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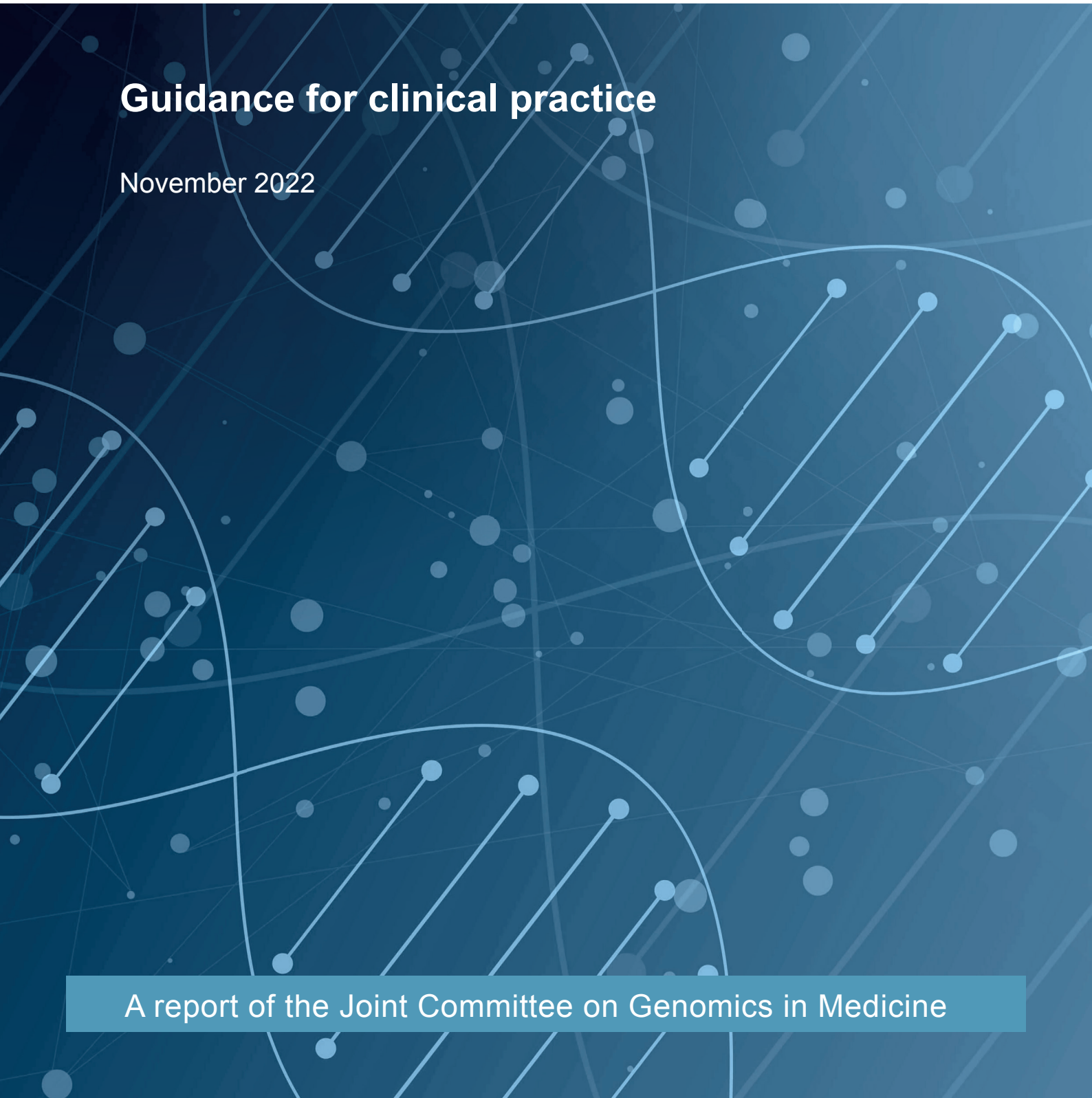
Ethical issues in prenatal genetic diagnosis



Guidance for clinical practice

November 2022

A report of the Joint Committee on Genomics in Medicine

About this report

Ethical issues in prenatal genetic diagnosis is the first report on this subject by the Joint Committee on Genomics in Medicine (comprising the Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine (including representatives from the Royal College of Obstetrics and Gynaecology and the Royal College of Paediatrics and Child Health)). It builds on related guidance *Consent and confidentiality in genomic medicine* published in 2019 by the Joint Committee on Genomics in Medicine.

Acknowledgements

This guidance was written by Ruth Horn, associate professor of ethics, Ethox Centre, Nuffield Department of Population Health, Oxford and Faculty of Medicine, Augsburg (GER); Alison Hall, senior humanities advisor, PHG Foundation, Cambridge, and chair of the Ethics and Policy Committee of the British Society for Genetic Medicine; and Anneke Lucassen, professor of genomic medicine, Nuffield Department of Medicine, Oxford.

We are grateful to the members of the working group: Lyn Chitty, Deidre Cilliers, Tara Clancy, Jane Fisher, Kate Glover, Sasha Henriques, Tessa Homfray, Alison Male, Michael Parker, Rosamund Scott, Sandy Starr and Sarah Wynn, who were participants at a workshop in Oxford in February 2020 where the key elements for this document were identified and discussed, and for the many helpful comments this group provided on multiple drafts. Special thanks to Rachel Horton for her significant input to the case studies.

We are also grateful to the executive committees of the BSGM and JCGM for their review of this document and to Anjana Kulkarni and Eamonn Sheridan for their input to specific sections.

Citation for this document

Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine. *Ethical issues in prenatal genetic diagnosis. Guidance for clinical practice.* Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPath and BSGM, 2022.

Review date: 2027

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Royal College of Physicians
11 St Andrews Place
Regent's Park
London
NW1 4LE
www.rcp.ac.uk
Registered Charity No 210508

Royal College of Pathologists
6 Alie Street
London
E1 8QT
www.rcpath.org
Registered Charity No 261035

British Society for Genetic Medicine
Royal Society of Biology
1 Naoroji Street
London
WC1X 0GB
www.bsgm.org.uk
Registered Charity No 1058821

Contents

Introduction

This document considers the ethical issues that can arise in prenatal genetic testing. Building on the Joint Committee for Genomic Medicine's *Consent and confidentiality* guidance,[1] it focuses on key steps of the prenatal testing pathway: the availability, request, offer and delivery of testing, the interpretation and communication of results and subsequent clinical management. By incorporating relevant legal principles, existing professional guidelines and practical sources of support, it aims to facilitate the decision-making processes for both professionals and patients.

The use of genetic and genomic tests to support reproductive choices during pregnancy and to guide potential treatment and management is increasingly a part of routine prenatal care. The focus in this document is therefore on testing *during* pregnancy (PND), although reference is made to testing in other contexts to support reproductive choices, for example, pre-implantation genetic testing for monogenic disorders (PGT-M).[2] These guidelines will be relevant to health professionals from a range of clinical specialties, including general practice.

While the ethical issues in the use of genetic testing in the prenatal setting[3] have much in common with those that arise throughout life, there are (at least) three important aspects that warrant special attention:

a. **Uncertainty:** The results of prenatal genetic tests may not give clear diagnoses or predictions. However, the choices that follow such testing are often binary: to continue with or to terminate the pregnancy (and sometimes to make decisions about treatment).

b. **Time pressure:** Decisions often need to be made in a matter of days or weeks and may be influenced by statutory limits on the availability of termination. Potential parents often have little time to reflect on and process challenging information before having to make decisions around how to respond to it.

c. **Legal status of the fetus:** Although such decisions will often focus on the impact of the results of testing on the potential future person, the fetus is in law a part of the pregnant woman's body until birth. Consent for any testing of fetal tissue must therefore come from the pregnant woman.

[1] Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine. *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic.* 3rd edition. Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPath and BSGM, 2019. https://www.rcp.ac.uk/projects/outputs/consent-and-confidentiality-genomic-medicine

[2] There are a range of overlapping terms which are used inconsistently. We have adopted the term pre-implantation genetic testing for monogenic disorders (PGT-M) which is recommended by the Human Fertilisation and Embryology Authority. https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/pre-implantation-genetic-testing-for-monogenic-disorders-pgt-m-and-pre-implantation-genetic-testing-for-chromosomal-structural-rearrangements-pgt-sr/

[3] Horn R, Parker M. Opening Pandora's box?: ethical issues in prenatal whole genome and exome sequencing. *Prenat Diagn* 2018;38:20–25. doi: 10.1002/pd.5114. Epub 2017 Aug 7. PMID: 28695688; PMCID: PMC5836985.

The terms genetic and genomic are overlapping, although genetics is often used to mean the study of single genes, while genomics is the study of the entire genetic code and its influence on growth and development. Nowadays tests using genomic techniques often analyse a particular genetic factor, or a small group of genetic factors. To aid readability, this guidance mainly uses the term ‘genetic’ to include both genetic and genomic technologies where appropriate.

This guidance includes 14 illustrative examples of patients experiencing different ethical issues around testing during pregnancy. The various scenarios have been included to illustrate common dilemmas and help guide clinical practice.

Types of genetic tests in the prenatal setting

A variety of screening tests are offered routinely to pregnant women during their pregnancy, which can take the form of scans and blood tests. For example, screening tests are available for a range of trisomies (eg Down's syndrome, Edwards' syndrome), thalassaemia and, depending on the patient's ancestry, sickle cell disease.[4,5] These are offered by a range of healthcare professionals involved in routine antenatal care. Clinical genetic health professionals may become involved where inherited disease is known about in the family, or the results from any of these screening tests suggest that the fetus may have a genetic condition.

Over the past two decades massive improvements in technologies to 'read' the genetic code, and the speed at which this can be done at affordable prices, mean that prenatal genetic testing is now offered and requested more frequently.

A move from targeted genetic tests to genome-wide tests

Although genome-wide approaches in the form of the cytogenetic technique of karyotyping have been available for decades, technological advances mean that the balance has shifted from targeted testing which is guided by a specific clinical question (eg testing for a specific genetic variant indicated by clinical features) to using a broad assay (such as whole genome/exome sequencing or detection of copy number variation mapping through microarrays).[6]

These genome-wide tests may introduce targeting at a later stage (through, for example, focusing on a panel of genes indicated by particular phenotypic findings in the fetus) or they may take a more agnostic approach.[7] For example, microarray testing of the fetus may be useful when the results are compared with similar testing of both parents (trio analysis) to identify which variants are new (*de novo*) and which can be ruled out as not clearly linked to the phenotype in question. In general, whole genome approaches will increase the complexity of interpretation. This can result in greater uncertainty about the significance of variants found as well as finding variants which may confer a risk rather than a diagnosis. This is particularly challenging in the prenatal context where there is no, or limited knowledge about the fetus's phenotype,[8] so that predicting what such findings may mean for the future child is uncertain.

[4] Antenatal Results and Choices. Tests explained: https://www.arc-uk.org/tests-explained/
[5] Office for Health Improvement and Disparities. Sickle cell and thalassaemia screening guidance: https://www.gov.uk/government/publications/screening-tests-for-you-and-your-baby/sickle-cell-and-thalassaemia
[6] See Annex 1 for more details on the nature and scope of the tests that are available.
[7] ie looking for variation throughout the genome, rather than targeting sections or certain genes because a particular condition is suspected.
[8] ie features in a fetus are not present or specific enough to help interpret the genotypic variants. In children/adults there has often been more time to see how phenotypic features develop to help narrow down, or exclude, particular genetic conditions.

Routes for collecting fetal genetic material for testing

Fetal genetic material can be obtained in a variety of ways: it may be derived from the fetus via placental tissue or by sampling the amniotic fluid surrounding the developing fetus. More recently techniques to analyse the sequence of cell-free fetal DNA from maternal blood have been incorporated in clinical practice. Cells may also be analysed directly from the developing embryo prior to implantation in the uterus (PGT-M).

Amniocentesis and chorionic villus sampling (CVS) ('invasive' tests)

Amniocentesis (a procedure in which a small amount of amniotic fluid is removed with a needle from the sac surrounding the fetus) has been available in clinical practice since the 1980s. It can be performed from the 15th week of pregnancy and carries a slight increased risk of miscarriage.[9] In the 1980s, sampling of the placental chorion villus was developed so that cells could reliably be obtained at an earlier stage of pregnancy (from week 11). This also carries a small increased risk of miscarriage. These techniques are usually offered to further investigate a prior suspicion of fetal abnormality (for example, from a screening result that indicates increased risk, eg an ultrasound scan, or from a family history of disease).

Cell-free fetal DNA screening from maternal plasma ('non-invasive' tests)

Non-invasive prenatal testing (NIPT) – where cell-free fetal DNA can be analysed via a blood test of the pregnant woman, has no associated miscarriage risk. Another advantage is that it can be performed earlier in pregnancy (from 9–10 weeks), and is now of sufficient sensitivity and specificity to be introduced as a second tier screening test in pregnancies with an increased risk for fetal aneuploidy in Wales, England and Scotland.[10] When this technique is used as a screening test it is recommended that results that indicate an increased possibility of an abnormality are confirmed with more invasive tests (ie CVS or amniocentesis[11]).

Yet because of the high accuracy of the NIPT test, fewer women will undergo these confirmatory invasive tests when they receive a lower risk result, compared with other screening tests.[12] The same technology can be used for a diagnostic test (NIPD), for certain single gene conditions (eg cystic fibrosis) and X-linked conditions (eg Duchenne muscular dystrophy, congenital adrenal hyperplasia), in which case a confirmatory test may not be needed.

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[9] Salomon LJ, Sotiriadis A, Wulff CB, Odibo A and Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. *Ultrasound Obstet Gynecol* 2019;54:442–51. https://doi.org/10.1002/uog.20353

[10] NIPT is offered as a second-tier test for those at high risk of aneuploidy: https://phescreening.blog.gov.uk/2021/01/28/nipt-procurement-and-launch-update Operational guidance: https://www.gov.uk/government/publications/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-non-invasive-prenatal-testing-nipt/screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome-nipt

[11] Amniocentesis may be the preferred option to confirm positive NIPT given that a false positive NIPT may result from placental mosaicism, which might then be repeated in a CVS but not amniocentesis test.

[12] Salomon LJ, Sotiriadis A, Wulff CB, Odibo A. and Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. *Ultrasound Obstet Gynecol* 2019;54:442–51. https://doi.org/10.1002/uog.20353

The use of NIPT allows increased ease of testing for patients, improved access and reduced costs. These features, coupled with increasing numbers of tests being made available directly to pregnant women via direct-to-consumer tests offered outside the NHS, and sometimes outside the UK, have altered the prenatal testing landscape: in the past, availability, cost and speed of results limited what could be offered. Now there is increasing emphasis on the interpretation of a broad genetic/genomic test result instead of a targeted one, which may complicate decisions about whether or not to terminate a pregnancy.

Pre-implantation genetic testing for monogenic disorders (PGT-M)

PGT-M involves testing a cell from an embryo that has been created through *in vitro* fertilisation (IVF). Such testing is available where embryos are at risk of a serious inherited disease and is regulated by the Human Fertilisation and Embryology Authority (HFEA). Only embryos that have been tested and found to be healthy are transferred into the woman's womb. Nearly 600 conditions have been approved for pre-implantation genetic testing in the UK by the HFEA.[13]

Genetic tests offered by the NHS

The range of genetic tests that can be offered prenatally through the NHS Genomic Medicine Service is set out in the National Genomic Test Directory.[14] In addition, targeted testing may be offered where there is a known familial cause, or a specific genetic condition is indicated. Where conditions are prevalent in a population, or where pathogenic variants for a condition are limited, a test to confirm a familial variant may not add value and therefore may not be necessary; the potential benefit offered by a test may be justified, even in the absence of a definitive family history (such as where testing for certain autosomal recessive conditions is carried out without carrier testing in both parents in routine screening for sickle cell disease).[15] The situation in the devolved nations is dynamic where some but not all of these tests might be available.

For adult-onset cancer susceptibilities, there is a lack of consensus about the provision of prenatal diagnosis and pre-implantation genetic diagnosis. For this reason, the Cancer Genetics Group, Fetal Genomics Group and BSGM have developed best practice guidance for cancer susceptibility gene variants.[16]

[13] Genome UK: the future of healthcare. 2020. https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare

[14] NHS England. The National Genomic Test Directory: Testing criteria for rare and inherited disease. 2022. https://www.england.nhs.uk/publication/national-genomic-test-directories/

[15] Public Health England. Sickle cell and thalassaemia: screening handbook. 2018. https://www.gov.uk/government/publications/handbook-for-sickle-cell-and-thalassaemia-screening

[16] British Society for Genetic Medicine. *Prenatal diagnosis and pre-implantation genetic testing for germline cancer susceptibility gene variants. Guidance for clinical practice.* Cancer Genetics Group and Fetal Genomics Group for the BSGM, guidance in development.

Consent to investigations during pregnancy

Medical interventions and investigations in a patient require consent. In clinical practice (as opposed to research) the process of obtaining consent is often integrated into a clinical consultation; at other times it is documented separately, eg in a specific consent form.

The person providing their consent must:

a. have been given sufficient relevant and appropriate information for them to be able to make a decision[17]
b. have the capacity, or competence to make that decision[18]
c. be free from coercion or undue influence by others.[19]

These elements must all be met for consent to be valid. Sometimes consent is documented with a signature on a specific form; at other times a consent discussion may be summarised in clinical records; or it may be an entirely verbal process.[20] In each case, what matters is whether the three criteria are satisfied, not whether there is a signed consent form, although the latter may provide [some] documentary evidence of such a discussion. The information provided to enable an individual decision should be sensitive, balanced, evidence-based and reflect the needs and values of the people offered a test.

Genetic testing in pregnancy to screen, diagnose or assess the future risk of a genetic condition in the fetus requires the consent of the pregnant woman. The fetus has no legal rights and is not a legal entity until it is born: since it does not have independent rights, it depends entirely on the rights given to the pregnant woman.[21]

[17] As regards the *validity* of consent, the person consenting must be 'informed in broad terms of the nature of the procedure which is intended': *Chatterton v Gerson* [1981] Q.B. 432, 443A. On the separate legal question of the *risks* of a procedure, see discussion of the *Montgomery* case below.
[18] This is presumed for those over 16: Mental Capacity Act 2005, s. 1(2) and s. 2(5). It can be rebutted with reference to ss. 2 and 3. For those aged below 16, the person has to demonstrate 'Gillick competence' discussed in more detail on page 13.
[19] See eg *Re T (adult: refusal of medical treatment)* [1992] 4 All ER 649 (CA).
[20] Regarding consent in the context of IVF and PGT-M, see the HFEA Code of Practice for particular requirements regarding consent forms.
[21] See eg *Re MB (Medical Treatment)* [1997] EWCA 1361.

1 Difference of opinion

Nadia is acting as a surrogate for her friends Emi and Isaac. She is 21 weeks pregnant. Her anomaly screen showed that the fetus has growth restriction and multiple anomalies, including enlargement of the ventricles in the brain, a heart defect, and short bones. Nadia has been offered amniocentesis and genetic testing to try to establish the cause of the medical problems in the fetus. In advance of Nadia becoming a surrogate, she had extensive discussions with Emi and Isaac where they agreed that if the fetus had serious medical problems then Nadia would have a termination of pregnancy. However, Nadia now feels she would want to continue the pregnancy unconditionally and does not want to have an amniocentesis.

Key points

- Ultimately, the clinician's primary responsibility is to Nadia, and it is Nadia's decision whether she has an amniocentesis, and whether she continues the pregnancy or not.
- Ideally, conflict can be avoided by detailed discussions prior to a surrogate pregnancy starting. However, sometimes people feel differently to how they thought they would feel when an eventuality actually arises.
- Opportunities to discuss the situation with clinicians and talk through the significance of the scan findings may help Nadia, Emi and Isaac to reach consensus on the way forward for them.
- Good communication and team working between different specialties will be important to support Nadia, Emi and Isaac and make plans for the pregnancy and potentially for the care of the child.

When planning fetal investigations, it is important to remember that consent needs to be sought for the *investigations/procedures* on the pregnant woman (for example, ultrasound, venepuncture to obtain blood samples, amniocentesis or CVS) and for the *tests or analysis* to be done on the biological material collected (blood, placental tissue, cells from amniotic fluid etc.). Consent for the procedure will often be quite specific, while consent for the range of possible findings and their possible implications as well as any limitations of the test, will often require lengthier and more detailed discussions.

Depending on the context, trio testing[22] may be necessary to optimise the interpretation of fetal tests. This means that consent from other individuals may also play an important role in the investigation of the fetus.

[22] Comparing results from the fetus with similar testing of both parents (trio analysis) can help to identify which variants are new (*de novo*) and which can be ruled out as not clearly linked to the phenotype in question. It can also help to resolve the interpretation of results for recessive conditions.

A. Sufficient relevant and appropriate information to be able to make a decision

Deciding what constitutes 'sufficient relevant and appropriate information' in a particular case is heavily dependent on context. In part, it is dependent on the nature of the investigation and the potential risks involved.

Beyond the question of information concerning the 'broad terms of the nature of the procedure' that is directly relevant to the *validity* of consent, there is the *separate question* of the patient's right to receive information relating to the *risks* of a procedure, so that he or she can decide whether to accept those risks. The law here is governed by the decision in *Montgomery*, which held that:[23]

> '*An adult person of sound mind is entitled to decide which, if any, of the available forms of treatment to undergo, and her consent must be obtained before treatment interfering with her bodily integrity is undertaken. The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.'*

Although risks are associated with all tests offered in pregnancy, as amniocentesis carries a risk of miscarriage it could be viewed as potentially more hazardous than a blood test. However, the results that might be generated from an amniocentesis test or those from a maternal blood test could have implications for reproductive decisions.

The information provided needs to take account of the possible results generated from the test and how certain it will be that they are diagnostic or predictive of ill health or disability in the future person. This needs to be done in such a way that the pregnant woman is able to make an informed decision about how to utilise the test results incorporating the fact that, in many cases, she will be faced with a binary decision – whether to continue with or to terminate the pregnancy. Many results will not give clear predictions – either because of variations in the severity or expression of the condition, because current knowledge is insufficient, or because the condition in question is not explained fully or reliably predicted by the particular result. The likelihood of uncertain or inconclusive results therefore requires careful discussion in advance, especially in the context of common societal discourses that a genetic code is a 'blueprint' and an expectation that its analysis will lead to clear-cut information.

In addition, the *Montgomery* ruling requires health professionals to seek out the views and perspectives of the patient in front of them when deciding the nature and amount of information that should be provided. That is to say, standard protocols or operating procedures

[23] *Montgomery (Appellant) v Lanarkshire Health Board (Respondent) (Scotland)* [2015] UKSC 11, para 87.

may need adapting to the particular patient. This includes taking special care when communicating genetic terms and procedures to patients who have communication impairments or a learning disability and may require additional skill and sensitivity.

2 Understanding the limitations of a genetic test

Elizabeth is 15 weeks pregnant. After a dating scan, her partner Shankar bought her a non-invasive prenatal test from a private provider as they wanted to check their baby was healthy and find out whether they were having a boy or a girl. They were very upset to be told that there was a high probability that the fetus had trisomy 13 (Patau syndrome). The test was advertised as being 99% accurate. Elizabeth calls her GP to request a referral for termination of pregnancy.

Key points

- Non-invasive prenatal tests (NIPT) can be used to screen for some fetal chromosomal conditions by analysing the relative proportions of fetal genetic material in the mother's blood.
- Such tests often have a good negative predictive value, ie if they say a fetus is likely unaffected by a particular condition they are probably right.
- Where tests detect a high probability of a condition, there is a substantial chance that this could be wrong – for Patau syndrome this chance is around 1 in 2 (although this will vary depending on the details of the test).[24] Elizabeth should be offered chorionic villus sampling or amniocentesis to confirm her NIPT result, and information and support as she makes decisions based on the result of confirmatory testing.
- People having prenatal genetic testing should be counselled in advance about the limitations of testing and encouraged to consider how they might respond to different possible outcomes and whether testing is the right decision for them. Where this may not have happened optimally in advance of testing, clinicians need to take particular care to ensure that people are subsequently given relevant and appropriate information to help them understand their results and consider how to respond.
- Tests motivated by an understandable wish for 'reassurance' can be problematic when the results only detect the probability of a condition.
- The claim that an NIPT test is 99% accurate may be correct but also misleading if used in the marketing of private tests, where the accuracy rates may be significantly reduced, especially for rare conditions.

[24] Nuffield Council on Bioethics. *Non-invasive prenatal testing: ethical issues*. London: NCB, 2017. www.nuffieldbioethics.org/wp-content/uploads/NIPT-ethical-issues-full-report.pdf

3 Unexpected outcomes

Priya is 22 weeks pregnant. Her 20-week scan detected multiple anomalies in her fetus. Priya gave consent to amniocentesis and a microarray to try to find a cause for the medical problems in her fetus. The microarray finds that the fetus has a deletion encompassing part of the *BRCA2* gene. This does not explain the fetal anomalies and, if the pregnancy were to continue, the *BRCA2* deletion would have no medical implications until adulthood, where it would confer an increased risk of developing various cancers. However, it may have been inherited from Priya or her partner Giovanni. If so, there might be screening or risk-reducing options that could benefit them or their wider families.

Key points

- Unexpected findings may arise from prenatal genetic testing, and this possibility should be discussed in advance of testing.
- Clinical practice should guide disclosure, and not a narrow interpretation of what the patient has consented to, although if the patient has made a clear decision to refuse feedback of information not pertinent to the medical issues in their fetus, this should be respected.
- Professional guidance does not recommend opportunistic prenatal *BRCA1* or *2* testing but this does not mean clinicians cannot report this if a cancer predisposing *BRCA1* or *2* variant is found by chance in a fetus. Responding to existing information is different to deciding to seek it out.
- Similar situations can arise when testing children, but the prenatal context may make this especially challenging as Priya and Giovanni potentially have to come to terms with unexpected information about their own health, while the anomalies found in their fetus remain unexplained.

B. Have the capacity, or competence to make that decision

There are several reasons that people may lack capacity or competence to make a decision about their care. Children may lack capacity because they lack the maturity to understand what is involved and weigh up the advantages and disadvantages of proceeding. Adults aged 16 or over are presumed to have capacity to make a particular decision unless a lack of capacity can be demonstrated.[25] Under the age of 16 the presumption is reversed: children and young people can consent to their own treatment if it can be demonstrated they have capacity, but the default is that they will not. Capacity in under 16-year-olds is often referred to as ‘Gillick’ competence.[26]

[25] Mental Capacity Act 2005 s.1(2). The Adults with Incapacity (Scotland) Act 2000 applies in Scotland and contains similar provisions.
[26] *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112.

Capacity may also be diminished through illness or disability. A lack of capacity may be permanent or fluctuating. Although discussions around capacity often suggest that it is an all-or-nothing state, it is important to remember that it is decision-specific. A person might have the capacity to decide about some medical interventions, yet not others: this might depend on what is at stake, and the extent of support which is provided to help that person achieve capacity. Legislation requires that all practicable steps are taken to support decision-making.[27] Capacity may also change over time.

4 Doubts about capacity

Felicity is 19 years old and 7 weeks pregnant. She has a 22q11.2 deletion, diagnosed in childhood when she had investigations for developmental delay. Her fetus has a 50:50 chance of having inherited this variant. Deletions of 22q11.2 can cause a wide spectrum of medical issues including learning problems and heart problems. Felicity is referred to discuss testing the fetus for the 22q11.2 deletion. She attends with her mother, Caroline. Felicity looks at Caroline whenever she is asked a question, and Caroline does all the talking. Caroline says that Felicity has a learning disability and Caroline supports her with everyday life, including potentially looking after a baby. Caroline is clear that Felicity wants a test.

Key points

- Felicity might have capacity to make a decision about having a prenatal test, but there is reason to be unsure about this, so a capacity assessment is needed.
- Clinicians should try to maximise Felicity's capacity to decide, for example by using simple language or pictures to help her understand the test and the reasons why she might or might not want it.
- If on further assessment, Felicity does not have capacity to decide whether to have a prenatal test, a decision will need to be made in her best interests. It would still be important to involve Felicity in the decision as much as possible.
- In some cases, this might involve discussing whether there are people who have been formally appointed to determine Felicity's best interests (including a donee of a lasting power of attorney (appointed by Felicity), or a court-appointed deputy, or an independent mental capacity advocate) and involving them in decisions. If there is serious doubt or dispute, clinicians should involve the Court of Protection.

C. Be free from coercion or undue influence by others

This component of consent is worth focusing on in the setting of genetics, given that tests may require samples from other family members for optimal interpretation, and the interests of others may therefore need to be taken into account. It is also important to note that prenatal

[27] Mental Capacity Act 2005 s.1(3).

testing is a stressful and potentially traumatic experience, and it is often invaluable for women to have their partners and other family members present to make decisions together or if bad news is being communicated. Sometimes however, it can be difficult to see the distinction between respecting the interests of others and the undue influence of others in a decision-making process. It is possible that a woman is under pressure from her partner or her relatives to have or not to have a test or termination of pregnancy. Women should be provided support in these cases to make sure they can make the decision they will be comfortable with, although this may often be intertwined with the partner's or family's views.

5 Free to decide?

Maria is 13 weeks pregnant. Combined testing indicates a high chance that her fetus has Down's syndrome (trisomy 21). She attends clinic with her husband Richard to discuss the possibility of further investigations. Richard is insistent that Maria should have CVS as soon as possible to establish whether the fetus has Down's syndrome. Maria says very little but is tearful during discussions around testing. When trying to explore what Maria thinks, Richard answers for her.

Key points

- Unexpected prenatal findings can be distressing, and Maria's tearfulness may simply be a reflection of that. However, it is essential to ensure that future plans genuinely reflect Maria's views, and at present it is unclear whether she agrees with Richard's wish for testing or not.
- It may be helpful to ask to speak to Maria separately, to try to give her an opportunity to share her views. When a couple disagree about how to respond to prenatal findings, it can be very challenging. Clinicians may be able to help the couple reach consensus by making time to sensitively talk through the significance of findings so far and providing balanced information on what a diagnosis might mean for them and their family. If disagreement persists, ultimately the clinician's primary responsibility here is to Maria.
- If there are concerns that Maria may be at risk of harm it is important to involve safeguarding teams.

Involving a multidisciplinary team for wider discussion provides support for difficult cases. The Genethics Forum is another potential source of ethical support in complex cases.[28]

[28] The Genethics Forum is a multidisciplinary clinical genetic group which meets regularly to discuss cases raising challenging ethical issues: https://www.genethicsUK.org

The Abortion Act

The result of genetic testing of a pregnancy may lead to consideration of whether to continue with the pregnancy or terminate it. Terminations of pregnancy (ToP) are regulated by the Abortion Act 1967 (as amended by the Human Fertilisation and Embryology Act 1990). There are different grounds for terminating a pregnancy. Under section 1(1)(d) (commonly known as Ground E[29]), the 'disability ground', a woman will be able to seek a ToP if two doctors judge in good faith 'that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped'.

If the pregnancy has not exceeded its twenty-fourth week, two doctors may instead sanction a woman's wish to terminate under section 1(1)(a), (commonly known as 'Ground C'), where they judge in good faith that 'the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family'. Box 1 shows the full wording of reasons for a termination. Only Ground C (section 1(1)(a)) has a time limit of 24 weeks. However, while ToP are legitimate in certain circumstances up until term, in practice few take place in the third trimester.[30]

Section 1(1) of the Abortion Act 1967 (as amended by the Human Fertilisation and Embryology Act 1990)

Subject to the provisions of this section, a person shall not be guilty of an offence under the law relating to abortion when a pregnancy is terminated by a registered medical practitioner if two registered medical practitioners are of the opinion, formed in good faith

a. that the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family; or
b. that the termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman; or
c. that the continuance of the pregnancy would involve risk to the life of the pregnant woman, greater than if the pregnancy were terminated; or
d. that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped.

It is important that women facing these choices understand the limits and degrees of uncertainty regarding the nature of the information generated from genetic tests, so that they can decide whether to proceed with a termination or not. If there is uncertainty as to whether

[29] In practice, rather than referring to the statutory grounds for termination under the Abortion Act, reference is made to the Ground E and Ground C in the abortion notification form available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/204071/HSA1-form.pdf

[30] In 2021 in England and Wales, 3370 abortions out of 214,256 (in total) were performed under Ground E at 24 weeks and over: https://www.gov.uk/government/statistics/abortion-statistics-for-england-and-wales-2021/abortion-statistics-england-and-wales-2021

there is a ‘substantial risk’ of a ‘serious handicap’, it is difficult to rely on Ground E (section 1(1)(d)) and only Ground C (section 1(1)(a)) would be potentially open to the woman and her medical practitioners.[31] Optimising communication to support the mother in the decision-making within a limited timeframe will be key.

There is no legal definition of what comprises a ‘substantial risk’ or a prescribed list of conditions which qualify as ‘serious handicap’ (Ground E, (section 1(1)(d)) above). Instead, the law relies on the informed judgement, in good faith, of practitioners. Under Royal College of Obstetricians and Gynaecologists (RCOG) guidance, they are to take account of factors such as the potential for effective treatment of the condition either before or after birth; the potential suffering of the future child; their ability to communicate with others; and the probability that they will be able to live independently without support.[32] The RCOG have emphasised the importance of a case-by-case appraisal taking into account all available clinical information. This may include seeking advice from maternal-fetal medical specialists, and also colleagues who specialise in treating the conditions in question, who could ‘counsel the parents’. When deciding whether the criteria of the disability ground of the Act are satisfied, doctors should attempt to take the views and interests of a woman (and her partner) into account. A recent legal case considering the legitimacy of relying on Ground E (section 1(1)(d)) concluded that this was for ‘responsible clinicians (to agree that in their good faith opinion the grounds for an abortion are met), the pregnant patient and, where relevant, her family’.[33] Where potentially more than one ground for termination might apply, it is important for clinicians to be clear about which of these will be relied upon in their discussions with patients.

[31] RCOG. Termination of pregnancy for fetal abnormality in England, Scotland and Wales. 2010.
[32] RCOG. Supporting women and their partners through prenatal screening for Down’s syndrome, Edwards’ syndrome and Patau’s syndrome. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/consensus-statement-prenatal-screening/
[33] In *Jepson v The Chief Constable of West Mercia Police Constabulary* [2003] EWHC 3318 a letter of the then Vice-President of the RCOG to the police was discussed, which stated, in part: ‘There is no precise definition of “serious handicap” and the decision is therefore one for the practitioner to make in consultation with the parents and other interested parties.’ See also Crowter, Wilson and *A v SOS Health and Social Care* [2021] EWHC 2536 (Admin), per Lord Justice Singh and Mrs Justice Lieven, para 17: ‘Whether an abortion should be carried out under section 1(1)(d) is a matter between the responsible clinicians (to agree that in their good faith opinion the grounds for an abortion are met), the pregnant patient and, where relevant, her family.’

6 What grounds for abortion before 24 weeks?

Freya is 6 weeks pregnant and refers herself to clinical genetics. Her husband Randall has a cancer predisposing *BRCA1* variant. The variant was first identified in the family when Randall's mother died of breast cancer when she was 45 and he was only 11. Freya and Randall want prenatal testing to establish whether Freya is carrying a female fetus with the cancer predisposing *BRCA1* variant. If she is, she would have a termination of pregnancy. In discussion about options, Freya explains that she would not want to bring a child into the world who would die of cancer in her 40s like Randall's mother. This leads to a discussion around grounds for termination of pregnancy and Freya and Randall are confused to hear that if Freya were to have a termination, the legal basis for this would be Ground C rather than Ground E.

Key points

- Prenatal testing for adult-onset risks can be controversial, especially where options are available to mitigate risk (for example, early breast screening and/or risk-reducing surgery for women with cancer-predisposing *BRCA* variants). The law confines Ground E to serious handicap in the fetus and it is not clear that an adult-onset predisposition fulfils this criterion.
- Clinicians should be mindful of a patient's lived experience – with Randall's experience of losing his mother at a young age it is very understandable that this couple might anticipate a cancer-predisposing *BRCA* variant in a female as being grounds for a termination of pregnancy on the basis of fetal abnormality. It is important that clinicians sensitively consider with Freya and Randall the options an adult woman with a cancer predisposing *BRCA* variant might now have to help her stay healthy.
- Freya and Randall should be supported to make whatever decision they feel is right for them, after a discussion about the possible long-term effects of this variant (likely chances of cancer and when, and uncertainties about interventions or treatment options over the next few decades).
- Where prenatal tests for adult-onset conditions are requested, it is important to have sensitive discussions about the reasons for this request given that such testing would not normally be offered during childhood. Unless the test is being done to decide about whether or not to have a termination, it should probably be deferred to a later stage, as it might, in effect, result in a predictive test for the future child.
- Where there is uncertainty or potential disagreement, it may be helpful to involve a multidisciplinary team. The Cancer Genetics Group and Fetal Genomics Group have developed best practice guidance on prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD) for cancer susceptibility gene variants.[34]

[34] British Society for Genetic Medicine. *Prenatal diagnosis and pre-implantation genetic testing for germline cancer susceptibility gene variants. Guidance for clinical practice.* Cancer Genetics Group and Fetal Genomics Group for the BSGM, guidance in development.

Communication and decision-making

Prenatal testing often reveals complex and uncertain information

Approximately two out of every 100 pregnancies result in a baby with a congenital anomaly.[35] Some, but not all of these will have a genetic explanation and some, but not all of these will be detectable with current genetic or genomic investigations. Hence, analysis has been increasingly moving from targeted to broad. With this, it becomes more likely that rare variants will be found whose significance is unclear or uncertain – a variant of uncertain significance or VUS (because we each have some 10,000 rare variants, many of which would be identified by using broad filters aimed at detecting a wide range of diseases). This uncertainty may remain or it might be clarified in the future as the result of research or clinical experience, so that a variant may shift from being uncertain to being assessed as clearly benign or clearly pathogenic.[36] Even where variants have clear evidence of associated pathogenicity this may require other (as yet unknown) factors for the pathogenicity to manifest, and the penetrance of many pathogenic variants may be much less than 100% (some people with the pathogenic variant will never manifest the associated condition). Other variants found during testing in pregnancy may indicate a high chance of future disease but one which does not manifest before adulthood, and which may be treatable (see ‘6 What grounds for abortion before 24 weeks?’ on p18). While interpreting genomic data can be complex and uncertain in any setting, the particular difficulty in pregnancy is that the opportunities to assess phenotype *in utero* are more limited. Deciding which genetic information constitutes a clinically useful result, and the extent to which that information can be relied upon when making related decisions (such as whether or not to continue with a pregnancy), can be difficult.[37]

[35] Public Health England, National Congenital Anomaly and Rare Disease Registration Service Congenital anomaly statistics 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1008030/NCARDRS_Congenital_anomaly_statistics_report_2018.pdf

[36] As mentioned above, trio testing may help to interpret the variant.

[37] Shkedi-Rafid S, Horton R and Lucassen A. What is the meaning of a ‘genomic result’ in the context of pregnancy? *Eur J Hum Genet* 2021;29,225–30. https://doi.org/10.1038/s41431-020-00722-8

7 What counts as information?

Frances is 21 weeks pregnant. Her anomaly scan found that her fetus has a heart defect and cleft lip. Frances and her partner Simon agree to a microarray in order to investigate this. The laboratory finds that Frances' fetus has a chromosomal microdeletion. The microdeletion encompasses 14 genes, but none are known to cause specific health problems when deleted. The microdeletion is rare, and the laboratory cannot find any data on health outcomes for people with a similar microdeletion. Parental samples were stored when Frances gave consent to the fetal microarray, and analysis of these shows that the fetal microdeletion is *de novo*.

Key points

- Our ability to generate genetic data is far greater than our ability to understand them. There are many genes for which impact on health is unknown.
- Multidisciplinary discussion and involving expert colleagues is important when interpreting genetic data. Sometimes steps can be taken to clarify the significance of a genetic finding (for example, if this microdeletion had been inherited from a healthy parent, it would be reassuring as it would demonstrate that a person can have the microdeletion and become a healthy adult).
- Ongoing communication between the laboratory team and clinicians is needed while a consensus is reached regarding whether it is appropriate to conceptualise this as a 'result', and how to write the microarray report. Where available, laboratory staff and clinicians should draw on professional guidelines.
- Where uncertain genetic data are discussed with prospective parents, careful planning is needed around communication. It is sometimes helpful to refer back to information that is relatively more 'certain'. For example, here the medical significance of the chromosomal microdeletion is unknown, but the impact of the heart defect may be somewhat easier to forecast.
- Patients will vary in their capacity to tolerate uncertainty. They should be enabled to discuss what the information means to them and be supported in their decision about whether to continue the pregnancy within the legal restrictions.

Diagnosis or prediction

New technologies make it possible to both diagnose genetic abnormalities that manifest from birth (eg trisomies or autosomal recessive conditions such as cystic fibrosis) as well as predict a heightened risk of later-onset conditions (eg familial cancer or cardiac conditions) and care needs to be taken to communicate the difference between these types of 'results'. Separate BSGM guidance on genetic testing in childhood outlines the ethical issues relating to when it may or may not be acceptable to use genetic testing to predict genetic conditions in the far future, particularly when there are no short-term interventions to ameliorate the course of the condition in question. These considerations may also be relevant to predictions made about the developing fetus *in utero*.

Even for conditions with onset in early childhood, there may be a wide range of possible manifestations of disease as well as degrees of severity. Moreover, the broader the investigation (and the less genetic testing is targeted to a particular clinical question) the more likely that vast swathes of data – with varying degrees of predictive power and uncertainty – might challenge effective communication and decision-making.

8 Different perspectives on the significance of genetic information

Alanna is 9 weeks pregnant. Her 6-year-old son Aiden has moderate developmental delay and challenging behaviour. Previous investigations into Aiden's developmental delay found that he had a chromosome microduplication, inherited from Alanna. At the time, Alanna and her partner Claire were counselled that the microduplication might be contributing to Aiden's difficulties, but that it had also been found in many healthy people (like Alanna) and there might be another cause for Aiden's difficulties that has not yet been found. Alanna is aware that her fetus has a 50:50 chance of having inherited the microduplication and requests a prenatal test. She understands that the microduplication is unlikely to be the full explanation for Aiden's difficulties, but she says she 'doesn't want to take any risk' and would terminate the pregnancy if the fetus had the microduplication.

Key points

- Interpreting genetic information is challenging and scientific interpretations may change over time.
- It is important that Alanna and Claire are given up-to-date information regarding the microduplication. This may involve discussing the uncertainty inherent in any pregnancy and challenging the idea that excluding a microduplication will remove 'risk', especially here where there may be another genetic cause for Aiden's difficulties that has not yet been found.
- Alanna cannot demand that a clinician perform a test if they do not think that it is medically indicated, though she does have the right to a second opinion. It is important to carefully consider her request and whether it would be appropriate to seek advice and/or discussion with other colleagues in clinical genetics and fetal medicine.

Ensuring that the patient is central in decision-making

Effective communication can be hard to achieve when decisions need to be made quickly. This is especially so where a prevailing public discourse holds that genetic testing is a matter of deciphering a 'blueprint'. The current reality of uncertainty, poor predictive value and changing interpretations of the clinical significance of many genetic variants can be difficult to

convey when a binary decision of whether or not to continue a pregnancy is the decision at hand. Questions of what is or is not a reasonable ground for termination of pregnancy are questions about which patients are likely to have their own views.

The *Montgomery* ruling, emphasises that reasonable care must be taken 'to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments', defining materiality as 'whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.' Arguably therefore, a one-off meeting with a pregnant woman to seek consent for genetic testing in pregnancy may be insufficient to satisfy this standard, and more time might be required. However, this may be challenging when the window for decision-making is inevitably limited during pregnancy. Where possible, conversations should take account of tight timescales and realistic turnaround times for the tests performed, while recognising that it may sometimes be challenging to communicate realistic expectations about tests and their possible results, especially if time and resources are limited.

9 Unexpected news with little time to decide

Holly is 18 years old. She has previously been treated for anorexia and thought her eating disorder and its treatment were the explanation for her lack of periods and increasing weight. At 21 weeks, she discovers that she is pregnant. She is referred for an anomaly scan. The scan shows that the fetus has a right-sided aortic arch, an anatomical variant that often causes no problems but that sometimes needs treatment (depending on other anatomy) and is associated with heart defects and certain genetic conditions. Holly decides to have an amniocentesis and genetic testing, which excludes common trisomies and 22q11.2 microdeletions. Detailed cardiac ultrasound finds no features suggestive of a heart defect. At 23 weeks, Holly asks for termination of pregnancy.

Key points

- Late discovery of pregnancy can put women and clinicians in a very challenging position. Here, right-sided aortic arch would be insufficient grounds for termination of pregnancy on the basis of serious handicap in the fetus. It could be argued that there is a risk, greater than if the pregnancy were terminated, of injury to Holly's physical or mental health, but at this gestation many centres would be uncomfortable making this judgement.
- Holly has had very little time to adapt to the idea of her pregnancy before being faced with unexpected scan findings, and consciousness of a 'deadline' at 24 weeks, beyond which she will have no option but to continue the pregnancy. It is possible that the prospect of her body changing as pregnancy progresses is additionally distressing for Holly (though important not to assume this).
- Multidisciplinary team working and clear communication is essential to support Holly and explore what options might be available to her.
- Psychological support should be offered to Holly.

Implications of prenatal genetic testing for others

Disclosure to family members

A prenatal genetic test can reveal information that is relevant not only to the fetus but also to the parents, siblings, and the wider family. Similarly, genetic testing outside the prenatal setting may generate information that might allow prenatal tests for other family members. Clinicians may feel a tension between their duty to focus on their patient and their duty towards others who may have an interest in this information.

10 Using familial information to facilitate prenatal testing

Abigail is 8 weeks pregnant. She is referred to clinical genetics after mentioning at her booking appointment that her sister Zara's 4-year-old son has developmental problems and has been seen by a geneticist. The clinical geneticist who calls Abigail asks about her family history. They recognise the name of Abigail's nephew, and know that he has Duchenne muscular dystrophy, a progressive genetic disorder that affects boys from early childhood and leads to early death. If Abigail is a carrier for Duchenne muscular dystrophy, there is a 1 in 4 chance that it will be affected with the condition (a 1 in 2 chance if her fetus is male). Abigail tells the clinical geneticist that she does not know the cause of her nephew's developmental problems. She says that a few months ago, Zara stopped answering messages or returning her calls. The geneticist speaks to a colleague who discussed the nephew's results at a recent meeting. The colleague recalls that Zara was distraught when she heard the diagnosis of Duchenne muscular dystrophy, and said at a follow-up appointment that there was no point discussing future prenatal testing as she would never have a termination of pregnancy.

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Key points

- Consent conversations should include making clear that genetic testing may generate information of relevance for family members, and that using such information to inform the care of family members is a standard aspect of clinical genetics practice and not something over which any one person has a right of veto.
- Genetic variants inherited by others within a family should be considered confidential to the family, rather than confidential to the individual in whom they were first identified. However, the medical consequences of a variant for an individual person (for example, the details of the difficulties Zara's son is experiencing) are confidential to them alone.
- Clinicians have a duty to weigh the interests of relatives in the balance with maintaining the confidentiality of the initial patient and need to be able to justify any decision to disclose and potential harm that this might cause.
- In this case, prenatal testing requires details of the genetic variant causing Duchenne muscular dystrophy in the family, so Abigail's geneticist cannot offer her a 'routine screen' for the condition.
- If, following team discussion, clinicians agree that Abigail should be offered a prenatal test, clinicians should try to protect Zara and her son's confidentiality as far as possible and should not disclose information about them or their medical care. The fact that Abigail is very likely to infer correctly that her nephew has Duchenne muscular dystrophy should not necessarily prevent the offer of a prenatal test.
- When a patient's personal information is being disclosed in the public interest without their consent, the General Medical Council (GMC) advises that the patient should be informed of this. In this complex situation, Abigail's pregnancy and associated plans are confidential, but the familial Duchenne muscular dystrophy variant is not personal to Zara and her son. Clinicians have assumed that Zara would stop the use of her son's information to facilitate Abigail's prenatal test if she had the right of veto. However, they should consider whether and how explaining to Zara that the familial Duchenne muscular dystrophy variant may be used to facilitate the medical care of others might be helpful.

One case where important information relevant to or about others could be revealed is where genetic parentage has been misattributed. This might come to light, for example, in the diagnosis of an autosomal recessive condition in the fetus, when the apparent father has not provided one of the variants found in the fetus. While such information is often considered as social information not relevant to the clinical discussion, it might have an important bearing on counselling of recurrence risks and so a real question about disclosure arises.[38] For example, an array could reveal excess homozygosity for which there may be a number of different explanations including structural genomic changes, consanguinity or potentially incest.[39] Thus, there is a balance to be struck between treating patient information as personal and confidential, and discussing potential familial information appropriately.

[38] Wright CF, Parker M and Lucassen AM. When genomic medicine reveals misattributed genetic relationships – the debate about disclosure revisited. *Genet Med* 2019;21:97–101. https://doi.org/10.1038/s41436-018-0023-7

[39] Genetic findings might indicate an incestuous relationship raising potential safeguarding concerns. If concerns arise, local and national guidelines should be followed, including consulting with colleagues or designated agencies or professionals. British Medical Association. *Adult safeguarding – a toolkit.* BMA, 2018. https://www.bma.org.uk/media/1792/bma-adult-safeguarding-full-toolkit-2018.pdf; General Medical Council. Adult safeguarding: ethical hub topic. https://www.gmc-uk.org/ethical-guidance/ethical-hub/adult-safeguarding

11 Misattributed paternity

Phoebe is 20 weeks pregnant. Her anomaly scan shows that her fetus has multiple contractures. Phoebe and her husband Kevin agree to trio exome testing to try to establish the cause of the contractures. The laboratory calls the referring clinician to say that trio testing failed quality control, but in view of the prenatal timeframe they proceeded to singleton analysis of the fetus and found variants in keeping with an autosomal recessive arthrogryposis (explaining the contractures).

Key points

- There are various reasons why genetic samples might fail quality control. A possibility here is that Kevin is not the biological father of the fetus (so his sample was not informative in screening variants from the fetal sample).
- While misattributed paternity is 'social' information, it may have medical implications, for example regarding recurrence risk for future pregnancies.
- The possibility that genetic testing might indicate that family relationships are not as reported, should ideally be made clear during the consent process. Whether this discussion happened should not necessarily have a bearing on disclosure decisions, but it may pre-empt such situations or make the possibility of misattributed paternity a little more straightforward to broach.

Another situation where a prenatal genetic test may reveal important information about either parent, or perhaps wider family members, is where broad techniques find, for example, a genetic variant associated with adult-onset cancer risks in the fetus as an incidental finding (ie it is incidentally 'stumbled upon' in the process of looking for a diagnosis). Where unrelated findings are deliberately sought, these findings are described as additional findings, and it is important to check whether the patient has consented to these findings being generated and returned or not. It may often be difficult to distinguish patient's views on generating findings and returning them, but in practice this is an important distinction.[40] It may also be important to check whether either parent, and subsequently their wider relatives, have the same variant, so that they might be offered appropriate surveillance.

In the UK, a recent court ruling[41] has confirmed professional guidance from the GMC that there is a duty to weigh the interests of relatives in the balance with the interest of maintaining the confidentiality of one person. While this case concerned a family in which disclosure was withheld, it makes clear that health professionals have a duty to consider (and keep a record of) the interests of [proximal] others when a potentially familial genetic result is found.

Questions about the impact of genetic tests for others are likely to become increasingly challenging as genetic testing becomes more routine, and it is important that such possibilities are raised at the outset so that patients have an understanding of what they can expect when results are returned.

[40] Shkedi-Rafid S, Dheensa S, Crawford G, Fenwick A, Lucassen A. Defining and managing incidental findings in genetic and genomic practice. *J Med Genet* 2014;51:715–23. doi: 10.1136/jmedgenet-2014-102435

[41] *ABC v. St. George's University Hospital NHS FT, SW London & St. George's Mental Health NHST and Another* (High Court, 28 February 2020 – Yip J.)

Broader aspects of patient care

Access to genetic testing and justice

A key principle underpinning the provision of healthcare in the UK is that it should be made available in a consistent manner to those in need. Avoiding inequality (differences in health status or outcomes between individuals or groups) or inequity (where the reasons for these differences are unjust or arise due to injustice) are important principles that inform healthcare provision across all clinical specialties but may be very challenging to address in practice. Identifying which women are likely to benefit from a particular test, and policy decisions about which tests should be funded, are the subject of ongoing debate. Although clinicians may feel uncomfortable about existing policies, they cannot – in their daily practice – change or override them. They can, however, make sure that all women receive accurate information about relevant genetic tests in pregnancy, and for those women who are eligible to access a test, support their decision-making.

12 Creating a two-tier system?

Anne is 5 weeks pregnant. Her 3-year-old son Tyler has Kabuki syndrome (a genetic condition which affects people in different ways but often causes learning disability and poor growth). Previous genetic testing found that Tyler's Kabuki syndrome is due to a *de novo* variant in *KMT2D*. Anne has been told that there is a roughly 1% chance that her current pregnancy will be affected by Kabuki syndrome, and requests prenatal testing. Her clinician offers her chorionic villus sampling or amniocentesis (once she reaches an appropriate gestation) on the NHS. The clinician also mentions the possibility of non-invasive prenatal diagnosis. Here, the laboratory would initially have to develop a bespoke test for Anne, which could then be used in this and any future pregnancy. The clinician explains that Anne would need to pay for the initial development of the bespoke test (costing around £1,000) but use of the test in pregnancies would then be covered by the NHS.

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Key points

- In this context, non-invasive prenatal diagnosis would be a clinically better option for Anne than chorionic villus sampling or amniocentesis, as it would give her similar quality information without exposing her and her pregnancy to the risks associated with an invasive procedure.
- Funding constraints mean that departments sometimes have to make difficult decisions about what investigations or treatments they are able to pay for.
- Here, clinicians are trying to facilitate Anne having the option of non-invasive prenatal testing, by offering NHS funding for prenatal tests based on this technology (in the same way that amniocentesis or chorionic villus sampling would be funded). However, this option is only available to people who are able to pay for development of the initial non-invasive prenatal test.
- Clinicians and commissioners may encounter difficult decisions as to whether it is better to refuse to pay for options that cannot be accessed by everyone who might benefit from them, or whether it is better to facilitate options that might be helpful for people at the risk of creating a two-tier system.

Legal provisions relating to pre-implantation genetic testing (PGT-M)

One example where equity of access is often evoked as a problem is preimplantation genetic testing for monogenic or single-gene disorders (PGT-M), a technique that allows the diagnosis of a genetic disorder in early embryos created through IVF, before transfer to the uterus. PGT-M is an option available on the NHS (subject to funding) for women and their partners. Legislation stipulates that PGT-M should be available where, in essence, there is a particular risk that an embryo may not be viable, or of a child having or developing 'a gender-related serious physical or mental disability… a serious illness, or… any other… serious medical condition', or of an embryo having an abnormality and 'there is a significant risk that a person with the abnormality will have or develop a serious physical or mental disability… a serious illness or any other serious medical condition'.[42] Testing is performed to determine whether an embryo is at risk of genetic disease and only unaffected embryos are transferred. PGD is an alternative to prenatal diagnosis for couples at risk for transmitting genetic disorders since termination of an affected pregnancy can most likely be avoided. What constitutes a serious condition is not defined but should be resolved by dialogue between clinicians and the people seeking treatment.[43] Currently, access through the NHS is not available if there is already a healthy child or children from the current relationship.

[42] Human Fertilisation and Embryology (HFE) Act 1990 (as amended by the HFE Act 2008), Sched. 2, paras. 1ZA(a), (c), (b) and 2).
[43] HFEA Code of Practice, 9th edition, paras 10.5, 10.6 and 10.9.

13 Eligibility problems

Leah and Marshall pay for preconception carrier testing after their best friend's baby dies from an autosomal recessive genetic condition. The test shows that Leah and Marshall are both carriers for Zellweger syndrome, a severe disorder that usually leads to death in infancy. This means that every time Leah and Marshall have a baby together, there is a 1 in 4 chance that the baby will have Zellweger syndrome. They have one healthy son, Adam, but want to have another baby, and after researching their options they decide on pre-implantation genetic diagnosis (PGD). When they are seen in a genetics clinic, they are distressed and angry to hear that they are not eligible for PGD on the NHS because they already have a healthy child. From their online research, they are aware of various examples where couples have accessed PGD on the NHS despite already having a healthy child.

Key points

- Commissioning guidance on accessing PGD[44] is implemented inconsistently across England and Wales. Existing rules do not support provision of PGD where there is an existing unaffected child from the current relationship.
- A new relationship or other criteria (such as maternal BMI or smoking status) can impact eligibility for PGD, and it might be difficult to understand the full picture from stories accessed via social media.
- These issues can pose significant challenges for families who often feel they have to resort to private providers in order to obtain access to PGD. Here, Leah and Marshall may understandably feel that they have tried to be responsible and save the NHS money in seeking out preconception carrier testing.
- Dealing with inconsistent provision is challenging for healthcare professionals working in this area.
- New commissioning guidance is currently being developed.

Implications of direct-to-consumer/private prenatal genetic testing for the NHS

Direct-to-consumer (DTC) or private prenatal genetic tests, including non-invasive prenatal tests (NIPT) or polygenic risk scores in pre-implantation genetic testing,[45] can mean that women access tests not available on the NHS. Although this is an issue for all genetic testing, the challenges are heightened in a prenatal setting, where timely decisions about the future of the pregnancy may have to be made, even though information is lacking.

[44] NHS England. Clinical Commissioning Policy: Pre-implantation genetic diagnosis (PGD). April 2014. https://www.england.nhs.uk/wp-content/uploads/2014/04/e01-med-gen-0414.pdf

[45] Forzano F, Antonova O, Clarke, A *et al.* The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice. *Eur J Hum Genet* 2022;30:493–95. https://doi.org/10.1038/s41431-021-01000-x

Private genetic companies may also offer susceptibility screening for conditions such as psychiatric conditions (eg Alzheimer's disease or schizophrenia) which are unlikely to occur in childhood and which cannot predict adult onset disease with any certainty because, usually, these conditions are not completely determined by genetic factors.[46] Difficulties may arise when parents turn to the NHS to seek help and find they are not eligible for such tests through the NHS.

The Royal College of General Practitioners (RCGP) and the British Society for Genetic Medicine (BSGM) recommend that healthcare professionals should exercise caution when asked to offer or provide clinical expertise about the results of private genomic or genetic testing.[47] They should inform the patients about the difficulties of relying on such tests and explain why they are not available on the NHS. However, referral should be considered if:

- a variant is found in a gene for which testing is offered on the NHS, or
- if both members of a couple are found to be carriers for a genetic condition, or
- if there are clinical signs, symptoms or a family history of disease.

Genomic services are generally able to provide advice where it is not clear whether a particular patient meets these referral criteria. Furthermore, healthcare professionals can refer women/couples to relevant charities for further information.[48]

Ongoing management and post-pregnancy follow-up

Prenatal testing potentially involves different healthcare professionals, and it is important that they work together to ensure that patients are treated in a consistent manner even if their care is managed by a range of different health professionals. For example, this could include arrangements to ensure that procedures are not undertaken without discussions about the range of findings they might reveal, and the implications for the patient at each stage. It may therefore be helpful for individual departments to identify members of their teams who can coordinate communication between these professionals as well as communication with the patients.

In order to ensure continuity in care and decision-making support, healthcare professionals should consider the various options available to the pregnant woman and how these might align with the information being communicated. Where possible they should ensure that further interventions (such as scans, tests or termination of pregnancy) can be offered promptly after results are given.

Healthcare professionals should offer their patients continued support after the birth of a child or after a pregnancy termination. Patients may require follow-up after the pregnancy to arrange for wider family members to be offered genetic testing or to plan further management for children born with a genetic condition, and to access potential sources of support, including

[46] Orchid Health genetic screening service https://www.orchidhealth.com/embryo
[47] RCGP and BSGM joint position statement on direct to consumer genomic testing. October 2019. https://www.rcgp.org.uk/representing-you/policy-areas/genomic-position-statement
[48] Antenatal Results and Choices. Tests explained. https://www.arc-uk.org/tests-explained/

patient groups. Sometimes follow-up contact is for ongoing results and outcomes of investigations such as fetal pathology. At other times emotional and bereavement support may be needed. Couples may also feel the need for further appointments before planning any future pregnancies and should be told how to re-establish contact with the team or arrange appropriate referral at a later point in time.

14 How far should you anticipate future wishes?

Amina is 20 weeks pregnant. Her anomaly scan shows that her fetus has multiple anomalies and she is counselled that, if the pregnancy were to continue to term, the baby would need multiple operations and would likely have significant lifelong medical problems. Amina and her partner Tom are devastated and decide to terminate the pregnancy. Clinicians advise that there may be a genetic basis for the fetus's health problems and offer a post-mortem and genetic testing. The couple are too distressed to engage with any discussions around this and say they just want to get the termination of pregnancy over with so that they can try to forget about it and try again.

Key points

- It requires sensitivity and judgement to balance supporting Amina and Tom as they go through a distressing experience, while also being mindful that addressing difficult decisions now might give them options in the future that could reduce the chance of them going through similar experiences again.
- Clinicians should try to keep options open for Amina and Tom where possible. For example, though they might not feel ready to discuss genetic testing, they may be willing to consider DNA storage from their fetus so that this possibility could be revisited in the future. Similarly, they might be more willing to consider medical photography or detailed imaging of their fetus (if available) than a traditional post-mortem.
- Clinicians should try to ensure continuity of care for Amina and Tom such that discussions around possible fetal investigations can evolve over time with the support of a clinician with whom they have an established relationship.

Key messages

- Consent discussions need to pay attention to both the procedure to obtain genetic material for testing and the **possible outcomes of testing**, including available treatments or interventions.
- Consent discussions should acknowledge that the **timelines of prenatal tests** are different from postnatal investigations and that a binary decision may need to be made on the basis of complex and uncertain information.
- Consent may also need to be **sought from others** in order to access samples to enable the most comprehensive interpretation of genetic findings in the fetus. For example, both prospective genetic parents, in addition to the fetus (trio testing), or other family members may be asked to provide samples for testing. The need for this should be communicated clearly from the outset.
- Prenatal genetic testing might reveal **medical information relevant to relatives**. The potential of such information arising needs careful consideration in advance of testing.
- Many types of genetic investigation generate **uncertain results**, and this will often need special emphasis, given that societal expectations about genetic tests are sometimes set too high.
- Communication should include **information about the limits** of the available genetic tests and that these do not always provide clear answers about the outcome, or whether implications for the child will emerge from birth or arise later in life.
- What constitutes a **'serious' condition** should be determined on a case-by-case basis, taking into account the views of the pregnant woman and advice from a range of different specialists.
- Relevant information should be given **as early and comprehensively as possible** in order to support the pregnant woman in her decision-making, including, if appropriate, seeking support from clinicians for termination of pregnancy.
- This information should include the **material risks** involved in any recommended treatment, and of any reasonable alternative.
- The **limited timeframe** to make decisions during pregnancy should be taken into account. Late terminations of pregnancy are more difficult emotionally and physically, and the legal grounds for them are narrower than for terminations that are carried out early in pregnancy.

- Patients who seek help with interpretation of the results from private genetic tests should be informed about the **difficulties of relying on such tests** and given an explanation of why they are generally not available on the NHS. However, referral should be considered where a variant is found in a gene for which testing is offered on the NHS, if both members of the couple are carriers or where there are clinical signs, symptoms, or a family history of disease.
- Patients should be able to access **emotional/psychological support** when dealing with difficult decisions about the future of their pregnancy and the consequences.
- Health professionals should discuss **difficult cases** with other colleagues or seek the opinion of clinical ethics teams or the UK Genethics Forum.

Annex 1: Glossary

Additional finding (AF) – sometimes known as secondary finding – is a finding not related to the patient's presenting phenotype or concern, that the laboratory has actively sought rather than merely stumbled upon.

Amniocentesis is a procedure in which a small amount of amniotic fluid is removed with a needle from the sac surrounding the fetus, which can be performed from the 15th week of pregnancy and carries a slightly increased risk of miscarriage.

Chorionic villus sampling (CVS) involves sampling and testing a piece of the placenta to determine fetal characteristics, by passing a needle into the mother's abdomen. This test can be performed reliably from the 11th week of pregnancy.

Diagnostic tests are targeted to make particular diagnoses, eg following an abnormal screening test, or if there is a family history of a particular (usually rare) genetic condition. Such tests often require invasive sampling, eg via chorionic villus sampling (CVS) or amniocentesis.

Genome-wide tests examine the whole genome for evidence of alterations in copy number (deletions or duplications) or alterations in DNA sequence. These (newer) tests may generate as detailed information as targeted tests but potentially – in a single step – about the whole genome. The technical challenges associated with these tests often arise from the interpretation of the findings rather than the generation of the information. Examples of these tests are microarray, karyotype and whole genome/exome sequencing.

Incidental finding (IF) is a genetic variant that has been identified in the course of primary genetic analysis and is not thought likely to be relevant to the patient's clinical symptoms or to the question being investigated but might be of medical relevance to them, or potentially to other family members, in the future.

Karyotyping is the profiling of a person's chromosomes to examine their appearance and number, particularly to look for large scale changes to the genome. These include aneuploidies such as trisomy conditions (for example, Down's, Edwards' and Patau syndromes) and sex chromosome deletion or duplications. They can also be used to identify large deletions, duplications or translocations of sections of chromosomes, which can lead to conditions such as leukaemia.

Microarray is a method of measuring gene expression or performing genotyping. Microarrays are particularly useful to look for copy number variants that may be missed using other genomic technologies.

Non-invasive prenatal diagnosis (NIPD) involves taking blood from a pregnant woman for analysis of cell-free fetal DNA in order to perform a diagnostic test, to confirm or exclude a specific condition in the fetus.

Non-invasive prenatal testing (NIPT) involves taking blood from a pregnant woman to carry out a test concerning the fetus using analysis of cell-free fetal DNA. This can be performed from 9-10 weeks and has no associated miscarriage risk.

Pre-implantation genetic testing can be performed on cells from early embryos created by *in vitro* fertilisation (IVF) so that those with a particular genetic feature are not transferred into the uterus. This might be screening for aneuploidies (pre-implantation genetic screening PGS) or more focused analysis of a genetic variant known to be present in a family (pre-implantation genetic diagnosis, PGD).

Screening tests are tests are used to screen populations of pregnant women (eg women over a certain age considered to be at higher risk of eg trisomies) or all pregnancies

Secondary finding – also known as additional finding – is a finding not related to the patient's presenting phenotype or concern, that the laboratory has actively sought rather than merely stumbled upon.

Targeted genetic tests focus on one or a few specific genes, to detect alterations in the DNA sequence of the protein-coding portions of the relevant gene(s).

Annex 2: Types of uncertainties

Sample mistakes
During any procedure where a sample of blood, prenatal tissue or amniotic tissue must be obtained there can be events that may inhibit the accuracy or indeed the return of any test results. Samples can be too small, of poor quality, or be inadequate due to other human error. This is an inherent limitation of any medical procedure.

Test failure
Due to the delicate nature of DNA and tissue obtained in prenatal situations results are sometimes unavailable due to a test failure. Examples of this include tissue that fails to grow in a lab setting or the malfunction of an assay or piece of equipment.

Penetrance
The quantitative ability of a gene alteration to elicit a given phenotype or set of clinical symptoms. For genetic changes with variable penetrance some individuals will remain asymptomatic.

Expressivity
Identical genetic variants due to other, often unknown, factors may produce a variable phenotypic spectrum among individuals who carry the variant even between those within the same family. This is known as variable expressivity.

Confined placental mosaicism
The placenta and the fetus usually have exactly the same chromosome complement. In a small percentage of pregnancies, the placenta can have a different chromosome makeup from the baby. This is called confined placental mosaicism (CPM). CPM is defined as the presence of chromosomal abnormalities in the extra-embryonic tissue which are absent from the fetal tissue. These chromosomal abnormalities are observed in about 1 to 2% of chorionic villus samplings (CVS).

False negative
A false negative error, or false negative describes a test result that incorrectly indicates that a condition is not present or a fetus is unaffected.

False positives
A false positive error describes when a test indicates the presence of a condition when it is not present.

Positive and negative predictive values
The statistical value that represents the power of a test to give true positive results is its positive predictive value. The highest possible positive predictive value is 100%. Negative predictive value is the ability of a test to make a negative prediction when the result is truly negative. The highest possible negative predictive value is also 100%.

Annex 3: Guidelines relating to genetic testing technologies containing ethical content

a. Rapid Exome Sequencing Service for acutely unwell children with a likely monogenic disorder – a guide for clinicians produced by University Hospital Southampton NHS Foundation Trust. www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Services/Genetics/Rapid-exome-service-clinicans-guide.pdf

b. Dempsey E, Haworth A, Ive L et al. A report on the impact of rapid prenatal exome sequencing on the clinical management of 52 ongoing pregnancies: a retrospective review. *BJOG: Int J Obstet Gy* 2021;128:1012–19.

c. Van den Veyver IB, Chandler N, Wilkins-Haug LE, Wapner RJ, Chitty LS. International Society for Prenatal Diagnosis Updated Position Statement on the use of genome-wide sequencing for prenatal diagnosis. *Prenat Diagn* 2022;42:796–803. https://doi.org/10.1002/pd.6157

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e. *Supporting women and their partners through prenatal screening for Down's syndrome, Edwards' syndrome and Patau's syndrome.* Consensus statement on pregnancy screening from the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Society and College of Radiographers. December 2020. www.rcog.org.uk/guidance/browse-all-guidance/other-guidelines-and-reports/supporting-women-and-their-partners-through-prenatal-screening-for-downs-syndrome-edwards-syndrome-and-pataus-syndrome/

f. Nuffield Council on Bioethics. *Noninvasive prenatal testing: ethical issues.* Nuffield Council: London, 2017. www.nuffieldbioethics.org/wp-content/uploads/NIPT-ethical-issues-full-report.pdf

Royal College of Physicians
www.rcp.ac.uk

Royal College of Pathologists
www.rcpath.org

British Society for Genetic Medicine
www.bsgm.org.uk