

A decorative graphic consisting of three blue circles of varying sizes and two thin blue lines. One line starts from the top left and extends towards the center, passing near the top and middle circles. Another line starts from the top right and extends towards the bottom right, passing near the middle and bottom circles. The circles are semi-transparent and have a slight gradient.

# **Ethical proposals for the implementation of whole genome sequencing**

Deliverable 5.3 DRAFT

**Samantha Leonard, Anne Cambon-Thomsen  
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## Introduction

### Background to recommendations

In deliverable 5.1, an in-depth literature search was carried out to identify the principal ethical issues being discussed with regards to whole genome sequencing and to uncover areas of convergence and dissent. “Return of incidental findings” was identified as the primary area of dissent, particularly with regards to returning incidental results for which no prevention or cure currently exists. More fundamentally, there was divergence in opinion as to how the benefits of the technology should be maximized. The American College of Medical Genetics (ACMG) advocated the use of WGS as a screening opportunity in addition to its role in seeking the answer to a specific clinical question (ACMG 2013). In Europe the European Society for Human Genetics recommended using targeted testing wherever possible (ESHG 2013). Following the publication of a number of articles arguing against opportunistic screening, a statement published by the ACMG changing their former stance that opportunistic screening should be obligatory each time that WGS is performed for any diagnostic purpose (ACMG 2014). Surveys showed that opinion generally among professional stakeholders was divided with regards to a number of issues, including the return of unsought incidental findings (Lohn et al 2013, Lemke et al 2013).

The available data regarding the attitudes of professional stakeholders came from North America. For deliverable 5.2, a web-based questionnaire was therefore developed to investigate the attitudes of European professional stakeholders. This revealed convergence in some areas, such as that opportunistic screening should be offered but not be mandatory, and that incidental findings for preventable or treatable disorders should be shared with both minor and adult patients. Return of other incidental findings and re-contact were areas where opinion diverged.

The aim of this deliverable is to make proposals for future guidelines, following consideration of the different ethical challenges posed by the offer of diagnostic whole genome sequencing. This was achieved through an ethical analysis of the issues identified through the literature search and based on experience with other genetic testing technologies, and will incorporate consideration of the different positions reflected in the questionnaire study.

## Proposal topics

### Informed consent

Whole genome sequencing offers the possibility of a wide ranging set of information about the person's genetic status and future health. However the test is generally performed in order to answer a specific clinical question. Medical consent procedures aim to give sufficient information to the patient to allow them to make an informed decision. Generally this involves talking through potential results of testing. It is expected that the number of incidental findings will be higher with WGS than with other forms of genetic testing, and it is important to determine the level of detail that is optimal for WGS consent. Counselling in detail regarding all of the possible predispositions for medical conditions that could potentially be detected by WGS is not feasible. One possible approach is that categories of disorders rather than individual disorders should be discussed.

Experience with genetic counseling has shown that preparation of patients for predictive tests poses particular challenges. Such tests are carried out in the context of a known family history of a particular condition for which the patient is at increased risk. The condition is therefore generally familiar to the patient, and they have often had some time to reflect on the meaning of that condition to themselves and to decide whether to take the test. Counselling prior to WGS for all of the potential clinically significant results that may arise that are predictive of serious and in some cases incurable disorders is potentially very complex and time consuming. A study counseling patients in a research setting for a diagnostic WGS test took several hours to counsel patients. The patients reported that they found the process overly long (Tabor et al 2012). There is therefore a need to develop a concise pre-test counseling procedure that gives patients sufficient information to make an informed choice, without overwhelming them to the point that making an autonomous choice is unreasonably difficult. Zeiler has argued that too much choice actually harms, rather than promotes, autonomy (Zeiler 2004).

The survey carried out for deliverable 5.2 indicated that 85% of participants were in favour of a more in-depth consent procedure for WGS than for current untargeted genetic tests such as array-CGH. Of those that were in favour of a more in-depth procedure, 88% felt that the explanation of possible results should be longer and 64% felt that there should be a more detailed consent form. Around a third of participants would consider incorporating more than one counselling session into a pre-test consent process and one third would consider using a web-based decision-aid tool.

**Proposal:** Care should be taken to allow for ample time for reflection about the test decision without subjecting the patient to an overly lengthy information-giving session. Patients should ideally be offered a two-step counseling process, with written information to be given after the first appointment. It is noted that some patients may find a two-appointment system burdensome, for example if they live far from the genetics centre or have a heavy schedule of appointments for a disabled child. In such cases, alternative approaches might be used such as telephone contact by a genetic counselor before or after the appointment, or the sending out of written material prior to the appointment. A further possibility is the use of web-based information and educational material to help patients to go to a single appointment with a basic understanding of the process and to allow them to begin thinking of the questions that they would like to ask their clinician.

## Opportunistic screening vs whole genome sequencing vs targeted testing

Although there appears to be consensus that if opportunistic screening will be offered it should be optional, we will here consider each of the four possibilities: WGS with compulsory opportunistic screening, WGS with optional opportunistic screening, WGS without opportunistic screening and targeted testing. Aside from the ACMG, all organisations whose guidelines were looked at in preparation for Deliverable 5.2 were in favour of targeted sequencing rather than whole genome sequencing when feasible. The argument in favour of performing opportunistic screening is that “reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing” (ACMG 2013, p.3). The reasons for not offering the possibility of opting out of this additional screening were listed as: 1. It would be too great a burden to perform the depth of genetic counseling necessary to respect patient preferences 2. It would be “unwieldy” for the laboratories to mask or ignore these medically significant results according to patient preference 3. Healthcare professionals have a “duty to prevent harm by warning patients and their families about certain incidental findings and that this principle supersedes concerns about autonomy just as it does in the reporting of incidental findings elsewhere in medical practice” (ACMG 2013, p. 11). The ACMG noted that this “may seem to violate existing ethical norms regarding the patient’s autonomy and “right not to know” genetic risk information” (ACMG 2013 p.11).

Arguments against this compulsory testing include the high cost of the additional pre and post test counseling in both financial and personnel terms, and the laboratory costs of analyzing additional data. From an ethical point of view, generally only the incapacity of the patient justifies overriding autonomy for his own benefit. Furthermore, Allyse and Michie (2013) argue that the offer of WGS on

the condition that opportunistic screening is accepted “borders on the coercive” (Allyse and Michie 2013 p.440). The concerns with such an approach were reflected in the survey of professionals working clinical genetics and related fields, carried out for deliverable 5.2, which showed that only 2% of participants were in favour of opportunistic screening without opt out.

Opportunistic screening **with the possibility of opting out** was supported by 55% of the survey respondents. In the workshop “When Opportunity Knocks: Understanding the ethical, legal and social aspects of clinical Whole Genome Sequencing” (3Gb-TEST/Genotoul societal Meeting May 4 2015 in Toulouse, France) a number of reasons not to offer such screening, even with an opt-out were highlighted. These included the difficulties of interpreting variants and emerging evidence that the penetrance of pathogenic mutations may be dependent on multiple genetic and environmental factors and that we cannot yet be certain of the impact of identified variants on patients’ health. In addition, if no mutations are identified, there is a risk that patients may be inappropriately reassured and cease to follow basic health advice such as not smoking, or participating in established national screening programs. A final argument was made that if opportunistic screening represents such great benefit for the patient, it is difficult to justify offering it exclusively to those undergoing WGS for other reasons, since members of the general public are equally likely to have significant secondary findings. The ensuing debate revealed mixed views but was generally not in favour of opportunistic screening in any form. Further arguments that have been advanced include the lack of a screening infrastructure (and the perceived lack of financial capacity to put in place such a structure) to support and follow up patients who have results predictive of future illness, and concerns regarding the insurance status of individuals with positive findings. In favour of opportunistic screening with opt out was the possibility of ensuring a healthy life for longer. If genetic opportunistic screening is thought of in a similar way to opportunistic screening in other fields of medicine, it seems desirable to derive the maximum possible benefit from a test that is taking place, in the same way that a radiologist will examine the whole film and not solely the area of interest. However the radiologist does not do a whole body scan for each patient, which might be seen as the equivalent of doing WGS and performing opportunistic screening, rather than doing WGS and returning incidental findings. An further argument in favour of conducting WGS and offering extra gene testing might be to increase the general knowledge and understanding of genetics in order to benefit society. However this knowledge can be gained through research and through the untargeted testing that is done for medical reasons. This argument to ‘increase in knowledge’ thus implies that patients should altruistically agree to expose themselves to the risks of additional testing (unwanted results, uncertainty) for the sake of others. Such an argument is difficult to justify when there are alternative ways to obtain this information.

**Whole genome sequencing without opportunistic screening** could be seen as an option that tries to balance the risks and benefits of opportunistic screening and masked testing. It would allow for some additional benefits to be derived from WGS but would avoid some of the problems associated with systematic searches for additional variants.

There are a number of reasons for favouring **targeted testing**. These include the complicated nature of interpreting whole genome sequencing results, and the potential problems engendered by uncovering susceptibilities to disorders for which preventative measures might either not exist or are unavailable for practical and financial reasons. In addition there is a justice argument that testing of the genome beyond the regions known to be related to the clinical indication (other than where it is judged to be necessary to increase diagnostic capacity) is not being done for medical need, and yet is not available to all equally, and so it cannot be justified in a state-subsidised healthcare system.

**Proposal:** In view of the difficulties of interpretation and the lack of an infrastructure for long-term follow up of healthy patients with predictions of future disease (and particularly in light of the fact that in such healthy patients without a family history penetrance of the known pathogenic mutations may well be decreased owing to selection bias of initial cases) it is proposed that tests should be targeted wherever possible, and that opportunistic screening not be offered at this time.

## The offer of results to adult patients

### *Classification of findings*

There are a range of potential results which could be offered to adult patients, from results relating solely to the clinical indication for testing to all of the information generated by the test. Results can be classified into categories:

- Results related to clinical indication for testing
- Results related to a treatable or preventable disorder unrelated to the clinical indication for testing (sometimes referred to as 'clinically actionable' results)
- Results related to a medically significant but non treatable or preventable disorder
- Carrier status
- Susceptibility loci
- Variants of uncertain significance (in any of the above categories)

- 'Social' findings such as the 'warrior gene'

#### *What is clinically actionable?*

In a number of articles written about whole genome sequencing, incidental findings have been classified into 'clinically actionable' and 'not clinically actionable' or some variation thereof. A 'clinically actionable' finding could be one such as the discovery of a BRCA 1 mutation, for which screening or prophylactic surgery may be available. A 'not clinically actionable' mutation might be one that is predictive of an incurable disease for which there are no preventative measures, such as Huntington's disease. However, although there may be no clinical action available, such information might be of 'actionable' value to some patients, who would plan their lives differently if they were aware of this risk. Others would not want to be given this kind of information under any circumstances. Experience with predictive testing shows that some patients want this kind of information whereas others choose to avoid it. This is in the context of a known disorder within the family and a high individual risk, where a careful staged pre-test counselling programme is generally offered. It is not known what the consequences might be of revealing this kind of predictive information to a previously low risk patient might be.

A number of conflicting concerns arise. On the one hand, it might be considered that patients have a right to know all of their medical information. On the other hand it might be considered burdensome or unnecessarily complex to return certain types of results, such as those of no known medical value. For certain categories of results there is an almost unanimous opinion that results should be returned. Such is the case for clinically significant preventable and treatable disorders in adult patients, and those that would be clinically actionable during childhood for paediatric patients. There is less accord over returning results showing an increased risk of a non-actionable but serious disorder such as a neurodegenerative disorder. Few participants in our survey were in favour of returning results regarding variants of uncertain significance or benign variants, or social findings such as paternity or tone deafness.

**Proposal:** Each laboratory and clinical department will need to decide (if there are no national guidelines) which results will be offered. Communication is essential here so that the patient is aware of which results will be made available. Ideally the patient should be given options for which categories they would like to receive if more than just the "results related to clinical indication" will be given.

## The offer of results to parents of minor patients

This is an issue that poses particular problems, and one which divided opinion in the survey carried out for deliverable 5.2. There is a strong tradition in clinical genetics of not testing children for adult onset conditions, the reason being the importance placed on the autonomy of the future adult. By not testing for adult-onset conditions, the future adult's choice to know or not to know their status is protected. However, in WGS the child is **not** deliberately tested for adult-onset conditions (unless opportunistic screening is being carried out), but the results are generated by untargeted WGS performed for a specific clinical indication. Arguments have been made that it is in the interests of the child for the clinician to share the information with their parents, firstly because it may get lost or forgotten by the time the child reaches adulthood, and secondly because their parents may carry the same mutation and therefore be at risk of illness. It is in the best interests of the child to have healthy parents. Against this it could be argued that the child is not directly benefiting from sharing the results in childhood, and that the risk of not protecting their future autonomous choice outweighs any future benefit. In the workshop held in the context of 3 Gb-TEST in Toulouse in May 2015, this topic was debated. The general (but not unanimous) consensus was that the problem of finding predictive adult-onset results in children is so serious and difficult to resolve that the best option is to mask genes known to be associated with adult-onset disorders so that these results are never produced. It was felt that, at least with the current state of medical knowledge, this action best protects the interests of the child.

**Proposal:** Until such time as the ability to interpret variants and to prevent adult onset conditions advances significantly, it is proposed that when children undergo WGS, results for genes known to be associated with adult-onset conditions but unrelated to the condition being tested for are masked. Parents need to be made aware of this so that they do not think that the child has been tested for those conditions.

## Recontact

There are a number of logistical as well as ethical constraints on the process of recontacting patients following whole genome sequencing when the state of knowledge regarding a variant has evolved. The logistical constraints are related to whether the data will be stored for years after the initial test or whether it is cheaper and more effective to re-sequence a new sample, and to the resources required to follow up patients each time that information regarding a variant has changed. It is likely

that requiring laboratories to recontact patients for every change in status of every variant found during their analysis would currently be too burdensome. However if a change in status leads to a change in the report issued **relating to the indication for testing**, it may be argued that the laboratory has a duty to update their report. In the 3 Gb-TEST survey 59.4% of the participants working in clinical genetics related fields felt that the clinical service ordering WGS have a duty to review previous results in the light of new information and to recontact patients (assuming consent has been obtained). However several participants expressed concerns about the practical challenges of such a procedure, and others commented that such duties should be limited to the original indication for testing, not for incidental findings. It remains to be assessed whether recontact is practically possible.

The possibility of recontact in the other direction should also be foreseen. Patients may benefit from being able to re-access their genomic data at a future point, either for the original test indication or for unrelated indications, for example for personalized pharmacogenetic data. A clinician wishing to prescribe a particular drug could, with the consent of the patient, request a re-analysis of the original data to look at up-to-date pharmacogenetic data, or ask that, in light of new discoveries, a sample is re-examined.

**Proposal:** Laboratories should not be expected to issue new reports related to variants outside of the indication for testing. However if the change is related to a variant reported in connection with the indication for testing then the laboratory could potentially be considered to have a duty to update the report. Whether such updating is practically feasible or not will depend on such factors as the capacity of the laboratory and their relationship with the prescribing clinicians. A decision therefore needs to be taken by each laboratory (where such a procedure is not already dictated by local law or professional guidelines) as to whether the laboratory will return results as a one-off report based on the state of current knowledge with no intention to update, or whether results could be subject to updating in the future. Whichever procedure is chosen, the patient must be informed at the time of testing whether their result is a 'snapshot' which reflects knowledge at the time of the test or whether it is an ongoing, evolving process liable to give rise to changing interpretations as knowledge advances. If possible data should be kept as part of the patient record so that the patient has the opportunity to benefit from their genomic data in the future.

## Solidarity and data sharing

Whole genome sequencing is expanding the paradigm of genetic testing. It was already the case that in order to provide answers for a patient, it was necessary to gather information about family members, and in some cases invite them for testing to better interpret results generated through tests on the patient. With whole genome sequencing we often need to look much further for answers. With so many variants being detected, and, for the moment, relatively limited knowledge of their significance in many cases, our ability to be able to make the fullest use of this data will depend on a cooperative endeavour on a global scale. This cooperation can occur at a number of different levels, from patient participation in research projects, to entry of rare variants into databases and sharing of appropriately anonymized and securised data between researchers.

**Proposal:** Opportunities for cooperation should be sought for and used as part of routine practice, as only this kind of large-scale effort will help to achieve more rapid understanding and translation of variant findings. Whilst care must be taken to avoid patients feeling under pressure to agree to participate in research protocols and databases, an explanation of the aims and nature of available cooperative opportunities whenever appropriate will allow more patients to benefit more quickly from genomic testing. Steps should be taken to facilitate sharing of data between research groups wherever this can be done without compromising the boundaries of consent and confidentiality. Work should be done on the design of consent and confidentiality in new research projects to consider the possibility of future collaborative efforts.

## Conclusion

Genetics has long been a rapidly evolving field, but with the advent of diagnostic whole genome sequencing, new frontiers of knowledge are before us. We are not yet ready to be able to reap the full range of benefits of all that the genome has for us. Before we can arrive at such a point, we need to go through a steep and probably laborious learning process, in which shifting interpretations of results may mean that incorrect reassurance or unnecessary investigations are put in place, or simply that we may be faced for some time with the possibility of regularly finding ourselves in a situation of returning uncertain results. It is important that progress is not hindered, and that we can continue to advance towards these new horizons with a sense of curiosity and anticipation.

Such anticipation should however be balanced by a realistic view of the challenges to overcome before we can access all of this anticipated benefit. For this reason these proposals remain cautious, and call attention to the realities of our abilities to interpret and understand genomic information. We must focus on the means of accomplishing the goal of mastering this interpretation and understanding: being open and clear with patients about what can be accomplished at present with this technology, and inviting them, when appropriate to participate in this acquisition of knowledge and experience by permitting data to be shared. As researchers and clinicians, we can help move towards our goal faster by taking the time to share data, clinical findings and experiences with the implementation and use of different policies for these issues whenever it is possible and appropriate to do so. Cooperation, both doctor- patient and between research teams will be the key to achieving successful use of this powerful tool.

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