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.

In this monograph:

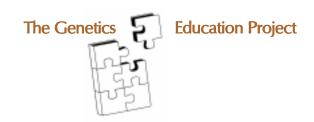
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Counselling Tip:

"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.

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.



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.

Prenatal Screening Tests for the Detection of Down Syndrome

Test		Down syndrome		Comments	Abbreviation AFP: Alp
		Detection Rate (DR)	False Positive Rate (FPR)		DIA: Din <i>f</i> βhCG: free of 1
IF	PATIENT PRESENTS BEFORE 14 WEEKS				Cho Go:
→	 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 	85-90%	2-4% ¹	 Results available in 2nd trimester Amniocentesis for diagnostic testing 	hCG: hun Go MS: Mai NT: Nu Tra mea ultr NTD: Net
→	 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 	80-90%	2-7% ^{1,2}	 Results available in 2nd trimester Amniocentesis for diagnostic testing Is available in most places where NT ultrasound is not available 	Defa PAPP-A: Preg Asso Prot uE3: uncc Estr Detection Ra Also known as probability tha with Down sy
Ļ	 First Trimester Combined Screening (FTS) First Trimester (11-13+6/7 wks) ↑NT - by certified sonographer MS: ↓PAPP-A, ↑fbhCG 	78-85%	3-9% ^{1,2,3}	 Results available in 1st trimester, earliest results CVS for diagnostic testing Does not screen for NTDs* 	
IF	PATIENT PRESENTS AFTER 14 WEEKS				detected by screening test
→	Maternal Serum Screen (Quadruple Screening) Second Trimester (15–20+6/7 wks) • MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA	75-85%	5-10%1,2,3	Results available in 2nd trimesterAmniocentesis for diagnostic testing	False Positiv
Ļ	 Maternal Serum Screen (Triple Screening -MSS) Second Trimester (15-20+6/7 wks) MS: ↓AFP, ↑hCG, ↓uE3 	71%	7% ⁴	Results available in 2nd trimesterAmniocentesis for diagnostic testing	The proportio unaffected p have positive

	tion Key:	
AFP:	P: Alpha-FetoProtein	
DIA:	Dimeric Inhibin-A	
3hCG:	free-beta subunit	
	of human	
	Chorionic	
	Gonadotropin	
CG:	human Chorionic	
	Gonadotropin	
AS:	Maternal Serum	
VT:	Nuchal	
	Translucency	
	measured by	
	ultrasound	
NTD:	Neural Tube	
	Defects	
APP-A:	Pregnancy-	
	Associated Plasma	
	Protein A	
E3:	unconjugated	
	Estriol	

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ate (DR):

is sensitivity, is the nat a fetus affected syndrome will be y the prenatal

ve Rate (FPR):

on of women with pregnancies who results.

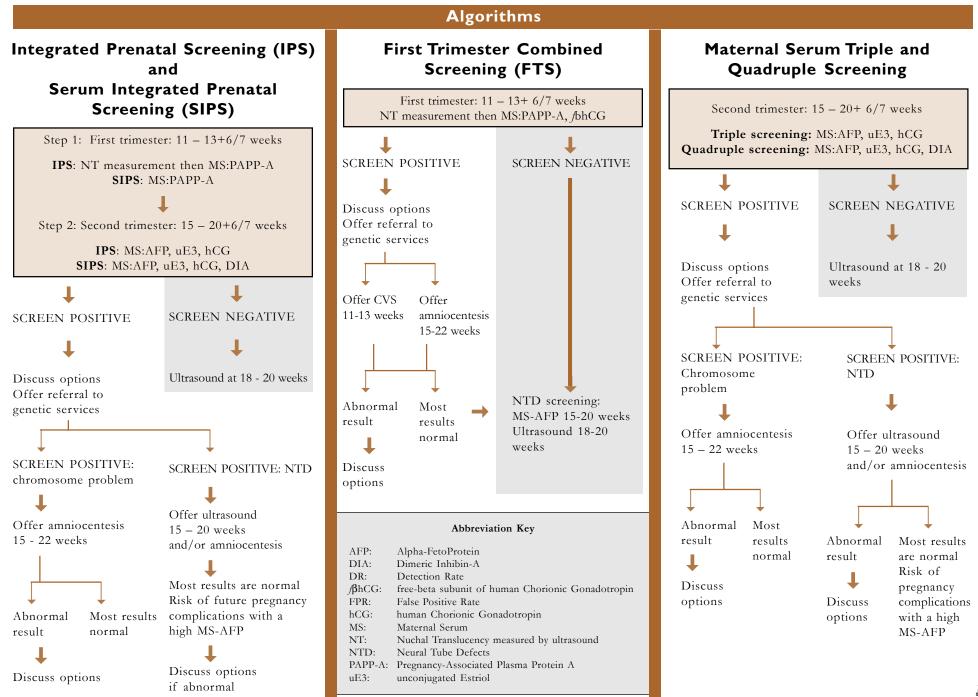
Testin	Testing for Open Neural Tube Defects and Trisomy 18				
	Open Neural Tube Defects	Trisomy 18			
MS	↑AFP	↑NT, ↓PAPP, \downarrow <i>fb</i> hCG, ↓AFP, ↓hCG, ↓uE3, ↓DIA			
DR	80% for each test except FTS which does not screen for $\rm NTDs^5$	Slightly lower than the DR for Down syndrome for each test			
FPR	Usually 5% or less for all tests except FTS^5	Lower than the FPR for Down syndrome for each test. Usually 1% or less	3		

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

Pregnancy Dating Ultrasound (U/S) dating is more accurate than LMP; a dating U/S will lower the FPR.

dapted from:

- Wald NJ, et al. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). J Med Screen 2003; 10:56 104.
- Malone FD, et al. First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med. 2005; 353:2001-11.
- Wapner R, et al. First trimester screening for trisomies 21 and 18. N Engl J Med 2003; 349:1405 1413.
- Summers AS, et al. Material serum screening in Ontario using the triple marker test. J Med Screen 2003; 10:107-11
- 5. American College of Obstetricians and Gynecologists. Clinical Management Guidelines for obstetrician-gynecologists. ACOG Practice Bulletin No. 44, Obstet Gynecol 2003; 102:203.



All pregnancies have a 2-3% risk for any birth defect; which may or may not be detected by prenatal screening

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Prenatal Diagnostic Testing:

Currently, pregnant women are eligible for amniocentesis or CVS if they are \geq 35 years, have a positive prenatal screening test, family history of genetic disease or certain ultrasound findings.

	Amniocentesis	CVS
Performed	15 -17 wks (ideal)but available up to 22 wks¹	11 - 13 wks ²
Sample	Amniotic fluid	Placental villi
Results available	2 - 3 wks	2 - 3 wks
Miscarriage rate	$0.01 - 0.5\%^3$	1%
Advantage	AccurateWidely availableTests for NTDs	 Accurate 1st trimester test – earlier results
Disadvantage	2nd trimester test - later results	 Availability varies Does not test for NTDs ↑ rate of repeat procedures due to ambiguous results

Amniocentesis may be available later than 22 weeks in certain circumstances.

2 The timing of CVS may vary between centres.

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 http://www.ghr.nlm.nih.gov/ 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_e.asp Practice guidelines.

Authors:

Dr. June Carroll, family physician Dr. Judith Allanson, geneticist Dr. Mary Jane Esplen, nurse Dr. Gail Graham, geneticist Dr. Wendy Meschino, geneticist Ms. Joanne Miyazaki, laboratory services Ms. Linda Spooner, nurse Dr. Sherry Taylor, molecular geneticist Dr. Brenda Wilson, epidemiologist

Ms. Andrea Rideout, genetic counsellor Dr. Sean Blaine, family physician Dr. Sandra Farrell, geneticist Dr. Jennifer MacKenzie, geneticist Dr. Fiona Miller, epidemiologist Ms. Cheryl Shuman, genetic counsellor Dr. Anne Summers, geneticist

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Risk Of Chromosome Abnormalities In Liveborn Infants at Term

III LIVEDOITI IIItantes at Territ					
Maternal	Risk of	Risk of any			
Age	Down	Chromosome			
(yrs)	Syndrome	Abnormalities			
20	1/1,650	1/530			
21	1/1,650	1/530			
22	1/1,430	1/500			
23	1/1,430	1/500			
24	1/1,250	1/480			
25	1/1,250	1/480			
26	1/1,175	1/480			
27	1/1,110	1/450			
28	1/1,050	1/430			
29	1/1,000	1/420			
30	1/950	1/390			
31	1/900	1/390			
32	1/770	1/320			
33	1/625	1/285			
34	1/500	1/240			
35	1/385	1/180			
36	1/300	1/150			
37	1/225	1/125			
38	1/175	1/100			
39	1/135	1/80			
40	1/100	1/65			
41	1/80	1/50			
42	1/60	1/40			
43	1/50	1/30			
44	1/40	1/25			
45	1/30	1/19			
46	1/23	1/15			
47	1/18	1/11			
48	1/14	1/9			
49	1/11	1/7			
Adapted from: Hook EB, Cross PK, Schreinemachers DM. Chromosomal					

abnormality rates at amniocentesis and in live-born infants. [AMA 1983;249:2034-38.

Hook EB. Rates of chromosomal abnormalities at different maternal ages. Obstet Gynecol 1981;53:282-85.

This monograph was prepared by members of The Genetics Education Project and the Education Subcommittee of the Ontario Multiple Marker Screening Committee in 2007. Health care providers must use their own clinical judgement in addition to the information presented herein. The authors assume no responsibility or liability resulting from the use of information in this monograph.

This monograph was partly funded by the Ontario Women's Health Council (OWHC). The OWHC is fully funded by the Ontario Ministry of Health and Long-Term Care. This monograph does not necessarily reflect endorsement of the Ontario Ministry of Health and Long-Term Care.