Reference Guide for Health Care Providers
Prenatal Screening Tests for the Detection of:
Down Syndrome, Trisomy 18 and Open Neural Tube Defects

Advances in prenatal screening have resulted in new tests that offer an improved detection rate and fewer false positives in the detection of chromosome abnormalities. These include nuchal translucency (NT) ultrasound, and new biochemical markers (PAPP-A and DIA). Timing of these tests beginning at 11 weeks’ gestation necessitates discussion early in pregnancy.

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Counselling Tip:
“A screening test can tell us if your baby has a higher than average chance of having a certain disorder. It does not tell us if your baby truly has the disorder or not. With screening, most babies with Down syndrome will be detected, but some will be missed.

What disorders are being screened for?
Prenatal screening gives a woman her individual risk of having a child with Down syndrome, trisomy 18 and open neural tube defects. It does not screen for all chromosome abnormalities, so some may be missed. Following positive results, women will need to decide whether to go on to have diagnostic testing (i.e. CVS or amniocentesis). Prenatal screening should be offered as part of a program where diagnostic testing, counselling and follow up are available.

Down Syndrome (trisomy 21):
Intellectual disability of varying severity, characteristic facial appearance, hypotonia & other less common congenital anomalies. The general population incidence of Down syndrome is 1 in 800, but varies with maternal age.

Prenatal ultrasound findings: congenital heart defects (40%), intestinal obstruction (12%), approximately 1/3 of affected fetuses will have normal ultrasounds at 18-20 weeks.

Trisomy 18 (Edwards syndrome):
95% of pregnancies will result in a miscarriage or stillbirth, 95% of liveborn infants die by 1 year. Surviving infants will have severe intellectual disability and multiple congenital anomalies. The general population incidence of trisomy 18 is 1 in 6,000, but varies with maternal age.

Prenatal ultrasound findings: congenital heart defects (90%), choroid plexus cysts, distinct hand posture, club feet, micrognathia, intrauterine growth retardation and others. Though rare, affected fetuses may have a normal ultrasound at 18-20 weeks.

Open Neural Tube Defects (NTD)
- including anencephaly and spina bifida:
Anencephaly is lethal. Most babies with spina bifida survive and may have problems ranging from hydrocephalus, paralysis and learning/intellectual disabilities to no physical or mental disabilities. Non-gestational diabetes mellitus, anticonvulsant medications, family history of NTD and hyperthermia result in a higher chance of an affected child. The general population incidence in North America is about 1 in 2,000, does not vary with maternal age.

Things to keep in mind:
• Informed choice - Before ordering the test, discuss benefits, risks and limitations.
• Autonomy - The patient should choose whether to have prenatal screening.
• What prenatal screening options are available in your area?
• What option is most suitable for your patient?
• Which test will provide the optimal care for your patient?
• A screening test is not diagnostic.
Prenatal Screening Tests for the Detection of Down Syndrome

### IF PATIENT PRESENTS BEFORE 14 WEEKS

**Integrated Prenatal Screening (IPS)**

- **First Trimester (11-13+6/7 wks)**
  - ↑NT – by certified sonographer
  - MS: ↓PAPP-A

- **Second Trimester (15–20+6/7 wks)**
  - MS: ↓AFP, ↑hCG, ↓uE3

**Serum Integrated Prenatal Screening (SIPS)**

- **First Trimester (11-13+6/7 wks)**
  - MS: ↓PAPP-A

- **Second Trimester (15–20+6/7 wks)**
  - MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA

**First Trimester Combined Screening (FTS)**

- **First Trimester (11-13+6/7 wks)**
  - ↑NT – by certified sonographer
  - MS: ↓PAPP-A, ↑fbhCG

### IF PATIENT PRESENTS AFTER 14 WEEKS

**Maternal Serum Screen (Quadruple Screening)**

- **Second Trimester (15–20+6/7 wks)**
  - MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA

**Maternal Serum Screen (Triple Screening -MSS)**

- **Second Trimester (15–20+6/7 wks)**
  - MS: ↓AFP, ↑hCG, ↓uE3

### Testing for Open Neural Tube Defects and Trisomy 18

<table>
<thead>
<tr>
<th>Open Neural Tube Defects</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td>↑AFP</td>
<td>↑NT, ↓PAPP, ↓fbhCG, ↓AFP, ↓hCG, ↓uE3, ↓DIA</td>
</tr>
</tbody>
</table>

**Detection Rate (DR):**
Also known as sensitivity, is the probability that a fetus affected with Down syndrome will be detected by the prenatal screening test.

**False Positive Rate (FPR):**
The proportion of women with unaffected pregnancies who have positive results.

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### Detection Rate (DR):

- **85-90% 2.4%**
- **80-90% 2-7%**
- **78-85% 3-9%**
- **75-85% 5-10%**
- **71% 7%**

### False Positive Rate (FPR):

- **5-10%**
- **5%**
- **4%**

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*NTDs can be screened for by MS-AFP and/or by ultrasound at 18-20 weeks*
**Algorithms**

### Integrated Prenatal Screening (IPS) and Serum Integrated Prenatal Screening (SIPS)

**Step 1:** First trimester: 11 – 13+6/7 weeks
- IPS: NT measurement then MS:PAPP-A
- SIPS: MS:PAPP-A

**Step 2:** Second trimester: 15 – 20+6/7 weeks
- IPS: MS:AFP, uE3, hCG
- SIPS: MS:AFP, uE3, hCG, DIA

**SCREEN POSITIVE**
- Discuss options
- Offer referral to genetic services

**SCREEN NEGATIVE**
- Ultrasound at 18 - 20 weeks

- SCREEN POSITIVE: chromosome problem
  - Offer amniocentesis 15 - 22 weeks

- SCREEN POSITIVE: NTD
  - Offer ultrasound 15 – 20 weeks
  - and/or amniocentesis

  - Most results are normal
  - Risk of future pregnancy complications with a high MS-AFP
  - Discuss options if abnormal

### First Trimester Combined Screening (FTS)

**First trimester:** 11 – 13+ 6/7 weeks
- NT measurement then MS:PAPP-A, fβhCG

**SCREEN POSITIVE**
- Discuss options
- Offer referral to genetic services

- Offer CVS 11-13 weeks
- Offer amniocentesis 15-22 weeks

**SCREEN NEGATIVE**
- Abnormal result
  - Most results normal
  - Discuss options
  - Abnormal result

### Maternal Serum Triple and Quadruple Screening

**Second trimester:** 15 – 20+ 6/7 weeks
- **Triple screening:** MS:AFP, uE3, hCG
- **Quadruple screening:** MS:AFP, uE3, hCG, DIA

**SCREEN POSITIVE**
- Discuss options
- Offer ultrasound 18 - 20 weeks

**SCREEN NEGATIVE**
- Ultrasound at 18 - 20 weeks

**SCREEN POSITIVE:** NTD
- Offer ultrasound 15 – 22 weeks
- Offer amniocentesis 15 – 20 weeks
- and/or amniocentesis

**SCREEN POSITIVE:** Chromosome problem
- Offer ultrasound 15 – 20 weeks
- and/or amniocentesis

- Abnormal result
  - Most results normal
  - Discuss options
  - Abnormal result
  - Most results are normal
  - Risk of pregnancy complications with a high MS-AFP
  - Discuss options

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**Abbreviation Key**
- AFP: Alpha-FetoProtein
- DIA: Dimeric Inhibin-A
- DR: Detection Rate
- fβhCG: free-beta subunit of human Chorionic Gonadotropin
- FPR: False Positive Rate
- hCG: human Chorionic Gonadotropin
- MS: Maternal Serum
- NT: Nuchal Translucency measured by ultrasound
- NTD: Neural Tube Defects
- PAPP-A: Pregnancy-Associated Plasma Protein A
- uE3: unconjugated Estriol

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All pregnancies have a 2-3% risk for any birth defect; which may or may not be detected by prenatal screening.
Prenatal Diagnostic Testing:
Currently, pregnant women are eligible for amniocentesis or CVS if they are ≥ 35 years, have a positive prenatal screening test, family history of genetic disease or certain ultrasound findings.

<table>
<thead>
<tr>
<th>Amniocentesis</th>
<th>CVS</th>
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<tbody>
<tr>
<td>Performed</td>
<td></td>
</tr>
<tr>
<td>15 -17 wks (ideal)</td>
<td>11 - 13 wks(^2)</td>
</tr>
<tr>
<td>- but available up to 22 wks(^1)</td>
<td></td>
</tr>
<tr>
<td>Sample</td>
<td></td>
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<tr>
<td>Amniotic fluid</td>
<td>Placental villi</td>
</tr>
<tr>
<td>Results available</td>
<td>2 - 3 wks</td>
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<tr>
<td>Miscarriage rate</td>
<td>0.01 - 0.5%(^3)</td>
</tr>
<tr>
<td>Advantage</td>
<td></td>
</tr>
<tr>
<td>- Accurate</td>
<td>- Accurate</td>
</tr>
<tr>
<td>- Widely available</td>
<td>- 1st trimester test – earlier results</td>
</tr>
<tr>
<td>- Tests for NTDs</td>
<td></td>
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<tr>
<td>Disadvantage</td>
<td></td>
</tr>
<tr>
<td>2nd trimester test</td>
<td>- Availability varies</td>
</tr>
<tr>
<td>- later results</td>
<td>- Does not test for NTDs</td>
</tr>
<tr>
<td>↑ rate of repeat procedures due to ambiguous results</td>
<td></td>
</tr>
</tbody>
</table>

1. Amniocentesis may be available later than 22 weeks in certain circumstances.
2. The timing of CVS may vary between centres.
3. Recent studies suggest that miscarriage rate is lower than 1 in 200 (0.5%).

Resources & Links

Mount Sinai Hospital Family Medicine Genetics:
http://www.mtsinai.on.ca/FamMedGen/Default.htm

Genetics Education Project website, downloadable version of this Guide available and other genetics resources for your practice.

Canadian Association of Genetic Counsellors:  http://www.cagc-accg.ca

Canadian Genetics Clinics list of contact and referral information.

Centre for Effective Practice:  http://www.effectivepractice.org/
Primary care resources for your practice.

The Genetics Home Reference Your Guide to Understanding Genetic Conditions
An excellent genetics educational site.

March of Dimes:  http://marchofdimes.com/
Excellent source of patient information for questions during pregnancy.

Motherisk:  http://www.motherisk.org/ or 416-813-6780
A teratogen information service.

Ontario Provincial Maternal Serum Screening Program:
http://www.lhsc.on.ca/programs/rmgc/mss/ Patient information on IPS, FTS and second trimester MSS.

The Society of Obstetricians and Gynaecologists of Canada:
http://www.sogc.org/guidelines/index_casp
Practice guidelines.

<table>
<thead>
<tr>
<th>Authors:</th>
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<tbody>
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<td>Dr. Mary Jane Esplen, nurse</td>
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<td>Dr. Gail Graham, geneticist</td>
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<td>Dr. Wendy Meschino, geneticist</td>
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<td>Ms. Joanne Miyazaki, laboratory services</td>
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<tr>
<td>Ms. Linda Spooner, nurse</td>
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Risk Of Chromosome Abnormalities In Liveborn Infants at Term

<table>
<thead>
<tr>
<th>Maternal Age (yrs)</th>
<th>Risk of Down Syndrome</th>
<th>Risk of any Chromosome Abnormalities</th>
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<tr>
<td>20</td>
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Adapted from: