

Information for Doctors

Screening for genetic disorders during pregnancy

This information is provided to assist doctors in discussing with their patients the risks of different genetic disorders in pregnancy. This document does not review the clinical features of these disorders, the technical performance of the screening tests available, nor the appropriate care pathway for women and couples having such testing.

(Please note, we have excluded two sex chromosome conditions, triple X (XXX) and XYY syndrome (XYY), from this summary, as the associated clinical features are so mild as to frequently be undetectable.)

Screening for genetic disorders during pregnancy

Screening for fetal trisomy is routinely offered to pregnant women in Australia. The common trisomies of chromosomes 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome) are usually *de novo* abnormalities, and they are more likely to occur with increasing maternal age. Non-invasive prenatal tests (NIPT) have revolutionised prenatal screening for these disorders.

NIPT can also screen for abnormalities of fetal sex chromosome number, such as Klinefelter syndrome (XXY) and Turner syndrome (XO). These, too, are usually *de novo*. Klinefelter syndrome is more likely to occur with increasing maternal age, while Turner syndrome does not demonstrate an association with maternal age.

NIPT can include a test for the most common microdeletion, that is, a microdeletion at chromosome 22q. These microdeletions are usually *de novo*, but can be familial. The risk of a 22q microdeletion does not change with maternal age.

A fourth area of screening is testing a couple for heritable genetic variants to determine if they are at increased risk of having a child with a serious childhood-onset autosomal recessive or X-linked disorder. Screening for carriers can be limited to common disorders, such as fragile X syndrome, cystic fibrosis and spinal muscular atrophy. Carrier screening can also be expanded to include hundreds of different disorders. The risk of having a child with an autosomal recessive or X-linked disorder does not change with maternal age.

This bulletin provides graphs that summarise the chance of a woman carrying a baby with one or more of these genetic disorders at term and at different maternal ages. We present the chances as:

- the absolute risk of a given disorder at term
- the combined risk of a number of disorders at term
- the relative risks of a number of disorders at term, that is, if a baby were to have a genetic disorder, what is the probability of it being each type of disorder.

The risks for some of these disorders will be higher at 10–14 weeks' gestation, that is, the time when screening tests are typically done. We have focused on the risks at term, as managing this risk is the principal goal of prenatal screening.

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Absolute risk of different chromosome disorders at term

Figure 1 shows the absolute risk by maternal age of a woman having a baby at term with a common chromosome disorder that can be detected by NIPT. These are the risks in the absence of any prenatal screening or other risk factors.

The risks of the three common trisomies (trisomy 21, 18 and 13) are combined, as are the risks of Klinefelter syndrome (XXY) and Turner syndrome (XO).

The risks are presented for mothers of different ages. Note that the risk of the common trisomies rises rapidly for mothers over the age of 35 years. The risk of fetal Klinefelter syndrome (XXY) also rises with maternal age, masking the fact that the risk of Turner syndrome does not change with maternal age.

The risk of a chromosome 22q11 microdeletion (0.1%) does not change with maternal age. For a woman under the age of 28 years, the risk of a fetal microdeletion of 22q is greater than the risk of the common trisomies, Klinefelter syndrome or Turner syndrome.

Combined risks of different chromosome disorders at term

Figure 2 shows the combined risk of a woman having a baby with one of the common chromosome disorders that can be tested by NIPT, that is, one of the common trisomies, Klinefelter syndrome (XXY), Turner syndrome (XO) or 22q11 microdeletion. The risks are presented at different maternal ages.

Relative risks of different chromosome disorders at term

Figure 3 shows the relative risks of these disorders at different maternal ages. In other words, if a woman has a child with one of the common disorders tested by NIPT (trisomies, Klinefelter syndrome (XXY), Turner syndrome (XO), 22q microdeletion), the figure shows the proportion of affected babies with each disorder.

For example, if a woman aged 30 years were to have a baby with one of these disorders, there is a 46% chance that the disorder would be one of the common trisomies, 16% chance that the disorder would be Klinefelter syndrome or Turner syndrome, and 38% chance that the disorder would be 22q11 microdeletion. You will note that the proportion of affected babies with Klinefelter syndrome or Turner syndrome changes little with maternal age (Figure 3), even though the absolute risk of these disorders does increase with maternal age (see previous figures).

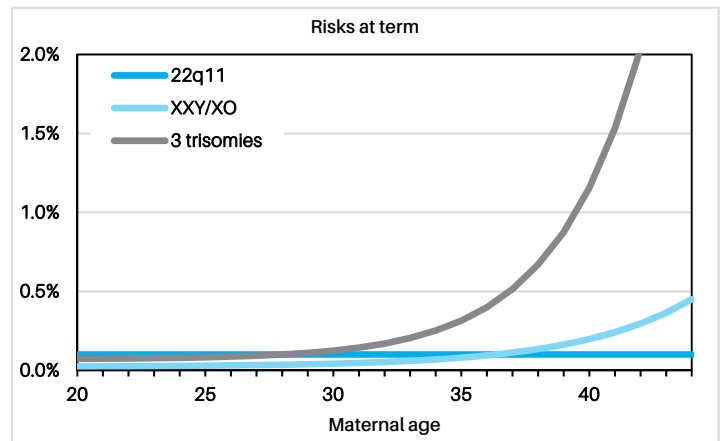


Figure 1. Absolute risks for baby at term having a chromosome disorder

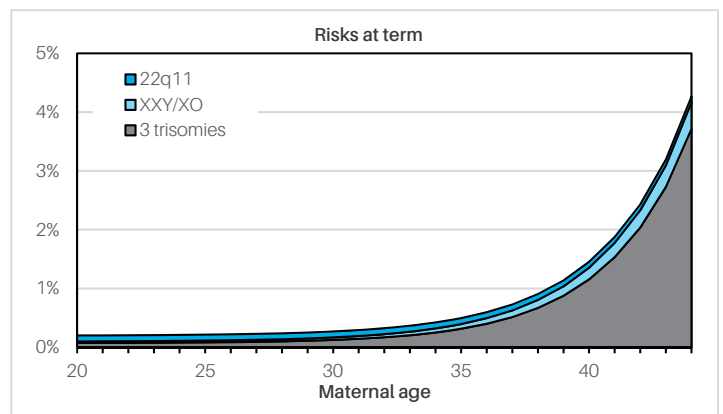


Figure 2. Combined absolute risk for baby at term having a chromosome disorder

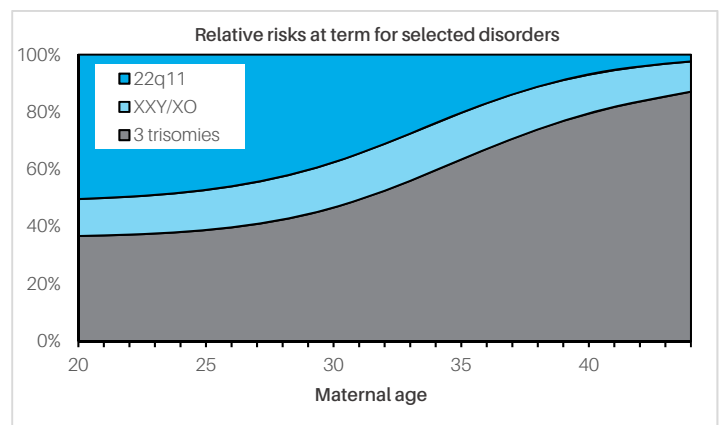


Figure 3. Relative risks for baby at term having a chromosome disorder

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The risk of other chromosome disorders at term

The common chromosome disorders tested by NIPT represent the majority of chromosome disorders identified after birth. There is a diverse group of microdeletions that is not routinely tested by NIPT. Each of these microdeletions is uncommon, having a frequency at birth of less than one in 1,000. Nonetheless, as a group they constitute a small but significant risk at term.

Figure 4 below shows the absolute risks of the disorders screened by NIPT and the combined risk of these other microdeletions. These are the risks in the absence of prenatal screening or specific risk factors. The risks are presented at different maternal ages.

Figure 5 shows the relative risks of these chromosome disorders and the rare microdeletions at different maternal ages. In other words, if a woman has a child with one of these disorders, the figure shows the proportion of affected babies with each disorder.

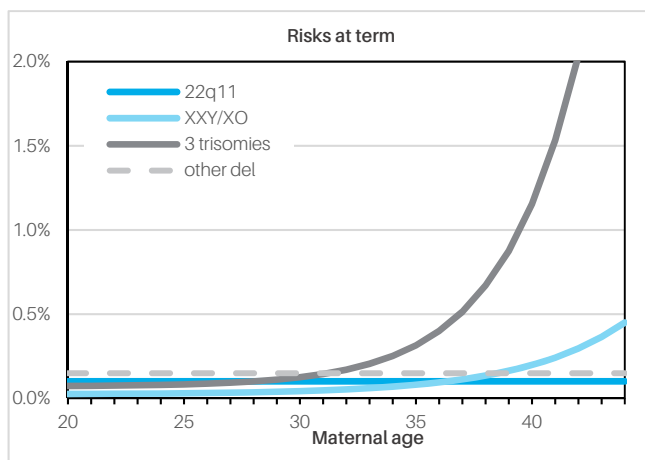


Figure 4. The risks for baby at term having other chromosome disorders

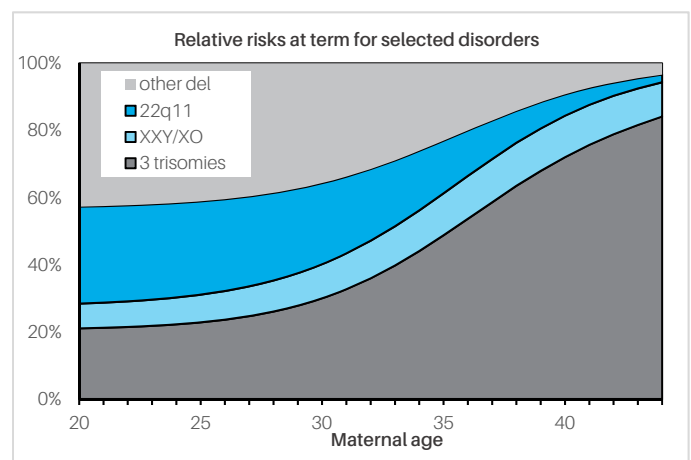


Figure 5. The relative risks of chromosome disorders and rare microdeletions

As yet, none of these rare microdeletions can be reliably detected by NIPT. The only means of reliably detecting these microdeletions is by invasive testing (chorionic villus sample or amniocentesis) and microarray analysis.

Absolute risk of autosomal recessive and X-linked disorders at term

Sonic Genetics provides carrier screening for couples for autosomal recessive and X-linked disorders. We provide two such tests. The first (3-gene carrier screen) covers three common disorders: cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS). Note that this screen does not include thalassaemia, which may be a significant risk in some ethnic groups.

The second test ('expanded carrier screen') covers these three disorders and a further 400 rarer disorders. In examining more genes, the probability that a couple will be identified as being at risk of having of an affected baby is increased. The genes included in this screen are restricted to genes responsible for serious childhood-onset disorders for which there are limited treatment options.

Figure 6 shows the absolute risks at term of various chromosome disorders (presented above, included here for comparison), the risk of having a child with one of the three common single gene disorders, and the risk of having a child with one of the 400 rare disorders.

The risks are shown at different maternal ages. These are the risks in the absence of any prenatal screening or specific risk factors. The risks of recessive disorders do not vary with maternal age.

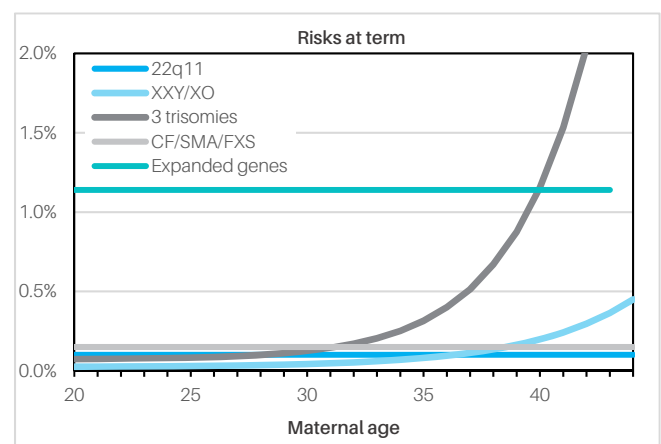


Figure 6. The absolute risk of recessive disorders at term

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Combined risks of different chromosome and autosomal recessive or X-linked disorders at term

Figure 7 shows the combined risk of a woman having a baby with one of the common chromosome disorders that can be tested by NIPT, the three common single gene disorders (CF, SMA and FXS) and the 400 rare disorders.

These are the risks in the absence of prenatal screening or specific risk factors. The risks are presented at different maternal ages.

Relative risks of different chromosome and autosomal recessive or X-linked disorders at term

Figure 8 shows the relative risks of the common chromosome disorders detected by NIPT and just the three common single gene disorders (CF, SMA and FXS) at different maternal ages. In other words, if a woman has a child with one of these disorders, the Figure shows the proportion of affected babies with each disorder.

Figure 9 shows the relative risks of the common chromosome disorders detected by NIPT, the three common single gene disorders (CF, SMA and FXS) and the 400 rare disorders at different maternal ages. In other words, if a woman has a child with one of these disorders, the Figure shows the proportion of affected babies with each disorder.

Disclaimers and sources of information

These Figures are derived from the sources detailed below. There are differences in the methods used to generate the data described in these sources, and so the summary statistics presented in this document should be regarded as indicative rather than definitive measures of the risk of a genetic disorder. The Figures incorporate the differences in risk associated with maternal age (as appropriate), but do not incorporate other differences, such as the carrier frequencies for different disorders in specific ethnic groups. Where possible, the carrier frequencies are representative of general Western populations. In particular, please note that these Figures do not make any allowance for personal or family history of either a chromosome or recessive disorder.

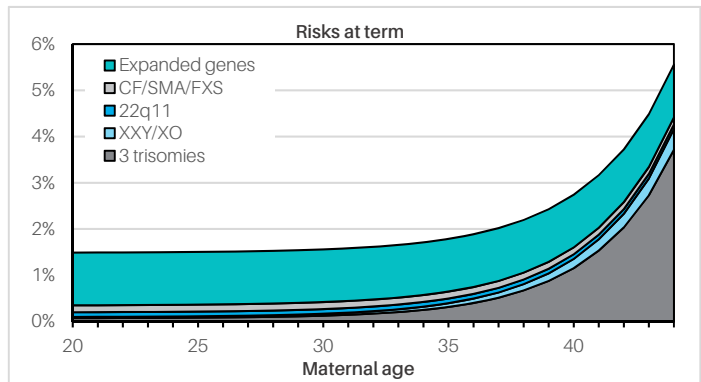


Figure 7. Combined risks of different chromosomes and recessive disorders at term

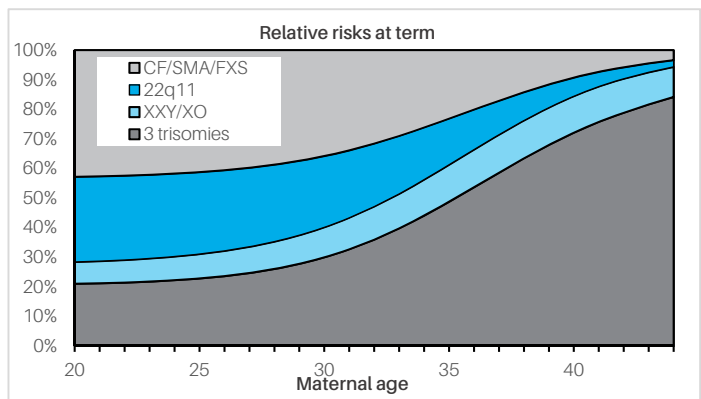


Figure 8. Relative risks of chromosome disorders and 3 recessive disorders

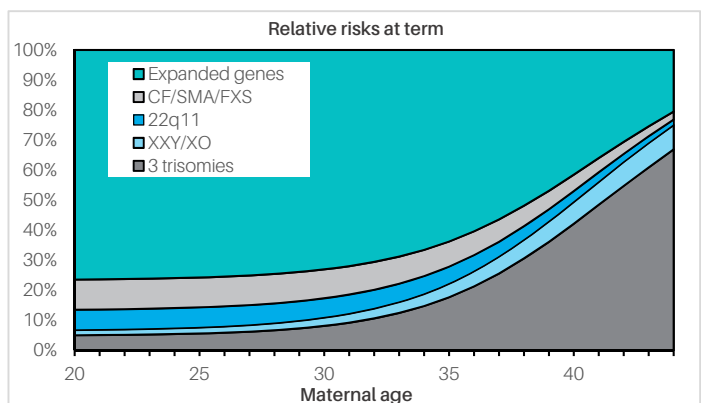


Figure 9. Relative risks of chromosome disorders and 400 recessive disorders

For further details, please refer to the Sonic Genetics website, www.sonicgenetics.com.au, speak with your local Client Liaison or contact Sonic Genetics on 1800 010 447 or email info@sonicgenetics.com.au.

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