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The British Society for Genetic Medicine

Genetic testing in childhood

Guidance for clinical practice

November 2022

A report of the Joint Committee on Genomics in Medicine

About this report

This guidance, *Genetic testing in childhood*, is a revision of a report first published by the Clinical Genetics Society in 1994 and subsequently revised in 2010. This report has been produced 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)) and builds on related guidance *Consent and confidentiality in genomic medicine*, published in 2019.

Acknowledgements

This guidance was written by Angus Clarke, professor and honorary consultant in clinical genetics, Cardiff University; Alison Hall, senior humanities advisor, PHG Foundation, Cambridge and chair of the Ethics and Policy Committee of the British Society for Genetic Medicine; and Rachel Hart, consultant clinical geneticist, Liverpool Women's Hospital.

We are very grateful for significant input from the members of the working group: Jo Bridgeman, Katherine Burke, Emma Cave, Tara Clancy, Gill Crawford, Isabelle Delon, Angela Fenwick, Lowri Hughes, Michael Parker, Katherine Shelton, Fiona Ulph, David Wright 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. This group helped to draft text, reviewed literature and gave many helpful comments on multiple drafts.

We are also grateful to Vicki McKay, Karen Low and the UK Cardiac Geneticists' group (for C8), and to Amrana Qureshi, Keith Gomez, Noemi Roy and Helen Stewart for their input on haematological disorders. In addition, we are grateful for comments from Ruth Horn, Gemma Chandratillake and Eamonn Sheridan, as well as the executive committees of the BSGM and the JCGM.

Citation for this document

Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine. *Genetic testing in childhood. 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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Introduction

This report provides guidance to healthcare professionals in the UK on genetic testing in childhood. It is a response to a reassessment of genetic testing in the light of developments in both molecular technologies and in society and the law, and aims to support best practice.

It updates existing guidance¹ from the British Society for Human Genetics (now the British Society for Genetic Medicine) and was triggered by the development of genome-wide genetic testing. Although the principles underlying the previous report have not changed, our collective experience of genetic testing in childhood has grown and genomic investigations have emerged from the earlier forms of testing which present new challenges. This report follows guidance on *Consent and confidentiality in genomic medicine* and addresses the very specific issues that arise in genetic testing in childhood.² A companion report on prenatal genetic testing and pre-implantation genetic diagnosis offers guidance on these related areas.³

In this report, when discussing genetic tests, we refer largely to investigations of a person's DNA sequence or chromosome structure, although other types of test may reveal genetic information, eg by imaging or biochemical tests. Indeed, specific clusters of clinical features may be so characteristic of a genetic condition that a DNA test is superfluous for diagnostic purposes, although it may still be helpful for other purposes. A genetic diagnosis may also be suggested by other types of investigation, eg immunohistochemistry of tumour specimens may point to the existence of an underlying genetic cancer predisposition syndrome. Rather than limit the term genetic test to any particular techniques, this report aims to cover circumstances where an investigation of any type will yield information about a patient's genetic constitution.

Genetic testing of children can play an important role in their care and treatment. For example, tests can be used as part of the diagnostic process when children present with health or developmental problems, or to determine whether surveillance strategies might be beneficial. In such situations, genetic tests can offer immediate clinical benefits and should be used in the same way as any other investigation to determine the best clinical care.

As well as being useful in establishing a diagnosis, genetic tests can also potentially generate information about children's health in the medium- and long-term future. This can relate to adult-onset disease and/or be relevant to reproduction and future generations, rather than current or imminent health problems. In this sense, genetic tests can differ from investigations carried out to investigate current health or disease status. **Decisions about the optimal time to carry out a genetic test can raise difficult issues for health professionals, for parents and for children and young people.** Delaying testing for childhood onset conditions may deprive children and their families of care and advice that promotes their wellbeing or may needlessly prolong concerns and anxieties. Testing too early may unnecessarily reduce a

¹ British Society for Human Genetics. *Report on the genetic testing of children*. BSHG, 2010.

² 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>

³ 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.

child's opportunity to decide for themselves whether they wish to know about their genetic makeup; it may also produce information that many adults prefer not to know. Choices made at different points in development will be incorporated into the child's life in different ways, dependant not only on their understanding but also on family context, peer view and other influences such as religion or culture. A genetic label, even a medically benign one, is not necessarily neutral in its effects.

The British Society for Human Genetics (BSHG) 2010 guidance was based on a report from the Clinical Genetics Society (CGS) published in 1994, which recommended that predictive genetic testing was appropriate where a medical intervention would be offered during childhood, but that such testing should not be undertaken for adult-onset disorders unless there were clear-cut arguments in favour in any particular case. Much of the 1994 guidance was based on clinicians' and families' experiences with Huntington's disease (HD) – an adult-onset condition for which there are still only limited treatment options. Most adults at high risk of HD choose not to undergo predictive or pre-symptomatic testing, although this may change as trials of promising treatments are in progress. Testing a young child for HD would remove the possibility of them making an informed decision not to be tested.

The 1994 report acknowledged that extrapolation from HD to other conditions might not always be appropriate and called for more evidence about the potential harms and benefits of childhood testing for later onset conditions. The 2010 report revisited the issues explored in 1994 in the light of subsequent developments. This report is now revisiting the issues again, taking account of subsequent clinical and genetic counselling experience, policy documents from other professional organisations^{4,5,6,7,8} and the development of genome-wide genetic testing technologies.

Professional concerns about testing a young child at the request of parents for disorders that typically present with clear signs of disease in childhood have lessened over the past two decades. At this time, testing is generally seen as a way of addressing parental concerns which may be worsened by possible early signs of the disorder. In these circumstances, testing during childhood is generally seen as being in the child's best interests if parents request it. As the child would be likely to manifest the condition during childhood, this approach does not compromise the child's future autonomy as an adult. There may still be questions about the optimal timing of the test, depending upon the precise circumstances, but this can usually be addressed by discussion with the parents and then support for their decision.

⁴ Borry P, Evers-Kiebooms G, Cornel MC et al. Genetic testing in asymptomatic minors: background considerations towards ESHG Recommendations. *Eur J Hum Genet* 2009;17:711–19.

⁵ European Society of Human Genetics. Genetic testing in asymptomatic minors: recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2009;17:720–1.

⁶ American Academy of Pediatrics and the American College of Medical Genetics and Genomics. Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 2013;131:620–2.

⁷ Ross LF, Saal HM, David KL et al. American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet Med* 2013;15:234–45.

⁸ Botkin JR, Belmont JW, Berg JS et al. American Society of Human Genetics Position Statement. Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents. *AJHG* 2015;97:6–21.

Professional concerns about testing an unaffected child for genetic carrier status in the light of their family history have also changed since 1994. It is important to differentiate between carrying an autosomal recessive disorder and carrying one of the other types (conditions resulting from sex-linked inheritance, a balanced chromosomal rearrangement, triplet repeat expansions or dominant disorders of reduced penetrance). In all categories of testing for carrier status, we would prefer to defer testing until the child can be involved in the discussion. However, it may sometimes be reasonable to agree to test a child for carrier status of an autosomal recessive disorder if parents persist with this request after careful exploration of the issues. Testing for carrier status in the other categories of 'carrier', where the risk to future children is inherited from only the carrier parent and is relatively high (50% for boys in sex-linked disorders) or where being a carrier might result in the disease being manifest, requires careful thought. In these circumstances, the discussion of whether and when to offer genetic testing is more complex.

Part A of this report summarises our conclusions and recommendations about genetic testing in childhood. Part B explains the legal and ethical rationale for those recommendations. Part C sets out the clinical contexts in which testing may be considered, explains the clinical rationale for our recommendations, and includes illustrative case studies to help guide practice.

Part A: Summary of conclusions and recommendations

A1. Legal and ethical principles (summary)

- > Parental rights to look after their children should be exercised in the child's best interests.⁹ This legal principle is based on the *Gillick* decision which also identified the importance of children's autonomy rights, including the right for children to participate in decision-making and to make certain decisions for themselves (see B1.2).
- > Decisions about genetic testing may require balancing of children's current and future interests, including their future autonomy. In the absence of a strong reason to take the decision earlier, genetic testing should be delayed until they can be involved in the decision (see B1.3).
- > Genetic testing in childhood needs to be authorised by appropriate consent. From the age of 16, young people are assumed to have mental capacity to give consent and can consent to medical treatment and ancillary matters such as testing, in the same way as an adult. Children under 16 can consent if they are 'Gillick competent' (see B2.1–B2.2).
- > Parents have legal responsibility to make healthcare decisions on behalf of young children who are not Gillick competent to make decisions themselves. In such cases, except in an emergency, proceeding without parental consent requires a decision from the court (see B2.3).
- > Consent should be informed. This means that the person consenting – whether an adult or child – should be appraised of the material risks, benefits and alternatives,¹⁰ including not having the test (see B2.4). They should be told the nature and purpose of the procedure, the scope and limits of testing, and likely outcomes and next steps. Efforts should be made to facilitate understanding of this information (see B2.6).
- > It is generally in the best interests of children for decisions on genetic testing to be delayed until they can be involved in the decision (see B3.3). Professional guidance suggests factors relevant to the child's best interests go beyond what is clinically indicated to include the views of the child, parents, health professionals and the wider cultural, religious or other beliefs of the child or patients (see B3.4).
- > If there is disagreement about what constitutes the child's best interests that cannot be resolved, the decision may be referred to the court. In arriving at a decision, the welfare and best interests of the child will be the judge's paramount consideration (see B3.6).
- > Delaying decisions on testing can provide an opportunity for the person to participate in the decision-making and may be relevant in cases where this consideration is not outweighed by a strong reason for an early test (see B4.3).
- > Health professionals have ethical duties to support parents but their primary clinical responsibilities are to the child patient. Taking account of the child's best interests may

⁹ *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112

¹⁰ *Montgomery v Lanarkshire HB* [2015] UKSC 11.

sometimes prompt safeguarding or child protection concerns which require further investigation or referral (see B5.4).

A2. Guidance to inform the clinical approach (summary)

- > Advances in genomics now allow detailed analysis across part or all of the genome. These can reveal various types of genomic changes including small variants, deletions, duplications or copy number variations (see C1.3).
- > These technical advances mean that a single assay can be used for multiple tests. This has resulted in an enormous expansion in the potential uses of genetic testing, highlighting a number of potential challenges: First, identifying which differences found in a patient are a significant cause of disease and which are benign, given the wide range of genetic variation between individuals. Second, while methods of detecting variants across the whole genome are relatively good at finding molecular explanations for clinical presentations with clear signs of disease, their ability to predict future disease in a healthy individual is much more limited. Finally, managing information that has not been sought by anyone but that simply emerges, such as misattributed family relationships (eg non-paternity), non-disease traits and projected information about future health problems (see C1.4).
- > Professionals, patients and families need to understand and accept that the use of genomics will provide useful clarity on some matters but may, at the same time, generate fresh uncertainties. Everyone involved in genomic investigations should understand their potential benefits and limitations (see C2.7). For example, it is important for a professional not to conduct 'predictive' tests on the basis of a variant of uncertain significance (VUS) (see C2.3).
- > **Genomic testing should only take place if it is in the child's best interests.** This requires consideration of what types of information it is helpful to generate about a child and what is best postponed, at least until the child can make their own decisions. This may involve taking account of the welfare of the child within their family and social context (see C3.1). Rarely, taking account of the child's best interests may prompt safeguarding or child protection concerns which require further investigation or referral (see C10.3–5).
- > Genomic testing can be very helpful in diagnosing a clinical disorder, but there may be circumstances in which genetic or genomic testing may be less helpful or simply inappropriate, because the patient is a child. Careful thought should be given to the added value from a genetic or genomic test to determine whether a healthy child carries an already known familial variant implicated as the cause of an inherited disorder (see C3.2).
- > Where there is no immediate clinical benefit to genetic testing but the possibility of testing has been raised, it is important to consider the timing of the test, and how information from the test will be conveyed to the child (see C4.1).
- > **Communicating awareness of a genetic condition in the family should be separate from any question of genetic testing, which may be sought much later, if at all.** Open discussions about a family's genetic risk for a particular condition may be just as helpful as the test itself (see C4.2).

- > Many parents take a drip-feed approach, giving children an early awareness that there is a possible condition ‘in the family’ and providing age-appropriate information in response to questions from the child (see C4.3).
- > Some parents avoid communication about their child’s predicted future because they find this difficult or stressful.¹¹ Addressing parents’ fears and concerns, rather than just ensuring they have sufficient facts about the condition or risk, can help promote communication within the family about genetic conditions (see C4.4).
- > Finding the ‘right time’ to convey information can be very challenging.¹² Knowledge of family illnesses can be a very important scaffold for children when given new genetic information.¹³ Both children and adults use this base of knowledge derived from their family to incorporate and act on new information from health professionals¹⁴ (see C4.8).
- > **It is especially important to see the individual’s knowledge of their risk – of their family history and its personal relevance to them – as entirely distinct from any question of being tested.** Regardless of whether genetic tests proceed, health professionals have an important role in supporting parents to provide children with helpful and appropriate information (see C4.11).
- > Healthcare professionals should aim to engage in an open discussion with parents and not to avoid or shut down difficult conversations or questions. Focusing on the child’s best interests using non-judgemental and probing questions, rather than why parents want their child to have a genetic test, will facilitate parents being able to talk about their perspective without being misunderstood from the outset (see C5.3).
- > Reframing parental requests in terms of finding the best timing for the test can be a useful strategy for discussion around harms and benefits (see C5.4).
- > When considering childhood predictive testing it is good practice to involve all relevant health professionals (eg for inherited cardiac conditions (ICC), input from clinical geneticists, genetic counsellors and cardiologists). In such cases, a ICC multidisciplinary team (MDT) meeting to discuss important decisions on an individual, case by case, basis would represent safe best practice (see C8.1).
- > Depending on the child’s age and maturity, it may also be desirable to seek consent or assent from the child as well as seeking informed consent from someone with parental responsibility (see B3.1). Many of the children and young people who undergo genetic testing have learning difficulties, which need to be considered when helping them to understand, and contribute to decisions about, any test that is proposed.
- > When a test is being considered for a teenager who could be Gillick competent, it will often be good practice to seek a conversation with them without their parents being present, even if only briefly.
- > When considering testing a child for carrier status, our preferred approach is to recommend openness and discussions within a family but often to defer testing, so that

¹¹ Goldman A, Metcalfe A, MacLeod R. The process of disclosure: mothers’ experiences of communicating X-linked carrier risk information to at-risk daughters. *J Genet Couns* 2018;27:1265–74.

¹² Manjoney DM, McKegnay FP. Individual and family coping with polycystic kidney disease: the harvest of denial. *Int J Psychiatry Med* 1978;9:19–31.

¹³ Ulph F, Leong J, Glazebrook C and Townsend E. A qualitative study exploring genetic counsellors’ experiences of counselling children. *Eur J Hum Genet* 2010;18:1090–94.

¹⁴ Ulph F, Cullinan T, Qureshi N and Kai J. Familial influences on antenatal and newborn haemoglobinopathy screening. *Ethnicity & Health* 2011;16:361–75.

important decisions are explicitly left to the young person to make for themselves. In this way, we believe, they are more likely to engage with the issues and make decisions with careful deliberation.

- > A recommendation not to test a child (for now) does not entail a recommendation not to discuss the topic with the child: in fact, we would strongly urge discussion in an age-appropriate fashion to prepare the ground for testing once the child can participate in the discussion (see C9.2).

A3. Clinical conclusions

- > Everyone involved in genomic investigations should understand their benefits, their limitations and the associated uncertainties. For those arranging testing for patients, an understanding of what the tests are, why consent is important and how to interpret results is imperative. Any professional discussing current genetic and genomic tests with a patient – or their parent – should be aware of four important aspects of genomic investigation: (i) variants of uncertain significance (VUSs), (ii) unexpected, incidental findings (IFs), (iii) the provisional nature of genomic results and (iv) whether (or not) additional, looked-for actionable findings will be reported (see C2.3–2.5).
- > Where genetic testing in childhood leads to better management of a child's condition, such as the initiation or cessation of surveillance or treatment, it is unlikely to be contentious. Possible longer-term consequences for the child and family should, where known, be discussed prior to testing.
- > Where genetic testing is primarily predictive of illness or impairment in the future, or is predictive of future reproductive risks, a cautious approach should be adopted. Here testing should normally be delayed until the young person can decide for themselves when, or whether, to be tested, because testing in childhood removes the opportunity of the future young person making their own choices. That opportunity should not be denied to them without good reason. Reframing parental requests in terms of finding the best timing for the test can be a useful strategy for discussion around harms and benefits.
- > This does not mean that childhood testing for such conditions should never be performed. Predictive genetic testing for a later-onset condition, that usually presents in adult life, should not happen unless there are specific reasons not to wait until a child is older, such as where the benefits of testing in childhood outweigh the harms. Less may be 'at stake' in other settings, such as for carrier status of an autosomal recessive disorder, and testing may be appropriate if parents remain convinced that it would be helpful.
- > In each case where parents request genetic testing of a child when this is of no direct or immediate medical benefit, an assessment should be made of the balance of harms and benefits of such testing, given that decisions ought to be made in the overall best interests of the child.
- > Even where a condition is likely to manifest during childhood, there may be good reasons to defer testing until surveillance might be implemented, to allow the child to participate in discussions. Where there is no realistic possibility of choice being exercised by the future young person before the condition might present clinically, the reasons to defer are weaker.

- > In many situations, making an immediate decision is unlikely to do justice to the complexity of the issues. Healthcare professionals and parents should have sufficient time to discuss the optimal timing of a predictive genetic test, including, where appropriate, discussions within the family. This is an important clinical consideration especially when resources are constrained. **Encouraging parents to talk to their children about their family history from a young age, so that they grow up knowing about it, will be integral to discussions about genetic testing.**

Part B: Legal and ethical considerations

This section describes the legal and ethical principles that provide the context for offering genetic testing to children. We start by describing those rights and interests that apply to children (B1) and go on to explore how ethical and legal principles determining consent (B2) or best interests (B3) are interpreted when applied to children. Some of these principles are embedded in best practice guidance; others are enshrined in legislation or emerge from legal cases in specific areas. Part B ends with a consideration of how these legal and ethical principles might be applied in practice to judgements about the timing and scope of genetic testing for children.

B1. Rights and interests of the child

- B1.1 All children have rights and interests by virtue of being human, whatever their age, gender or status. Children do not have all the rights an adult has (such as to vote), and they can claim extra rights and protections by virtue of being young. The UN Convention on the Rights of the Child (UNCRC), an international treaty first adopted in 1989, sets out principles that guide decision-making about children. These include the right to life, survival and development (Article 6), the primary consideration of their best interests (Article 3), and the right of children capable of forming a view to be heard (Article 12).
- B1.2 When a child is young, parents have strong claims to make decisions on their behalf because they have primary responsibility for their child and usually know their child best. However, the *Gillick* decision in 1985 established that parental rights are held to enable parents to carry out their responsibilities to look after their children. These should be exercised in the child's best interests.¹⁵ The *Gillick* decision also identified the importance of children's autonomy rights. These include the right for children to decide the extent to which they wish to participate in decision-making and to make certain decisions for themselves.
- B1.3 Decisions about genomic testing may require balancing of children's current and future interests, including their future autonomy. The recommendations in this report give weight to the legal recognition of the value of the autonomy rights of children and young people by suggesting that, in the absence of a strong reason to take the decision earlier, genetic testing should be delayed until they can be involved in the decision.

B2. The basis of consent

- B2.1 Like all medical tests (other than in an emergency where the necessity of immediate life-saving treatment may override the requirement for consent), genetic testing in childhood

¹⁵ *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112

needs to be authorised by appropriate consent.¹⁶ Health professionals are liable in law if they treat or test without consent. They are also accountable to their regulatory bodies for their practice and need to take into account ethical guidance to ensure that they act professionally.

- B2.2 From the age of 16, young people are assumed to have mental capacity to give consent,¹⁷ and can consent to medical treatment and ancillary matters such as testing, in the same way as an adult.¹⁸ The *Gillick* decision established that children under the age of 16 who have sufficient understanding of the matter to be decided have the legal authority to consent to treatment that is in their best interests.¹⁹ Where a child refuses an intervention that is very important to their health, the courts and potentially the child's parents may provide the necessary consent and override the child's refusal if it is in the child's best interests to do so.²⁰
- B2.3 Parents generally have legal responsibility to make healthcare decisions on behalf of young children who do not have Gillick competence or mental capacity to make decisions themselves. In such cases, except in an emergency, proceeding without parental consent requires a decision from the court. Some children, who are not able to provide consent, may still be able to participate in the decision in which case Article 12 of the UNCRC protects their right to do so where it is in their best interests.
- B2.4 To protect the person's autonomy interests, foster trust, and to comply with the law, consent should be informed. According to the law of negligence, it is important that the person consenting – whether adult or child – is appraised of the material risks, benefits and alternatives,²¹ including not having the test. In light of the Supreme Court decision of *Montgomery v Lanarkshire HB*,²² care should be taken to disclose information in response to what matters to the particular patient. Where material risks are difficult to predict, this fact should be acknowledged and communicated. Where research is offered alongside clinical testing, the consent process should distinguish between the two where that is feasible. If that is not feasible, then it should be made clear when consent is sought, that any clinical testing necessarily entails agreeing to participate in research.
- B2.5 The General Medical Council (GMC) produces guidance for all doctors on decisions involving children and young people. It advises that doctors should provide children with information that is easy to understand and appropriate to their age and maturity, covering issues such as the child's condition(s), the purpose of investigations and what they involve, and the risks associated with different options.²³

¹⁶ *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112. For the emergency exception, see also *Re S* [1994] 2 FLR 416, at 420.

¹⁷ Mental Capacity Act 2005, section 1(2).

¹⁸ *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112

¹⁹ This position has been codified in Scotland in the Age of Legal Capacity (Scotland) Act 1991.

²⁰ *Re R* [1991] 4 All ER 177; *Re W* [1992] 4 All ER 627; *Re X (No 2)* [2021] EWHC 65 (Fam).

²¹ *Montgomery v Lanarkshire HB* [2015] UKSC 11.

²² *Montgomery v Lanarkshire HB* [2015] UKSC 11. And see General Medical Council. *Decision making and consent*. GMC, 2020.

²³ General Medical Council. *0-18 years: guidance for all doctors*. GMC, 2007, updated 2018, para 8.

B2.6 The Joint Committee on Genomics in Medicine 2019 guidance on consent sets out general principles of consent which also apply to children. These can be summarised as follows:

- > The process of seeking consent ensures that a person understands the nature and purpose of the procedure or intervention thereby asserting a right to self-determination [section 3].
- > Consent is often integrated into a clinical consultation and may be evidenced by good documentation but a signature on a form will not necessarily indicate what consent has been given. Model forms to record consent discussions are provided.
- > Modifying such forms with additional riders or boxes is inappropriate for clinical practice and may compromise the actual consent obtained.
- > The many possible outcomes from a genetic test, now and in the future, anticipated or unexpected, individual or familial, can mean that 'fully informed, specific' consent is difficult to achieve. Broad consent can still be valid consent.
- > When considering using a genetic test, the following elements might usefully be included in a discussion with a patient [section 3.1]:
 - Test results may predict future health as well as diagnose current problems.
 - Results may be relevant to other family members.
 - Genetic test results may take longer than other medical tests: patients should be given likely timescales for availability of test results, or components of the results.
 - The scope and limits of the proposed testing (ie what will, and will not be tested for and communicated, as well as when and how).
 - Genetic (and especially genomic) tests may generate unexpected or incidental findings ie findings not related to the reason for testing.
 - Outcomes from genetic testing may be uncertain or unclear.
 - Interpretation of genetic (especially genomic) results may be updated in the future and may need periodic re-evaluation.
 - DNA samples are routinely stored and may be routinely used as quality assurance for clinical testing in others.
 - It is often necessary to compare genomic data across the NHS or outside it to gather evidence to inform genomic interpretation; absolute anonymisation may not be possible and might compromise the utility of data sharing.²⁴

B3. Best interests of the child

B3.1 Parents who make decisions on behalf of their child about their medical treatment, including genetic testing, make these decisions in the exercise of their parental

²⁴ RCP, RCPATH and BSGM. *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic*. 3rd ed. Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPATH and BSGM, 2019, pp 6-7, and see in particular 3.5.1–3.5.2.

responsibility.²⁵ They must make these decisions according to the welfare or best interests of the child (the terms are used synonymously).²⁶ Health professionals are also under a duty to act in the best interests of the child.²⁷ Usually decisions about a child's best interests are made by parents and health professionals together. This ensures that the decision takes into account not only clinical considerations but also the particular needs and wishes of the child now and in the future (as far as this is possible) and the values and beliefs of the child and their family.

B3.2 Parents and health professionals may sometimes disagree about the timing of a predictive genetic test for a condition that is likely to manifest later on in childhood but is not yet apparent. In the past, health professionals caring for a family with children at risk of a childhood onset disease may have preferred to delay testing until symptoms had developed. Now it is recognised that there are practical and emotional reasons why parents might wish to know whether a child has inherited a high chance of developing the condition for which they are already known to be at an increased familial risk. Indeed, this may help the topic to be introduced appropriately into family discussions and facilitate open communication within the family which can be of benefit to the child. However, if the test is effectively of carrier status – the result being solely of reproductive significance for the child as a future adult – health professionals may, on balance, prefer to defer testing on the basis that such questions should be left for the child to decide when they are older.

B3.3 The starting point is that it is generally in the best interests of children for decisions on genetic testing to be delayed until they can be involved in the decision. However, it has to be determined that this is in the best interests of the child, for example, that there are not strong reasons to take the decision earlier. Consideration should be given to the child's current and their medium- and long-term interests, given that testing may generate information affecting the child's medical treatment and care in the future. Testing too early or too late can both be problematic, as discussed above.

B3.4 There are no legal guidelines as to the factors relevant to determination of a child's best interests when the decision is reached by parents and professionals. The General Medical Council's *0-18: guidance for all doctors* states that in addition to what is clinically indicated, doctors should also consider:

- > the views of the child or young person, so far as they can express them, including any previously expressed preferences
- > the views of parents
- > the views of others close to the child or young person
- > the cultural, religious or other beliefs and values of the child or parents

²⁵ Defined in the Children Act 1989, s 3(1): 'In this Act "parental responsibility" means all the rights, duties, powers, responsibilities and authority which by law a parent of a child has in relation to the child and his property.' This applies to England and Wales.

²⁶ *Gillick v West Norfolk & Wisbech AHA* [1986] AC 112; Children Act 1989, s.1.

²⁷ *Re Wyatt* [2005] EWHC 2293.

- > the views of other healthcare professionals involved in providing care to the child or young person, and of any other professionals who have an interest in their welfare
- > the choice, if there is more than one, which will least restrict the child or young person's future options.²⁸

B3.5 Where parents and professionals have different views about genetic testing of a child which cannot be reconciled even after referral to mediation services if appropriate, the decision may be referred to court. The courts are not bound to follow parental views, even if they are reasonably held,²⁹ but must make an independent assessment of the course of action that is in the best interests of the child.³⁰ The judge will decide according to the facts and evidence so it is not possible to draw conclusions about what a court might decide from previous cases. This is particularly so because previous cases have been concerned with a child's medical treatment rather than whether it is in a child's best interests to undergo genomic testing.

B3.6 In deciding upon the child's best interests, the judge will place the welfare or best interests of the child (the terms are used synonymously) as the paramount consideration. Judges determining the best interests of a child will use the following approach:

'Best interests are used in the widest sense and include every kind of consideration capable of impacting on the decision. These include, non-exhaustively, medical, emotional, sensory (pleasure, pain and suffering) and instinctive (the human instinct to survive) considerations.'³¹

The Children Act 1989 requires courts, when determining the welfare of a child, to have regard to,

- a. his or her ascertainable wishes and feelings considered in the light of his/her age and understanding;
- b. his or her physical, emotional and educational needs;
- c. the likely effect on him or her of any change in his or her circumstances;
- d. his or her age, sex, background and any characteristics which the court considers relevant;
- e. any harm which he or she has suffered or is at risk of suffering.³²

The views of the child are given weight but these are only one of the factors to be considered and can be overridden in the child's best interests. The judge will consider the child's current and future interests.

²⁸ General Medical Council. *0-18: guidance for all doctors*. GMC, updated May 2018.

²⁹ *Re T (a minor) (wardship: medical treatment)* [1997] 1 WLR 242.

³⁰ *Re W (A Minor) (Medical Treatment: Court's Jurisdiction)* [1993] Fam 64.

³¹ *Re MB* [2006] EWHC 507.

³² Children Act 1989, s.1(3).

B4. Decision-making

B4.1 Ideally, decisions to test a child, like those about a child's medical treatment, should be made by parents and health professionals together, in the interests of the child. As Lord Donaldson stated:

'No one can dictate the treatment to be given to any child, neither court, parents nor doctors. The doctors can recommend treatment A in preference to treatment B. They can also refuse to adopt treatment C on the grounds that it is medically contra-indicated or for some other reason is a treatment which they could not conscientiously administer. The court or parents can refuse to consent to treatment A or B or both, but cannot insist on treatment C. The inevitable and desirable result is that choice of treatment is in some measure a joint decision of the doctors and the court or parents.'³³

B4.2 An effective partnership between parents and health professionals depends upon effective communication, listening and the sharing of information to arrive together at a decision about the child's best interests (see C4 on communication).

B4.3 Consideration should be given to the extent to which the child is able to participate in discussions. Article 12 of the UNCRC provides that:

'A child who is capable of forming his or her own views [has] the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.'

While older children may benefit from being involved in discussions about genetic testing, such discussions may arise in relation to children who are clearly too young to be capable of forming a view on the question. However, it is our view that this participation right provides an independent reason for delaying decisions on testing until later childhood in cases where it is not outweighed by a strong reason for an early test. Where the child is over the age of 16 and thus presumed to have the competence to make decisions about medical treatment and ancillary matters such as testing, or the child is assessed as Gillick competent, health professionals should take care to determine the extent to which they wish for a parent to continue to be involved in discussions. They should also take care to determine whether the child wishes to make the decision, to share decision-making responsibility with a parent or for their parent to make the decision on their behalf in their best interests.³⁴ The case of *Axon* established that Gillick competent children and those aged 16 or 17 have a right to confidentiality should they wish to exercise that right.³⁵

³³ *Re J (A Minor) (Wardship: Medical Treatment)* [1991] Fam 33.

³⁴ Ulph F, Leong J, Glazebrook C & Townsend E. A qualitative study exploring genetic counsellors' experiences of counselling children. *Eur J Hum Genet* 2010;18:1090–94.

³⁵ *R. (on the application of Axon) v. Secretary of State for Health & Another* [2006] EWHC 37.

B5. Professional duties of care

- B5.1 Health practitioners should comply with good practice guidance from their regulatory bodies. Medical practitioners must comply with guidance from the General Medical Council, *Decision making and consent* (2020) which applies to 'every health and care decision' including genetic testing (para 1).³⁶
- B5.2 Health professionals will need to exercise their professional judgement as to the best course of action in every case to determine whether the presumption against testing young children should be rebutted. However, applying the guidance will provide reassurance that the individual professional is acting in accordance with the considered views of colleagues and following accepted practice.
- B5.3 Parental consent can authorise an intervention but cannot mandate it if it contravenes the child's rights and is not in the child's best interests. The courts have stated that neither a parent nor a judge can require doctors to provide treatment contrary to their professional judgement.³⁷ The application of this principle to medical or genetic testing has not been tested in the courts. By complying with professional guidance and by seeking the views of colleagues, health professionals can ensure that their professional judgement is in accordance with accepted practice. Potentially useful resources include multidisciplinary team meetings, regional meetings of colleagues, clinical ethics committees and the UK Genetics Forum.
- B5.4 Health professionals have ethical duties to support parents, but their primary clinical responsibilities are to the child patient.³⁸
- B5.5 Certain genetic findings might indicate an incestuous relationship between a parent and child in which case local and national guidelines on safeguarding should be followed (see C10.3–5 and C11.7).^{39,40} This may involve consulting with colleagues and other agencies having appropriate expertise, or getting advice on safeguarding from a designated professional if they are not sure how to ensure that the best interests of children are protected.⁴¹
- B5.6 Recent case law (the *ABC* case) shows that health professionals may also have obligations to other members of a patient's family, at least where those family members are also the health professionals' patient(s).⁴² At its most extreme, such obligations could include requiring professionals to balance the risks to, and interests of, different members of the family, and potentially disclosing the nature of the patient's illness to other relatives. Alternatively, it may be possible to alert family members that they are at risk of disease without disclosing details of a patient's illness.⁴³

³⁶ General Medical Council. *Decision making and consent*. GMC, 2020.

³⁷ *Re J (A Minor) (Child in Care: Medical Treatment)* [1992] 3 WLR 507.

³⁸ British Medical Association. Children and young people toolkit. A toolkit for doctors. BMA, 2021: p24–25. <https://www.bma.org.uk/media/4666/bma-children-and-young-people-ethics-toolkit-oct-2021.pdf>

³⁹ British Medical Association. Adult safeguarding – a toolkit. BMA, 2018. <https://www.bma.org.uk/media/1792/bma-adult-safeguarding-full-toolkit-2018.pdf>

⁴⁰ General Medical Council. Adult safeguarding: ethical hub topic. <https://www.gmc-uk.org/ethical-guidance/ethical-hub/adult-safeguarding>

⁴¹ General Medical Council. *Protecting children and young people: the responsibilities of all doctors*. GMC, 2012 updated 2018. <https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/protecting-children-and-young-people>

⁴² *ABC v St George's Healthcare NHS Trust & Ors* [2020] EWHC 455.

⁴³ RCP, RCPPath and BSGM. *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic*. 3rd ed. Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPPath and BSGM, 2019.

Part C: Clinical context and considerations

C1. Genetics and genomics

- C1.1 The first genetic investigation available for the purposes of clinical diagnosis was a genomic investigation, the karyotype, which allowed assessment at only a very crude level, initially the counting of chromosomes. However, as staining methods were refined, scientists became able to assess the presence of deletions, duplications, translocations and inversions.
- C1.2 More focused investigations employed molecular methods to detect sites of variation in the DNA sequence of chromosomes. These genetic methods focused more and more precisely on single genes and the DNA sequence within specific genes. Now very small genetic alterations in the DNA coding sequence of genes can be identified, establishing their role in causing Mendelian (single gene) disorders.
- C1.3 The emergence of genomics over the past decade represents the ability to use a single assay to generate detailed single gene tests simultaneously across the whole genome or to target specified subsets of the genome. The information generated can represent the relative copy number of different segments of DNA (by chromosomal microarray, to assess whether a section of the genome shows any deletions or duplications) or the DNA sequence of all or parts of the genome. What must be kept clearly in mind is that much more information may be generated and held in the laboratory IT system than is ever analysed and reported in the course of a specific investigation.
- C1.4 These technical advances mean that the potential uses of genetic testing have expanded enormously. There are challenges associated with these developments. First, given the enormous amount of 'normal' genetic variation between healthy individuals, how can we determine which of the many differences found in a patient are acting as significant causes of disease and which are entirely benign? Second, while the methods of detecting variants across the whole genome are relatively good at finding molecular explanations for clinical presentations with clear signs of disease, their ability to predict future disease in a healthy individual is much more limited. Finally, the bulk of data generated about patients can lead to information that has not been sought by anyone but that simply emerges, as with information about misattributed family relationships (eg non-paternity), consanguinity and incest, and potentially many non-disease traits as well as projected information about future health problems. How should such information be managed?

C2. Genomic uncertainties

C2.1 A practitioner can request and make the arrangements for a genomic investigation without necessarily understanding the full complexity of either the molecular technologies employed or the bioinformatic processing of raw DNA sequence data that eventually leads to a diagnostic laboratory report. However, interpretive steps are required to make sense of the raw data. Any professional discussing current genetic and genomic tests with a patient – or their parent or consultee – should be aware very specifically of four important aspects of genomic investigation: (i) variants of uncertain significance (VUSs), (ii) unexpected, incidental findings (IFs), (iii) the provisional nature of genomic results and (iv) whether (or not) additional, looked-for actionable findings will be reported. For those wishing to arrange testing for their patients an understanding of what the tests are, why consent is important and how to interpret results is imperative. Additional resources are available through national education programmes.⁴⁴

C2.2 **Likely pathogenic variants** – Many of these have only a 90% probability of pathogenicity, though for some variants the probability may be higher. Individual judgement should be exercised as to the threshold at which predictive testing is appropriate. In general terms a decision to withdraw surveillance on the basis of a test with only 90% probability may not be in a child's best interests and it may be more appropriate to defer predictive testing until the status of the familial variant is more clearly established as definitively pathogenic or uncertain or to continue with surveillance even in the face of a negative predictive test.

C2.3 **A variant of uncertain significance (VUS)** is a variant (genetic alteration) found in a patient but whose significance in causing the patient's disease is unclear. Clarifying this may involve seeing whether the same variant has been found in previous studies of similarly affected patients or in large population databases of healthy individuals, whether it has arisen as a new mutational event in the patient or tracks with disease through the family, and how it influences the outputs or function from the gene. Despite such efforts, the pathogenicity of the variant may remain unclear for some time, perhaps years, only becoming clear when the same variant is found again in a similarly affected patient or in some perfectly healthy adult individuals.

It is important for professionals not to conduct 'predictive' tests on the basis of a VUS. Testing an at-risk child for a genetic VUS found in an affected family member may be appropriate if the child has been found to be definitely affected, as that helps to interpret the variant, but if the child appears unaffected then any result will be open to misinterpretation and is likely to cause confusion.

C2.4 **An incidental finding (IF) or unexpected finding** 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 disease phenotype – to the question being investigated – but might be of medical relevance to them in the future or, potentially to other members of the family. There is much debate about if, when and how to report these. We understand that guidance on managing unexpected findings will shortly be published by NHS England.

⁴⁴ <https://www.genomicseducation.hee.nhs.uk/>

1 'Incidental finding' risk of early-onset dementia

Tom, aged 3 years, has mild global delay and a suggestion of some autistic behaviours. He is seen by a paediatrician, who requests chromosome analysis. The analysis is performed by chromosomal microarray analysis (CMA) and a duplication is found that encompasses the coding region of the *APP* gene on chromosome 21 but includes no other genes. This is not thought to account for Tom's neurodevelopmental problems but the laboratory raises the question with the clinical genetics team of whether this finding should be included on the CMA report. The concern is that, if it is included in the report but not disclosed to the family, it might be revealed inadvertently on a later occasion.

The report is issued with a recommendation for referral to clinical genetics for discussion of an incidental finding, without the nature of the finding being disclosed. The referral goes ahead and the family history contains no suggestion of early-onset dementia. The significance of the duplication is considered highly likely but not completely certain to be pathogenic. This is discussed with Tom's parents, and it is explained that testing could be made available to them should they wish to attempt to clarify the situation. Some years later, they had not yet sought testing. A subsequent CMA report is issued to the paediatrician that includes details of the duplication.

Key points

- > Incidental findings (IFs) cannot be altogether avoided and consideration of how, or whether, to report such findings and how to approach the return of results are key.
- > An IF should be considered in the context of the family history as well as the scientific context.
- > Incidental findings are likely to increase with the use of genomic testing techniques and clear policies should be in place locally to handle them, eg discussing at MDT and/or with the referring clinician the appropriateness of reporting such findings.
- > Keeping discussions open for review later provides a safety net and reduces pressure to make an immediate decision.
- > Ensure that all information given to the parents is available to all the patient's healthcare providers.

C2.5 An **additional finding** (AF) or **secondary finding** (SF) is a finding, not related to the patient's presenting phenotype or concern, that the laboratory has actively sought rather than merely stumbled across. This practice is sometimes known as 'opportunistic genomic screening' and the European Society of Human Genetics has guidance on this.⁴⁵ Some laboratories actively examine the sequence of a set of genes that are

⁴⁵ de Wert G, Dondorp W, Clarke A et al. Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2021;29:365–377.

thought to have met the standards of AFs that should be disclosed as being of high penetrance and being medically ‘actionable’.⁴⁶

C2.6 Reinterpretation. A final complexity to the reporting of genomic investigations reflects the rapid progress in the field: these reports are usually provisional and carry a warning that the interpretation of identified variants may change in time. The systems required for the laboratory to issue a revised report proactively – without external prompting – are not yet established, and there is currently no means of achieving this without systematic planning and sustained investment.

C2.7 These challenges mean that the clinical application of genomic investigations often leads to uncertainties. Professionals, patients and families need to understand and accept that the use of genomics will provide useful clarity on some matters, but may, at the same time, generate fresh uncertainties. This is not a reason for rejecting the use of genomics but it is important for all involved in genomic investigations to understand its limitations and the uncertainties it can generate as well as those it can dispel.

C3. What is special about genetic and genomic testing for children?

C3.1 The premise of this document is that testing should be in the child’s best interests. We need to consider what types of information it is helpful to generate about a child and what is best postponed, at least until the child can make their own decisions. In addition, we need to consider how to take account of the welfare of the child within the family context, instead of trying to consider the child as if they exist in an artificial vacuum, detached from their family and social world. There is a tension between providing a consumer-choice service to parents with no checks or balances, and generating antagonism through obstructing tests that are legitimate and helpful for all concerned. Good practice may involve creating opportunities for dialogue and reflection about a child’s long-term best interests with the child’s parents, and where possible the child.

C3.2 Making the diagnosis of a clinical disorder will always be important and genomic testing can be very helpful in achieving this. In this document, however, we also highlight the circumstances in which genetic or genomic testing may be less helpful or simply inappropriate, because the patient is a child. There are several circumstances in which careful thought may be required to make the best decision, such as determining whether a healthy child carries an already known familial variant implicated as the cause of an inherited disorder.

C4. Communication

C4.1 In many situations where there is no immediate clinical benefit to genetic testing but the possibility of testing has been raised, an immediate decision about testing is unlikely to do justice to the complexity of the issues. Perhaps a parent has suggested or requested

⁴⁶ The American College of Genetics and Genomics curates a list of such genes annually, currently known as ACMG73, but these are not used routinely in the UK.

that a genetic test be performed on their child. In such a case, ample time should be allowed for full discussion among all relevant parties. If testing is to happen, consideration should also be given to the timing of the test. Central to this should be a discussion around how information from the test will be conveyed to the child to whom it pertains, and how to ensure that parents are aware of the impact and perhaps burden of being the messengers.

- C4.2 Discussion about a genetic condition in the family may focus on ‘the test’ while neglecting the need for good familial communication. In relation to late-onset genetic disorders, where predictive tests may be feasible, health professionals and parents should consider together whether such a test may be helpful and, where appropriate, facilitate discussions within the family about this. They may then go on to consider the optimal timing of such a test. The process of communication and awareness should be seen as quite separate from any question of genetic testing, which may be sought much later, if at all. These open discussions in the context of a family’s genetic risk for a particular condition may be just as helpful as the test itself, if not more so. It is difficult to conceive of circumstances where openness within a family is unhelpful, although some parents will seek to ration or even to block information in an attempt to protect their (often adult) children.^{47,48} Of course, young children need to be given information in an age-appropriate fashion which may benefit from building foundations and then scaffolding further information in line with their current level of maturity and insight into their own physiology, identity and social dynamics, but that is not the same as attempting to impose secrecy.
- C4.3 Supporting parents to hold open conversations with children from an appropriate age and at an appropriate level, so that the child grows up knowing about the inherited condition in their family, is integral to discussions about genetic testing. Many parents take a drip-feed approach, giving children an early awareness that there is a possible condition ‘in the family’ and providing age-appropriate information in response to questions from the child. This can be helpful to the child’s subsequent adjustment and their coping as an adult.⁴⁹ Information transfer should be ‘child-led’, allowing the child to set the agenda in terms of both content and timing. Conveying information will require multiple conversations and the child’s needs for information are likely to change as they mature. Thus, parents should be supported in opening up family discussions and communicating risk information to their children over time. Using developmentally appropriate strategies helps to promote children’s understanding of, and their ability to cope with, genetic information. In turn this can lead to them being able to participate fully in any decision to be tested and make their own autonomous decisions when appropriate.

⁴⁷ Ulph F, Cullinan T, Qureshi N & Kai J. Familial influences on antenatal and newborn haemoglobinopathy screening. *Ethnicity & Health* 2011;16:361–75.

⁴⁸ Middleton J, Calam R & Ulph F. Communication with children about sickle cell disease: A qualitative study of parent experience. *Br J Health Psychol* 2018;10.1111/bjhp.12311

⁴⁹ Hayes B, Hassed S, Chaloner JL, Aston CE, Guy C. Duchenne Muscular Dystrophy: a survey of perspectives on carrier testing and communication within the family. *J Genet Couns* 2016;25:443–53.

C4.4 Parents often feel a responsibility to help their children adjust to their genetic risk and to tell them of their genetic carrier status prior to the possibility of reproduction.⁵⁰ Overall, the majority of parents do inform their children, or plan to do so.^{28,51} However, research evidence suggests that this communication is challenging; even if parents inform their child, they may avoid the most vital information in an attempt to protect their child from distress. There are recurrent findings in the research literature of parents struggling to convey information that indicates loss or risk impacting on their child's predicted future, so that communication around the topic is avoided.⁵² Another manifestation of this is the way that parents' fear can shape what they tell the child, which in turn may influence the young person's decision about testing.⁵³ Thus, parent-to-child communication is not just about conveying information or education in the same way as a health professional might inform and support a patient. Rather, parents often aim to protect their children as well as informing them. This may influence the process, sometimes distorting it, especially if the parent needs to protect themselves as well as the child. If parent-child communication within the family about their genetic condition is to be improved, more emphasis should be put on addressing parents' fears and concerns rather than just ensuring they have sufficient facts about the condition or risk, as having 'sufficient information' does not necessarily lead to its being passed to the child.⁵⁴ How to communicate results to their child is a key area where many parents seek guidance.⁵⁵

C4.5 Failing to pass on information to their children also leads parents to feel distress: non-communication (failure to confront the issue) avoids the immediate challenge but is no solution.⁵⁶ Furthermore, while in many families mothers and fathers have different roles vis-à-vis communication, both parents may need support in order to fulfil this task. Their success in transmitting information to their children may depend upon how well supported they are, not only by health professionals but by many other sources of personal support. The level of confidence felt by the parent may be important, with greater confidence making disclosure more likely.⁵⁷ This seems not to be a question of confidence in the facts but more a question of overall sense of self-efficacy.

⁵⁰ Ulph F, Cullinan T, Qureshi N & Kai, J. Informing children of their newborn screening carrier result for sickle cell or cystic fibrosis: Qualitative study of parents' intentions, views and support needs. *J Genet Couns* 2014;23: 409–20. doi: 10.1007/s10897-013-9675-2

⁵¹ Tercyak KP, Mays D, DeMarco TA et al. Decisional outcomes of maternal disclosure of BRCA1/2 genetic test results to children. *Cancer Epidemiology Biomarkers & Prevention* 2013;22:1260–6.

⁵² Goldman A, Metcalfe A, MacLeod R. The process of disclosure: mothers' experiences of communicating X-linked carrier risk information to at-risk daughters. *J Genet Couns* 2018;27:1265–74.

⁵³ Rowland E, Plumridge G, Considine AM, Metcalfe A. Preparing young people for future decision-making about cancer risk in families affected or at risk from hereditary breast cancer: A qualitative interview study. *Eur J Oncol Nurs* 2016;25:9–15.

⁵⁴ Lowe GC, Corben LA, Duncan RE, Yoon G, Delatycki MB. "Both sides of the wheelchair": The views of individuals with, and parents of individuals with Friedreich Ataxia regarding pre-symptomatic testing of minors. *J Genet Couns* 2015;24:732–43.

⁵⁵ Dennis A, Howell S, Cordeiro L, Tartaglia N. "How should I tell my child?" Disclosing the diagnosis of sex chromosome aneuploidies. *J Genet Couns* 2015;24:88–103.

⁵⁶ Rowland E, Metcalfe A. Communicating inherited genetic risk between parent and child: A meta-thematic synthesis. *Int J Nursing Studies* 2013;50:870–80.

⁵⁷ Hamilton JG, Mays D, DeMarco T, Tercyak KP. Modeling the dyadic effects of parenting, stress, and coping on parent-child communication in families tested for hereditary breast-ovarian cancer risk. *Familial Cancer* 2016; 15: 513–22

- C4.6 Support groups may promote effective family communication by acting as a prompt or trigger to initiate communication, although they may not impact on the quality of communication.⁵⁸
- C4.7 Other triggers to communication may be situational, such as the recognition that a child is becoming sexually active, or parents finding themselves in a situation – a ‘crunch’ moment of decision – where they have to choose between disclosure and secrecy.⁵⁹
- C4.8 Even when parents express a sense of responsibility, perhaps also claiming the right to be the one to disclose the information to their child, they may find it difficult to ‘find the right time’ to put this into action. They may acknowledge this as a weakness or decide that they do not want their own child to be given such painful information. However, such blocks to communication – such family secrets – can blight the children’s health and prove deeply damaging to relationships.⁶⁰ Knowledge of family illnesses can be a very important scaffold for children when given new genetic information.⁶¹ Both children and adults use this base of knowledge derived from their family to incorporate new information from health professionals.⁶² If the knowledge base is unsound, it becomes much more difficult to accept and act on additional information provided by others, including health professionals.⁶³ Maladaptive family communication can be more problematic than simple ignorance.⁶⁴ It is difficult to correct misinformation; attempts to do so may trigger distress or a rejection of new information that conflicts with what families have told their child. This is an example of a more general phenomenon, also seen when young adults struggle to assimilate new information if they have no prior knowledge.⁶⁵
- C4.9 It is interesting that children/young people often agree with their parents that genetic testing is important for making reproductive decisions and building relationships. However, they also tend to favour testing at a later age than parents would like and to express more concerns about the psychological risks associated with testing.⁶⁶
- C4.10 Most discussions on the predictive genetic testing of children and young people in the absence of any clear medical benefit have focused on the question of who has the right to make the decision and the impact of testing on the child’s (future) autonomy. The conventional view within genetic services is the wish to preserve this future autonomy of

⁵⁸ Plumridge G, Metcalfe A, Coad J, Gill P. The role of support groups in facilitating families in coping with a genetic condition and in discussion of genetic risk information. *Health Expectations* 2012;15:255–66.

⁵⁹ Lowe GC, Corben LA, Duncan RE, Yoon G, Delatycki MB. "Both sides of the wheelchair": The views of individuals with, and parents of individuals with Friedreich Ataxia regarding pre-symptomatic testing of minors. *J Genet Couns* 2015;24:732–43.

⁶⁰ Manjoney DM, McKegney FP. Individual and family coping with polycystic kidney disease: the harvest of denial. *Int J of Psychiatry in Medicine* 1978;9:19–31.

⁶¹ Ulph F, Leong J, Glazebrook C & Townsend E. A qualitative study exploring genetic counsellors’ experiences of counselling children *Eur J Hum Genet* 2010;18:1090–94.

⁶² Ulph F, Cullinan T, Qureshi N & Kai J. Familial influences on antenatal and newborn haemoglobinopathy screening. *Ethnicity & Health* 2011;16:361–75.

⁶³ *ABC v St George’s Healthcare NHS Trust & Ors* [2020] EWHC 455.

⁶⁴ British Medical Association. *Children and young people toolkit. A toolkit for doctors*. BMA, 2021 p24-25. <https://www.bma.org.uk/media/4666/bma-children-and-young-people-ethics-toolkit-oct-2021.pdf>

⁶⁵ Noke M & Ulph F. Young adults’ pre-existing knowledge of cystic fibrosis and sickle cell diseases: implications for newborn screening. *J Genet Couns* 2013;23:121–30. doi 10.1007/s10897-013-9622-2

⁶⁶ Santerre-Theil A, Bouchard K, St-Pierre D et al. Development of a tool to guide parents carrying a BRCA1/2 mutation share genetic results with underage children. *Journal of Cancer Education* 2018;33:569–75.

the child as an adult. On the other hand, parents have the right to make decisions on behalf of their children because they have primary responsibility for their child and they know their child best. The evidence that would be required to make a fully evidence-based assessment of the psychosocial harms and benefits of testing in childhood is difficult, if not impossible, to collect.⁶⁷ As a result, existing guidelines are based on practical experience of what constitutes good practice rather than clear empirical evidence. While children want to be involved in communication and decisions, the idiosyncratic circumstances of particular families and settings make it difficult for the analysis of practice to lead to robust, generalisable insights.

- C4.11 Ultimately there remains the wish to respect and support parents, alongside the wish to see children given helpful and appropriate information. It is especially important to see the individual's knowledge of their risk – of their family history and its personal relevance to them – as entirely distinct from any question of being tested. Indeed, more attention should be focused on the first of those categories as the second may then be easier to manage.
- C4.12 One proposed benefit of testing young children for serious inherited conditions is that the untested child has lost the opportunity to grow up with and adapt to genetic knowledge during his/her formative years and that not testing may cause harm if parents remain anxious and the young person finds uncertainty difficult.⁶⁸ On the other hand, the knowledge that you have about having definitely inherited a high chance of developing schizophrenia in your teenage years, or a neurodegenerative disorder in your 40s, or a fatal cardiac dysrhythmia provoked by exercise, has the potential to be deeply destructive for a growing person. Knowledge that you are at risk of a serious disorder is not good but an imposed certainty from an early age may sometimes be worse.
- C4.13 We argue that it is more productive to encourage open communication about the condition in a family and to discuss with the parents (and the child) what they have identified as the benefits and the drawbacks of testing or of not testing, rather than to focus on testing itself. We recommend that discussions with parents (and their children) should be framed around the competing tensions discussed above. It may be more helpful to consider when (or under what circumstances) might be the best timing for the test rather than focusing on the binary choice of whether or not it should take place. This will often avoid confrontation and lead to an agreement to defer the decision, especially if an offer is made to review the family situation and the parents' request at a later date. Parents should also be advised that they and/or their child can request appointments with genetic services at any time in the future for further discussions, should they wish. On some occasions it may be appropriate to see children separately from their parents as well as with them.⁶⁹ This is especially important when children who are Gillick competent or young people over 16 years request tests for adult-onset conditions or some types of genetic carrier status.

⁶⁷ Clarke AJ. Commentary on predictive genetic testing of minors: by Mand et al. *Journal of Medical Ethics* 2012;38: 527–8.

⁶⁸ Ulph F, Leong J, Glazebrook C and Townsend E. A qualitative study exploring genetic counsellors' experiences of counselling children *Eur J Hum Genet* 2010;18:1090–94.

⁶⁹ Ulph F, Leong J, Glazebrook C & Townsend E. A qualitative study exploring genetic counsellors' experiences of counselling children *Eur J Hum Genet* 2010;18:1090–94.

C5. Challenging conversations with parents

C5.1 Parents may request genetic testing when their child has no symptoms and/or when there is no treatment or prevention available during childhood. This can create a tension between parents and healthcare professionals about what is in the child's best interest now and as an adult. Having an insight into why parents request such tests can help healthcare professionals frame the subsequent discussions.

C5.2 Parents might want or expect genetic testing for their child for several reasons:

- > Reassurance – that their child does not carry the genetic change and will not develop the condition.
- > Knowledge – knowing that the child does carry the genetic change means parents can be alert to the development of symptoms and/or measures to help their child (eg prevention, lifestyle changes, the prompt introduction of therapies or interventions if/when necessary).
- > Preparation for the child – many parents want their child tested to prepare themselves and their child. Parents may find that introducing the family history to a young child means the child grows up knowing about and accepting it. Even so, parents may have concerns about leaving genetic testing until the child is able to understand more and be part of the decision; this is often in the early-mid teenage years when the child may be struggling with the changes experienced in adolescence.
- > Preparation for the parents – some parents say they need to know their child's genetic status for their own mental wellbeing and the integrity of their family.
- > Decisional authority – parents may feel that the decision to test or not test is theirs to make on behalf of their child (just as they make many other decisions on their behalf).

C5.3 Poor/suboptimal communication is a key factor underlying conflict between healthcare professionals and parents. It is important for healthcare professionals to engage in an open discussion with parents and not to avoid or shut down difficult conversations or questions. This maximises the chance that both parties see each other as focusing on the child's best interests. It is important that healthcare professionals suspend assumptions about why parents want their child to have a genetic test. Adopting a non-judgemental approach alongside probing questions/statements, will facilitate parents being able to talk about their perspective without being misunderstood from the outset. Discussions about genetic testing in childhood can evoke strong feelings and reactions for both parties; reflecting on, rather than reacting to these, gives health professionals an insight into the parents' experience.

C5.4 Reframing parental requests in terms of finding the best timing for the test can be a useful strategy for discussion around harms and benefits. This includes deferral of testing to when the child would be old enough to be involved in the decision. This reframing can enable health professionals and parents to engage in a discussion that involves both addressing the ethical issues and discussing the consequences of testing.



2 Reframing the request as ‘when’ not ‘if’ in neonatal testing for *BRCA1*⁷⁰

Beverley’s husband is known to have a *BRCA1* mutation. This comes up in discussion with her midwife during Beverley’s pregnancy and the midwife wonders whether a prenatal diagnostic test might be available. However, Beverley makes it clear that she would decline this even if it were offered, on the basis that she would not want to terminate the pregnancy. Once her daughter is born, Beverley asks for a genetic test for her daughter but is told that, because the disease is highly unlikely to manifest before adulthood, testing should be deferred. Beverley cannot understand why the test would be available during her pregnancy but declined after her daughter was born.

Key points

- > While a woman is pregnant, the law does not recognise an independent status for the unborn child. This means that prenatal diagnosis is permissible, especially where the woman might modify her reproductive plans on the basis of the test results. Once a child has been born, the law requires that the interests of the child are considered independently of the parents’ wishes.
- > Those interests include protection against the restriction of the child’s future autonomy unless there is a clear and specific reason to do so.
- > Here, the question is whether or not to carry out a predictive test for a condition that is only likely to manifest in adulthood. The predictive testing of a young child for this adult-onset condition is controversial. Two options are available:
 - (i) Test for the *BRCA1* mutation as a baby or young child
 - (ii) Delay testing until the daughter can decide for herself.
- > Testing after birth cannot alter the risk to the daughter and so no benefit would accrue to her as a child. Testing would, however, deprive the daughter of the opportunity to decide for herself whether and when she wished to know the genetic information. We know that when adults are offered such a choice, they do – after appropriate counselling – reach different conclusions. This strongly suggests that the choice is a valuable one, which should not be removed without good cause.
- > This is why there is a presumption that testing should be deferred until the person to be tested can make her own decision; that, in turn, accounts for why this consideration carries very considerable weight. In this case, no reason has been identified to displace that presumption, and if one were offered it would need to be clear and precise to justify removing the daughter’s future autonomy at this early age. Accordingly, we support option (ii).

⁷⁰ Adapted case 4 from *Report on Genetic Testing of Children* British Society for Human Genetics, 2010.

2 Reframing the request as ‘when’ not ‘if’ in neonatal testing for *BRCA1*⁷⁰ (cont)

- > Having a clear record of past discussions about predictive or diagnostic genetic testing would have been useful in this case. It is now recommended that prenatal diagnosis (PND) or pre-implantation genetic testing (PGT) is discussed as standard with all individuals/couples of reproductive age who are at risk of having a child with a cancer susceptibility syndrome.⁷¹
- > While prenatal diagnosis is not usually offered for this late-onset risk of cancer, PGT is sometimes considered and that might be possible in a future pregnancy. It may be helpful to involve a multidisciplinary team to enable further discussion.

C6. Diagnostic testing

- C6.1 For diagnostic testing, a child will have clinical features of a disorder and a diagnosis may help inform treatment or management. For these scenarios, traditional, targeted genetic testing is similar to any other diagnostic test. While this type of test may lead to some uncertainty, eg variants of uncertain significance (see C2.3), it will not identify anything in other genes as it is targeted to certain specific genes relevant to the condition.
- C6.2 Recent advances mean that it is now possible to look across the whole genome in more detail than in the past. Tests include the whole genome sequence (whole genome sequencing, WGS) or all the transcribed and protein-coding sequences (whole exome sequencing, WES) or the number of copies of widely dispersed sequences from across every chromosome (chromosomal microarray, CMA) or the alleles at a large number of dispersed single nucleotide polymorphisms (SNPs) (as often used in genome-wide association studies, GWAS). The results of targeted genetic tests are usually much simpler to interpret than whole genome tests where the massive quantity of data generated requires much work to filter the findings and yield a clinically relevant interpretation that can be applied to support the management of a patient’s condition.
- C6.3 The aim of genomic testing is also diagnostic but it may be more likely than targeted tests to identify incidental findings or variants whose significance is unknown, as well as having the potential to identify additional findings (see C2.3–2.5). When performing a whole genome sequence, the laboratory will generate much more information than is usually interpreted; the decision about what elements of the overall sequence data are interpreted and then reported, and which elements are not analysed, may be crucial.

⁷¹ 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.

Decisions about the scope of the test may, in turn, influence whether information is generated which might have an impact on the child's future health as an adult.

C7. Predictive testing

- C7.1 A predictive test is a test offered for a known genetic diagnosis in a family. It may be that there are no current physical signs or symptoms but these may become apparent over time. If there is no medical action to be taken until well into adult life, and testing a young child brings no clear medical benefit until later, then it is argued that testing the child is denying them the opportunity to make their own decision about genetic testing once they are adult or mature. Raising the child in the knowledge that there is a genetic condition in the family and that they can find out more about it when older may be a better route than testing the young child. This is especially true when many or most adults at risk choose not to be tested, as applies in the context of Huntington's disease, where less than 20% of adults at risk choose to have predictive testing.⁷² If safe and effective treatments exist or become available, the context is different: it may then be entirely appropriate to test children, so that they can access appropriate care. Indeed, it would then be important that they are not denied such opportunities.
- C7.2 There are circumstances where families wish to 'protect' a child from knowledge of their risk of an inherited condition, especially if this may impact their choice of career or access to life insurance. Such blocks to communication can increase the risk of health problems as well as jeopardising family relationships in the future. They regularly arise in the context of autosomal dominant polycystic kidney disease. See also C4.8.^{73,74}
- C7.3 A point of concern is around the accuracy of our understanding of certain genetic conditions and gene variants. While the cardiac section (see C8) highlights a specific area of concern, this consideration is relevant in predictive testing for many conditions. It should be remembered, especially if screening and intervention decisions are made on the basis of these variants, that our understanding is still changing and the interpretation of many variants – even some that appear to have firm interpretations – may be subject to change.

⁷² Quarrell O, Clarke A, Compton C et al. Predictive Testing of Minors for Huntington's Disease: The UK and Netherlands Experiences. *Am J Med Genet B Neuropsychiatr Genet* 2018;177:35–39.

⁷³ Manjoney DM, McKegnay FP. Individual and family coping with polycystic kidney disease: the harvest of denial. *Int J Psychiatry Med* 1978;9:19–31.

⁷⁴ Clarke A, Sarangi S, Verrier Jones K. Voicing the lifeworld: Parental accounts of responsibility in genetic consultations for polycystic kidney disease. *Soc Sci & Med* 2011;72:1743–51.

3 ‘Predictive’ testing for an inherited cardiac condition: beware the misinterpretation (published case report)

A variant in *LQT1* (*KCNQ1*) is found in Deepak, whose brother Ali died suddenly aged 13. The variant is thought to be responsible for Ali’s sudden cardiac death, so a defibrillator is inserted in one family member and others are identified as being at risk. It subsequently emerges that the variant is benign and is not carried by Ali, who had a *de novo* pathogenic variant in the gene encoding desmin (*DES*) which was the likely cause of his sudden death.⁷⁵

Key points

- > Careful variant interpretation is needed by clinicians and laboratory scientists working together to ensure that inappropriate assumptions are not made about variant pathogenicity. This will help to ensure that decisions about patient management are based on a sound understanding of variant pathogenicity
- > Without proper scrutiny, assumptions can have implications for family members if results are cascaded through the family, as happened in this case where it led to inappropriate, invasive and costly procedures and to delays in recognising and acting on the true family pathology.

C8. Predictive testing for inherited cardiovascular conditions

C8.1 Children at-risk of inherited cardiovascular conditions (ICCs) are increasingly undergoing predictive genetic testing in order to inform ongoing clinical management, including surveillance, as well as to inform career choices, lifestyle management and exercise advice. However, predictive testing of children for ICCs remains highly contentious within the cardiac genetics community with a polarisation of opinion regarding almost all aspects of testing. In part, this is because many inherited cardiac conditions display reduced penetrance, so a child who carries a pathogenic variant may never display a clinical phenotype but might curtail their activities and life choices on the basis of a test result. Children who carry a pathogenic ICC variant may be treated differently by their schools and restricted from undertaking certain sports or taking up specific careers, such as the military. Although this may be appropriate, it is essential that this possibility is discussed with families before any predictive testing is undertaken. Thus, determining what is in the best interests of the child may be extremely difficult and heavily dependent on the family context.

⁷⁵ Ackerman, BA, Bartos DC, Kapplinger JD et al. The promise and peril of precision medicine: phenotyping still matters most. *Mayo Clin Proc* 2016;91:1606–16.

The UK Cardiac Geneticists' Group proved unable to establish a broad consensus position for this document, noting that there was a dichotomy of views on every point. It is therefore essential that, when considering childhood predictive testing for ICCs, there should always be full discussion with the family, with input from clinical geneticists and genetic counsellors as well as cardiologists. In addition to informed consent from the family, there should be consent or assent from the child if possible. Prior discussion within an ICC MDT on an individual case by case basis would represent safe best practice.

C8.2 Despite the lack of an overall consensus position, there was agreement that the following points should be considered when offering predictive testing for inherited cardiac conditions:

- > Ensure that both the phenotype and the genotype in the family have been confirmed before considering any predictive testing in a child.
- > Families must be counselled that variant classification can be subject to change.
- > Discuss with families the potential limitations on the child's activities and life choices before any predictive testing is undertaken.

The only area in which there was majority consensus was regarding the clear clinical utility for predictive testing in children for long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT).

- > For other ICCs, such as the cardiomyopathies, families may wish to consider earlier predictive genetic testing where the family phenotype is severe, early-onset or syndromic or where early medical treatment can alter the course of clinical features.
- > There is now good evidence that the inheritance of Brugada syndrome is complex, influenced by both rare and common variants. An apparently pathogenic *SCN5A* variant may not fully explain or predict a Brugada syndrome phenotype in some families, and further testing, including negative clinical testing, may be justified.

4 Beware the non-Mendelian disorder

A regional clinical genomics service receives a referral to carry out predictive genetic testing on James, aged 3. James is at risk of Brugada syndrome (BrS), as his father is reportedly affected by the syndrome. James is fit and healthy, but the parents would like him to have a genetic test to prove he's not at risk.

Key points

- > It is important to start by reviewing the clinical details of the phenotype in an affected parent before considering ICC predictive genetic testing in a child, as reported phenotypes may differ. For example, an apparent diagnosis of BrS may turn out to be long QT syndrome.
- > Even if BrS is likely, clinical interpretation may be difficult since many variants in the main BrS gene *SCN5A* are classified as VUSs.
- > As BrS is now understood to be more oligogenic than Mendelian (ie potentially influenced by a number of genes of substantial effect, and potentially also environmental factors), there are relatives within families who have been shown not to carry a familial, pathogenic *SCN5A* variant but still display a phenotype.
- > For all these reasons, the clinical utility of 'predictive' genetic testing for BrS in children is not established and remains controversial; expert input from an ICC MDT is recommended.
- > ICC MDT input can help to elucidate the phenotype of the affected parent and wider family. Clinical cardiac assessment may be more reassuring to families than a predictive genetic test, especially if a normal ECG can be obtained on a child during fever as this reduces the likelihood of a severe BrS phenotype. In such cases, after counselling, families may opt not to go ahead with genetic testing.
- > The uncertain clinical utility of genetic testing for BrS means that cardiac surveillance for BrS may be offered by some ICC centres, even after a negative test result for the putative family variant in a child.

C9. Carrier status testing

C9.1 Testing a young child to determine their carrier status for a known autosomal recessive disorder in the family is not 'needed' when they are young but would be appropriate to be offered to young people as they become sexually mature. Some parents would prefer to find out this information about their children well in advance; it may guide conversations within the family.

C9.2 Our preferred approach is to recommend openness and discussion within a family but to defer testing, so that important decisions are explicitly left to the young people to make

for themselves. In this way, we believe, they are more likely to engage with the issues and make decisions with careful deliberation. In addition, there may sometimes be emotional costs to being identified as a carrier in terms of guilt (when the child has affected siblings) or stigmatisation (within the wider family and community)⁷⁶ although such responses will (hopefully) become less common once more people appreciate that we all carry some deleterious genetic alterations and are all carriers for at least one serious autosomal recessive condition. Furthermore, the harm likely to result from testing young children is not often severe. Accordingly, we might agree to requests to do this, after a frank discussion with the parents and a period of reflection. This may be preferable to sacrificing our professional relationship with the family. It must be emphasised that a recommendation not to test a child (for now) does not entail a recommendation not to discuss the topic with the child: in fact, we would strongly urge discussion in an age-appropriate fashion so as to prepare the ground for testing once the child can participate in the discussion.



5 Reporting carrier status from a diagnostic test

Twelve-year-old Dan is brought to the emergency department by his parents with a history of fatigue, loss of appetite, joint pain, weight loss, anaemia and jaundice. His symptoms and further investigations suggest Wilson's disease, a disorder of copper metabolism, and Dan is tested and copper chelation therapy is commenced to prevent further damage. Dan has two siblings, aged 8 and 15. The parents would like both children to be tested to check whether either is affected. The question is whether carrier status should be reported if they are not affected. The parents are keen that the full results including carrier status are released, even though the younger child cannot make a decision for herself until she is older. The multidisciplinary team caring for the family are undecided whether to report carrier status for both children.

Key points

- > Patients with Wilson's disease can deteriorate rapidly and, since treatment is available, encouraging a child to be tested and the results to be available to the clinical team is advisable. However, carrier status will not be of importance until later in life at the point of planning a family.
- > Like other predictive tests involving children and young people, if a child is able to make their own decision about having the test, then they should be consulted, recognising that they may want their parents to be involved in the decision as well. If appropriate, genetic testing should then proceed.
- > It would be advisable to discuss with the parents, before performing the investigation, that the carrier status of the younger at-risk child would inevitably be revealed by testing.

⁷⁶ Ulph F, Cullinan T, Qureshi N and Kai J. Familial influences on antenatal and newborn haemoglobinopathy screening. *Ethnicity & Health* 2011;16,361–75.

5 Reporting carrier status from a diagnostic test (cont)

If they prefer not to know the result at this point, they could be given a 'not affected' result and arrange to return once the child is older to be given the full, carrier-status result.

- > In practice, whether or not carrier status is revealed when the result becomes available, it may be helpful to arrange an appointment once the child is in their late teens/adulthood to give them a full explanation of carrier status, so that they have ownership of the result.
- > This points to the need for services to have robust infrastructures and processes to provide follow-up services for transition clinics where young people may be offered investigations that have been deferred until they are more mature, or to provide an explanation about genetic tests that have already been performed.

C9.3 In the setting of preconception population screening for recessive disorders, similar considerations apply in that testing adolescents and young people can be appropriate when they have sufficient understanding to participate and give consent for themselves. It is important that the offer of screening is not made in a pressurised or coercive environment or in a context in which carriers are stigmatised, whether this is in a group environment or involves individuals or couples. There are numerous examples of good practice in this area, in both the UK and other countries, sometimes as part of a community screening programme.

C9.4 Newborn screening programmes will usually identify all carriers of sickle cell disease (SCD) and a much smaller proportion of carriers of cystic fibrosis. The information is generated while screening to identify affected infants. Generating such information is unavoidable in the case of cystic fibrosis screening so the results are disclosed to families. In the case of screening for SCD a deliberate decision has to be made if this information is not to be generated. We know that families want to convey these results to their children but that they also want help from health professionals; some families may also forget about the newborn screening results if there are no affected family members, so the information may not reach the child. Some parents may also need to see genetic specialists (either genetic counsellors or clinical geneticists) to help them understand what it means to be a carrier.

C9.5 When testing a child for carrier status of a sex-linked disorder, a chromosome rearrangement or an autosomal dominant disorder of reduced or age-dependent penetrance, the situation is somewhat different from testing for autosomal recessive carrier status as the biological responsibility for having an affected child rests exclusively with the identified carrier. This contrasts with the context of autosomal recessive disorders where both parents of an affected child will be carriers and it is easier to

perceive the responsibility as being shared. The prospect of personal difficulties – especially blame, guilt and stigmatisation – is therefore potentially greater with these conditions than with autosomal recessive disorders (although that is not always the case), and so the reasons for deferring tests until the child can participate fully in the discussion are perceived as stronger. On the other hand, there is the possibility that the child may not only carry the problem but also – to some extent – be affected by it. That would be true in sex-linked disorders and in carriers of some translocations, even if they appear on karyotype or microarray to be ‘balanced’. Therefore, if the child has problems that might be the result of the genetic variant, testing may be appropriate as a diagnostic investigation. Such circumstances can arise in conditions such as Duchenne muscular dystrophy, fragile X syndrome and Huntington’s disease.

C10. CMA for chromosomes

C10.1 Over the past decade, chromosomal microarray (CMA) – delivered originally via array-comparative genomic hybridisation (aCGH) technology, and more recently via single nucleotide polymorphism (SNP)-based arrays – has become the mainstay for the diagnosis of cytogenetic anomalies associated with unbalanced chromosomal rearrangements. The karyotype is still required for the detection of other chromosomal rearrangements, such as balanced translocations and inversions, although these can in principle be detected by whole genome sequencing. Considered a significant technological advance,⁷⁷ CMA has been used in clinical genetics and in the paediatric clinic setting. Its strength is in increasing diagnostic yield in unexplained developmental disorders, including intellectual disability, autism and multiple congenital abnormalities. It is much more sensitive than the karyotype in detecting microdeletions and microduplications, known as copy number variants (CNVs). Such testing may detect a potentially pathogenic variant but of reduced penetrance, whose relevance to the child’s presenting problems may be unclear. Furthermore, CMA can also detect changes that are unexpected, eg a deletion or duplication encompassing a known disease-causing gene, such as a deletion of or within a *BRCA* gene. Such a deletion may (or may not) explain the problem with which the child has presented but there will still be a need for family counselling, leading to genetic testing in the child’s parents. The child will need to be informed about this finding once they are mature enough to understand its significance and – if female – will also benefit from specific surveillance for the risk of breast cancer. If the child’s mother carries the same deletion, she would also be offered appropriate surveillance.

⁷⁷ Miller DT, Adam MP, Aradhya S et al. Consensus Statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2019;87:749–764

6 Unexpected future health risks identified via broad genetic testing

Rosie is a 3-year-old girl with short stature, heart problems and a cleft palate. Her paediatrician requests chromosomal microarray (CMA) to investigate her health problems. This finds that Rosie has a deletion encompassing part of the *BRCA2* gene, such that she only has one working copy of the *BRCA2* gene. This has no clinical relevance for Rosie in childhood, and would not explain her short stature, heart problems or cleft palate. However, the *BRCA2* deletion might confer an increased risk of developing breast cancer in adult relatives, some of whom might be eligible for screening and/or risk-reducing surgery (these interventions would be considered in young adulthood at the earliest).

Rosie may have inherited her *BRCA2* deletion from one of her parents. They or their relatives may be at high risk of cancer and might benefit from screening or risk-reducing surgery but they might not know to access this if the *BRCA2* finding is not communicated. For Rosie, there are no recommended actions until adulthood, yet current NHS systems cannot be relied upon to store this information until it is clinically relevant, or to ensure future communication of her genetic risk at an appropriate time in the future.

Key points

- > Broad genetic tests (eg CMA or genome sequencing) may reveal unexpected health risks, or information of relevance to other family members. The relevance to other family members may sometimes be more immediate than for the person tested. This possibility should be discussed up front, as part of the consent process, wherever it may be relevant. This may require support and training for non-genetics specialists.
- > Since this result is unexpected, but in a gene known to be disease causing and with management options available, the decision whether or not to disclose it to the family would take account of the best interests of the child but would also take account of the potential implications for the child's parents as well as the future interests of the child. In the context of WGS in the UK, a pathogenic variant in this gene is regarded as a looked-for additional finding.
- > If a *BRCA2* deletion had previously been found in Rosie's parent, current guidance would be that Rosie should not be tested for this – or that the result should not be reported if it would be revealed by the investigation – until Rosie is able to make her own decision regarding testing. If the laboratory had been informed of the familial variant and were asked not to disclose it, the laboratory report should state that it would not indicate the presence or absence of the previously known familial variant and that follow-up should be arranged for this to be considered at an appropriate point in the future.



6 Unexpected future health risks identified via broad genetic testing (cont)

- > As broad genetic testing will sometimes result in generating information outside the referrer's expertise, professionals should be clear about how they can obtain relevant advice if this occurs.
- > An MDT discussion may be valuable if the variant is likely to be of moderate penetrance.⁷⁸
- > In this case, the clinical actionability of the test is a consideration in deciding whether or not to disclose the test result. Had the result revealed a likely finding of early-onset dementia for the child (for example from a variant in *PSEN1* or a duplication of the *APP* gene), the decision to disclose the result would have been less clear-cut based on the current lack of actionability of the result.
- > Different professional duties may arise when responding to existing information than when considering whether potential information should be sought and communicated.

C10.2 If a fetus with congenital abnormalities has had CMA performed, with no CNV identified that could explain the anomalies, then the paediatrician or geneticist who assesses the child after birth may need to consider requesting a reinterpretation of the CMA analysis. This is because a report issued prenatally may have used different (more restrictive) criteria for reporting possible CNVs than would apply postnatally (see below). The same situation will also arise in relation to sequencing the fetal exome or genome.

C10.3 Recent approaches to CMA have started to detect the DNA sequence at specific variable sites in the patient's genome (SNPs) instead of the relative binding of the patient's sample versus a control to oligonucleotide sequences (aCGH). This means that additional information is produced, potentially of relevance to the generation of polygenic risk scores (PRS), and also giving information about runs of homozygosity. This in turn can yield information of potential social (not merely medical) significance. If the runs of homozygosity are long, then this may indicate that the patient's parents were close relatives, so that the child's father might be the mother's own father or brother. If the CMA indicates this as a possibility, there may be implications for safeguarding of the mother (and possibly also of the patient and any siblings). For further discussion of what these responsibilities for child protection and safeguarding may entail, see B5.5.

⁷⁸ 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.

- C10.4 If the degree of homozygosity occurs in a community that practises customary consanguinity, then familiarity with the background level of consanguinity for that community will be pertinent to considerations about incest, abuse or safeguarding.
- C10.5 If the patient's mother is clearly adult and no longer living in her original family home, then raising the question of past sexual abuse with her will be delicate. A strong network of support would need to be in place before such a question could be broached.

C11. Whole genome sequencing

- C11.1 Next generation sequencing (NGS) technology can be broadly divided into genomes, exomes or more targeted gene panel screens. The genome is the entirety of the genetic material of an organism which can be examined through a whole genome sequencing test (WGS). The exome is the portion that codes for proteins (nearly 2% of the genome), which can be examined through whole exome sequencing (WES). These intensive testing technologies are more often used for non-specific problems as they have a higher rate of identifying a likely cause for the disorder in question, but also a higher rate of finding a variant of uncertain significance or of incidental findings (see C2.3–2.4). For people with more specific problems (or phenotypes), targeted gene testing is often more appropriate, as it is more focused on specific, relevant genes and is often hardly less sensitive. Increasingly, large gene panel tests are being conducted using WGS or WES as the underlying technology, with an *in silico* gene panel being applied bioinformatically.
- C11.2 Sequencing technologies produce results in the form of raw sequence code but the analysis of this data in a diagnostic laboratory, in the form of bioinformatics, is organised into virtual gene panels, according to the phenotypic information provided about the patient's problems (as in the 100,000 Genomes Project). Variants are also filtered according to the mode of inheritance of the gene, the allelic frequency in 'normal' or 'control' populations and the predicted consequences for the protein's function, or tiered by likelihood of pathogenicity, to try to distinguish the one or two potential diagnostic variants that are responsible for a disease in an individual case from all the many thousands of other variants, most of which will represent normal variation.
- C11.3 As with other genetic testing technologies, there may be occasions when pathogenic variants are identified that had not been specifically sought. This might indicate a risk for an adult-onset condition or a condition not yet diagnosed. It may seem in a patient's best interests to feed this information back to the family, if surveillance or treatment is available. However, where conditions do not have treatment options, it is unclear whether the duty to avoid harm (by not revealing that particular result) outweighs the value of autonomy (the patient's right to choose whether to be given the information). To avoid difficult discussions and decisions once the results have been reported, it is

advised that a full discussion is held beforehand – at the time of taking consent for the test – about the different possible types of results that may be produced by the test.⁷⁹

C11.4 ‘Additional findings’ may be actively sought when a child has WGS or WES performed for diagnostic purposes. The American College of Medical Genetics and Genomics (ACMG) recommended in 2013, 2016 and 2021 that additional findings of highly penetrant, definitely pathogenic and ‘actionable’ variants be sought with any whole genome or whole exome sequencing of children as well as adults.^{80,81,82} In Europe and the UK, there remains considerable debate about this approach and there is still no consensus on whether parents should receive these results. If not through the parents, how and when should we ask children whether they want these ‘additional sought’ or ‘secondary’ findings? If this information is seen, in part, as family information, can you deny parents the opportunity to have genetic variants identified that could result in better health outcomes for them and their wider family? If a child is tested in infancy, how can we ensure that the child, once an adult, is given those results and access to the appropriate genetic counselling, and interventions such as risk surveillance? This will need to be considered in any pilot programme of WGS as part of the neonatal screening programme.

C11.5 While opinions may differ as to which variants in which genes should be included in the active search for additional findings, the principle of searching for such variants in a child is novel and important. It is sometimes termed ‘opportunistic genomic screening’ (OGS). Although the test may be understood as a form of screening, the setting also differs from a true, population screening programme as only modest numbers of children will be tested and the costs of screening are not high because the added costs are the marginal costs of additional variant assessments in a pre-specified list of genes. Against this one must weigh the lack of infrastructure for such additional analyses and the lack of even a UK-wide consensus on whose obligation this would become. The return of a limited number of such additional actionable findings has been explored via the 100,000 Genomes Project, but the results have not yet been fully evaluated. While we prefer a cautious approach to the full-scale introduction of such OGS, the scope exists for a limited and carefully monitored form of this to be introduced alongside a programme of service evaluation.

C11.6 It would be good practice to check whether a child is already known to be at high prior risk of an inherited condition known in the family. In that case, it may be preferable to delay reporting these results and further investigation until the child is mature enough to be involved in a discussion about testing.

⁷⁹ RCP, RCPPath and BSGM. *Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic*. 3rd ed. Report of the Joint Committee on Genomics in Medicine. London: RCP, RCPPath and BSGM, 2019. See especially the set of case studies.

⁸⁰ American College of Medical Genetics and Genomics (ACMG). Incidental findings in clinical genomics: a clarification. A policy statement of the ACMG. *Genet Med* 2013;15:664–6.

⁸¹ Kalia SS, Adelman K, Bale SJ et al; on behalf of the ACMG Secondary Findings Maintenance Working Group. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update: a policy statement of the ACMG. *Genet Med* 2017;19:249–55.

⁸² Miller DT, Lee K, Chung WK, Gordon AS et al and ACMG Secondary Findings Working Group. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021;23:1381–90. <https://doi.org/10.1038/s41436-021-01172-3>

C11.7 In addition, WGS (and even WES) may – as with SNP-based CMA – reveal runs of homozygosity. The same considerations then arise as already discussed in C10.3, 10.4 and 10.5.

C11.8 Experience is being gained with rapid whole genome or exome sequencing (WGS/WES) of very sick infants, especially in neonatal or paediatric intensive care units. WES/WGS is particularly applicable to critically ill children due to the often non-specific presentation, and the clinical utility of this testing method has been shown worldwide.^{83,84,85,86,87}

With ever-growing knowledge of gene-disease associations but incomplete understanding of the natural history of disorders in the neonatal period, the analysis of WGS/WES data using an agnostic rather than panel-driven approach has proven useful. However, it is acknowledged that this may result in more uncertainty if findings cannot be readily related to a clinical phenotype.

C11.9 WGS/WES can give very helpful results in the neonatal/paediatric intensive care unit (NICU/PICU) context that feed effectively into the management of the infant's care. While practical difficulties can arise, neonatologists are working with their genetics teams to improve the use of the service. Areas of improvement for an effective service include choosing the appropriate timeframe for the test and the eligibility criteria,⁸⁸ the clinical genetics support required in intensive care settings to understand and consider results within the critical care decision-making process and the clinical genetics pathway for children diagnosed as inpatients.^{85,89,90}

C11.10 The process by which parents give consent to such acute testing is difficult and must – even more than in other circumstances – be regarded as a process. Decisions must be made in a limited time at a moment of crisis when parents may be both distressed and deprived of sleep, which may affect their ability to make informed decisions and present a further emotional burden in the already stressful ICU environment. The question of consent and the way in which results may (or may not) emerge should be discussed on a number of occasions on the ICU and again at follow-up appointments,

⁸³ de Wert G, Dondorp W, Clarke A, et al. Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2021;29:365-377.

⁸⁴ Stark Z, Schofield D et al. Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. *Genet Med* 2019;21:173–180.

⁸⁵ Stark Z, Ellard S. Rapid genomic testing for critically ill children: time to become standard of care? *Eur J Hum Genet* 2022;30:142–49. doi: 10.1038/s41431-021-00990-y

⁸⁶ NICUSeq Study Group, Krantz ID, Medne L, Weatherly JM et al. Effect of whole-genome sequencing on the clinical management of acutely ill infants with suspected genetic disease: A randomized clinical trial. *JAMA Pediatr* 2021;175:1218–26. doi: 10.1001/jamapediatrics.2021.3496

⁸⁷ Dimmock DP, Clark MM, Gaughran M et al. An RCT of rapid genomic sequencing among seriously ill infants results in high clinical utility, changes in management, and low perceived harm. *Am J Hum Genet* 2020; 107:942–952.

⁸⁸ The NHS England national genomic test directory for rare and inherited disease sets out eligibility criteria for accessing genetic and genomic tests. The directory can be accessed at <https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-3.1-August-2022.pdf>

⁸⁹ Stark Z, Nisselle A, et al. Attitudes of Australian health professionals towards rapid genomic testing in neonatal and paediatric intensive care. *Eur J Hum Genet* 2019;27:1493–1501.

⁹⁰ Raymond FL. Clinical genomics in critically ill infants and children. *JAMA* 2020;323:2480–82.

acknowledging that the timeframe and setting for pre- and post-test counselling may differ from more classical genetic testing.^{91,92,93}

- C11.11 As part of the discussion around the rapid genome/exome sequencing of sick children, the parents should be prepared for a result that may amplify any sense of uncertainty; in addition, their expectations of the test may not align with what is currently possible to achieve. Counselling should include information about the technology, its capabilities and limitations, and should include both the significance of a negative result and the implications of trio testing as it is usually performed. This is of course familiar across all of medicine but may be especially distressing in these circumstances. A clear and important result may be found that is of great relevance not only to the sick child but also to the parents (in terms of health or the risk of recurrence) or to other members of the family. It is possible that the diagnosis is very rare, so that little information is available about the condition and the associated prognosis, and it is difficult to build it into the care pathway for the infant.
- C11.12 However, test results may, in conjunction with the clinical picture, give clear information about the child's prognosis. If this indicates a poor outlook, the implications for management will have to be considered with great care. Communication and discussion with the family will need to be conducted very gently and with particular sensitivity. A transition to palliative care is not always acceptable to the family, even when intensive care seems futile to professionals; both parents and staff may find that these situations cause great anguish. The time that may be needed to adapt to such information and learn to 'cope' may not be readily available in the intensive care environment.
- C11.13 Experience of using WGS in the neonatal and paediatric intensive care setting has highlighted the following points to take into consideration:

Pre-test

- > Evidence shows that a significant proportion of children in NICU and even more in PICU have an underlying rare disease as indicated by diagnostic rates from several projects. Determining clear eligibility criteria for WGS is difficult, and national guidelines (ref R14) will need to be kept under regular review. Where a child has already had an exome analysis as a fetus (R21 criteria), the sequence data could be reanalysed using postnatal (R14) criteria.⁹⁴
- > For this reason, clinical genetics gatekeeping is the current norm in the UK and clinical genetics input is also required to interpret complex genetic results.

⁹¹ Ayres S, Gallacher L, Stark Z, Brett GR. Genetic counseling in pediatric acute care: Reflections on ultra-rapid genomic diagnoses in neonates. *J Genet Couns* 2019;28:273–82.

⁹² Clowes Candadai SV, Sikes MC, Thies JM *et al*. Rapid clinical exome sequencing in a pediatric ICU: Genetic counselor impacts and challenges. *J Genet Couns* 2019;28:283–91.

⁹³ Gyngell C, Newson AJ, Wilkinson D *et al*. Rapid challenges: Ethics and genomic neonatal intensive care. *Pediatrics* 2019;143(Suppl 1):S14–S21.

⁹⁴ NHS England national genomic test directory for rare and inherited disease R14 –acutely unwell children with a likely monogenic disorder; R21 refers to fetal anomalies with a likely genetic cause. <https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-3.1-August-2022.pdf>

- > For many conditions, WGS is not a substitute for metabolic biochemistry testing or imaging. The ready availability of WGS testing for children receiving intensive care should not supersede these more traditional but evidence-based diagnostic pathways. Indeed, these approaches may complement each other.
- > Parents of children in ICU may find decision-making difficult. Feeling great anxiety and distress, and being in a stressful environment, may compromise or undermine their ability to give valid consent. Careful thought should be given to providing sufficient support (through genetic counselling) or, in emergency cases, considering proceeding either without consent (if parents are unavailable) or with consent but deferring its full documentation.
- > Counselling may also be important in understanding the key motivation of parents or guardians for testing.

Test

- > Where the phenotype may not yet be very well defined, or where the natural history of a disorder in the neonatal period is yet to be described, trio testing with agnostic interpretation or a very large panel may be the most effective approach.
- > Trio testing pipelines which screen out dominant inherited variants largely reduce the risk of incidental findings but will miss inherited causative variants of variable penetrance or parental mosaicism⁹⁵. This can be mitigated by adopting a 'white list' of known pathogenic variants together with the careful assessment of the parental phenotype; a gene list drawn up in conjunction with a clinical geneticist can be applied in addition to trio analysis in some cases.
- > Interpretation of variants is sometimes more difficult with young children, when phenotypes may be less specific, and when genetic findings may be on the border between diagnostic or predictive of later onset childhood disorders, which may or may not be causing the neonatal phenotype.

Post-result

- > The results may prompt multiple sources of uncertainty for the family and health professionals: preparing for diagnosis of ultra-rare disorders with no known prognosis or treatment; managing the implications when results of trio testing have direct consequences for other family members; and creating uncertainty for the medical profession about how to incorporate the result in the case management.
- > Physicians are already accustomed to dealing with complex/uncertain results through other tests (eg CT scans) which raise similar difficulties of interpretation, and the possibility of incidental findings.
- > Parents may need additional support and time to adapt to test results outside the ICU setting, especially if WGS reveals the diagnosis of a fatal condition.
- > Testing may have long-term implications for parent-child bonding and relationships.

⁹⁵ Wright CF, Prigmore E, Rajan D et al. Clinically-relevant postzygotic mosaicism in parents and children with developmental disorders in trio exome sequencing data. *Nat Comm* 2019;10:2985
<https://doi.org/10.1038/s41467-019-11059-2>



7 Genetic testing in neonatal intensive care (NICU)

Mina, a baby in NICU is identified as eligible for rapid exome testing. This testing identifies a pathogenic variant in *NKX2-1*. This is associated with choreoathetosis, hypothyroidism and neonatal respiratory distress. This is a variable condition which gives rise to different clinical symptoms in different individuals. In Mina's case it was inherited from her father. Her father had symptoms assigned to cerebral palsy but, in retrospect, they are likely due to this genetic variant. He had a child from a previous relationship who died in the neonatal period. He had wanted that child's DNA tested but wasn't in touch with the mother, so a provisional diagnosis was never confirmed.

Key points

- > Variable conditions may present very differently in different individuals.
- > In this case Mina's father had been told he had a different condition and it was difficult for him to adjust to a new diagnosis. Identifying a genetic condition which contradicts a person's understanding of their lifelong issues will often need support for the process of adjustment.
- > The father needed to adjust to finding out that he had passed on a gene alteration that may have caused one child to die and led to another being in the NICU.
- > Sharing information which may not change care but may have an impact on understanding, psychological adjustment and relationships outside the immediate situation may be an issue and will need follow up and support.
- > A genetic test on one individual can have a significant but unanticipated effect on others.

C12. Newborn screening programme: conventional programmes and whole genome sequencing

C12.1 The UK's conventional newborn screening (NBS) programme screens babies for preventable or treatable early onset conditions; currently nine conditions are screened for across the UK.⁹⁶ Decisions about which disorders should be included in such screening have been made over the years by the National Screening Committee on the basis of an updated version of the Wilson and Jungner criteria for screening (1968),⁹⁷ which requires screening to be for the direct health benefit of the individual identified through screening. Strict adherence to these criteria ensures both public goodwill and that the process of consent does not require lengthy discussion or complex thought, as health professionals can wholeheartedly recommend the newborn programme as being important and to the direct benefit of each infant. At present, the UK newborn

⁹⁶ Public Health England. Newborn blood spot screening: programme overview. PHE, 2013.

<https://www.gov.uk/guidance/newborn-blood-spot-screening-programme-overview> (accessed 1 March 2022).

⁹⁷ Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: WHO, 1968.

- screening programme for metabolic and genetic disorders is much more restricted in scope than the equivalent in many other developed countries because it adheres strictly to the Wilson and Jungner criteria for benefit to the individual infant.
- C12.2 The availability of cheap and accurate genomic tests, in addition to further applications of tandem mass spectrometry methods, raises the possibility of broader newborn screening, including additional conditions such as various metabolic syndromes.
- C12.3 While genetic testing of the newborn screening blood spot occurs regularly as a second-tier test in screening for cystic fibrosis, genetic analysis has not until now been a standard part of newborn screening in the UK. However, a pilot project incorporating whole genome sequencing into the newborn screening programme is in progress in the USA and a similar initiative, exploring the scope for adding a genomic dimension to the existing newborn blood spot programme is planned for the UK. It is likely that WGS as part of UK newborn screening would not be an open-ended exercise in genome interpretation (except perhaps as part of a research add-on) but would seek to identify a set, pre-defined list of disorders.
- C12.4 Incorporating WGS into the newborn screening programme is a possibility for the future but much debate remains around the practicalities. Additional screening would require a substantially greater focus on the process of information and explanation to ensure valid and informed parental consent, with the potential introduction of different tiers of consent depending on which conditions are screened for. There would be a relatively simple discussion about those disorders for which screening was offered for the direct benefit of the child, the 'Wilson and Jungner' type of screening, and a more complex discussion about screening offered for other purposes, such as achieving a rapid diagnosis of essentially untreatable disorders or to support parents' future reproductive decisions. Note that WGS would have to supplement conventional screening; it could not replace the metabolic elements of newborn screening as (i) the commonest and most readily treatable abnormality, congenital hypothyroidism, often does not have a simple genetic cause, (ii) having a phenotype (whether a biochemical, metabolic phenotype or, potentially, a proteomic phenotype) alongside DNA sequence data helps greatly with the interpretation of variants,⁹⁸ and (iii) the timescale for reporting actionable results is usually much shorter for biochemical analyses. Reconciling and interpreting the results from different modalities may be a challenge.⁹⁹
- C12.5 Newborn screening should therefore be kept under review as new developments arise and pilot schemes are assessed and reported. There are several arguments in favour

⁹⁸ Adhikari AN, Gallagher RC, Wang Y et al. The role of exome sequencing in newborn screening for inborn errors of metabolism. *Nat Med* 2020;26:1392–97.

⁹⁹ Wojcik MH, Zhang T, Ceyhan-Birsoy O et al. Discordant results between conventional newborn screening and genomic sequencing in the BabySeq Project. *Genet Med* 2021;23:1372–75.

of only screening for conditions that can be prevented or treated in childhood.^{100,101,102} For other diseases, a lack of prevention or treatment in childhood must be weighed against the potential benefits of early detection. These include: avoiding the often long delay between first concerns about a child's health and a diagnosis being made (the so-called diagnostic odyssey); the opportunity for natural history studies and clinical trials for very rare conditions; and, parents having the choice to use the information for their future reproductive decisions.¹⁰³

C12.6 Newborn screening does not always distinguish between early and later onset versions of the same condition. For example, it cannot distinguish between infantile onset and late onset Pompe disease.¹⁰⁴ Families do not necessarily experience newborn screening negatively as a result of this but there is evidence that, when late onset Pompe disease is identified, parents experience problems including being 'patients-in-waiting', increased fear/anxiety, and uncertainty about their child's future and when to start treatment.¹⁰⁵

C12.7 Evidence will be needed to inform policy decisions about the incorporation of WGS into the conventional programmes of newborn screening. The types of evidence required about the utility of WGS for newborn screening include:^{100,101,103}

- > accurate interpretation of variants identified (ie distinguishing disease-causing and benign variants of all genes screened)
- > test sensitivity, specificity, and positive predictive value, taking account of different ancestries in the population
- > cost-effectiveness (immediate and longer-term costs)
- > an assessment of lives saved and quality of life gained
- > finding the most helpful approach to integrating family history information, or previous genetic findings in the parents, with what is found by WGS of the infant
- > the impact on children, parents and families
- > public acceptability
- > resolution of ethical and policy issues (disclosure of incidental findings; ownership, storage and sharing of genomic data, potential to exacerbate health disparities etc).

¹⁰⁰ US President's Council on Bioethics. The changing moral focus on newborn screening 2008 <https://repository.library.georgetown.edu/bitstream/handle/10822/559367/Newborn%20Screening%20for%20the%20web.pdf?sequence=1&isAllowed=y>

¹⁰¹ Howard HC, Knoppers BM, Cornel MC et al. Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. *Eur J Hum Genet* 2015;23:1593–1600.

¹⁰² Friedman JM, Cornel MC, Goldenberg AJ et al. Genomic newborn screening: public health policy considerations and recommendations. *BMC Med Genomics* 2017;10:9–21.

¹⁰³ Genetic Alliance UK. Fixing the present, building for the future: newborn screening for rare conditions. GA UK, 2019. <https://geneticalliance.org.uk/wp-content/uploads/2020/01/Newborn-Screening-Report.pdf>

¹⁰⁴ NHS Cambridge University Hospitals. Pompe (inherited metabolic disorders). <https://www.cuh.nhs.uk/our-services/pompe-inherited-metabolic-disorders>

¹⁰⁵ Pruniski B, Lisi E, Ali N. Newborn screening for Pompe disease: impact on families. *J Inherit Metab Dis* 2018;41:1189–1203.

8 Newborn screening recognition of MCAD deficiency

Alice, the first child of teenage parents tests positive on newborn screening for MCAD deficiency (medium chain acyl CoA dehydrogenase deficiency, MCADD). She is well and the parents are informed about the diagnosis and given guidance about how to prevent metabolic decompensation in the event of dehydration, fever or other illnesses. Alice's mother becomes very anxious and concerned about how to manage her baby when Alice 'possets' (small regurgitations of milk) or becomes 'snuffly'. Her parents do not live nearby and are not available for practical support. She brings the baby to the emergency department for very minor episodes and is difficult to reassure. The baby is admitted overnight on two occasions, to provide reassurance rather than from any clinical indication.

The baby's father is much more relaxed, being perhaps overly reassured by the information that as many as half of those affected 'biochemically' never run into any problems: he is 'optimistic'. The health visitor becomes concerned about the resulting tensions between the couple and considers placing the infant on the risk register.

Key points

- > This case demonstrates the practical difficulty of managing the diagnosis, especially for inexperienced parents. Families will differ greatly in the amount and type of support they require.
- > The ethical issues arise not so much from considering whether or not to screen for MCADD but about the appropriate package of information and support that must be made available not only through the programme itself but additionally by the local community and primary care services.
- > Setting the biochemical threshold is also critical, with the need to balance sensitivity against the positive predictive value of the test.
- > Too many biochemical diagnoses made without clinical manifestation will detract from the programme.
- > Harm can be done if the newborn screening is considered simply as a testing service without a very full consideration of the whole programme, including the implications of a diagnosis for families and local health and social care services.



9 Late diagnosis of methylmalonic acidaemia (MMA)

Neville, aged 3, has a history of lethargy, weight loss and poor muscle tone. After several visits to his GP, he is referred to the local district general hospital and is admitted to the paediatric ward. He has started to feed poorly and has occasional episodes of vomiting. Routine investigations are inconclusive and he is discharged home after 1 week without a diagnosis. After being sent home he seems relatively well for the first few days but then develops a cold. Over the following 24 hours his breathing becomes rapid and he stops feeding. Neville's parents bring him back to his local hospital in the early evening. He is admitted and treated with intravenous fluids and antibiotics and discharged after 2 days.

One week later Neville becomes increasingly drowsy and is again taken to hospital. On this occasion he is seen by another doctor who has experience of metabolic disease who discusses his case with the regional specialist in inborn errors, who arranges for further investigations. A diagnosis of methylmalonic acidaemia is then quickly made by the specialist laboratory and he is transferred to the PICU at the regional centre. By the time he reaches the unit, Neville is very ill, has encephalitis, is acidotic, and has a high blood ammonia. He requires major intensive care support, including ventilation and haemofiltration. Although he makes a gradual recovery, and commences on a low-protein, high-calorie diet, vitamin B12 and L-carnitine, he suffers serious and permanent brain damage.

It is explained to his parents that Neville has a serious inherited metabolic disease which, in his case, is associated with neurological and renal disease and needs lifelong treatment in order to limit further complications.

Key points

- > Many inherited metabolic diseases can present in similar ways to other common childhood conditions. Seemingly innocuous symptoms, such as vomiting or raised temperature, can be dismissed by health professionals.
- > Awareness of metabolic disease is needed in the adult and paediatric medical communities to ensure appropriate and timely investigation and management.
- > Once the diagnosis is made, simple clinical management can significantly improve outcomes with specialist advice and can mitigate longer term complications. Failure to make a diagnosis may lead to significant morbidity and mortality.
- > Although metabolic diseases can present at any age, they can present after the newborn period and often require specialist management.
- > Parents of children with inherited metabolic diseases may require support in managing their children's symptoms appropriately to avoid over medicalisation.

C13. Prenatal genetics

C13.1 There are three potentially problematic contexts in which important genetic information may be known about a child before they are born.

- > When a genome-based test is performed in an attempt to diagnose a fetal abnormality, perhaps detected on fetal ultrasound scans, genetic abnormalities of uncertain significance or unrelated to the original indication for the test may be identified. This will be especially true if fetal WES or WGS is carried out, and will arise less often if CMA or more targeted molecular testing, such as a gene panel, is used.
- > When fetal carrier status is revealed by prenatal diagnosis for autosomal recessive or sex-linked disorders or for unbalanced chromosomal rearrangements, many parents will want to know the results in full and will therefore be aware of the carrier status of their healthy infant (see C9 and case study 5).
- > When prenatal diagnosis is performed for a late-onset disorder and the pregnancy is continued after the fetus is predicted to be affected. In the context of Huntington's disease, this usually reflects a change of heart in the pregnant woman or couple regarding their intention to terminate an affected pregnancy, especially if the results are delayed. This occurs in about 10% of pregnancies in which prenatal testing has shown that the fetus is affected or at high risk¹⁰⁶ and can lead to a very difficult situation for the family once the child is born. Unfortunately, families then often break off communication with the genetic counselling team despite their need for support.

C13.2 The same difficulties do not arise when a couple continues their pregnancy after the prenatal diagnosis of a congenital disorder or a disease of early childhood onset. Indeed, some families prefer to know in advance whether their child will be affected by a familial condition without any thought of terminating the pregnancy in the event of a positive result. The contexts are very different. It is also important for maternity services to ensure that women and couples who have decided to continue their pregnancy have that decision respected, when the fetus has been diagnosed with a chromosomal condition (such as an autosomal trisomy) or a malformation (whether it is regarded as lethal or potentially treatable). If they are questioned at each clinic attendance about this decision, they can feel that their wishes are not being respected and that staff are trying to persuade them to terminate the pregnancy.

C13.3 In some cases, it would be entirely reasonable for the laboratory report of fetal WES/WGS only to report clearly pathogenic variants that relate to the indication for testing. Any incidental findings, or findings of uncertain significance, that are revealed in the analysis could be made available to the parents and/or a paediatrician after the birth of the child, if they had indicated their wish to access such findings when the test was discussed with them and they gave their original consent to the test. More

¹⁰⁶ Wadруп F, Holden S, MacLeod R et al on behalf of the UK Huntington's Disease Predictive Testing Consortium. 2019. A case-note review of continued pregnancies found to be at a high risk of Huntington's disease: considerations for clinical practice. *Eur J Hum Genet* 2019;27:1215–24.

information about prenatal testing and pre-implantation genetic testing can be found in new guidance for clinical practice.¹⁰⁷

C14. Looked-after children and children adopted from care

- C14.1 Looked after children are likely to have greater health needs than their peers^{108,109,110} in addition to other possible challenges such as adverse prenatal exposures and postnatal neglect or abuse. Many children needing placement with a family have health problems. These include physical disabilities, developmental delay, learning difficulties, behaviour problems and genetic conditions (including being at risk of an inherited disorder). Knowledge of personal and family health information may be important to understanding a child's present or likely future health needs but, for children in the care system, access to this information may be lost, the information may be misunderstood, or it may be withheld by parents.¹¹¹
- C14.2 The reason for testing is important to consider. Diagnostic testing is suggested when an individual has a manifest health problem whether physical and/or developmental, and a genetic test result may make or confirm the diagnosis. When children are in the looked-after system, this testing may need the support and consent of birth families or social workers and the local authority. In general, the starting point for considering genetic investigations in a looked-after child would be to take the same approach as for any other child. If the clinical process is to be managed differently, there should be a clear reason for this departure from standard practice. It may be difficult to obtain samples from a child's biological parents so, in many cases, the advantages of trio WES or trio WGS may not be available.
- C14.3 If a child taken into care shows signs of delayed development and the cause is unclear – whether this is the result of genetic constitution, prenatal exposures or postnatal factors – it is important for the limitations of genetic testing to be appreciated.¹¹² A period of observation may be helpful. Genetic testing will often have a role in the investigation of developmental delay but its limitations must be kept in mind. For example, chromosomal microarray testing of a child with neurodevelopmental problems will provide no information about alcohol exposure *in utero*. Uncertainty may be introduced if a copy number variant (CNV) is found that is of reduced penetrance or of uncertain significance (ie a chromosomal VUS). Such uncertainty may be more of an obstacle to securing permanence for children (through placement with adoptive parents) than the developmental delay itself, especially if it introduces concerns about

¹⁰⁷ 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.

¹⁰⁸ Children in Care Statistics. NSPCC, 2014. <https://www.nspcc.org.uk/preventing-abuse/child-protection-system/children-in-care/statistics/> (accessed 8 December 2015).

¹⁰⁹ Bazalgette L, Rahilly T, Trevelyan G. *Achieving emotional wellbeing for looked after children: a whole system approach*. London: NSPCC, 2015.

¹¹⁰ *Promoting the health and well-being of looked-after children. Statutory guidance for local authorities, clinical commissioning groups and NHS England*. Department for Education and Department of Health, 2015.

¹¹¹ Barnes C. *Genetic testing and adoption. Practice note No. 50*. London: British Association for Adoption and Fostering, 2006.

¹¹² Parker MJ, Teasdale K, Parker MJ. The genetic assessment of looked after children: common reasons for referral and recent advances. *Archives of Disease in Childhood* 2016;101:581–84.

future health, development or neuropsychiatric problems that cannot be resolved or assuaged.

- C14.4 There is a consensus that predictive genetic testing for a late-onset disorder present in a child's birth family should not be performed unless it has a direct health implication for that individual in childhood. This maintains a child's autonomy to decide for themselves, once 'mature', if and when they want the information. Predictive testing for a disorder likely to manifest in childhood is different as the child's future autonomy as an adult is not at stake; the decision will often be best made by the parents/guardians after appropriate genetic counselling but there might be unusual circumstances that would justify testing before a child is placed for adoption.
- C14.5 Where a child is being considered for adoption, it could be argued that the best interests of the child might be achieved through genetic testing for a disorder in the birth family, even where there would be no immediate health benefit. To support successful adoption, it is good practice to make as much information as possible available to prospective adoptive parents, and genetic testing that has already been performed should not be treated any differently in this regard. The question then arises as to whether it may be appropriate and in the child's best interests to make arrangements for testing for a genetic condition or genetic variant known to be present in the birth family, in the expectation that this would support matching and placement with a family who can support their individual needs, both present and future.^{113,114} Here, genetic testing can be seen as improving the chances of a successful placement. Prospective adoptive parents face multiple uncertainties about any child they adopt; the desire to reduce uncertainty, when this is possible, is understandable.
- C14.6 Opposed to these considerations is the argument that, while it would benefit children with 'good news' results, it may be even more difficult to find a placement for those with adverse results, who would then be further disadvantaged. The claim is sometimes made that genetic testing will enable a better 'match' between child and adoptive parents, although there is no evidence base to support this.¹¹⁵ A family willing to adopt a child at risk of an inherited disorder and to find out about their genetic status over time, as happens in other families, would appear preferable to a family that sets genetic conditions upon accepting a child. Testing for a VUS known to be present in the birth family would be difficult to justify under any circumstances.
- C14.7 It is difficult to specify circumstances in which it would be appropriate for genetic tests to be undertaken for adoptive children, where they would not usually be carried out at that stage for children in the care of their birth families. We recommend caution for carrier testing (of future reproductive significance only) and even more so for predictive testing for later onset conditions (with no useful medical interventions in childhood). Where decisions depart from usual practice, there would need to be clear and explicit

¹¹³ Jansen L, Friedman Ross L. The ethics of pre-adoption genetic testing. *Am J Med Genet* 2001;104:214–228.

¹¹⁴ Arribas-Ayllon M, Clarke A, Shelton K. Professionals' accounts of genetic testing in adoption: a qualitative study. *Arch Dis Child* 2020;105:74–79.

¹¹⁵ Arribas-Ayllon M, Shelton K, Clarke A.. Can genomics remove uncertainty from adoption? Social workers' and medical advisors' accounts of genetic testing. *Br J Social Work* 2021;52:719–37. doi: 10.1093/bjsw/bcab017

reasons for this. We are not aware of any circumstances arising in which the predictive testing of a looked-after child for Huntington's disease or a similar neurodegenerative disorder has been justified.

C14.8 Multi-party and multidisciplinary discussions may be useful at an early stage of the child's health assessment, with consideration of whether testing might have a legitimate role. These discussions may include medical advisers, paediatricians, social workers and prospective adoptive parents, alongside genetic counsellors and geneticists, birth families, carers and the children concerned. It may be appropriate to arrange referral of prospective adopters for genetic counselling, as discussion in a large, multi-professional group may not do justice to the sensitivities involved. These discussions, in one format or another, allow concerns to be addressed openly, and for exploration of the additional potential risks to the child that may result from genetic testing. Such open discussions often help understanding and support informed decision-making, resolving difficulties without the need for genetic testing. It may also allow signposting to appropriate support groups, third sector organisations or systems such as the hospital's clinical ethics committee.

C.14.9 Testing (C16) in an attempt to determine the genetic ancestry of a looked-after child on the premise of aiding in their placement is a fundamentally flawed practice and should be strongly discouraged.^{116,117}



10 Microarray results in adoption

Sam, a 2-year-old boy, is seen by the adoption medical adviser with his foster parents, as part of an assessment for adoption. He has been diagnosed with global developmental delay by a community paediatrician, and is under the care of the multidisciplinary team, including physiotherapy and speech and language therapy. A chromosomal microarray is undertaken as part of the investigation into Sam's global developmental delay and shows a copy number variant. This is a variant of uncertain significance and parental testing is recommended.

Despite significant input from social workers, the birth parents have not attended to provide samples to establish if the variant is *de novo* or inherited. Family-finding social workers are concerned that this genetic variant will impact on their ability to find a permanent family for Sam, as 'there is too much uncertainty about what this variant means for Sam going forward'.

¹¹⁶ Lucassen AM, Hill CM and Wheeler R. 'Ethnicity testing' before adoption; a help or hindrance? *Arch Dis Child* 2010;96:404–405. doi:10.1136/adc.2009.168989

¹¹⁷ Merredew F and Sampeys C (eds). *Promoting the health of children in public care*. British Association for Adoption and Fostering, 2015.

10 Microarray results in adoption (cont)

Key points

- > Finding a permanent family for Sam that can support his complex needs should be the priority.
- > Establishing whether the variant is *de novo* or inherited will not have implications for Sam's immediate care needs, which are well characterised, given that he has a good support package in place.
- > The family-finding social workers have misunderstood the significance and implications of clarifying the nature of the variant: even if the inheritance pattern is confirmed it is unlikely to resolve uncertainties about Sam's future prognosis. Speaking with the clinical genetics team could help resolve some of these misunderstandings.
- > Repeated efforts to obtain information or samples from the birth parents could heighten distress under already difficult circumstances. A balance needs to be struck between causing distress to birth parents with repeated requests on behalf of a child who may have been forcibly removed, with the potential benefit for the child of receiving more definitive information to guide prognosis and future care. Retaining a relationship with the birth parents may also be important for Sam when he is older.

C15. Recontact issues and infrastructure

C15.1 Genomic investigations frequently identify genetic variants of uncertain significance. The interpretation of such variants will often change over time as more data become available. A VUS may then be recognised as more clearly pathogenic or more clearly benign. Such altered interpretations of a variant may have direct implications for the health and the healthcare of individuals in whom that variant has been found. However, there may be no ready mechanism for passing this altered interpretation to those who need to be aware of it, ie the patients and the medical professionals caring for them.

C15.2 More appropriate solutions to the problem of variant re-interpretation need to be found. One possible approach is for genomic medicine laboratories across the UK to keep a record of all reports issued so that, when a clinically important reinterpretation of a variant occurs, all those cases potentially impacted are readily identifiable. The clinicians who referred those patients could be passed this information by the relevant laboratory and they, in turn, could contact the patient to discuss the implications.

C15.3 This requires substantial investment in appropriate IT infrastructure. Alongside this a system in primary healthcare for triggering the communication of personal and family

genetic information when a child becomes adult or when an adult moves from one general practice to another could promote a much more effective use of family history and genetic information within healthcare in the UK.



11 Testing children for *BRCA*?

Ann is diagnosed with terminal breast cancer aged 44, after having investigations which reveal a primary breast cancer and multiple metastases in her spine and brain. A pathogenic *BRCA2* variant is identified. As the cancer has spread to her spine and brain, and she is not responding to chemotherapy, she knows that her prognosis is poor. She asks for her children, two girls aged 8 and 10, to be tested so they have this information for the future and she can be comforted knowing they would know whether they are at risk or not. Although she has confidence in her husband to look after her children after she has died, she feels that he would not be able to cope with them having *BRCA* tests once they were older. She feels that it would be better for the family if the girls' *BRCA* status could be clarified while she is still able to participate.

After discussions with the clinical genetics team, including a genetic counsellor who helps set up a structure for future communication (and also with a counsellor, who helps Ann to come to terms with her own death), the children are not tested for *BRCA* but are put on review for discussion in their late teens.

Key points

- > The mother's request for testing is to ensure her family has the information they need for the future as she will not be around to prompt them. Setting up a commitment to review the children's case in their late teens and putting other measures in place provides Ann with sufficient reassurance that the options for testing will be fully discussed and that testing will be carried out at an appropriate time.
- > As well as arranging for future review, letters from Ann are kept for future reference by the unit and by the family, so that they can be proactive about seeking future review. Copies of these letters and discussions are also sent to the GP with a request to put an alert on their file and, in the case of a move to another practice, for the alert to go with it.
- > This mother has valid concerns about possible future house moves and practical obstacles to referrals in the future, such as her husband not knowing who to contact or having difficulty in broaching the topic of *BRCA* gene tests, as well as limitations in the understanding of their risks and their options by young adults.
- > This illustrates the importance of communication, empowering patients to trigger recontact but also trying to put safety nets in place for them. A system to provide a recontact service is becoming increasingly important and urgent.

C16. Direct-to-consumer genetic testing

C16.1 Direct-to-consumer (DTC) tests are now widely available to the public, and there is currently no legislation preventing parents from buying tests for use on their children. Different companies offer to provide tests to reveal people's ancestry and some offer testing for additional health information. Results from the latter need to be treated with care for a variety of reasons: 'risk' information – information about disease susceptibility – will not necessarily mean that a person will develop a particular condition. Information of this sort is open to frequent misinterpretation, as concepts such as relative risks, conditional information and the measures that describe the performance of a test (sensitivity and specificity, and positive and negative predictive values) are often not well understood, even by health professionals.¹¹⁸ Furthermore, test provider companies have different policies in relation to pre- and post-test counselling. In relation to testing for children, parents are able to submit their child's samples and then receive their children's test results, as well as their own. Parents may therefore receive predictive information about adult-onset conditions for their children, or at least information about disease susceptibility if it is not firm enough to count as predictive information. Questions will then arise as to how this information is best managed in the clinical setting. Indeed, a recent report has recommended that the government consider limiting direct-to-consumer access to genomic tests for asymptomatic children to those that meet the criteria of the UK National Screening Committee.¹¹⁹

C16.2 The position statement on direct-to-consumer (DTC) genetic testing from the BSGM and Royal College of General Practitioners advocates treating DTC test results with caution.¹²⁰ The underlying ethical concerns about predictive testing for adult-onset conditions in children remain the same for DTC testing, with the added caution that many such tests, especially polygenic risk scores, have little or no demonstrated clinical utility and so would often be regarded as illegitimate in a healthcare context. This is especially true for pre-implantation or prenatal testing of fetal polygenic risks.¹²¹ With DTC testing, parents may already have an increased risk result and may request clinical follow up. Routine follow up in such cases should not be an expectation; however, there may be circumstances where it would be appropriate to arrange clinical referral, especially in situations where NHS testing would normally be offered.

¹¹⁸ Horton R, Crawford G, Freeman L et al. Direct-to-consumer genetic testing. *BMJ* 2019;367:l5688 doi:10.1136/bmj.l5688

¹¹⁹ House of Commons Science and Technology Committee. Direct-to-consumer genomic testing. First Report of Session 2021–22. HC94.

¹²⁰ <https://www.rcgp.org.uk/-/media/Files/CIRC/Clinical-Policy/Position-statements/RCGP-position-statement-on-direct-to-consumer-genomic-testing-oct-2019.ashx?la=en>

¹²¹ Forzano F, Antonova O, Clarke A et al on behalf of the Executive Committee of the European Society of Human Genetics and the Public and Professional Policy Committee of the European Society of Human Genetics. 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>



12 'I want to know my children's future health risks'

Part one

Doreen, a 41-year-old single mother, decides that she would like to get more information about her genome, especially as she is aware that a number of family members have had cancer diagnoses and diabetes. She buys a direct-to-consumer testing kit (via the internet) and, at the last minute, thinks she might just as well include samples from her two children, David aged 13 years and Sara aged 10. The instructions indicate that all three just need to provide a saliva sample and she subsequently sends these off to the company. Three weeks later the reports for the family are available online for Doreen to review. Because of her family history of cancer, Doreen is particularly interested to find out about the option that relates to cancer predisposition and clicks on this link. There she discovers that a variant has been found in a gene called *MSH6* that is associated with a diagnosis of Lynch syndrome, which increases the risk of developing bowel and womb cancer. As this appears to be a very serious condition, Doreen wants to review her children's results straight away and is very upset that they indicate that Sara has inherited the same gene variant, although it does not appear that David has. After searching online, she learns that people with Lynch syndrome should have bowel screening from the age of 25 and, as she is already 41, she is worried that she may already have cancer. She immediately calls her GP to make an appointment for the following day and her GP makes a referral to her local clinical genetics service.

Key points

- > UK clinical genetics services are advised to exercise caution when asked about the results of direct-to-consumer testing and may decide to reject a referral. Testing for Lynch syndrome is available through NHS genetic services for people with a relevant personal or family history of cancer or where there is a proven familial genetic variant. Doreen's family history of cancer may not meet the clinical criteria for Lynch syndrome testing and she would therefore not be offered testing under the NHS.
- > In general, if a direct-to-consumer test has reported a variant in a high-risk cancer predisposition gene for which genetic testing is routinely offered and effective interventions are available, a referral would be accepted.
- > As Lynch syndrome is an adult-onset condition, a predictive genetic test is not usually offered until a child at 50% risk has reached adulthood and can decide the best time to proceed with testing. As there is no medical benefit to testing in childhood and delaying the test would protect the child's future autonomy and decision-making, this position is in line with the ethical principles underpinning this guidance.
- > The analytical validity, sensitivity and clinical utility of results generated by a direct-to-consumer test may be much lower than in clinical service laboratories. It is therefore possible that subsequent testing in the NHS – in a quality-assured laboratory – may

12 ‘I want to know my children’s future health risks’ (cont)

- > reveal that the result is incorrect.¹²² The original reported finding will have generated significant anxiety for the family and it can be difficult for patients to accept a second, negative result.
- > If the Lynch syndrome variant is confirmed, Sara (aged 10) will be recommended to start bowel screening at 25 years. The genetic test result will need to be discussed with Sara as she gets older. Issues to consider include: Who will inform and/or reiterate the result to Sara and when? What is the role in this process for family members, primary care and specialist services? Where will the genomic data be stored and who has access to it? In addition, there may be concerns that the information could be used in a discriminatory way in the future if, for example, Sara applies for health insurance or employment. Is there a risk of the information being ‘lost’ and Sara not being informed of her increased risk of cancer, and receiving recommendations for screening and other management options?

Part two

The genetics service arranges to see Doreen and, subsequent to NHS testing, the original result is confirmed and Doreen is referred for bowel screening. Since Doreen’s positive predictive test for an adult-onset condition has been validated by the NHS laboratory, this could influence Sara’s eligibility for a test. Doreen tells the genetic counsellor that she had originally told Sara the saliva sample was to determine the family’s roots and had said nothing about health information. She requests that Sara also has a confirmatory test.

Key points

- > If Sara has a confirmatory test, then she may become aware of the previous direct-to-consumer test result arranged by her mother. It is likely that, as her mother’s test was confirmed, Sara’s will be as well. Sara has had a predictive genetic test without the usual pre- and post-test genetic counselling and without the opportunity to make an informed choice about whether or when she would like to have testing. The clinical genetics service could at this point decline the request to confirm Sara’s result as this test would not usually be offered to children. However, as there is already a result available on Sara it may be that Doreen and Sara would benefit from genetic counselling to explore the associated implications, and to discuss when it might be appropriate to have the test.
- > As Doreen told Sara she was having an ancestry test, the genetics team will need to work with Doreen on how to manage the introduction of health and cancer risk information with Sara in an age-appropriate way.

¹²² Horton R, Crawford G, Freeman L et al. Direct-to-consumer genetic testing. *BMJ* 2019;367:l5688 doi: 10.1136/bmj.l5688

C17. Emerging or contentious developments

- C17.1 Emerging science and technologies can bring new solutions to health problems. While some of these will be pertinent to children, many are at such an early stage in their development that their clinical utility is not clear, and their effectiveness is unproven. Similar issues have arisen with earlier genetic technologies but have been amplified greatly by the move to genomic technologies.
- C17.2 Additional challenging issues include how best to manage the storage of, and access to, large quantities of personal data; the transmission of information within families; and inequities in health and healthcare.
- C17.3 Following a diagnosis is the desire for disease management, treatment and even cure. As more is understood about genetic diagnoses, the natural history of the associated clinical conditions and the underlying mechanisms of disease, it is likely that treatments will emerge. This may generate additional pressure to undertake testing at earlier points in childhood. Careful review of the benefits of treatment and the influence of treatments on the natural history of the specific condition will need to be balanced with any potential harms. It will be an important professional responsibility to remain alert to the potential scope for the emotional and financial exploitation of vulnerable individuals and families through an economy of inflated expectations and false hopes.
- C17.4 While genetic testing has in the past focused largely on single gene disorders, there is now growing interest in the application of genomic technologies to achieve an understanding of the many common, complex disorders (such as the common cancers, cardiovascular and cerebrovascular disease, diabetes mellitus, hypertension, Alzheimer's disease, many inflammatory disorders). There is great interest in how the interaction of genes and environment affects disease. The use of 'polygenic risk scores' in research settings to quantify these effects is an active area of research, motivated by a wish to improve the understanding of the underlying disease mechanisms. It remains uncertain whether some useful clinical applications will emerge for the modest shifts in risk estimates that polygenic risk scores for these complex diseases can generate, given that the heritability of the common complex diseases is often around 40–50% and the fraction of this that PRSs can incorporate is usually less than half of that.
- C17.5 Gene editing is the technology used to modify specific sequences of DNA. The underlying concept is that one stretch of genomic sequence can be removed and replaced by another sequence. This is in widespread use in the research laboratory but in principle it could also be used therapeutically. A sequence containing a specific pathogenic variant could be replaced with the normal protein-coding sequence, or a section of regulatory sequence could be altered. These technologies hold great promise, initially for somatic gene editing as a treatment for an individual with disease. In the future, germline editing may become a reality, which has the potential to change the genomes of the embryos that are treated, as well as future generations. This remains highly contentious but has the potential to bring great health benefits. We must remain alert to signs both of progress and of potential harms as developments continue.

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