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Predictive genetic testing in children: where are we now? An overview and a UK perspective

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Many different professional guidelines have responded to the issue of predicting risk of disease, or future reproductive risks, in children through the use of genetic tests.

In 1994, the UK Clinical Genetics Society (CGS) [1] recommended that such testing should only be done if the onset of the condition was likely to occur in childhood or if there were useful medical interventions that could be offered to treat, delay the onset, or ameliorate the course of the disease. Twenty-six further national and international guidelines (reviewed by Borry et al. [2]) similarly recommend that testing should be deferred until such time there is medical benefit, or until the child is old enough to make an autonomous decision [2–4].

Despite this almost unanimous guidance, clinical practice suggests that predictive genetic testing does occur in childhood and that practitioners can find it difficult to know how to respond to parental requests for genetic testing [5, 6]. This, and the expansion of genetic services over the past 2 decades prompted The British Society of Human Genetics (which now incorporates the above mentioned CGS, as well as genetic counsellor and laboratory specialist societies) to call for a review of their 1994 guidance to see if, and how, these should be updated.

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Most of the guidelines on childhood-testing base their recommendations on the need to protect children's best interests, and conclude that these are not served if there is no medical benefit to be gained from testing. Potential adverse psychosocial consequences, including altered parent–child relationships, anxiety, possible discrimination (for example, by the insurance industry), depression and altered self concept, are cited as possible harms and reasons to defer testing [7, 8].

Although professional guidelines have been unanimous in their recommendations, the debate has also acknowledged both potential benefits of childhood-testing for adult onset conditions and potential harms of postponing testing until adulthood [9–11]. It has also acknowledged that the guidelines reflect a cautious approach, based on largely theoretical concerns, and that they should be reviewed once further research evidence about the harms and benefits of testing has been gathered. Therein lies a problem however; practitioners have been reluctant to test on a routine basis, and more importantly perhaps, to study the consequences of testing in the rare cases where such testing does take place, because of the very existence of the guidelines.

Further, although there is broad consensus, there are also subtle differences between the guidelines. For example, guidance issued by the European Society of Human Genetics [4] suggests that a predictive genetic test in childhood may be indicated if the onset can be expected at this age AND if medical measures can be taken to prevent or treat the disease or complications, whilst the 1994 CGS guidelines suggest it might be appropriate if the onset of condition is in childhood OR there are useful medical interventions that can be offered [1]. Testing for conditions such as Li–Fraumeni syndrome (which can have an onset in childhood, but for which there are no evidence based

surveillance or treatment options), would therefore be in accordance with UK but contravene European guidance.

It is worth remembering that in the early 1990s (when many childhood testing guidelines were first compiled), the number of available genetic tests was small. Much of the debate focused on testing for Huntington's disease (HD), an adult onset neurodegenerative disorder with, as yet, limited beneficial intervention, surveillance or treatment. Of adults coming forward for testing, only a small proportion (15%) decided to pursue predictive testing once the advantages and disadvantages of such testing had been discussed with them [4, 12, 13]. This was in contrast to the vast majority of the same group indicating—prior to the discovery of the HD gene—that they would like a predictive test where one to become available [12]. The discrepancy between those expressing an initial interest, and actual numbers tested was a major factor in the cautious approach to predictive testing in childhood. It was reasoned that many children might grow into adults who would decide not to be tested, and that this choice would be removed from them if their parents had them tested as children. Thus, the concern about a child's future autonomy was heavily influenced by these data. The CGS report of 1994 also held that, on balance, the risk of harm was likely to be underestimated by parents and non-geneticists whilst the benefits of the test, for example the usefulness of the knowledge, or the usefulness of surveillance, were likely to be overestimated. Blood tests in children are usually done to ascertain something about their state of health—or disease—at that point in time. Genetic tests are more likely to predict possible health consequences (or reproductive consequences) at some point in the future, perhaps not even till adulthood. Was this distinction clear to parents? Might they think that such knowledge would decide surveillance, treatment or lifestyle choices in childhood? Would they be aware that a test result could affect family relationships? Guidelines about genetic testing in childhood served to highlight these issues and to encourage at least some consideration of possible adverse consequences before testing.

The ensuing years have seen genetic services, and the number of genetic tests, expand substantially. Furthermore, genetic testing has spread outside the confines of the small speciality of clinical genetics. For example, national neonatal screening programmes, oncology and haematology services are now involved with genetic testing and general practitioners are increasingly asked about genetic tests. Neonatal screening programmes for autosomal recessive conditions such as the haemoglobinopathies, cystic fibrosis and rarer genetic disorders such as MCAD (Medium-chain acyl CoA dehydrogenase) deficiency have now rolled out across the UK. Such screening relies on genetic tests to diagnose affected children in the newborn period. However, in doing so, many entirely healthy unaffected 'carrier' children are also identified. The UK National Screening Committee has concluded that the carrier status of newborns should be disclosed to their parents. In part this is because the detection of carriers might facilitate preconceptual risk counselling through identification of carrier parents by cascade screening. There was also concern that non-disclosure would mean withholding information from parents unnecessarily, certainly without clear evidence that such disclosure would be harmful. Further, disclosure to parents would be a more effective way of ensuring that the child would find out about her possible future reproductive risks than by assuming health services would inform young adults of results found during the neonatal period. Here then was an example of routine genetic testing in childhood where there were no medical or therapeutic consequences for the child. However this has lead to further apparent inconsistencies: Parents are informed of the carrier status of their children born after the introduction of neonatal screening programmes whilst their elder children are not usually tested because there are no medical interventions to offer that child, and there is no risk of the disease during childhood. To date, clinical genetics services have held that this difference in practice is legitimate because the detection of healthy carriers is a 'side-effect' of neonatal screening whereas a carrier test for other siblings would be intentional, yet of immediate benefit to the child or her family.

Although there has been relatively little research investigating the long term sequelae of the discovery of carrier status in childhood, that which has been done—albeit on small numbers of families, suggests that the mother/baby relationship, anxiety or wellbeing was not adversely affected by testing [14], and that most parents are interested in the carrier status of their children and want their children to be tested before adulthood [15]. However, other studies also suggest that communication of carrier status between parent and carrier does not always take place effectively; for example, a long term study of the impact of carrier testing for x-linked conditions in childhood found that a significant proportion of daughters had not been told about their test result [16].

Surveys of practice have found that childhood-testing before likely onset of a disease (or its prevention or surveillance) does happen: clinicians believe that requests must be considered on an individual basis and adopt a cautionary but variable position—some support the 'rule of earliest onset' (testing at or just before, the youngest age that symptoms manifest), others favour a wider parental discretion [17–20]. An international survey of practice found that testing in childhood did occur before likely onset, treatment or surveillance, since although clinicians agreed with the guidelines they also believed each case

must be considered individually [21]. Whilst some of these studies were hypothetical questionnaire studies with 'would you?' rather than 'have you?' questions, anecdotal reports from UK practice indicate that testing in childhood does happen on a regular basis and particularly so within UK cancer genetics services.

Two regular UK meetings of relevant health care professionals indicate that parents regularly request testing of their children well before a medical intervention might be offered. The UK Cancer Genetic Group (CGG), a constituent body of the British Society for Human Genetics addressed the issue of childhood genetic testing for cancer predisposition syndromes at their annual conference in May 2007, at a conference held jointly with the Dutch Cancer genetics group. Attendees reported regular requests from parents to test their children, citing their anxiety, or an interest in knowing what genetic predisposition they have endowed their children with [6].

The UK Genethics Club (www.genethicsclub.org), a multidisciplinary forum for the discussion of ethicolegal issues in clinical genetic practice, also indicates that clinicians throughout the UK are regularly asked about childhood predictive genetic testing and that they sometimes find it very difficult to know how best to handle such requests. Parker in this issue of the journal gives a detailed description of the types of cases brought to genethics club for discussion [22] Clinicians are aware that an assessment of medical best interests may be too narrow, and that there may be wider best interests at stake. Although they may not be best placed to judge these wider interests, they also see themselves in a gatekeeper or vetoing role. In response to the 1994 UK guidelines the Genetics Interest Group argued that "Parents are responsible for welfare of children and at the end of the day most are better equipped to decide what is in the best interests of their child and family than outsiders are" [23].

Within cancer genetics, requests for childhood testing that cause dilemmas for the clinician appear to fall into two broad groups:

(a) Those where the onset of the disease is not till adulthood. For example, hereditary breast (BRCA1/2) or bowel (HNPCC/Lynch) families.
(b) Those where the onset is usually, or possibly, in childhood, but where testing is requested well before the average age of onset. For example, requests for testing babies/infants for Familial-Adenomatous-Polyposis, von-Hippel-Lindau disease or Multiple endocrine neoplasias, or where there is no evidence based intervention to offer as a result of testing. For example, predictive testing for Li-Fraumeni syndrome.

Table 1 shows three anonymised scenarios of the types of cases which clinicians can find difficult to manage. These types of examples are explored in greater detail in other papers in this issue. Cases discussed at CGG and at Genethics Club also indicate that the interpretation of the guidance varies between, and sometimes within, different genetic services. For some, the guidelines have taken on a quasi legal status; a rule that should not be transgressed for fear of legal repercussions; for others they serve to highlight possible risks to be discussed, but are not seen as prohibiting testing. One UK regional genetics service representative reported at one such meeting that approximately ten cases had been tested in their service 'in breach' of guidance, indicating that some view guidance as perhaps more proscriptive than it was designed to be. Fenwick in this issue of the journal describes how the existence of professional guidance can create this hazard and this is perhaps exacerbated because of the plethora of international publications with the same conclusions [24]. In the UK certainly, this may have an indirect effect on the legal interpretation of any cases examined by the courts; If

Table 1 Three anonymised scenarios of the types of cases arising in cancer genetics which clinicians can find difficult to manage. These types of examples are explored in greater detail in other papers in this journal

Peter has attenuated familial polyposis with a known mutation in the APC gene. Both he and his father have had bowel surgery in their 20s. Peter has a 1 year old son—Ethan, and would like him to be tested so that the family can prepare him early for hospital visits if he has inherited the condition. Ethan is unlikely to be affected until his late teens. Peter and his wife are persistent in their request for testing now and cannot see why it should be delayed until Ethan is older. They know that practitioners will agree to test him before he is fully competent to decide for himself and therefore cannot see why they cannot be relieved of their 'unbearable uncertainty' now
Shane is 6 months old and in foster care awaiting adoption. His mother has drug and alcohol dependency. His father lives elsewhere but is known to have Multiple endocrine neoplasia type 1 (MEN1). Social workers have asked that Shane has a predictive test for MEN1 so that prospective adopters are better informed. Shane would not be offered any screening for the condition until approximately aged 10 because the earliest onset of the disease is not till after this age. The genetics service thinks that testing now would not be of medical benefit. See http://www.bbc.co.uk/radio4/science/ethicscommittee_20080820.shtml for detailed debate on this case
Rupert has recently been shown to have inherited the BRCA2 mutation present in other members of his family. He and his wife Jayne attend the genetics clinic to ask that their 3 sons aged 7 9 and 11 are tested with mouth swabs to see whether they have inherited the gene fault. They wish to know what they have endowed their children with and enquire about private or internet based testing when they hear that current guidelines suggest their sons should not be tested yet

geneticists were seen to have a consensus on the approach to be taken to cases where testing was requested in childhood then the courts might interpret that this serves to define the limits of good practice. At the same time, practitioners may be faced with parents who do not understand the reluctance to test their child and who view current guidelines as too prohibitive. This is perhaps not surprising in the context of a shift in health care approaches over recent years to one which is more 'consumer' focussed and where parents can access testing privately or over the internet without too much difficulty.

Recent reports of predictive genetic testing for cancer of a child under a court order [25] in the face of clinicians' and medical ethicists' disagreement, provides further evidence of a disparity between lay and professional opinions about childhood-testing which need to be addressed in up to date professional guidelines. Given that the guidance on genetic testing was largely based on the experience with HD, is this approach too cautious in cancer genetics? Most cancer syndromes have some surveillance or treatment that can delay onset or improve treatment of the condition. The uptake of predictive testing in adults for cancer syndromes such as Lynch/HNPCC or BRCA1/2 is much higher than for Huntington's [26].Therefore, urging caution on the basis that a child may not grow into an adult who would want such testing carries less weight. On the other hand, most adults have a predictive genetic test for cancer predisposition around the age at which screening or other interventions are available. For cancer conditions such as familial polyposis (FAP), in which the onset is usually in childhood so that testing is routinely done before a child is [fully] competent to decide for themselves. Whilst they are likely to be more involved in this decision at the age of 11 than they are at the age of 1, and this is of course desirable, a delay at the age of 1 can not be justified on the grounds of concern about future autonomy.

What is clear for the UK at least is that there is no national collation of numbers of requests for predictive testing in childhood, numbers tested, reasons behind such requests, or long term follow up of the sequelae of decisions made. Attempts to research this systematically have failed at the research funding stage because funders have thought it inappropriate to study an area apparently already clearly delineated by professional guidance.[1]

Despite the apparent differences in practice referred to above, a remarkable degree of consensus was achieved at the BSHG workshop in March 09. Twenty-five experts including representatives from the clinical genetics community, neonatal screening service, law, medical ethics, and social science discussed revised guidance. Where genetic testing is predictive rather than diagnostic, adopting a position of caution about such testing to allow time to highlight potential problems was still thought to be appropriate in 2009. Guidance should not be seen as a set of outcome rules which delineated what could and could not be done in certain situations. Rather guidance could be seen as a means to delineate a decision framework. A default position of caution would serve to ensure that decisions were adequately informed but in some situations practitioners might be persuaded of the potential benefits of testing more easily than in others. Practitioners should support families in maximising their child's autonomy, protecting them from harm and securing the best available care, rather than be seen as vetoing desired testing because of the presence of guidelines. Framing discussions more around the timings of a test rather than whether or not it could happen was also thought to be more conducive to such a support role. At the same time, health administration systems will need to be such that children who are not tested in childhood, can be offered appropriate testing when they reach adulthood.

Whilst larger and longer term studies delineating the sequelae of testing, or not testing, in childhood are clearly desirable, a short term outcome of the BSHG workshop has been to survey the current views and practices of UK practitioners as well as seek the opinion of the consultative panel of the Human Genetics Commission (HGC). The HGC is a UK government advisory group on genetics and its consultative panel consists of lay members who have experience of living with a genetic condition.

The outcome of these two exercises is awaited and will be incorporated into updated guidelines on the genetic testing of children for the UK.

[1] Personal experience of authors.

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