibin $> 2$ MoM
  - $uE3 < 0.5$

Abnormalities followed up sequentially with individualized monitoring based on level of risk
Although meta-analyses show that uterine artery Doppler analysis can predict women at increased risk of placental dysfunction, it is not recommended to be used for screening purposes.

Improved identification of women at increased or decreased risk of a disease that cannot be prevented and has no treatment other than delivery is unlikely to improve maternal or fetal outcome.

Furthermore, the false positive rate of these test is quite high, leading to excessive patient anxiety and health care costs.
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - HIGH AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - LOW AFP = T18 + Down (Merkatz, AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

Ultrasound

- NT
- NB, DV, TR, fronto-maxillary angle…
NT Scan

Professor Kypros Nicolaides
Founder 11 to 14 week Scan Project
Director Fetal medicine Foundation
“the skin is deficient in elasticity. . . . . too large for the body”

Langdon Down


**Increased NT at 11-14 wks**

\[(n=4,767)\]

- **Abnormal karyotype**
  - Normal Karyotype
    - IUD / NND / Defects
  - Snijders et al, 1998  \(n=96,127\)

- **Normal karyotype**
  - Souka et al, 2001  \(n=1,320\)

**NT**
- 2.5
- 3
- 3.5
- 4
- 4.4
- 4.5
- 5.4
- 5.5
- 6.4
- \(>6.5\) mm

- 19%  33%  50%  64%  
- 50%  33%  23%  69%  

- 3%  19%  33%  50%  
- 14%  23%  33%  69%  

Snijders et al, 1998  \(n=96,127\)

Souka et al, 2001  \(n=1,320\)
Ultrasound Detection of Fetal Anomalies in the First Trimester

- NT > 95th centile
  - Multiple anomalies – 100%
  - Body-stalk anomalies – 100%
  - Lethal skeletal dysplasia – 50%
  - Diaphragmatic hernia – 37%
  - Cardiac defects – 28%

Syngelaki et al, 2011
Grande et al., 2011
Pregnancy-Associated Plasma Protein - A

- A large glycoprotein tetramer produced by the trophoblast
- Metalloprotease cleaving Insulin-like growth factor binding protein-4
- Increases the bioavailability of insulin-like growth factor
Secondary Prevention - Screening for Trisomy 21

Aims

Reduce invasive testing rate & increase detection rate

Risk vs. Years

β-hCG
Estriol
AFP
Inhbin
15-20 wks

Nuchal translucency
11.5-14 wks

β-hCG / PAPP-A
11.5-14 wks
One-Stop Clinic for Assessment of Risk for Trisomy 21

Results

Maternal age

False positive rate (%)

Sensitivity (%)

NT + MA+
β-hCG + PAPP-A

90%
79%
60%
31%

NT +
MA

β-hCG + PAPP-A + MA+

Bindra et al 2002
Integrated Prenatal Screening

• Combine FTS w/ MSS and give one result for OSB, Down syndrome and Trisomy 18/13 (NT, PAPP-A, AFP, uE3, hCG, IA)

• benefits: more accurate- i.e. increased detection rate and less false positives

• (92% for 5% FPR)

• Timing- waiting until 2nd trimester and need woman to return
Integrated Serum Screening (ISS)

- Papp-A, AFP, uE3, hCG, +/- Inhibin A
- benefits: more accurate- i.e. increased detection rate and less false positives
- Timing- 1\textsuperscript{st} and 2\textsuperscript{nd} trimester
- VERY GOOD when no access to NT
- (DR - <35 yrs: 79%; 35 – 39 yrs: 92%; cutoff 1:300; FPR 5%)
Politics and health care in Ontario

- 5 biochemical laboratories
- Freedom to have a variety of screening tests mainly according to the HCP choice
- Lack of QA for NT decreased the detection rate
- Interaction with a commercial company and paying royalties for IPS increased the provincial expenses
Suggestions

- Prenatal Screening:
  - Screening for Down syndrome + T13/T18
    - Use FTS to provide early results and avoid having two blood tests and thus decreased compliance
  - Screening for Fetal structural abnormalities
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - HIGH AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - LOW AFP = T18 + Down (Merkatz, AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

Ultrasound

NT

NB, Ductus venosus, TR, fronto-maxillary angle…
Nasal bone

Normal nasal bone

Abnormal nasal bone

Absent nose bone
History of Prenatal Screening and Biomarkers

1960’s - Maternal age associated with risk for having a baby with Down syndrome

1972 - HIGH AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - LOW AFP = T18 + Down (Merkatz, AJOG)

1990’s - Multiple biomarkers (AFP, uE3, hCG, DIA…)

Ultrasound

NT

NB, DV, TR, fronto-maxillary angle…
<table>
<thead>
<tr>
<th>Ultrasound “soft markers” (evidence and classification)</th>
<th>Aneuploidy (LR)²</th>
<th>Congenital/Anomaly Association³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screenning scan (16-20 weeks)</td>
<td>T21</td>
<td>T18</td>
</tr>
<tr>
<td>Nuchal fold (III, A)</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>Echogenic bowel (I-II, A)</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Ventriculomegaly (II-2, A)</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Echogenic cardiac focus (III, A)</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Choroid plexus cyst (II, A)</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Single umbilical artery (III, A)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Enlarged cisterna magna (II, A)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Renal pylectasis (II-2, A)</td>
<td>—</td>
<td>OFD, MG, DiG</td>
</tr>
<tr>
<td>B. Comprehensive scan (calculation; detail)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinodactyly (II-2, A)</td>
<td>5.5</td>
<td>—</td>
</tr>
<tr>
<td>Humerus (short) (II-2, A)</td>
<td>7.5</td>
<td>skeletal dysplasia; IUGR</td>
</tr>
<tr>
<td>Femur (short) (II-2, A)</td>
<td>2.7</td>
<td>skeletal dysplasia; IUGR</td>
</tr>
<tr>
<td>Nasal bone absent/hypo (II-2, A)</td>
<td>51</td>
<td>—</td>
</tr>
<tr>
<td>C. Research/Not useful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachycephaly (III, B)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Iliac angle (II-2, A)</td>
<td>TED</td>
<td>—</td>
</tr>
<tr>
<td>Ear length (II, B)</td>
<td>3-5</td>
<td>—</td>
</tr>
<tr>
<td>Sandal toe (III, B)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

²LR: Likelihood ratio; TBD: to be determined.
³CF: cystic fibrosis; CNS: central nervous system; GI: gastrointestinal; OFD: oro-facial-digital syndrome; MG: Meckel Gruber Syndrome; DiG: Di George Syndrome; IUGR: intrauterine growth restriction; AC: agenesis corpus callosum.
Multiple LR’s can be combined

• Risk LR’s can be multiplied to give new risk.

• New risk = initial $\times LR_1 \times LR_2 \times LR_3 \times \ldots \times LR_n \times LR$ modifiers$^*$

  e.g.

• Down = age risk $\times LR_{NT} \times LR_{PAPP-A} \times LR_{\beta-hCG} \times LR$ modifiers$^*$

• LR modifiers: smoking, weight, diabetes, history, ethnicity, fetal number.
The mean percentage of mothers >35 years of age increased from 10.9% in 1993 to 18.8% in 2004.

The total mean prevalence of DS (still births, live births, and ToP) increased from 13.1 to 18.2/10,000 births.

The total mean prevalence of DS births remained stable at 8.3/10,000 births, balanced by a great increase of ToP.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. Births</th>
<th>Maternal age &gt;35 years</th>
<th>Newborn DS</th>
<th>Terminations</th>
<th>Total DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, 1993</td>
<td>1,554,529</td>
<td>10.89%</td>
<td>8.29/10,000</td>
<td>4.78%</td>
<td>13.08/10,000</td>
</tr>
<tr>
<td>All, 2004</td>
<td>1,564,501</td>
<td>18.77%</td>
<td>8.32/10,000</td>
<td>9.92%</td>
<td>18.24/10,000</td>
</tr>
</tbody>
</table>
Prenatal Diagnosis
Secondary “Prevention”

- Screening for Down syndrome and other fetal chromosome abnormalities
- Screening for Open Neural Tube Defects
  - Spina bifida, Anencephaly
  - Abdominal wall defect
- Screening for structural fetal abnormalities
Should we tell her?
Among 45,191 studied pregnancies, 44% of the anomalies (213/488) were detected in the first trimester.

Syngelaki et al, 2011
Grande et al., 2011
The 18 - 20 week ultrasound scan

- Standard of care in Canada
- Screen for birth defects

“*The Genetic Sonogram*”
Trisomy 13

Trisomy 18

Trisomy 21

Major Defects

Spinal lesion T12-S1

Normal karyotype
Assessment of Risk

18 - 20 wk scan - Number of abnormalities

Chromosomal Defect  301/2086 (14%)

Nicolaides et al 1992
Noninvasive Prenatal Diagnosis

- Fetal Cells in Maternal Blood
- Cell-free DNA in Maternal Blood
  - Chromosome abnormalities - T21 and others
  - Rh Disease
  - Sex determination for X - linked & X-limited disorders
  - Single Gene disorders
Sequenom launched MaterniT21 Down Syndrome Test as LDT, Publishes Clinical Validation Study
October 19, 2011
Private Sector

- BGI
- Harmony™ Prenatal Test
- verifi™ Prenatal Test
- natera™

MOUNT SINAI HOSPITAL
# NIPT - Performance

## Table 1. A comparison of aneuploidy screening options

<table>
<thead>
<tr>
<th></th>
<th>First trimester screen traditional</th>
<th>Second trimester maternal serum screening</th>
<th>NIPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>When is the test performed?</td>
<td>11–14 weeks</td>
<td>15–23 weeks</td>
<td>After 9 weeks</td>
</tr>
<tr>
<td>Who is the test available to?</td>
<td>All patients</td>
<td>All patients</td>
<td>Patients with a risk factor</td>
</tr>
<tr>
<td>What does it screen for?</td>
<td>Down syndrome</td>
<td>Down syndrome</td>
<td>Down syndrome</td>
</tr>
<tr>
<td></td>
<td>Trisomy 18</td>
<td>Trisomy 18</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td></td>
<td>Trisomy 13</td>
<td>Open spina bifida</td>
<td>Trisomy 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monosomy X: ~88% [8*]</td>
</tr>
<tr>
<td>What is the screen positive rate?</td>
<td>5%</td>
<td>5%</td>
<td>&lt;1% [7]</td>
</tr>
</tbody>
</table>

NIPT, non-invasive prenatal testing; SNP, single nucleotide polymorphism

Hardisty and Vora, 2014
NIPT not only for common aneuploidy
Submicroscopic deletions

- 22q deletion syndrome (DiGeorge)
- 5p (Cri-du-chat syndrome)
- 15q (Prader-Willi/Angelman syndromes)
- 1p36 deletion syndrome
- 4p (Wolf-Hirschhorn syndrome)
- 8q (Langer-Giedion syndrome)
- 11q (Jacobsen syndrome)
- Trisomy 16
- Trisomy 22
NIPT – Points to remember

• It is a screening test
• Pre and post-test counselling is essential including discussion of false positive and false negative
• The PPV is at the most 85%
• No irrevocable obstetrical decision should be made in pregnancies with a positive NIPT result without confirmatory invasive diagnostic testing.
• Further consideration needed regarding:
  • Test performance on multiples
  • Turnaround times
  • Economic aspects
NIPT – Indications/suggestions

• Maternal age ≥ 40 at delivery
  (we should we go for 35)

• Ultrasound anomalies associated with an increased risk for aneuploidy
  (with the low risk associated with CVS/amniocentesis we should offer invasive testing in these cases)

• A prior pregnancy with aneuploidy

• Parent is a known carrier of a translocation involving chromosome 13 or 21

• High risk result for aneuploidy on FTS, IPS, SIPS, MSS (including adjusted risk with soft signs)
Prenatal Diagnosis

Prevention
• Primary
• Secondary

Diagnosis

Treatment
Invasive testing in pregnancy

Risk of miscarriage up to 1%

Risk of miscarriage < 0.5%
Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Akolekar et al., UoG 2014

The weighted pooled procedure-related risks of miscarriage:

- Amniocentesis - 0.11% (95% CI, -0.04 to 0.26)
- CVS - 0.22% (95% CI, -0.71 to 1.16)
Metaphase Spread
Advantage of ACGH

- Much higher resolution

- 25-50 Mb
- 5-8 Mb
- 0.05-0.1 Mb
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of cases studied</th>
<th>Cases with pathogenic CNV</th>
<th>Cases with unclear CNV (VOUS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiorentino et al., 2011</td>
<td>1037</td>
<td>9 (0.9%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Shaffer et al., 2012</td>
<td>4406</td>
<td>207 (5.3%)</td>
<td>163 (4.2%)</td>
</tr>
<tr>
<td>Wapner et al., 2012</td>
<td>3822</td>
<td>35 (0.9%)</td>
<td>61 (1.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US Abn – 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMA/Abn screening – 1.7%</td>
<td></td>
</tr>
<tr>
<td>Scott et al., 2013</td>
<td>1049</td>
<td>13 (1.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US Abn – 4.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMA/Abn screening – 1.2%</td>
<td></td>
</tr>
<tr>
<td>Fiorentino et al., 2013</td>
<td>3000</td>
<td>7/120 (6%)</td>
<td>1 (0.03%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17/2880 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>
US Abn – 6%; LMA/Abn screening – 1.7%
0.8% = 1/125 cases sampled for AMA or positive screening had CNVs associated with cognitive impairment and psychiatric diseases
All Pregnancies are High Risk

<table>
<thead>
<tr>
<th></th>
<th>By Predetermined Listings</th>
<th>VOUS Adjudicated by CAC or Clinical Geneticist</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathogenic</td>
<td>Total</td>
<td>Likely Benign</td>
</tr>
<tr>
<td>AMA N=1965</td>
<td>9 (0.5%)</td>
<td>62 (3.2%)</td>
<td>37 (1.9%)</td>
</tr>
<tr>
<td>Positive Screen N=727</td>
<td>3 (0.4%)</td>
<td>22 (3.0%)</td>
<td>13 (1.8%)</td>
</tr>
<tr>
<td>US Anomaly N=757</td>
<td>21 (2.8%)</td>
<td>40 (5.3%)</td>
<td>16 (2.1%)</td>
</tr>
</tbody>
</table>

Wapner et al., 2012
Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature

*De Wit et al., UOG 2014*

## Pooled prevalence of pathogenic submicroscopic CNVs in a specific anatomical system

<table>
<thead>
<tr>
<th>Isolated anomalies</th>
<th>Cardiac</th>
<th>Resp</th>
<th>CNS</th>
<th>Facial</th>
<th>MSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled prevalence (95% CI)</td>
<td>22/476 4.6% (2.7-6.5)</td>
<td>5/81 6.2% (0.9-11.4)</td>
<td>35/563 6.2% (4.2-8.2)</td>
<td>6/113 5.3% (1.2-9.4)</td>
<td>24/305 7.9% (4.8-10.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolated anomalies</th>
<th>GIT</th>
<th>Urogenital</th>
<th>NT &gt;3.5 mm</th>
<th>Cystic hygroma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled prevalence (95% CI)</td>
<td>7/105 6.7% (1.9-11.4)</td>
<td>9/153 5.9% (2.2-9.6)</td>
<td>5/162 3.1% (0.4-5.7)</td>
<td>12/262 4.6% (2.0-7.1)</td>
<td>125/2220 5.6% (4.7-6.6)</td>
</tr>
</tbody>
</table>
The Use of Microarray Analysis in the Prenatal Setting

• The use of microarrays has not only increased the identification of pathogenic CNV (chromosome abnormalities), it has also identified copy number variants (CNVs) that are clearly benign.

• The identification and classification of these novel alterations have become challenging, especially in the prenatal setting.
## Counselling issues
### Variants Of Uncertain Clinical Significance

<table>
<thead>
<tr>
<th></th>
<th>VOUS</th>
<th>Pathogenic</th>
<th>Likely Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2007 Study Classification</strong></td>
<td>94 (2.5%)</td>
<td>35 (0.9%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>2012 Classification</strong></td>
<td>57 (1.5%)</td>
<td>64 (1.7%)</td>
<td>8</td>
</tr>
</tbody>
</table>
On the Horizon

Diagnostic capability of genetic tests
prenatal diagnosis

Currently available

Standard karyotype
Able to detect large, extra, or missing chromosomes (i.e. down syndrome)

MicroArray
Able to detect small deletions or duplications (i.e. 22q11 deletion syndrome)

On the horizon

Genomic technologies

Intron Intron Intron
3'
Exon Exon Exon
Whole genome sequencing

- VS -

Intron Intron Intron
5'
Exon Exon Exon
Exome sequencing

Hardisty and Vora, 2014
Thank You