

GENETIC COUNSELLING: REPRODUCTIVE GENETIC CARRIER SCREENING AND 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 or woman planning pregnancy

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 woman's/couple's medical and family history
- Offer woman/couple 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
 - inconclusive NIPS result/s

Reproductive Genetic Carrier Screening (RGCS)

- Discuss the option of RGCS with low risk (i.e. no family history) woman/couple $\leq 11^{+0}$ weeks gestation as outlined in Appendix 1. See RGCS in educational notes
- Refer couples to private services (Appendix 2) when there is no family history reported but couple are interested in carrier screening

Aneuploidy Screening

- Offer woman the option of screening for aneuploidy regardless of age. (Appendix 3)
Discussion should include:
 - cFTS
 - NIPS as a primary screen
 - utilisation of NIPS in a contingent screening model
 - early ultrasound assessment of fetal anatomy at 12-14 weeks' gestation
 - the role of the formal morphology assessment at 20 weeks' gestation

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- Discuss options with woman outlining each test and its distinct advantages, disadvantages and limitations:
 - cFTS:
 - preferred primary screen at RHW
 - performed between 11⁺⁰-13⁺⁶ 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 (β hCG)
 - 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% (or 2.5% if nasal bone incorporated).
 - ultrasound component also determines:
 - gestation (if not already established)
 - number of fetuses (if not already established)
 - viability
 - presence of some congenital anomalies
 - Medicare rebates are available, and in some centres, cFTS is completely covered by Medicare
 - Non-invasive prenatal screening (NIPS):
 - performed after 10 weeks' gestation
 - involves collection of maternal blood to analyse cell-free fetal DNA
 - an ultrasound for dating (if not already established) and viability is recommended at the time of blood collection
 - can be used as the primary screen 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
 - 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%
 - fetal sex determination and screening for sex chromosome aneuploidy should be discussed, as it may also report some sex chromosome abnormalities at a much higher false positive rate compared to autosomes with a low positive predictive value
 - self-funded (at time of publication)
 - requires redraw of blood/no result in up to 3-5% of cases
 - does NOT include routine serum biochemistry (PAPP-A and β hCG). 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 PAPP-A and β hCG performed, it needs to be requested in addition to NIPS
 - First trimester structural ultrasound and/or second trimester morphology ultrasound – used in isolation, are 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
- Ensure follow up arrangements are in place for all results

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If any screening results show one or more of the following:

High risk cFTS ($\geq 1:300$)

NIPS suggestive of aneuploidy

NT ≥ 3.5 mm

Structural abnormality on ultrasound

- Inform woman of her risk assessment and refer for genetic counselling, which will be provided within seven days
- 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, and 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). A woman considering TOP should be aware of surgical and non-surgical methods of TOP which are determined by gestation
- 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 ≥ 3.5 mm
 - the free β hCG 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
 - repeated NIPS failure
- Explain limitations of diagnostic procedures:
 - counsel regarding possibility of variant of uncertain significance (VUS) in up to 5% of cases and devise a follow up plan if a VUS is detected, including parental samples required in a timely manner
 - in the case of a VUS on array, arrange consultation with genetic counsellor and/or geneticist to establish possible phenotype, prior to blood being taken from parents for parental segregation studies
 - inform woman an amniocentesis is the recommended procedure after a high-risk NIPS result when no structural anomalies are seen on US
- Perform diagnostic testing with a high-risk NIPS results, prior to any irreversible action such as termination of pregnancy (TOP)
- Provide documentation to referring doctor and/or clinic following genetic counselling and document in medical records

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- Ensure other appropriate investigations/referrals are arranged as needed:
 - referral to maternal fetal medicine (MFM) if fetal anomaly detected on ultrasound
 - 16-week ultrasound in MFM if NT \geq 3.5mm
 - second trimester morphology ultrasound (all women)
 - second trimester morphology ultrasound at tertiary ultrasound centre if NT \geq 3.5mm
 - fetal echocardiogram if NT \geq 3.5mm
 - third trimester ultrasound for growth assessment if PAPP-A $<$ 0.334 MoM

If any screening results show low risk cFTS but with either of the following:

T21 risk 1:300-1:1000

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
- Arrange through one of the following, if woman elects NIPS for further information:
 - her GP
 - a private ultrasound service
 - Department of Medical Imaging RHW
 - antenatal clinic

6 DOCUMENTATION

- Medical records
- Antenatal card

7 EDUCATIONAL NOTES

Reproductive Genetic Carrier Screening (RGCS)

- Refer to updated 2018 RANZCOG/HGSA Statement 'Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions' Recommendation 15:
<https://www.hgsa.org.au/documents/item/6110>
- Carrier status screening of women with a low probability for the more common genetic conditions (e.g. cystic fibrosis, spinal muscular atrophy, fragile X syndrome) should be discussed with a woman planning pregnancy or in the first trimester of her current pregnancy.
- There is currently (at time of publishing) no Medicare rebate for carrier screening, and costs vary between providers.

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 \geq 1 in 300 is considered "high risk", and a risk $<$ 1:300 considered "low risk". The lowest possible risk for a woman is \geq 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.

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- 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 $\geq 3.5\text{mm}$, or if serum biochemistry results are abnormal.

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, rate of redraw/no result (3-5%), 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.
- Positive Predictive Values change based on maternal and fetal factors e.g. age, testing platform, ultrasound findings
- Can usually be performed in twin pregnancies, although has not been clinically validated in HOMP.
- 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 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, which have 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 between providers.

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.
- VUS are reported up to 5% of prenatal arrays. Pre-test counselling should inform the parents of this possibility and the possible request of parental bloods to clarify inheritance.
- All reports of VUS should be discussed with genetics (geneticist or genetic counsellor) prior to taking parental blood samples to tailor counselling e.g. query particular issues in the family history.
- 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

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8 RELATED POLICIES / PROCEDURES / CLINICAL PRACTICE LOP

- NSW Health Policy Directive: Prenatal Testing/Screening for Down Syndrome & Other Chromosomal Abnormalities, 2007
- Referral to the Department of Maternal Fetal Medicine: Fetal Indications
- Anaemia and haemoglobinopathies in pregnancy
- Termination of pregnancy – framework
- Pregnancy – Framework for Terminations in New South Wales. Public Health Organisations 2014. PD2014_022
- Congenital Conditions Register – Reporting Requirements
- Fetal Echocardiography indications and referral

9 RISK RATING

- Low

10 NATIONAL STANDARD

- Standard 5 – Comprehensive Care

11 REFERENCES

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3. Human Genetic Society of Australasia (HGSA)/ RANZCOG Position Statement on Prenatal Assessment of Fetal Structural Abnormalities, 2015
4. Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions RANZCOG. C-Obs 59). Revised August 2018
5. Analysis of Cell-Free DNA in Maternal Blood in Screening for Aneuploidies: Meta-Analysis M.M. Gil, R. Akolekar, M.S. Quezada, B. Bregant, K.H. Nicolaidis. Fetal Diagn Ther 2014; 35:156–173
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15. *Ultrasound Obstet Gynecology* 2016; 47:45–52 Clinical implementation of routine screening for fetal trisomies in the UK NHS: cell-free DNA test contingent on results from first-trimester combined test. M M Gil, R Revello, LC Poon, R Akolekar and KH Nicolaides

REVISION & APPROVAL HISTORY

Title changed from *Genetic Counselling : Aneuploidy Screening including the non-invasive prenatal screening (NIPS) test* - Reviewed and endorsed Maternity Services LOPs group 5/11/19

Approved Quality & Patient Care Committee 19/10/17

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

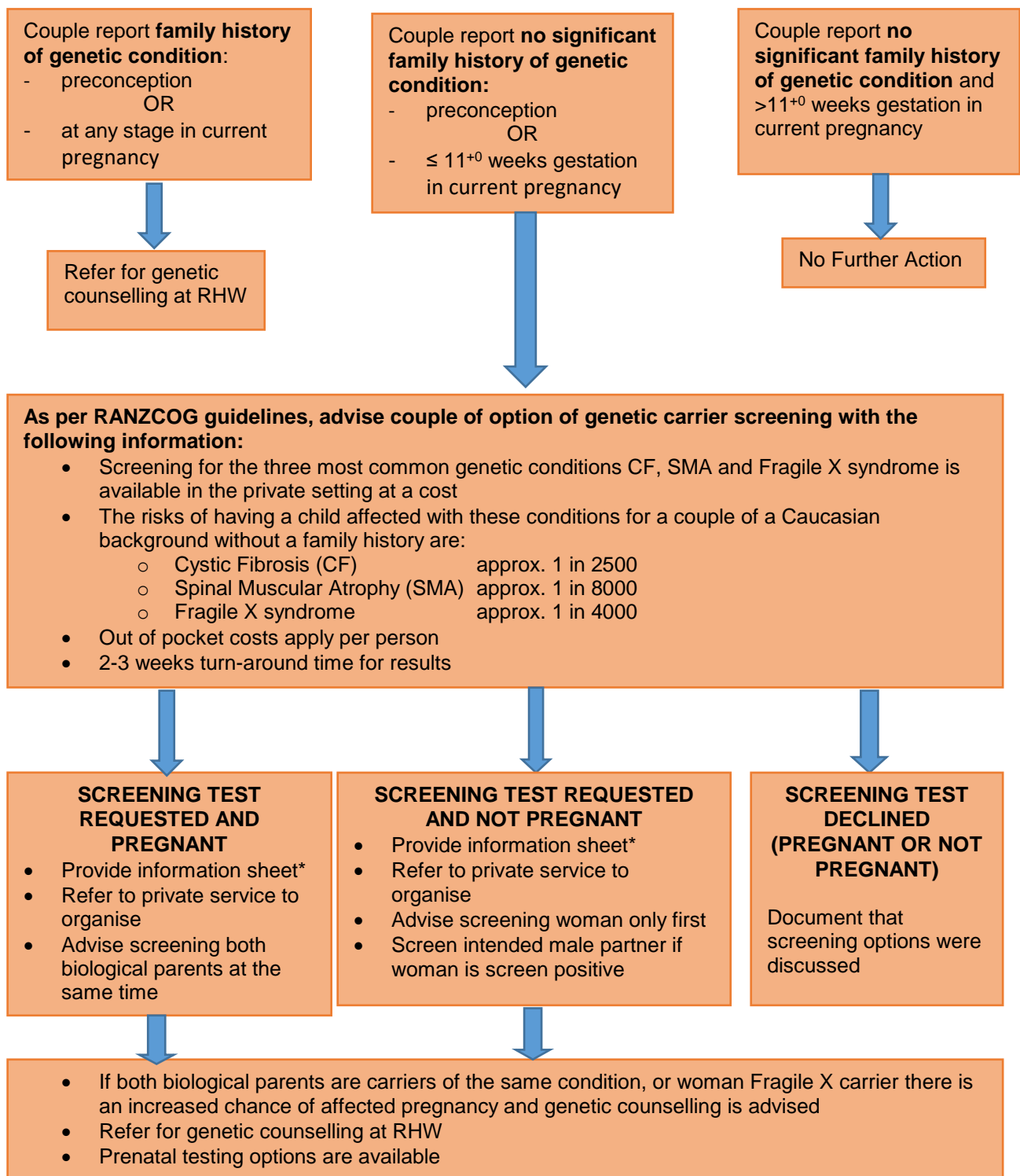
Trisomy 21 Screening, including non-invasive prenatal testing (NIPT) – approved Quality & Patient Safety Committee 20/11/14 – endorsed Maternity Services LOPs group 4/11/14

FOR REVIEW: NOVEMBER 2024

APPENDIX 1 REPRODUCTIVE GENETIC CARRIER SCREENING

Reproductive genetic carrier screening is an optional test that provides information about the chance of a couple having a child with a genetic condition.

The 2018 RANZCOG/HGSA joint position statement - *Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions* has been updated to include recommendations that all couples planning or in the first trimester of a pregnancy should be provided information about reproductive genetic carrier screening - <https://www.hgsa.org.au/documents/item/6110> (see **recommendation 15**)



*NSW Health Fact Sheet 65, 'Reproductive Carrier Screening':

<http://www.genetics.edu.au/publications-and-resources/facts-sheets/FS65REPRODUCTIVECARRIERSCREENING.pdf>

APPENDIX 2 REPRODUCTIVE GENETIC CARRIER SCREENING PROVIDERS

Reproductive genetic carrier screening is not currently publicly funded, at time of printing, unless there is a reported family history.

This information sheet is intended as a guide only and does not endorse any particular company or option and is current at the time of publication

This information sheet is to accompany the NSW Health Fact Sheet 65 titled, 'Reproductive Carrier Screening':

<http://www.genetics.edu.au/publications-and-resources/facts-sheets/FS65REPRODUCTIVECARRIERSCREENING.pdf>

There are out-of-pocket costs for all screening/testing options listed below when there is no reported family history. These can be requested by GPs or some ultrasound, IVF and private clinical genetic services or laboratories.

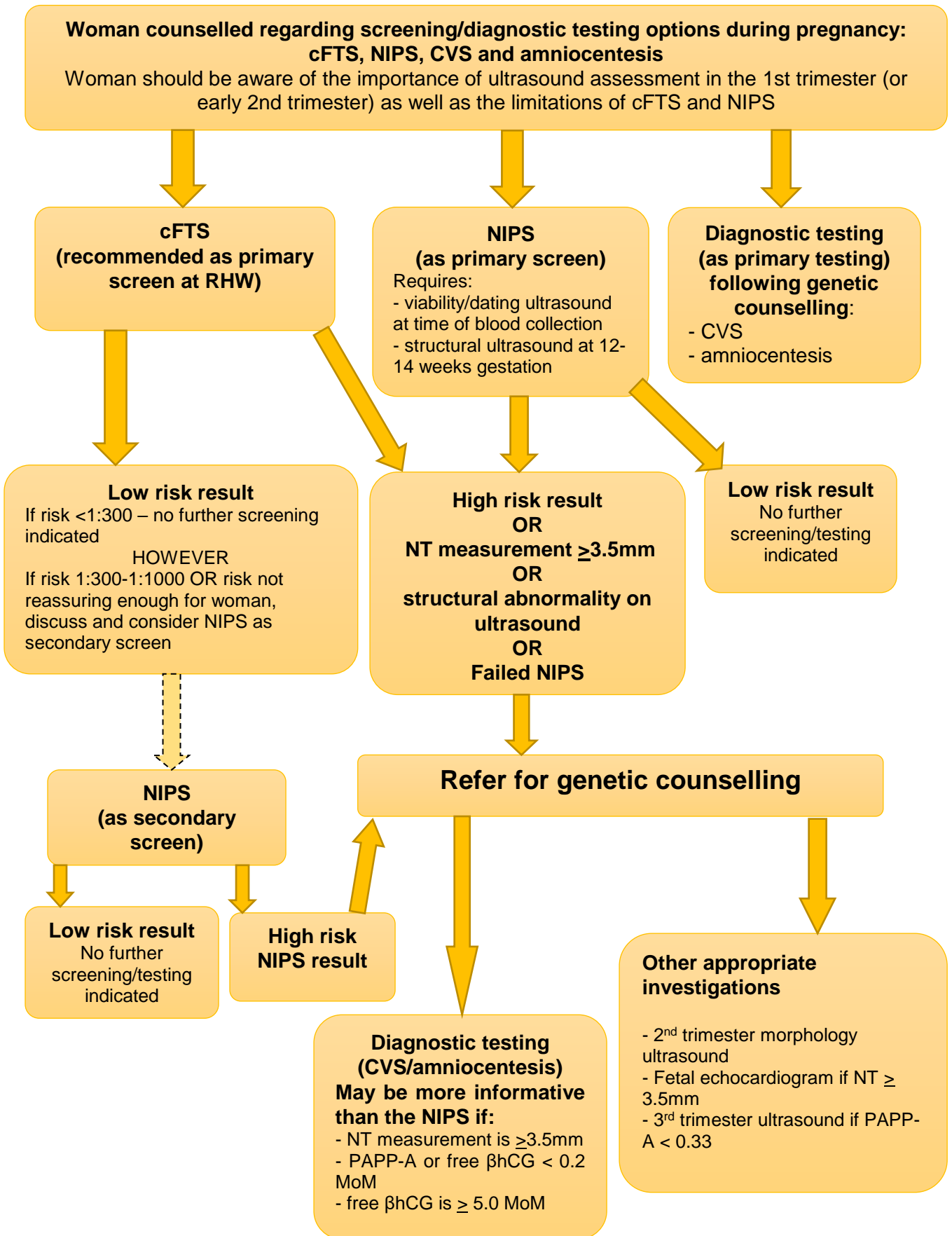
Private services facilitating testing and include counselling:

- <https://eugenelabs.com/>
- <http://www.thegeneticclinic.com.au/>
- <http://www.sufw.com.au/>
- <https://www.ultrasoundcare.com.au/>
- <https://www.ivf.com.au/about-fertility/how-to-get-pregnant/preconception-screen>
- <https://www.privategenetics.com.au/about-us/>

Carrier screening providers for the three most common genetic conditions (cystic fibrosis (CF), spinal muscular atrophy (SMA) and Fragile X syndrome) laboratory only:

- <https://www.vcgs.org.au/tests/prepair>
- <https://www.sonicgenetics.com.au/tests/preconception-carrier-screening-panel-cf-sma-fragile-x/>
- <https://www.virtusdiagnostics.com.au/specialist-genetic-testing/virtus-genetic-screen-vgs/>

**APPENDIX 3
ANEUPLOIDY SCREENING/DIAGNOSTIC TESTING**



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