Clinical Ethics Committee Case 8:

Should we carry out a predictive genetic test in our young patient?

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Biographical Information
Dr Ainsley Newson is Senior Lecturer in Biomedical Ethics in the Centre for Ethics in Medicine at the University of Bristol. She has a PhD in Medical Ethics and Bachelors degrees in Science and Law. Her research interests include clinical and reproductive decision-making in genetics and synthetic biology. Ainsley is a member of the European Clinical Ethics Network, the Board of Trustees of the UK Clinical Ethics Network and the Editorial Committee of this journal. She has been a member of Clinical Ethics Committees for 6 years; and is a CEC member at the Royal United Hospital in Bath.

Introduction
This is the eighth of a series of cases provided and discussed by UK clinical ethics committees. All clinical ethics committees registered with the UK Clinical Ethics Network may submit a case, which is then discussed by another committee. To safeguard confidentiality, if a case is based on an actual clinical scenario, consent from *all* parties is necessary. To the same end, the committee referring a case will not be identified (as this would provide a geographical indicator of identity), but we do name the committee discussing the case. A member of the editorial committee attends the discussion of the case and writes the summary to be published in *Clinical Ethics*, once the discussing committee and the journal editors have approved it. Committees interested in participating should contact the Case Studies editor Ainsley Newson (ainsley.newson@bristol.ac.uk).

The Clinical Ethics Committee at Southampton University Hospitals Trust agreed to discuss the following case. The Southampton University Hospitals trust (SUHT) Clinical Ethics Committee (CEC) was established in 2000 and serves a large teaching Hospital in the South of England. Committee membership comprises hospital clinicians (doctors and nurses), a chaplain and a medical ethicist. The CEC provides a consultation service, education for hospital staff and offers review of hospital policies where ethics input is required. The committee meets monthly, but members of the committee are also available at times in between to receive referrals and give advice. In the nine years the committee has been operating it has discussed approximately 200 cases. 'Live' CEC consultations may take place at the bedside, at meetings of a small group from the committee, or by e-mail (with anonymised details). Cases have included end of life issues, refusal of treatment in adults and children and physician-patient (or family) conflict as well as genetic issues. All cases and notes of CEC deliberations are recorded and minutes taken of every meeting

Referral to the Clinical Ethics Committee: A request for genetic testing in childhood.

S, a five-year old boy, has recently been seen with his mother C in the paediatric outpatient clinic. Sadly his father N died from metastatic cancer a few months ago, aged 30 years. Other members of N's family have died in childhood or early adulthood from various forms of cancer. While N was unwell, it was discovered that he carried a mutation in the *TP53* gene associated with Li-Fraumeni Syndrome (LFS).

LFS is a cancer predisposition syndrome leading to a high risk of various aggressive cancers, including leukaemia, melanoma, soft-issue sarcoma and pancreatic, colon, brain or breast cancer. LFS runs in families and is inherited as an autosomal dominant trait, such that any child of a person with the *TP53* gene change will have a 50% risk of inheriting the same mutation and a resultant high chance of developing one of these cancers. The type or age of onset of these cancers cannot be predicted.

When N was unwell, his oncologists suggested that S be referred to a clinical genetics service for genetic testing for LFS. At that time the clinical team thought it was appropriate that testing should go ahead, however the laboratory that received the sample for testing let it be known that they thought it was not appropriate to test because S was a minor and that guidelines on genetic testing in children suggested such a test should not be done routinely. Testing therefore did not go ahead.

The genetics team then referred S to a consultant paediatrician, recommending annual surveillance in accordance with professional guidelines written by a paediatric oncology society. This surveillance includes a thorough physical examination, routine blood tests (which may reveal leukaemia, for example), abdominal ultrasound to detect intra-abdominal malignancy and other indicated organ-specific surveillance tests. However, none of these measures have been shown to be effective in reducing morbidity or mortality for LFS.

When we (the paediatricians) met S and his mother C in the outpatient clinic, we explained the surveillance programme, but indicated that a cancer, if it were to occur, might reveal itself between the annual checks, and might not be detected even if present. We discussed that there is little evidence that surveillance would improve the prognosis even if her son did carry the TP53 gene change. C was also warned that some screening methods, such as CT scanning, produce radiation in high doses and so could actually increase his risk of cancer if he was affected over and above detecting any abnormality. However, MRI scanning would be used when possible.

During this recent appointment, C expressed her disappointment that S was not able to receive a genetic test for LFS. She was finding it difficult to manage his at-risk status and was particularly worried that whenever he developed an illness, or abdominal pain (both relatively common in childhood), he would require potentially complex and unpleasant tests. C said that if she knew his gene status, not only would she have greater certainty about what the future held, but unnecessary investigations might be avoided.

We established that S was thriving and was not displaying any signs of ill health. We discussed the various issues with C, and although we felt that gene testing was a reasonable option we were concerned that to test now would deny S any say in the matter and that he might (when old enough) decide he would rather not know his risk status. On the other hand, we were also sympathetic to the idea of C's parental autonomy to make decisions that were best for her family. If S's status could be established now then he may be able to avoid further screening, although the uncertainty over the benefit of screening is also a difficult issue to resolve.

We are approaching the ethics committee with the following questions in mind:

1. Should S be tested now for Li-Fraumeni syndrome?
2. In cases like this, how should we balance the interests of S with those of C or their wider family?
3. If we decide not to test S, how should this be managed in the clinic and with S over time? Or, If we do test him, how should this result be disclosed to S and when?
4. How should intra-disciplinary conflicts, such as a disagreement between the laboratory and the clinical team, be handled in practice?

Response from the Southampton General Clinical Ethics Committee

Thank you for your referral, which we considered at our meeting on 6 May 2009. This case prompted an interesting discussion, particularly those aspects of the case which involved S's best interests and C's parental authority. You proposed five questions for consideration, which we used to structure our discussion.

Background

LFS is an inherited condition in which those who have inherited the faulty gene have a high risk of developing various aggressive cancers. A key clinical issue is variation in age of cancer onset, as this can present in children or adults. If a person has the relevant gene change (a mutation in the *TP53* gene) then he or she will have an extremely high lifetime risk of cancer and a considerable risk of cancer in childhood. For a woman, this risk is 85-90% in her lifetime - with most cancers arising before the age of 50. For a non-smoking man the lifetime risk of cancer is 65-70%, reflecting the increased risk of breast cancer that the gene change confers in women. The general population risk of cancer is about 30% but most of this percentage is due to cancers arising after the age of 60.

In children with LFS, there is a relatively high risk of cancer before adulthood. There is a peak for cancer onset in childhood and then an additional peak in adulthood. Cancers arising from this syndrome have, for example, been observed in children as young as three years of age. However, there is little to no evidence that any screening regimes have an evidence base proving their effectiveness. In reality, screening will provide a further mechanism for confirming an established cancer rather than offering a reliable method of detecting a cancer at a more treatable stage than it would be if presenting through symptoms.

There are some 28 national and international guidance documents relevant to genetic testing in children. There is remarkable unanimity amongst these documents: unless there is a medical benefit to testing, that is to say, unless the test will make any difference to the management of current clinical care of the child then it is preferable to delay testing until the child can decide for themselves. This is because the child may grow into an adult who does not wish to know his or her inherited risk and because there might be adverse psychosocial consequences to testing in childhood when no interventions can be offered as a result. Although a test may be technically easy, a presumption of caution where there is no medical benefit is appropriate in children. However, if it is going to be deleterious for a child as he or she grows up *not* to be tested, then testing should not necessarily be precluded, but the clinical team should ensure that such decisions are as informed as they can be.

Should S be tested now for Li-Fraumeni syndrome?

Had medical screening not yet commenced for S, given the lack of a good evidence base for this we would actually have recommended that it *not* commence at all. This is because screening may not provide the necessary reassurance; it could be practically difficult; it would be performed without clear guidance as to frequency; and could in fact be harmful to S. We would therefore be interested to know a

little more about why screening was considered for S in the first place, as in our view it may not be in S's current best medical interests.

If S had not already commenced screening, our answer to this question may have been different. That is, guidance would have recommended that as testing would not change S's clinical management, then it may be more appropriate to delay testing. But here a genetic test in S could lead to screening being ceased (there is a 50% chance of this), and this is a significant factor to consider in favour of testing. An alternative would be to withdraw the screening that has already started, but given that C is already disappointed with the previous decision not to test S, this may be seen as a further departure from her wishes.

In general, genetic testing may not be fundamentally different from other kinds of testing in medicine; however they are divisible into tests that are diagnostic of current health and those that predict future health. It can be tempting for parents to ask for predictive genetic testing in their children because they think that obtaining the information about a condition now will be helpful, even though that condition may not present for some time and even though there is no treatment for it.

We would therefore want to know a little more about C's rationale for requesting this test. This could be explored with her in more detail, in conjunction with a thorough discussion of the clinical context and professional guidelines. Why does C desire for S to be tested *now* as opposed to at some point in the future? A key factor to discomfort over predictive genetic testing in children is the weight of their future autonomy. But, as screening has commenced, is this enough to outweigh the other considerations? For example, S will continue annual screening for the foreseeable future.

S's competence is also relevant to this decision. There may be good reasons to delay testing S for the TP53 mutation until he can be more involved. But it will be possible to seek S's views on testing from a relatively young age, and he may be able to have more involvement in this decision than we may initially think – in particular he will be aware that his father has died and that he is having annual checks. S's experiences of LFS in his family will place him at a different level of understanding than any other 5 year-old. Additionally, were testing postponed until S reached adolescence, you would then also have to consider his potential involvement in testing at *that point* in his life, with all the other changes and challenges that adolescence brings.

We also discussed the potential for the test to change S's management. If, for example, S was found to carry the TP53 mutation, were he to then present with symptoms that could indicate a cancer, then the information about his genetic status might change the management of these symptoms. For example bone cancer is extremely rare in the young general population, but much more common in LFS. Knowledge of this increased risk may lead to a speedier diagnosis. But on the other hand, if testing was done at the time these symptoms presented, it would be considered as more of a diagnostic test which would be performed if clinically indicated.

In summary, we are not making a 'yes' or 'no' recommendation about testing, but there is a need for a frank discussion with C about timing. It would be important not to just grant this test immediately (taking this request at face value) but to explore C's reasoning behind her request in detail. If C goes through a sustained process of deliberation and still wants the test, and she understands the issues and alternatives to testing, then testing may be acceptable. For example, if C has requested the test for 'reassurance' then she needs to understand that there is a 50% chance she will not receive this. The key challenge will be to work with C to determine the best timing for the test.

In cases like this, how should we balance the interests of S with those of C or their wider family?
A consideration of interests is very important to this case. Any assessment of interests will have to take account of not just medical interests but social and psychological interests as well.

The interests of S and C may conflict. S's best medical interests would be to avoid screening if possible. This may justify testing. However his social and psychological interests would necessitate a consideration of whether S may choose to determine his risk status if testing was postponed until he was an adult. Many adults at risk of an inherited disease decide, on reflection, that they don't want to know their result. This is because there is a 50% chance of a 'bad' result being received. But many do appreciate knowing that the test is available. Therefore it will be necessary to weigh up the possible anxiety for S arising from him growing up at risk (which can have a significant impact on one's developing sense of personal identity), with the potential problems that may arise if he was tested and shown to carry the TP53 mutation. Weighing these in the balance, which may be preferable?

C's interests draw on her role as a sole parent who has lost her husband and faces the prospect of illness in her child. If they haven't already done so, the clinical team should discuss C's expectations of testing in some detail, including how she may react if a mutation is found. How is C currently coping with any symptoms of illness in S? Does she feel any concerns are taken seriously by medical staff? It may be that her initial desire for testing is not sustained over time and so it may dissipate once she has had additional time to reflect, in particular on the pitfalls of testing 'for reassurance.'

Exploring C's anxiety will also be important, as this may now be at a point where it may be better to test S, so as to relieve uncertainty. The nature of any anxiety, the effect that this is having on C's relationship with S and the potential for this to further manifest over time should be discussed with her. The clinical team should sensitively explore the possibility of C still experiencing grief and a consequent desire to feel in control of her situation. This exploration alone may also help to alleviate any anxiety, in particular by focussing on the previous decision not to test and whether now may be the right time to move forward with it or not.

In addition to C's interests, we should also be mindful that she is solely responsible for S and has the privilege of bringing him up to the best of her ability. For C, it may be that she needs as much knowledge as possible to do this. This authority has been reflected in some previous legal cases. For example, in the case of *Re T*[1](which involved parents refusing a liver transplant for their young son), Dame Butler Sloss commented that "the best interests of this child require that his future treatment should be left in the hands of his devoted parents."(at p249). We might therefore suggest that as C is taking a responsible approach to his care, her desire for testing should be taken seriously. Although this may appear to be a case of C's rights overriding S's future autonomy, taking a wider view of S's best interests may accept him being tested.

In summary, a consideration of S's and C's interests is necessarily a balancing exercise. It may be in S's strict medical interests to test, as there is a 50% chance that testing could cease the need for screening. Additionally, many of S's wider interests (such as an interest in good quality of family life) will be compatible with those of C. There is, however, a need for research to follow up children who have been tested in childhood, especially because practice guidelines are based on a hypothetical potential of harm.

If we decide not to test S, how should this be managed in the clinic and with S over time? Or, If we do test him, how should this result be disclosed to S and when?

If we do not test S, his current management in clinic would not change. However, it would be important to ensure that contact is maintained and that his status is explained to him when it becomes appropriate to do so.

If we do test S, disclosure to him should be up to C but with appropriate support from clinical services. C will require expertise and help from someone who is experienced in communicating with children, as there are sensitive and gentle ways in which disclosure can take place. The type of discussion to be held may change depending on the result obtained, but no result should be withheld from him for too long. Planning for disclosure of the test result, including longer-term follow-up, should form part of the pre-test counselling with C. S could also be invited back to clinic in his own right once he reaches early adolescence, to ensure he has a good understanding of his risk.

How should intra-disciplinary conflicts, such as a disagreement between the laboratory and the clinical team, be handled in practice?

We found it interesting that the laboratory in this case expressed a negative view on the request for testing. In our experience it is not usual practice for a laboratory to make what is arguably a clinical decision like this. Laboratory staff can, and are encouraged to, raise concerns about samples that come in to the laboratory. But given that this particular test had already been considered by a clinical geneticist (as opposed to a clinician not trained in genetics), raising such a question is unusual. Debate on these kinds of issues is to be welcomed, but such an impasse should not necessarily lead to a test being prevented from going ahead. We would emphasise that guidelines over childhood genetic testing are not proscriptive; but laboratory staff may have interpreted them differently to clinical staff.

Therefore, conflict resolution methods should be used to attempt to resolve this problem, as they would be for any other professional conflict in health care practice. This could involve an inter-disciplinary meeting to discuss the problem and hear different points of view. This will 'de-role' the professionals involved and serve as an educational opportunity for the team as a whole, not to mention preventing similar conflict in future. Individual team members should also be offered counselling. It is important to recognise that seemingly minor cases like this, if adversarial, can take up lots of time and impact future working relationships.

Concluding remarks

The nature of the dilemma presented in this case necessitates a sensitive and careful consideration of interests and maintenance of good communication with C, S and the wider clinical team. In our response, we have not provided a strict 'yes' or 'no' answer to any of the questions you proposed, although we have adopted a permissive approach to this test going ahead. This stance reflects the nature of this dilemma, the fact that we haven't met the family personally and the nuances that arose in our discussion.

In seeking to resolve this case, do bear in mind that it may not be possible to achieve this in one single further meeting with C. Rather, it will be beneficial to all concerned to maintain ongoing contact with her and with S as he gets older. Feelings of trust will be important to foster for all concerned.

Ultimately, we do not desire to see professional guidelines being implemented at the expense of recognising parental authority and minimising long-standing anxiety. If C's request for S to be tested has been thoroughly explored and sustained over time, then it may be appropriate for him to be tested.

Whenever the decision to test S is made, be it now or in years to come, it will need to be done with appropriate support and incorporation of wider views and perspectives. The process of making this kind of decision at any point is likely to be imperfect and we will need to accept that this decision may lead to a mistake being made.

Members of Southampton University Hospitals Trust Clinical Ethics Committee who discussed this case:
Professor Anneke Lucassen, Consultant in Clinical Genetics
Mr Robert Wheeler, Consultant Paediatric Surgeon and Medical Lawyer
Dr Tom Woodcock, Consultant Anaesthetist
Dr Angela Fenwick, Senior Lecturer in Medical Ethics and Education
Rev Richard Lowndes, Senior Manager for Spiritual Care
Mr Henrik Steinbrecher, Consultant Paediatric Neurologist
Ms Karen Swanson, Divisional Risk and Safety Coordinator
Ms Sally Boxall, Consultant Nurse in Prenatal Diagnosis and Family Support

[1] *Re T (A Minor) (Wardship: Medical Treatment)* [1997] 1 WLR 242.