JAMES COOK UNIVERSITY AUSTRALIA

Celebrating 50 YEARS 1970 - 2020

General Practice Training Queensland

HEALTH PROFESSIONALS WEBINAR SERIES

Antenatal Screening Unplugged

TUESDAY, 23 JUNE 2020

7:00PM QLD/NSW/ACT/VIC, 6:30PM SA/NT, 5:00PM WA

An update on preconception and antenatal screening

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Case study 1 – 'Rachel'

32yo Rachel attends your practice in far western QLD with her husband for a pregnancy planning visit. She has no significant risk factors for genetic abnormalities. She is wondering if there are any tests she should have done prior to her getting pregnant. You rattle off a series of investigations including her varicella and rubella serology, but then you recall the last RANZCOG statement that stated that all couples should be offered carrier screening for common genetic conditions.

How do you proceed?

RANZCOG Recommendations

- Information on carrier screening ***should be*** offered to all women planning a pregnancy or in the first trimester of pregnancy.
- Options for carrier screening with a panel for a limited selection of the most frequent conditions (i.e. cystic fibrosis, spinal muscular atrophy and fragile X syndrome) or screening with an expanded panel that contains many disorders (up to hundreds).

REF: RANZCOG. (2019). Genetic carrier screening. Retrieved 22 June 2020, from https://ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Genetic-carrier-screening(C-Obs-63)New-March-2019_1.pdf?ext=.pdf

What is reproductive carrier screening and why is it important?

- Reproductive carrier screening:
  - tests healthy adults: ? increased chance of having a child with an autosomal recessive or X-linked genetic condition before conception, or prior to birth.
- Hundreds of inherited genetic conditions that present in infancy or early childhood.
  - Most are rare.
- Grouping these conditions together, they affect about 1 in 400 people (Stenson et al., 2017)
- **Most children born with these conditions are born into families with no other affected family members.**

Ref: Stenson PD, Mort M, Ball EV, et al. The human gene mutation database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136(6):665-677.

What do we need to decide?

- Individual vs. couple?
- Preconception vs. Pregnant?
- Limited vs. expanded?

Test type	Limited panel	Expanded panel
Conditions screened	Cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS)	~300+ specific conditions (including CF, SMA and FXS)
Sample type	Saliva/Blood	Saliva/Blood
Cost	~$385 (Medicare rebate if family history of CF*)	Varying costs through different platforms
Turn-around-time	~14 days	~21 days

Case study1: 'Rachel'

- 'Rachel', G0P0
- After discussion, Rachel and her partner opt for the expanded carrier screening panel.
- The couple are found to be at a high probability (25%) of having a child with Pontocerebellar Hypoplasia.
  - What is Pontocerebellar Hypoplasia?
    - Causes abnormal brain development (underdevelopment of the pons and cerebellum), microcephaly, intellectual disability, decreased muscle tone, and vision loss
    - Life-limiting (death in infancy or early childhood)
- They are shocked, but relieved to have this result prior to pregnancy
- Options including pre-implantation genetic testing (PGT-M) and/or prenatal diagnosis discussed.

Monash IVF Group Experience

- 721 individuals screened with expanded panel:
  - Negative screen: 187 (26%)
  - Positive carrier result: 534 (74%)
  - Carrier couples: 20 (2.8%):
    - SMA
    - Galactosemia
    - Cystic Fibrosis
    - X-linked Retinoschisis
    - Non-syndromic hearing loss
    - Batten syndrome
    - Fragile X syndrome
    - Pontocerebellar Hypoplasia
- Other clinically significant results:
  - Homozygous for hereditary haemochromatosis
  - Affected with Factor V Leiden
- What we have learned:
  - Screening by age, ethnicity and family history is not a good indicator

Case study 2 – 'Marissa'

After uneventful pre-conception counselling, Marissa returns several months later approximately 8 weeks pregnant. She asks about first trimester screening options but wants you to know that due to COVID, money is tight as both her and her husband has lost his job.

What are her options?

Case study 2 – 'Marissa'

Marissa elects to have a nuchal translucency test at the nearest facility 400km away which returns a result of 1/200 risk for Trisomy 21.

What does this mean for Marissa's pregnancy?

What options does she have to proceed, keeping in mind her location and budget?

Prenatal screening

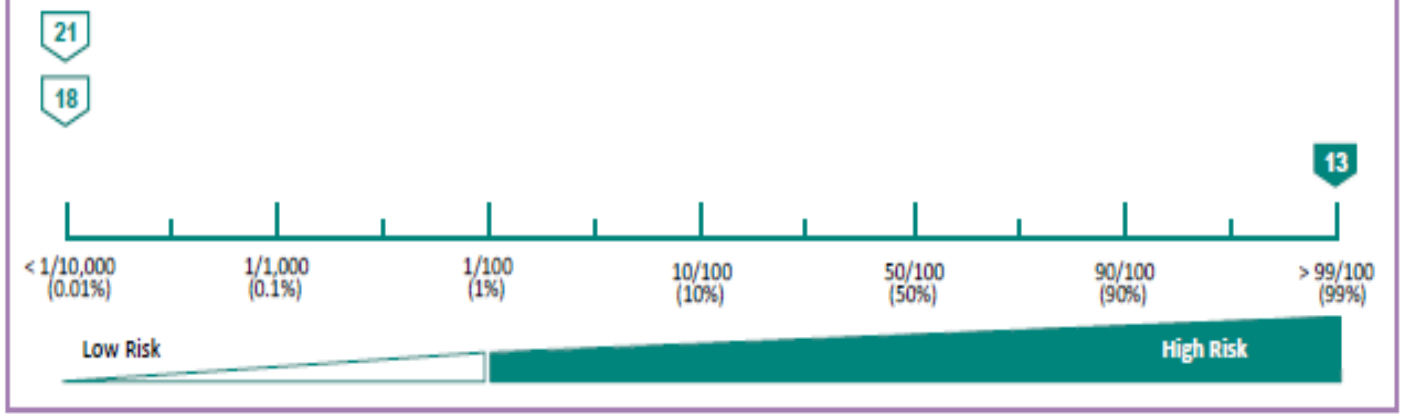
Screening test	Non-invasive prenatal testing (NIPT)	Combined first trimester screening (CFTS)	Second trimester maternal serum screening (2TMSS)
Method	• Maternal blood taken from 10 weeks GA onwards. • Examines cell-free DNA released from the placental into the maternal blood stream	• Maternal blood taken between 9-13 weeks GA to measure PAPP-A and free beta-HCG • Nuchal translucency ultrasound 11-13 weeks GA • Maternal age, weight and GA	• Maternal blood taken between 14-20 weeks GA (best done between 15-17 weeks) to measure alpha-feto protein, unconjugated estriol, free beta-HCG and inhibin A. • Maternal age, weight and GA.
Conditions screened	T21, T18, T13 and sex chromosome aneuploidy. Some platforms additionally all autosomes for aneuploidy, as well as segmental gains/losses >7mb.	T21, T18 and T13	T21, T18 and neural tube defects
Detection rate	99% (for T21)	85-90%	75-80%
Cost	~$450	$90-120	$79-88
12-13 week ultrasound	Strongly recommended	Required	Strongly recommended

Case study 3: 'Emily'

- 'Emily' G2P1, 31yo
- Indication for NIPT: Maternal preference
- Pre-NIPT scan reveals incorrect dates (9+5/40).
- Returned the following week for blood draw at 10+5/40

Test Results — **Fetal cfDNA Percentage: 5.6%**

CHROMOSOME	RESULT	PROBABILITY	RECOMMENDATION
Trisomy 21 (T21)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 18 (T18)	Low Risk	Less than 1/10,000 (0.01%)	Review results with patient
Trisomy 13 (T13)	**High Risk**	**Greater than 99/100 (99%)**	**Genetic counseling and additional testing**
Fetal Sex	No Result	No Result	No Result
X,Y Analysis	No Result	No Result	No Result



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Case study 3: 'Emily'

- Could this be the reason the fetus was behind dates?
- Emily was informed of these results and was understandably shocked/upset
- Discussed the main clinical features of Trisomy 13
- Discussed that invasive genetic testing is recommended to confirm these results
- Scan performed the following day, no abnormalities detected
- PPV for T13 and possibility of confined placental mosaicism (CPM) discussed
- Emily decided to proceed with amniocentesis

PPV in action

https://www.med.unc.edu/mfm/nips-calc/

University of North Carolina at Chapel Hill

Positive Predictive Value of Cell Free DNA Calculator

Baseline Risk
(•) Age-related risk ( ) A priori risk

Maternal Age (31)

20 22 24 26 28 30 32 34 36 38 40 42 44

Gestational Age in Weeks (10)

10 12 14 16 18 20

Test
(•) Harmony® ( ) Materniti 21® ( ) Panorama® ( ) Verifi®

	Trisomy 21	Trisomy 18	Trisomy 13
Age-related risk	1:409	1:1014	1:3228
Test Sensitivity	99	98	80
Test Specificity	99.97	99.93	99.9
PPV	89%	58%	20%

Disclaimers:

- The calculator is a counseling tool and is meant to be an adjunct to, not a replacement of, in-person counseling.
- The calculator is an estimate of the positive predictive value and does not account for errors in estimation of the maternal age/gestational age-related risk of aneuploidy or the confidence intervals around each tests' sensitivity and specificity.
- Age and gestational age-related risk tables were used from: Snijders RJ, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risk for chromosomal defects. Fetal Diagn Ther 1995;10:356–67.
- This calculator is designed as a teaching tool to demonstrate the relationship between a priori risk, sensitivity and specificity and to underline that cell-free DNA screening **is not a diagnostic test**. Therefore, it is critical for patients with abnormal test results to be offered **diagnostic** testing such as a CVS or amniocentesis.
- The sensitivity and specificity for each test is based on clinical validation trials. As these studies vary significantly in their sample size, study design, and data analysis, this calculator **should not be used as a tool to compare the different testing platforms**.
- These estimates are based on high risk results ("aneuploidy detected", "Positive", or increased risk results (99/100)) and PPV for results reported with an intermediate increased risk (such as "aneuploidy suspected", >1% but
- For more information about this calculator please see: Grace, M. R., et al. (2015). "Cell free DNA testing-interpretation of results using an online calculator." Am J Obstet Gynecol 213(1): 30 e31-34.

Verifi® is a registered trademark of Illumina, Inc.

Harmony® is a registered trademark of Ariosa Diagnostics.

Ref: Grace, M. R., et al. (2015). "Cell free DNA testing-interpretation of results using an online calculator." Am J Obstet Gynecol 213(1): 30 e31-34.

Case study 3: 'Emily'

- Lab performed two types of analysis on sample:
  - Normal FISH (reported within 24-28 hours)
  - Normal Molecular Karyotype

*Prenatal diagnosis is recommended when:

- High probability NIPT
- Abnormalities on Ultrasound
- Nuchal measurement ≥3.5mm
- Increased probability FTCS (1:2 – 1:50)

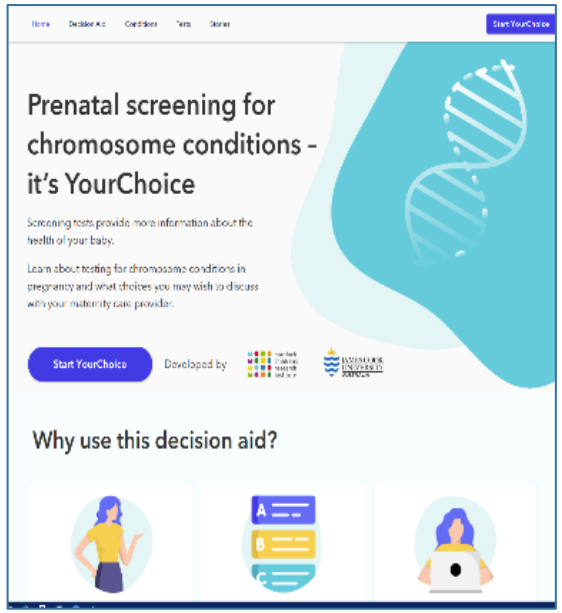
Microarray analysis is the preferred cytogenetic technique for prenatal diagnosis

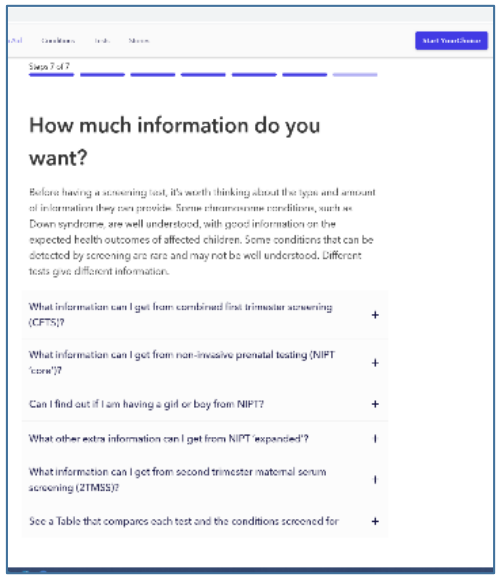
What did we learn?

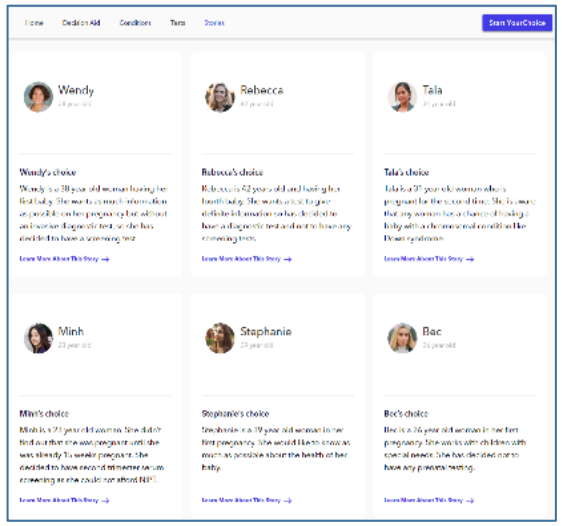
- Tertiary ultrasound is paramount: most Trisomy 13 fetuses present with phenotypic features which in experienced hands, can be identified with transabdominal in combination with high frequency transvaginal ultrasound assessment.

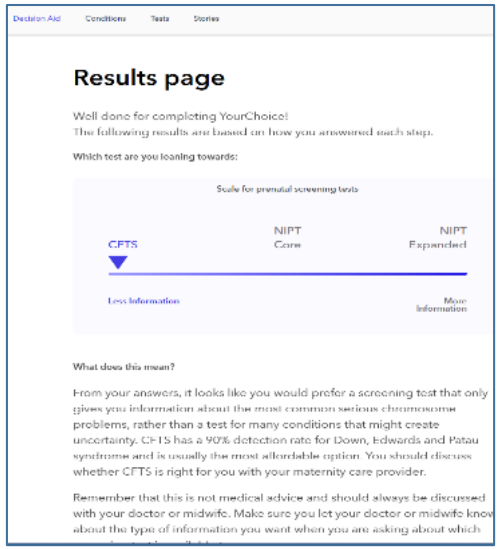
- In the event of a normal ultrasound:
  - Amniocentesis is preferred due to chance of placental/fetal mosaicism
  - Other explanations: co-twin demise, or a statistical false positive result with no apparent biological cause.

- Calculating the positive predictive value in these cases can be a useful counselling tool.









Decision Aid

- Value based decision support
- Adjuvant to clinical care
- Evidence based
- Risks, benefits and consequences

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Thank you

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