

# Prenatal Genetic Screening in BC.

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Dept of Medical Genetics  
C&W

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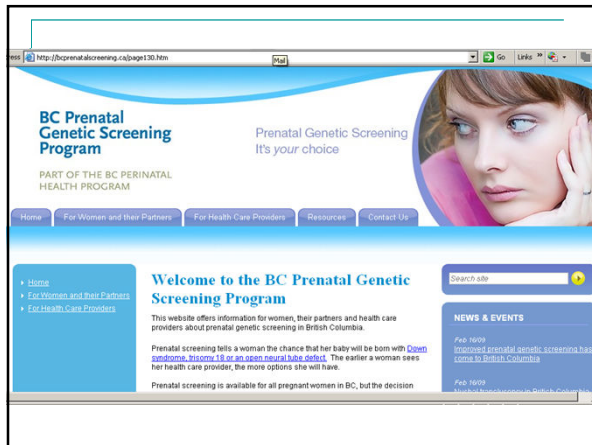
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## By the end of the session, participants will be familiar with:

- the concept and tests available for prenatal screening for Down syndrome, trisomy 18 and open neural tube defect
- the practical issues related to screening for Down syndrome
- the screening tests available for some of the more common autosomal recessive disorders.

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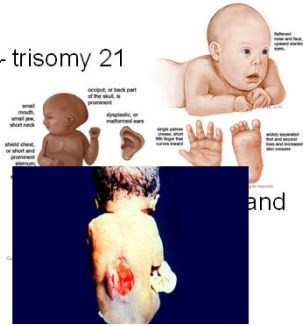
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## What are we screening for?

- Down syndrome – trisomy 21
- Trisomy 18
- Open neural tube spina bifida.



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## Estimating risk of Down syndrome.

- Patient a priori risk – age related risk.
- Modify the “a priori risk” by factoring in the results of the “markers” measured.
- Patient’s Down syndrome risk in this pregnancy.

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## How are we screening?

- We measure a combination of markers for which the levels seen in a normal population differ from those seen in a population of Down syndrome pregnancy.

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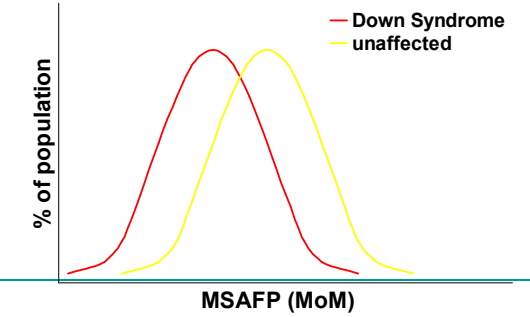
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**MSAFP levels in maternal serum at a specific gestational age**




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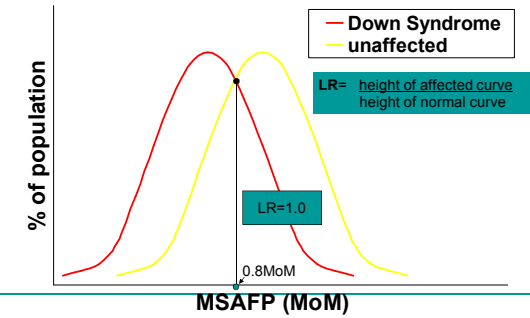
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**MSAFP levels in maternal serum at a specific gestational age**




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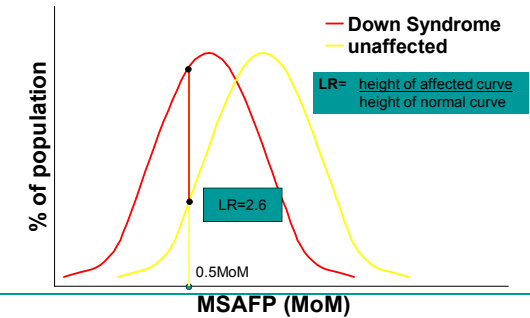
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**MSAFP levels in maternal serum at a specific gestational age**




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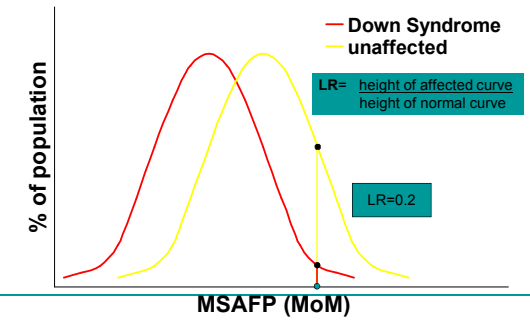
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### MSAFP levels in maternal serum at a specific gestational age




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### Patterns of markers

Condition	PAPP-A	AFP	uE3	hCG	InhibinA
ONTD		↑↑			
Down syndrome	↓	↓	↓	↑	↑
Trisomy 18	↓	↓	↓	↓	↓

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### Nuchal Translucency



- Gestation 11-14 wks
- CRL 45-84 mm
- Mid-sagittal view
- Image size: calipers 0.1mm
- Neutral position
- Away from amnion
- Maximum lucency
- Callipers on-to-on

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**Example of T21 risk calculation**

Maternal age at delivery is 30 years old

A priori risk = 1/900

SIPS screen with MoM for 5 markers

Likelihood ratios are:

PAPP-A LR 1.1

AFP LR 2.5

uE3 LR 1.5

hCG LR 0.80

Inhibin A LR 1.0

Quad screen Down's risk is:

$$1/900 \times 1.1 \times 2.5 \times 1.5 \times 0.80 \times 1.0 = 1/272$$

**"Positive Screen"**

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**Based on all available markers for Down syndrome – a number of tests available.**

- Quad screening in 2<sup>nd</sup> trimester - **QUAD**
- Serum integrated screening - **SIPS**
  - 1<sup>st</sup> and 2<sup>nd</sup> trimester biochemical markers
- Integrated prenatal screening – **IPS**
  - NT and 1<sup>st</sup> and 2<sup>nd</sup> trimester biochemical markers

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**BC Prenatal Genetic Screening Options**

Screening Options	Risk cut-off	DR	FPR	Negative Predictive Value
<b>SIPS</b>	1:300	87%	5%	99.9%
<b>IPS</b>	1:200	89%	2.5%	99.9%
<b>QUAD</b>	1:385	87%	8%	99.9%

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## BC Prenatal Genetic Screening Options

- Tests available:

Screening Options	Risk cut-off	DR	FPR	Negative Predictive Value
<b>SIPS</b>	1:300	<35 - 78% ≥35 - 92%	<35 - 3.3% ≥35 - 10%	99.9%
<b>IPS</b>	1:200	<35 - 83% ≥35 - 92%	<35 - 1.4% ≥35 - 5%	99.9%
<b>QUAD</b>	1:385	<35 - 75% ≥35 - 91%	<35 - 5.6% ≥35 - 18%	99.9%

These figures apply for Down syndrome and assume dating by US in women ≥35 years.

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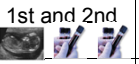

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## BC Prenatal Genetic Screening Options

- Tests available:

Screening Options	How	11 – 13 <sup>+</sup> 6	10-13 <sup>+</sup> 6	15 – 20 <sup>+</sup> 6
<b>SIPS</b>	1st and 2nd 		PAPPA	AFP, HCG, UE3 and Inhibin A
<b>IPS</b>	1st and 2nd 	NT U/S	PAPPA	AFP, HCG, UE3 and Inhibin A
<b>QUAD</b>	2nd 			AFP, HCG, UE3 and Inhibin A

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## Some factors to consider

- ~ 25,000 women have prenatal screening
- 7000 are women 35 years or older - “ higher risk”
- NT requires training, certification and maintenance of competence.
- Limited ultrasound capacity in BC – limited capacity for NT for next few years.

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**BC Prenatal Genetic Screening Options**

- Test to be offered will depend:
  - Age of the patient at time of delivery
  - Gestational age at first prenatal visit
  - Singleton vs multiple gestations
  - Presence of absence of other risk factors: e.g. previous history of trisomy 21, 18, or 13.

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**BC Prenatal Genetic Screening Options**

- Singleton pregnancies that present before 13 weeks 6 days offer:
  - Serum Integrated Prenatal Screen
  - If  $\geq 35$  years or increased risk by family history or obstetrical history AND NT available, add NT to SIPS = IPS

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**BC Prenatal Genetic Screening Options**

- Singleton pregnancies that present after 13 weeks 6 days and before 20 wks 6 days offer:
  - QUAD

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## Screening in Multiple Gestations

- Most reliable marker in twins is NT as allows assessment of each twin individually
- Regardless of maternal age, twin gestations qualify for **IPS** if diagnosed in first trimester

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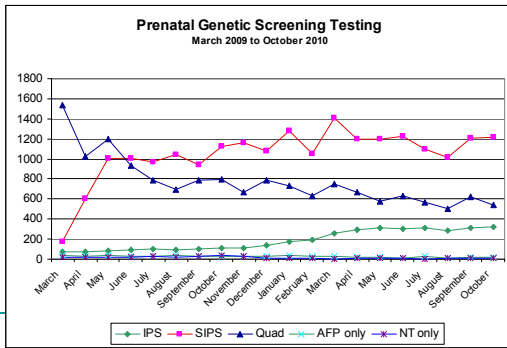
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## Screening Stats 2009 / 2010




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## Uptake of screening

Age	2009	2010
<35	46%	51%
35-39	58%	66%
40+	62%	69%
Total	50%	55%

Baseline: 43% uptake for <35 yrs; 37% for ≥35yrs  
 2 yr target: 48% uptake for <35 yrs; 61% for ≥35yrs  
 5 yr target: 50% uptake for <35 yrs; 64% for ≥35yrs

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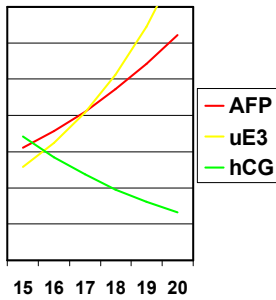
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**Maternal Serum Median Values**



Medians for all analytes vary with gestational age.

**Because of this accurate dating is crucial**

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**Dating**

- Screening performance is improved with U/S dating compared to LMP dating.
- If dating ultrasound done, CRL should be provided and will be used above LMP for risk calculation.
- If no dating scan done and 2<sup>nd</sup> trimester U/S shows dating discrepancy of 8 days or more, contact the laboratory for reinterpretation.

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### Timeline .....

- Results within 10 days of second blood draw
- negative result - reassuring.
  
- positive screen results requires additional testing.
  - Amniocentesis
  - Option of termination available until 23<sup>+6</sup> wks

Prompt "dispatching" of samples is crucial.

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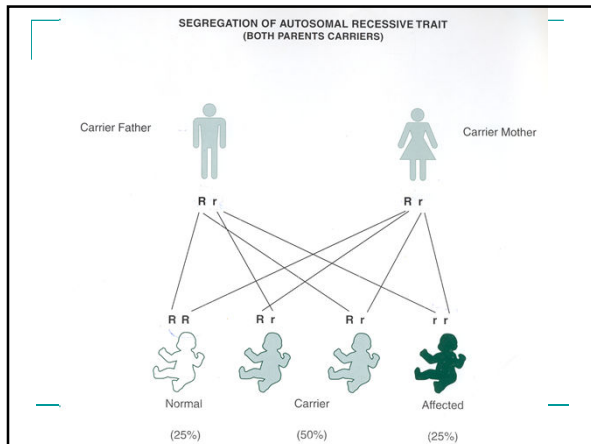
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**Genetic screening**

- **For single gene disorders**
  - review of the family history
  - specific testing based on ethnic background

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**Genetic screening**

- **For single gene disorders**
  - review of the family history
  - specific testing based on ethnic background

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Identify carriers who are at risk of having an affected child so that specific prenatal diagnosis can be offered.

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### Tay - Sachs disease



- more common amongst Ashkenazi Jewish individuals
- carrier frequency of 1/30 (compared to 1/250 -1/300 in non-Jews.)
- severe disease : neurodegenerative which starts between 3-6 months, death by 4 years.

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### Carrier screening for Tay Sachs

- DNA testing for the common mutations in the *HEX A* gene seen in Ashkenazi Jewish individuals – picks up 98% of carriers.
- prenatal testing is possible by DNA analysis of CVS or amniotic fluid.

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### Canavan disease

- seen in all ethnic groups but more common amongst Ashkenazi Jewish individuals
- carrier frequency of 1/37 - 1/57 (disease freq. of 1/5476 - 1/12996)
- severe disease : neurodegenerative which starts around 3- 6 months, hypotonia, spasticity, death in childhood.

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**Canavan disease**

- carrier testing: in the Ashkenazi Jewish population - 3 mutations account for 98% of alleles.
- prenatal testing is possible by DNA analysis of CVS or amniotic fluid.

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**Familial Dysautonomia**

- Autosomal recessive condition seen almost exclusively in Ashkenazi Jewish population
- Carrier freq. of 1/32
- Severe neurological disorder affecting the the sensory and autonomic system. Affects swallowing, digestion, pain sensation. Death is usually before age 30.
- carrier testing: in the Ashkenazi Jewish population - 2 mutations account for 99% of alleles.
- prenatal testing is possible by DNA analysis

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**Ethnic specific carrier testing  
Ashkenazi Jewish Individuals**

- **If both members of the couple are AJ:**
  - DNA testing for Tay Sachs, Canavan, Familial Dysautonomia, Fanconi Anemia - Ashplex panel
- **If only one member is AJ: offer TaySachs screening only – can be done by enzymatic assay Hexoaminidase A**

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### Sickle cell disease

- more common amongst African Americans
- carrier frequency of 1 in 12
- Also increased in Middle East, Mediterraneans
- definite burden of disease: bone pain, chest pain from occlusive disease in lung, stroke, hepatosplenomegaly, anemia, aplastic crisis
- carrier testing:
  - Hemoglobin electrophoresis
- Prenatal diagnosis by DNA testing



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### Thalassemia: $\beta$ and $\alpha$



- more common Mediterraneans, Arabian peninsula, Turkey, Iran, Africa, India, South-East Asia, Southern China.
- carrier frequency:  $\beta$  thal in Cyprus and Sardinia - 14%  
in chinese - 2-4%  
 $\alpha$  thal in chinese - 5%
- Beta thalassemia: severe anemia – transfusion dependant
- Alpha thalassemia: fetal hydrops.

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### Thalassemia: $\beta$ and $\alpha$



- Carriers of  $\beta$  and  $\alpha$  thalassemia present with a low MCV on their CBC. MCV<80
- Carriers of  $\beta$  thalassemia have increased HbA2 on Hemoglobin electrophoresis.
- Prenatal diagnosis by DNA testing if both partners are carriers.

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**Ethnic specific carrier testing**

- African Americans, Mediterraneans, Middle Eastern, South East Asians, Western Pacific

Should have CBC and Hb Electrophoresis.

(Everyone except Northern Europeans, Native Americans, Japanese, Koreans)

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**For more information**

- [www.bcprenatalscreening.ca](http://www.bcprenatalscreening.ca)
- [www.elabhandbook.info](http://www.elabhandbook.info)

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