GENETIC COUNSELLING: ANEUPLOIDY SCREENING, INCLUDING THE NON-INVASIVE PRENATAL SCREENING (NIPS) TEST

This LOP is developed to guide clinical practice at the Royal Hospital for Women. It should not be taken as medical advice. Clinicians need to tailor their decisions to meet individual patient needs.

1 AIM
- To ensure woman is given appropriate counselling regarding her screening options for trisomy 21, other chromosomal anomalies (aneuploidy) and genetic conditions

2 PATIENT
- Pregnant woman

3 STAFF
- Medical and midwifery staff
- Genetic Counsellors

4 EQUIPMENT
- Ultrasound machine

5 CLINICAL PRACTICE
- Establish gestation and accurate expected date of delivery (EDD)
- Take a comprehensive history at booking regarding couple’s medical and family history
- Offer woman a referral for genetic counselling for the following indications:
  - personal or family history of genetic condition
  - current or previous pregnancy affected by aneuploidy and/or fetal anomalies
  - maternal or clinician request
  - high risk screening results e.g. combined first trimester screen (cFTS), NIPS, haemoglobinopathy (thalassemia)
    - inconclusive NIPS result/s
- Offer woman the option of screening for aneuploidy regardless of age
- Discuss options with woman outlining that each test has distinct advantages, disadvantages and limitations:
  - Combined first trimester screening (cFTS):
    - preferred primary screen at RHW
    - performed between 11½-13½ weeks gestation
    - involves:
      - ultrasound measuring nuchal translucency (NT), +/- nasal bone
      - serum biochemistry for Pregnancy Associated Plasma Protein-A (PAPP-A) and free beta human chorionic gonadotropin (βhCG)
    - screens for trisomies 21, 18 and 13
    - has a detection rate for Trisomy 21 of approximately 90% with a false positive rate of approximately 5%
    - ultrasound component determines gestation and number of fetuses (if not already established), viability, and identifies some congenital anomalies
    - Medicare rebates are available, and in some centres, cFTS is completely covered by Medicare
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- Non-invasive prenatal screening (NIPS):
  - performed after 10 weeks gestation
  - involves collection of maternal blood to analyse cell-free fetal DNA
  - an ultrasound for gestation (if not already established) and viability is recommended at the time of blood collection
  - can be used as primary screening for aneuploidy (Trisomy 21, 18 and 13 and sex chromosome aneuploidy) in conjunction with structural ultrasound at 12-14 weeks gestation
  - can also be used for secondary screening after cFTS
  - does NOT include routine serum biochemistry (PAPP-A and ßhCG). (The additional benefit of serum biochemistry remains undetermined but may detect fetuses at risk of atypical aneuploidy and growth restriction. If the woman wishes to have this performed, it needs to be requested in addition to NIPS)
  - has a detection rate of approximately 99, 97 and 92% for Trisomy 21, 18 and 13 respectively and an overall false positive rate of 0.4%
  - it may also report some sex chromosome abnormalities with a detection rate of approximately 95% and a much higher false positive rate compared to autosomes
  - self-funded (at time of publication)
- First trimester structural ultrasound and/or second trimester morphology ultrasound:
  - used in isolation, is not accurate compared to cFTS or NIPS

- Offer referral to genetic counsellor for woman who presents too late in gestation for the cFTS and has not already had NIPS/early structural ultrasound, to consider other options
- Ensure woman is aware when and how she will receive her results
- Ensure woman is aware not all results will be low risk and this can be quite stressful

High risk cFTS (> 1:300), NIPS suggestive of aneuploidy, NT ≥ 3.5 mm, and/or structural abnormality on ultrasound

- Inform woman of her risk assessment and refer for genetic counselling within a timely manner
- Provide counselling and emotional support
- Encourage the woman to bring her partner or other support person to the consultation
- Allow the woman time to consider her options
- Inform the woman that referral to the genetic counsellor is for discussion of further options. This sometimes takes several appointments
- Ensure woman is aware genetic counselling will cover the following issues:
  - provide a clear explanation of the implications of her result
  - provide information regarding the risks and limitations of further screening and diagnostic testing (chorionic villus sampling (CVS), or amniocentesis)
  - give an expected timeframe for results
  - provide verbal as well as written information
  - explore options to be considered if the result is abnormal
  - acknowledge the individual nature of decisions with regard to the pregnancy. This would include a balanced discussion about continuing the pregnancy as well as the option of termination of pregnancy(TOP). Woman considering TOP should be aware of surgical and non-surgical methods of TOP which are determined by gestation
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- Inform woman of (small) risks of miscarriage associated with diagnostic testing. Advise the woman that diagnostic testing provides more frequently clinically significant information in cases where:
  - the NT measures ≥ 3.5mm
  - the free βhCG measures greater than ≥ 5.0 MoM or < 0.2 MoM
  - the PAPP-A measures < 0.2 MoM
  - the combined cFTS risk is > 1:100
  - structural anomaly is detected on ultrasound (even if NIPS is low risk)
  - maternal age > 45 years
- Verify high risk NIPS results with diagnostic testing prior to any irreversible action such as TOP
- Provide documentation to referring doctor and/or clinic following genetic counselling and document in medical records
- Ensure other appropriate investigations are arranged as needed:
  - second trimester morphology ultrasound
  - fetal echocardiogram if the NT measures ≥ 3.5mm
  - third trimester ultrasound for growth assessment if PAPP-A < 0.4 MoM

Low risk cFTS result but with T21 risk 1:300-1000, and/or with a risk number that the woman is not reassured by:
- Inform woman this is a low risk result
- Discuss and consider NIPS as secondary screen, if woman is not reassured by her result
- If woman elects NIPS for further reassurance, this can be arranged through her GP or a private ultrasound service

6 DOCUMENTATION
- Medical records
- Antenatal card
- Obstetric database

7 EDUCATIONAL NOTES
cFTS
- Nuchal translucency plus free β hCG and Pregnancy Associated Plasma Protein-A (PAPP-A) +/- nasal bone is the recommended primary aneuploidy screening for singleton and twin pregnancies at RHW as it is covered by Medicare. A cFTS risk ≥ 1 in 300 is considered “high risk”, and a risk < 1:300 considered “low risk”. The lowest possible risk for a woman is >20 x less than her age related risk. If she has a result in-between e.g. 1:300-1:1000 then she may wish to consider further screening (NIPS)
- Can also be used in twin pregnancies with a slightly lower detection rate. Aneuploidy screening for triplet and higher order multiple pregnancies (HOMPs) should be performed with first trimester ultrasound markers only (without bloods)
- The role of cFTS as a screening tool for pre-eclampsia is uncertain.
- The preferred approach at RHW is that of contingent screening, whereby women start with the cFTS and then consider their options for further testing/screening based on the results of the cFTS. Current evidence suggests this model will detect a higher proportion of clinically significant aneuploidies as well as avoiding an unnecessary increase in the cost of screening.
- For women with a high risk cFTS, diagnostic testing may give a more clinically significant result, particularly if the adjusted risk is > 1:100, the NT measures ≥ 3.5mm, or if serum biochemistry results are abnormal.
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NIPS
- Does not have sufficient accuracy to replace diagnostic testing (CVS and amniocentesis). Although it has high sensitivity and specificity for Trisomy 21, Trisomy 18, Trisomy 13 and sex chromosome aneuploidies, the positive predictive value for all aneuploidies vary from 35 to 90%.
- Pre-test counselling should include information about the possibility of false positive and false negative results, as well as the ability to identify fetal sex and sex chromosome aneuploidies (SCA). Some services give women the option of opting out of receiving a result for fetal sex/SCA.
- Can usually be performed in twin pregnancies, although has not been clinically validated in HOMPs.
- Inaccurate results may occur due to confined placental mosaicism, twin demise or vanishing twin, maternal malignancy, low fetal fraction, maternal mosaicism, and prior organ transplant. Relevant clinical information should be included on the referral.
- There is a test failure rate of up to 5%. This increases as body mass index (BMI) increases. The test failure rate is likely to be 50% at a maternal weight of 160kg. In women with test failure there is an increased risk of aneuploidy.
- Not all laboratories will offer the NIPS to women who have conceived by donor egg or embryo. This information needs to be included on the referral.
- Has not been clinically validated for microdeletion studies, has poor performance, and should not be ordered prior to genetic counselling.
- There is currently (at time of publishing) no Medicare rebate for the NIPS and costs vary.

Diagnostic testing
- CVS or amniocentesis, with prenatal microarray, is diagnostic for significant chromosomal anomalies as well as some known genetic disorders that cannot be detected by NIPS.
- When fetal anomalies are detected on ultrasound, microarray will identify clinically significant chromosomal abnormalities in approximately 6% of the fetuses that have a normal karyotype. For this reason, chromosomal microarray analysis is now the primary test (replacing conventional karyotype) for women undergoing prenatal diagnosis.
- Carries a small risk of miscarriage, usually quoted at 0.5-1%. Recent literature suggests the risk of procedure-related miscarriage may be significantly lower.

8 RELATED POLICIES / PROCEDURES / CLINICAL PRACTICE LOP
- Referral to the Department of Maternal Fetal Medicine-Fetal Indications
- Anaemia and haemoglobinopathies in pregnancy
- Termination of pregnancy – framework
- PD2012_055 Congenital Conditions Register - Reporting Requirements.

9 RISK RATING
- Low

10 NATIONAL STANDARD
- CC - Comprehensive Care
LOCAL OPERATING PROCEDURE
CLINICAL POLICIES, PROCEDURES & GUIDELINES

Approved by Quality & Patient Care Committee
19/10/17

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11 REFERENCES

1. Human Genetic Society of Australasia (HGSA)/ RANZCOG Position Statement on Prenatal Diagnosis and Screening. 2015, amended 2016
4. Prenatal screening and diagnosis of chromosomal and genetic conditions in the fetus in pregnancy. RANZCOG. C-Ob 59). Revised 2016

REVISION & APPROVAL HISTORY
Reviewed Maternity Services LOPs group October 2017 – replaced the following :
Genetic Counselling following a high risk first trimester screen – approved Quality & Patient Safety Committee 20/9/12 – endorsed Maternity Services LOPs group 11/9/12
Trisomy 21 Screening, including non-invasive prenatal testing (NIPT) – approved Quality & Patient Safety Committee 20/11/14 – endorsed Maternity Services LOPs group 4/11/14

FOR REVIEW : OCTOBER 2022
**ANEUPLOIDY SCREENING/DIAGNOSTIC TESTING**

**Woman counselled regarding screening/diagnostic testing options during pregnancy:**
- cFTS, NIPS, CVS and amniocentesis

**Woman should be aware of the importance of ultrasound assessment in the 1st trimester (or early 2nd trimester) as well as the limitations of cFTS and NIPS.**

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**cFTS** *(recommended as primary screen at RHW)*

**NIPS** *(as primary screen)*

**Diagnostic testing** *(as primary testing) following genetic counselling:*

- CVS
- amniocentesis

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**Low risk result**

If risk <1:300 – no further screening indicated

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If risk 1:300-1:1000 OR risk not reassuring enough for woman, discuss and consider NIPS as secondary screen

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**Refer for genetic counselling**

**NIPS** *(as secondary screen):*

**Diagnostic testing** *(CVS/amniocentesis)*

**Other appropriate investigations**

- 2nd trimester morphology ultrasound
- Fetal echocardiogram if NT > 3.5mm
- 3rd trimester ultrasound if PAPP-A < 0.4

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**Low risk result**

**High risk result**

**OR**

NT measurement ≥3.5mm

**OR**

structural abnormality on ultrasound

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**Refer for genetic counselling**

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**Abbreviations:**
- cFTS: Combined first trimester screen
- NIPS: Non-invasive prenatal screen
- CVS: Chorionic villus sampling
- NT: Nuchal translucency
- PAPP-A: Pregnancy Associated Plasma Protein A
- βhCG: Beta human chorionic gonadotropin