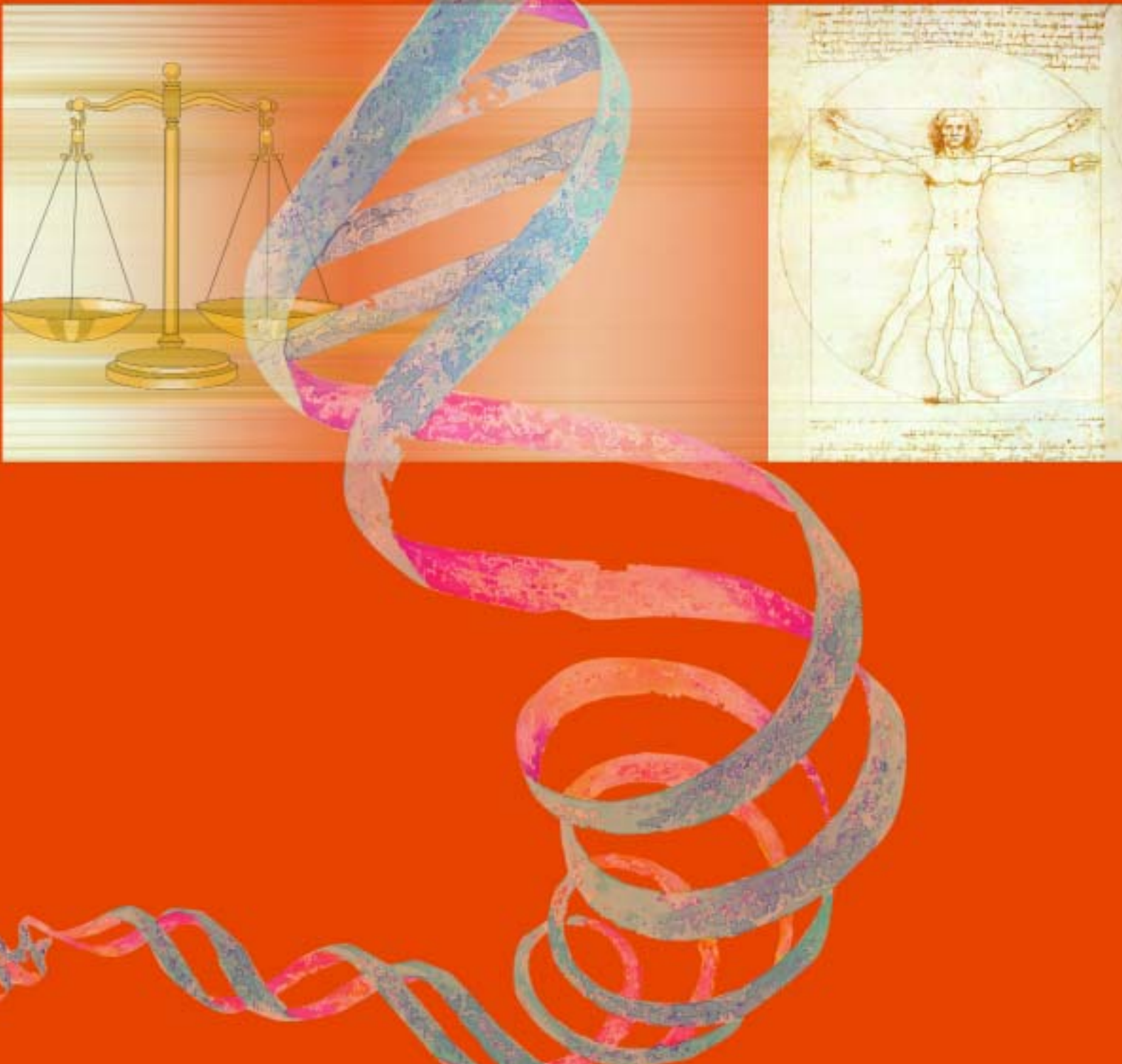


Policy for the Quality Management of Prenatal Screening and Diagnosis of Down syndrome in Western Australia



This policy was endorsed by the State Health Management Team in February 2004

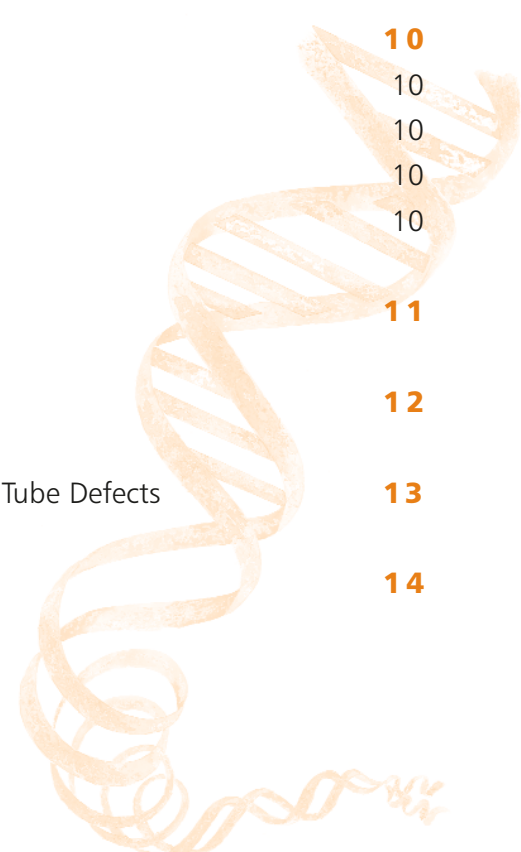
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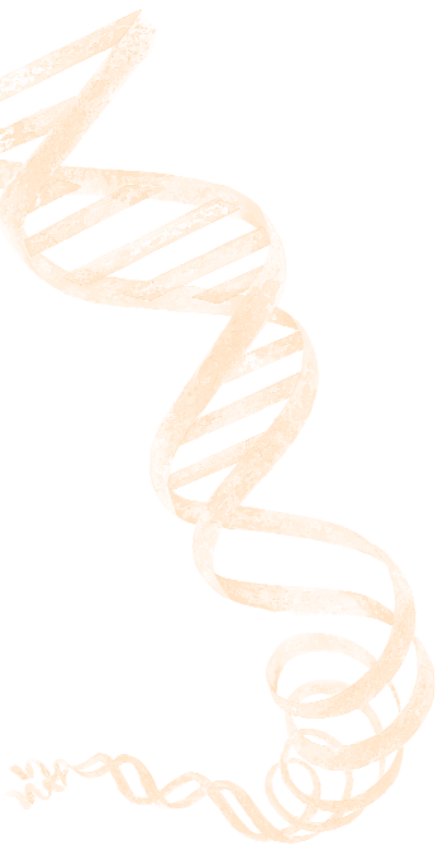
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Abbreviations

AFP	Alpha-fetoprotein
CRL	Crown Rump Length
CVS	Chorionic Villus Sampling
DR	Detection rate
FMF	Fetal Medicine Foundation
free bhCG	Free beta human chorionic gonadotropin
MoM	Multiples of the Median
NATA	National Association of Testing Authorities, Australia
NT	Nuchal Translucency
PAPP-A	Pregnancy Associated Placental Protein-A
UE3	Unconjugated estriol





FOREWORD

Down syndrome, which has a birth prevalence of 1:445 in Western Australia¹, is the most common form of mental retardation and many affected infants have major structural abnormalities.

Since the late 1980s, screening programs involving ultrasound and biochemical markers have been used in early pregnancy to determine whether a fetus is at 'increased risk' for a chromosomal disorder such as Down syndrome (Trisomy 21).

Diagnostic tests such as amniocentesis or chorionic villus sampling can reveal whether a fetus has the disorder. These test results and pregnancy outcome information are used to determine the effectiveness of screening tests.

Using biochemistry at 15-18 weeks gestation, second trimester maternal serum screening has a detection rate of 70-80% with a false positive rate of 5%.

Using a combination of ultrasound and biochemistry at 10-13 weeks gestation, first trimester screening provides an 83% detection rate with a false positive rate of 3.7%.

A population screening program, like prenatal Down's screening, involves close coordination between ultrasound, biochemistry, genetics, cytogenetics, obstetrics and primary healthcare providers. The information acquired through screening can assist parents and professionals in preparing for the birth of a baby who may require postnatal medical or surgical care or in considering other management options for the pregnancy.

Deciding whether to undergo testing is a complex process, dependant upon a variety of personal factors. For some, testing may provide the information necessary to prepare for their future. For others, it may lead to more questions and serious considerations. Still others may choose not to undergo testing at all. There are no right or wrong choices.

It is important that women considering prenatal testing make an informed choice, appropriate for them. Making an informed choice means having balanced information: not only knowing about the options testing can provide, but also recognising the potential of people with disabilities to lead full and rewarding lives.

March 2005.



PART 1: Policy

There are three principles that support the prenatal screening program for fetal anomalies such as Down syndrome:

- All women should have access to prenatal screening;
- Prenatal screening aims to maximise detection and minimise the false positive rate, which determines the number of referrals for diagnostic interventions (amniocentesis or chorionic villus sampling) and therefore the number of unaffected fetuses lost; and
- Every woman has the right to choose a test determined by her own values as well as by the test's performance criteria.

The screening test offered to each woman will depend on her gestation and the resources available, particularly the availability of high quality ultrasound to measure nuchal translucency (NT). At this time, the tests that provide acceptable performance with respect to effectiveness, safety and cost-effectiveness are:

- First trimester screening (Combined Test: NT measurement with maternal serum PAPP-A and free β hCG) for women who attend prenatal care in the first trimester (10-13 weeks gestation); and
- Second trimester maternal serum screening (Triple Test: maternal serum AFP, free bhCG and unconjugated estriol) for those women who present for prenatal care for the first time in the second trimester (14-18 weeks gestation).

Down syndrome screening should be offered as a comprehensive service, which includes:

- The most effective and safe method of screening as early as possible in pregnancy;
- Quality assured screening, including both laboratory and ultrasound components;
- Provision of both amniocentesis and chorionic villus sampling with sufficient volume to minimise the risk and maximise the acceptability of the procedure and its consequences;
- Appropriate pre- and post-test counselling through midwives, accredited genetic counsellors or clinicians and information pamphlets which explain the procedures and outcomes;
- Cytogenetic services that integrate with genetic counselling, screening and obstetric components of the service;
- Monitoring of the program performance and quality assurance; and
- Ongoing education, certification and audit of health professionals involved in providing prenatal screening and diagnosis.

This prenatal screening policy has been based on best practice recommendations and guidelines available through national and international programs²⁻⁹.



A broad range of stakeholders have been involved in the prenatal screening policy development process. This policy should be disseminated widely to professionals involved in providing prenatal screening and should be easily available to pregnant women or others who wish to read it.

1.1 Information and support for women and their partners

In order to facilitate informed decision making about the options available, women and their partners should be provided with clear written and verbal information from a suitably qualified health professional. The information provided should be available before pregnancy occurs or as early as possible in pregnancy before women are faced with making decisions.

Women's understanding of and satisfaction with the current screening methods, counselling and associated procedures has been evaluated in Western Australia in order to tailor appropriate information and education¹⁰⁻¹⁴.

Personal information contained on the screening test request form that accompanies a referral is required for risk assessment and program evaluation. Ultrasound and laboratory test results and sometimes, additional information from the doctor, may be requested to complete testing and audits. Accordingly, all Department of Health prenatal screening pamphlets contain the statement; *"To improve the accuracy of the screening program, results and outcomes will be monitored. Your personal information will remain confidential"*.¹⁵

Counselling is a necessary prerequisite to ensure women have a thorough understanding of the screening test and its accuracy. The level of post-test counselling support needed may vary with the type of result and the resources of the referring practitioner to deal with the issues surrounding an abnormal result. Women receiving an increased risk test result in particular, require adequate post-test counselling.

1.2 Education and training for staff

Ideally, professionals providing prenatal screening and services have received appropriate education for their roles and responsibilities.

The Fetal Medicine Foundation (FMF) has introduced a process of comprehensive training, support and audit for the proper implementation of many aspects of the screening program.

The appropriate certificate is awarded to sonologists (minimum 2 years obstetrics experience) who have:

- Attended a theoretical course and passed the examination;
- Submitted a logbook of images of relevant scans; and
- Attended a clinical session in the presence of an approved examiner; and demonstrated their ability to carry out the relevant scans.



The theoretical course is open to all those involved in obstetric ultrasound, including obstetricians, radiologists, radiographers, genetic counsellors, general practitioners and midwives.

It covers such topics as:

- Principles of screening;
- Biochemistry;
- Multiple pregnancies;
- Nuchal Translucency and chromosomal defects;
- Increased Nuchal Translucency with normal karyotype;
- Pathophysiology of increased Nuchal Translucency;
- Diagnosis of fetal abnormalities in the first trimester scan;
- Amniocentesis and Chorionic Villus Sampling; and
- Counselling issues.

Experienced operators with appropriate training will conduct all procedures.





PART 2: Choice of Screening Tests

2.1 Women at increased risk for aneuploidy

Women who are considered to be at increased risk for aneuploidy, based on advanced maternal age or previous affected pregnancy should be offered diagnostic testing, either chorionic villus sampling or amniocentesis.

2.2 Women at population risk of aneuploidy

Women who are at population risk of aneuploidy should be made aware of screening tests for Down syndrome and other chromosomal abnormalities including first and second trimester screening, the relative advantages and disadvantages of which, are best discussed with their practitioner.

Table 1: Results of first and second trimester screening in Western Australia¹⁶

Screening test	Total women screened	Detection rate	Women at 'increased risk' of having a Down syndrome pregnancy	Chance of missing Down syndrome in 'population risk' women	Chance of detecting Down syndrome in 'increased risk' women
First trimester	22,280	50/60 (83%)	3.9%	1 in 2,227	1 in 17.5
Second trimester	21,000	18/23 (76%)	6.5%	1 in 2,135	1 in 63


Ultrasound assessment for indications of aneuploidy other than Down syndrome should be performed according to a standard scanning protocol. Scans should be done as close to 19 weeks gestation to maximise the time available for further testing and counselling if there is an abnormal scan result.

2.3 Sequential testing

First trimester screening followed by second trimester serum screening is not currently recommended as a population screening method due to likelihood of a high false positive rate.

2.4 Procedure for first trimester screening:

The combination of ultrasound (NT measurement) and serum screening (free b-hCG and PAPP-A) is recognised as the most effective screening measure for Down syndrome in the first trimester.

- 
- First trimester blood between 10 weeks and 13 weeks 6 days though 10 to 11 weeks gestation is optimal; and
 - First trimester ultrasound between 11 weeks and 13 weeks 6 days, though 12 weeks gestation is optimal.

2.4.1 Fetal nuchal translucency (NT)

- NT measurements should only be performed by trained operators who are accredited with the Fetal Medicine Foundation¹⁷, using a risk assessment program that incorporates NT, Crown-Rump Length (CRL) and maternal age. This test should be done when the fetus has a CRL of 45 to 83mm, which corresponds to the period 11 weeks 4 days to 13 weeks 6 days;
- In a pregnancy in which the fetus has a significantly increased NT ($\geq 3\text{mm}$ at 12 weeks) but the fetal karyotype is subsequently shown to be normal, women should visit a tertiary qualified and experienced obstetric clinic at 19 weeks for a detailed anatomy scan. This is recommended since there may be significant fetal abnormalities in the presence of normal chromosomes;
- If the NT measurement is $\geq 4\text{mm}$ at 12 weeks, a 16 week scan should be offered;
- NT measurements alone should not be used for population screening programs; and
- An increased NT result can predict other aneuploidies such as Trisomy 13, Trisomy 18 or Monosomy X.

2.4.2 Biochemical analysis

Pregnancy Associated Placental Protein-A and free b-hCG should be collected between 10 weeks and 13 weeks 6 days. Currently the Fetal Medicine Foundation software can accept biochemistry results expressed in absolute values (U/L) or Multiples of the Median (MoM) when measured on Kryptor or Wallac (Delfia) platforms. The gestational age or crown rump length is required to calculate the MoM of each analyte.

2.4.3 Nasal bone assessment

The detection of a fetal nasal bone and incorporation into the risk calculation algorithm is NOT recommended at this time. There is no consensus between the results of large multicentre trials in the UK and USA concerning the value of including fetal nasal bone detection in the risk calculation for Down syndrome. Therefore, until more evidence becomes available, the recommendation is to not incorporate fetal nasal bone detection into the risk algorithm at this time.



2.5 Procedure for second trimester screening:

2.5.1 Biochemical analysis

Though the 16th week is optimal, maternal serum alpha-fetoprotein, free β -hCG and unconjugated estriol measurement can be undertaken between 14 and 18 weeks.

2.6 Risk calculation for Down syndrome

2.6.1 Calculation of risk in the first trimester

Risk calculations should only be performed using software approved by the Fetal Medicine Foundation and all laboratories must ensure that they only take nuchal translucency or CRL measurements from sonographers who hold FMF Certificate of Competence in the first trimester scan. The percentage of total screened cases identified with a risk of 1 in 300 or greater should be monitored on a monthly basis. The screen positive rate should be between 3%-6% depending upon the age of the population being screened.

The risk calculated at the time of the NT measurement is recommended for first trimester screening, rather than the risk at term. Since up to a third of Down syndrome pregnancies spontaneously abort between 10-40 weeks gestation the risk at screening will be higher than at term.

2.6.2 Calculation of risk in the second trimester

Laboratories that routinely measure risk for Down syndrome and neural tube defects during the second trimester should use software that is validated and audited by participating in an external quality assurance program (such as the National External Quality Assessment Service). Laboratories should perform at least 1,000 screening tests annually to be able to statistically review MoMs. Smaller volume laboratories should work with laboratories that perform 10,000 or more tests annually to monitor performance (medians, MoMs, detection rates and false positive rates).

2.6.3 Diagnostic tests

If the results indicate that the fetus is at increased risk of Down syndrome, post-test counselling and further diagnostic tests (amniocentesis and chorionic villus sampling) should be offered to determine the fetal karyotype. Risk of spontaneous fetal loss after such a procedure ranges from 0.5 to 2%.



PART 3: Laboratory Quality Assurance

3.1 Code of practice

Accreditation with the National Association of Testing Authorities, Australia (NATA) is essential for laboratories providing a prenatal screening and diagnosis service. However,

- Fetal Medicine Foundation accreditation;
- Senior laboratory staff responsible for internal quality control with defined lines of accountability for all laboratory aspects of the service; and
- Participation in external quality assurance programs such as the UK National External Quality Assurance Service,

is also recommended.

3.2 Epidemiological monitoring

This includes the collection of the following data:

- Medians of analytes;
- False positive rate;
- Detection rate;
- Ultrasound NT data;
- Maternal age distribution of the screened population; and
- Uptake of screening and prenatal diagnosis.

3.3 Sample collection

Samples should be accompanied by the following information:

- Patient demographics including full name, referring clinician, date of birth, history of previous Trisomy and weight; and
- Blood sample date of collection and reference number.

First trimester screening samples also require:

- Site of ultrasound performing the NT measurement; and
- Ultrasound scan data including date, name of sonographer, fetal crown-rump length, fetal nuchal translucency, number of live fetuses.



3.4 Program performance

The Down syndrome screening program must be continuously monitored and always seek to improve in quality.

Overall audit and monitoring of the prenatal screening programs should be performed.

All providers of biochemical and ultrasound-based screening tests for Down syndrome and other fetal aneuploidy should maintain comprehensive records and appropriate follow-up of cases to enable them to know their own screening test characteristics. Continuous audit of their screening practice, and being able to provide the users of their service with accurate and current information on the numbers of pregnancies screened, the detection rate and the false positive rate, is also considered best practice.



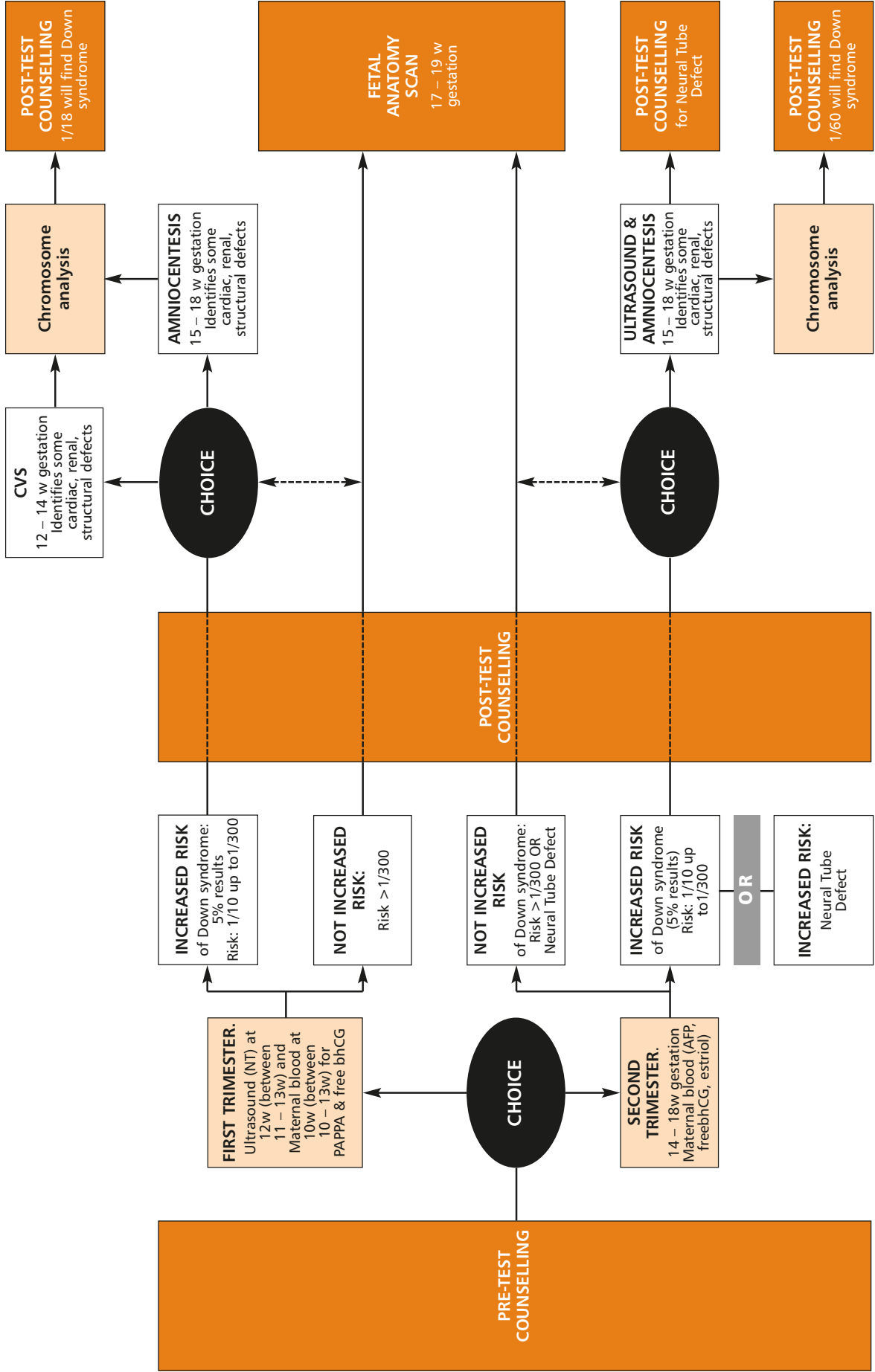


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Appendix A: Prenatal screening for Down syndrome and Neural Tube Defects



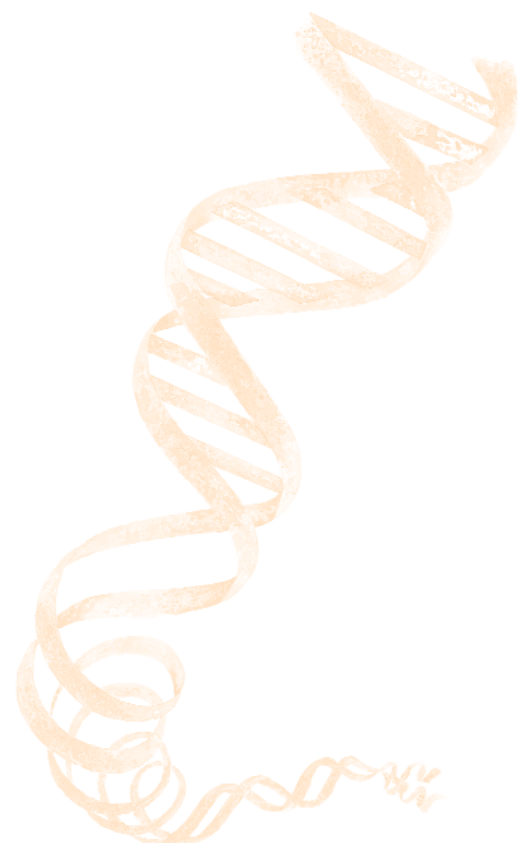


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