3Gb-TEST

CONVERGENCE AND DISSENT IN WHOLE GENOME SEQUENCING

Deliverable 5.2

Samantha Leonard, Anne Cambon-Thomsen

10/31/2014

Table of Contents

Introduction

In deliverable 5.1 we examined the guidelines and recommendations issued by professional and government bodies related to the clinical use of WGS. We also looked at some of the commentaries published by healthcare professionals and ethicists in reaction to these guidelines. The guidelines revealed several areas in which common values could be seen across different cultures. They also revealed areas of dissent, both across cultures and within cultures. The most obvious example of the latter was the publication of the American College of Medical Genetics guidelines recommending the obligatory use of WGS to provide opportunistic screening in all those undergoing testing for any reason, and their subsequent withdrawal after dissent by the members of the College.

This deliverable will look in more detail at areas of dissent and convergence among healthcare professionals and other stakeholders regarding the clinical implementation of WGS. One of the major areas of discussion around WGS relates to the handling of what have variously been termed incidental findings, secondary findings and unintentional findings among others. For the purposes of this Deliverable we will use the term 'incidental finding' (IF) to refer to any genetic change considered as likely to be pathogenic which is not related to the disorder for which the test was requested.

Incidental findings are not, of course, a new phenomenon, nor one that is unique to genetic tests – they date back to the first time a physician examined a patient for one complaint and noticed signs of another, unrelated disorder. The debate in relation to genetic testing became particularly acute when array CGH was introduced as it was anticipated that IFs would arise with greater frequency. WGS was predicted to lead to an even greater rate of IFs; however when the debates started there was little knowledge of the actual incidence of such findings. As time has gone on, such data is available, and is likely to impact on planning and recommendations. Studies indicate that just fewer than 2% of adults have clinically actionable IFs (Kullo et al 2014).

This deliverable will examine areas of convergence and divergence from a number of perspectives; the areas that emerged from the review of guidelines and recommendations, a literature review looking at studies of the views of genetics professionals and patients on these areas, a survey of European professionals involved with genetic testing or its development and evaluation and input from patient associations.

Overview of areas of convergence and dissent drawn from the recommendations reviewed in Deliverable 5.1

A review of the literature aimed at identifying new commentary and surveys among stakeholders involved with WGS was carried out using ovidSP. The review of recommendations, guidelines and commentaries identified principle areas of ethical discussion including opportunistic screening, return of incidental findings in adultes, and testing and return of results for children.

Opportunistic screening and return of results to adult patients:

Interestingly the committees selected by the American College of Medical Genetics and the European Society of Human Genetics to produce recommendations regarding clinical implementation of WGS came to very polarised conclusions: the ACMG viewed WGS as an opportunity to provide additional benefits to patients, and felt that this potential benefit was great enough to justify overriding patient autonomy regarding the choice to access this additional information. The ESHG regarded WGS as potentially harmful, and recommended that where possible, targeted sequencing should instead be carried out. As we shall see below however, it seems that their members are in reality much closer together on this issue. The ACMG eventually amended their recommendations to allow patients to opt out of opportunistic screening, but the tone of the amendment remained strongly in favour of providing such screening. The Danish council of Ethics did not support opportunistic screening, and the Presidential Committee for the study of bioethical issues was in favour of tailoring tests to the needs of the individual patient.

Return of results for paediatric patients:

The ACMG recommendations clearly state that it is in children's best interests to have results indicating risk of clinically actionable adult-onset conditions returned to their parents. Although this appears to go against their previous stance regarding testing children for adult-onset conditions, they distinguish between the two contexts, saying that deliberately testing a child for a known familial condition is different as they will have the opportunity to have the test later on, and their

relatives are already aware of the risk and so there is no potential gain from early testing. In contrast incidental findings which are actionable provide valuable information to the family, and the child will benefit from action being taken to prevent or treat serious illness in their parents. In addition if information about risk of an adult-onset condition is not shared at the time of the initial test, the child may lose the opportunity to express their autonomy and decide to receive these results later on, as they may lose contact with the genetics department. The ESHG has a similar stance with regards to sharing incidental findings, although as discussed above they do not advocate purposely looking for additional information. The recommendations highlight the need for guidelines to establish which results should be shared in order to balance autonomy and the need of the child and parents to know or avoid knowing information that could have implications for future offspring or other family members (van El CG et al 2013 p. 582). Bowdin et al (2012) raise a number of concerns regarding informing a family of a child's predisposition to adult-onset conditions including altered relationships with friends and family, and negative impacts in areas such as future employment.

Surveys of providers of genetics services

Laboratories and reporting results

Jamal et al (2013) found wide variation in practice between certified laboratories in the USA providing exome sequencing. 5 of the 6 laboratories surveyed return medically actionable results. One laboratory provided no secondary or incidental findings. Two of the laboratories required expression of patient preferences for return of results at a single clinic visit whilst a third gave patients up to 6 months to decide to receive secondary results. No laboratory gave patients direct access to their results. All laboratories provided updated interpretations of the results, some at their own instigation, some requiring action by the requesting professional. One laboratory provided a publicly accessible online tool for looking up reclassifications of variants.

Return of results by the clinician

A number of surveys of genetics professionals have been carried out in the USA and Canada. These mostly concern return of results and indicate a high level of consensus regarding the return of incidental findings where the condition is serious and treatment is available (the vast majority would return such findings) and also for conditions where the information had only social implications (a very large majority would not return such findings) (Lohn et al 2013, Lemke et al 2012), but far less consensus where untreatable conditions were concerned, particularly in paediatric patients. A study by Lemke et al (2012) showed that the majority of USA genetics professionals would return results

regarding treatable adult conditions to the parents of paediatric patients. Lemke et al differentiate the discovery of treatable adult onset conditions in children during the process of WGS from the deliberate testing of minors for adult onset conditions, pointing out that this second process is done in a different context, of deliberately looking for a condition for which the child is known to be at risk. They express concerns regarding how withheld information will be transferred to the child when they reach majority, citing logistical problems with this approach. The study by Lohn et al (2013) demonstrated a strongly favourable view towards giving patients options for receiving results at the time of obtaining informed consent.

Other commentaries on return of results – paediatric patients

As the surveys demonstrate, there is a good degree of consensus regarding return of incidental findings to parents where these are actionable during childhood. There is however less consensus on return of results when no action will be required until adulthood. Genetic practice in Western countries has long been to avoid testing children for adult-onset conditions. The principle arguments around not returning results relate to protection of the autonomy of the child. This is based on the right of the child to make the decision for themselves whether or not to take the test when they reach adulthood. This situation has previously arisen in the context of recognised Mendelian disorders within the family. As Evans (2013) points out, in this situation there is no compelling reason to override the child's autonomy; the condition is known, the information is available and other family members can choose to have testing. He contrasts this with the situation of incidental findings. Here the condition is not known in the family. Withholding the information brings a number of risks – the information may be lost or forgotten and so the child may miss their opportunity to express their autonomy in deciding to receive the results as an adult. Secondly, with some conditions there is a risk that other family members are unknowingly also affected and would benefit from surveillance or treatment. Evans argues that two negative consequences could thus arise – the parents may suffer a condition which could have been prevented or treated earlier, and the child may suffer through the avoidable illness or loss of a parent. If the results are shared, the child will lose the right to make a decision for themselves about receiving the information, but they will benefit from the continued good health of their parent as well as a higher chance of access to prevention as an adult. Bowdin et al (2014) lists several potential negative consequences of returning adult onset results to the parents of a child undergoing testing, including altered parent-child relationship and problems with finding employment and obtaining insurance. They note

however that the ethical discussion may be altered by the different context of whole-genome sequencing versus in-family testing.

Survey of European genetics professionals and other interested stakeholders carried out in the context of 3Gb-TEST

All currently available surveys of attitudes towards clinical use of whole genome sequencing identified by the literature search included North American or Canadian participants. In order to examine the identified areas of ethical discussion around whole-genome sequencing from a European perspective, a survey was designed and sent out, using networks and contacts built up through 3Gb-TEST, another European project (TECHGENE) and professional contacts. Genetics professionals were targeted, but also other professionals belonging to these networks and having an interest in WGS. The survey consisted of 6 questions aimed at eliciting views on various ethical aspects of whole genome sequencing, as well as standard demographical questions.

Survey results

130 people from 23 countries across Europe responded to the survey. The majority were clinical geneticists and clinical laboratory staff, but included in the 'other' category were bioinformaticians, neurologists, oncologists, genomics researchers and translational scientists among others. 38.9% were using WGS in their clinical practice at the time of answering the survey. Participants ranged in age from 20-30 up to >60, with the majority of respondents falling in the 31-50 age range. 54.3% were female.

Areas of convergence and divergence:

Return of results to adult patients: There was a lot of divergence regarding the issue of screening for a predetermined panel of genes. 56.3% of participants thought patients should be offered such a panel but with the option of opting out, whereas 34.4% thought the offer of testing should be limited to the clinical reason of origin. Only 1.6% thought that the panel of additional genes should be routinely performed without on opt-out opportunity. Regarding incidental findings, 96% of participants felt that adult patients should be given the option of receiving IF results for clinically significant preventable or treatable disorders. Only a small minority (3.9% and 6.3% respectively)

thought that competent adults should be given the option of receiving IFs relating to VOUS and benign variants, or social findings such as paternity, tone-deafness etc.

Return of results to parents of minors: 96% of participants were in favour of returning IF results regarding clinically significant treatable or preventable disorders of childhood onset. Opinion was divided on the issue of return of results for non-treatable childhood onset disorders, and also for carrier status, with 41.7% and 46.5% stating that parents should have the option to choose to receive these results. There was disagreement regarding the return of IFs for adult onset disorders, with only 50% saying that such results should be returned to the parents. In contrast there was almost unanimous agreement that IFs conveying non-clinical information should not be returned.

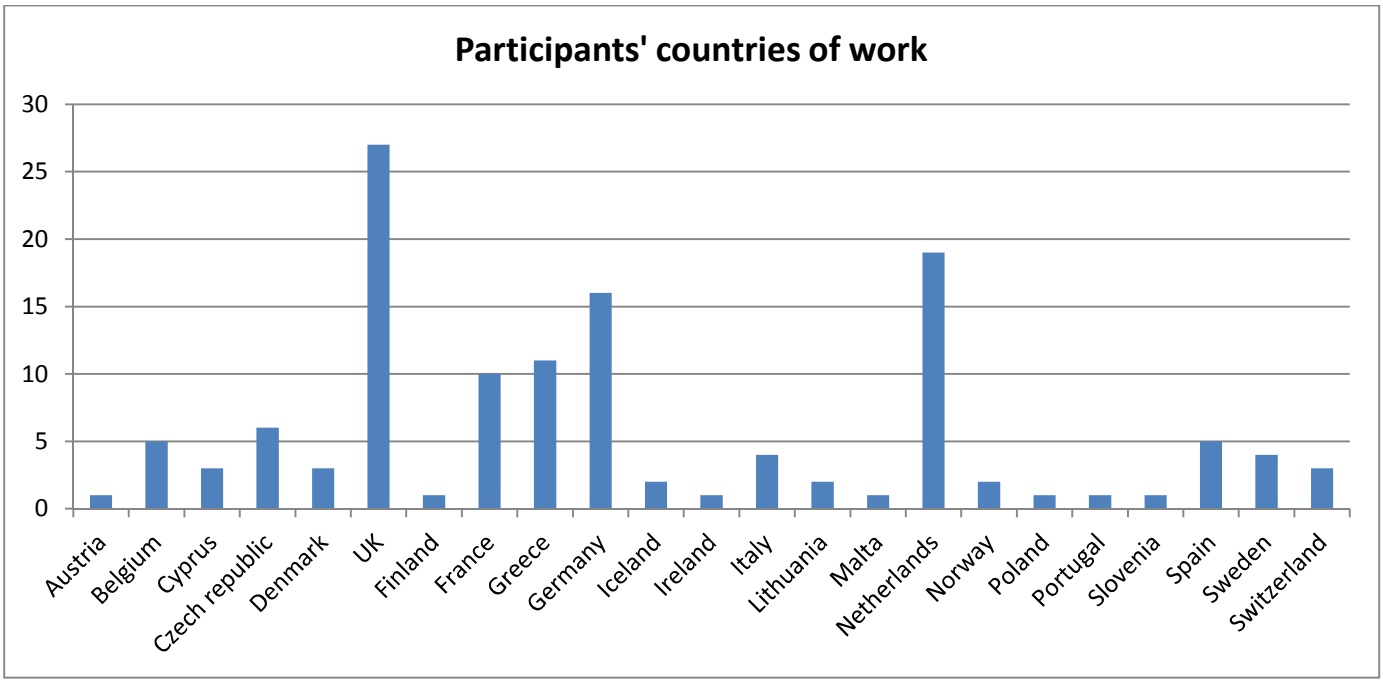
Informed consent for WGS:

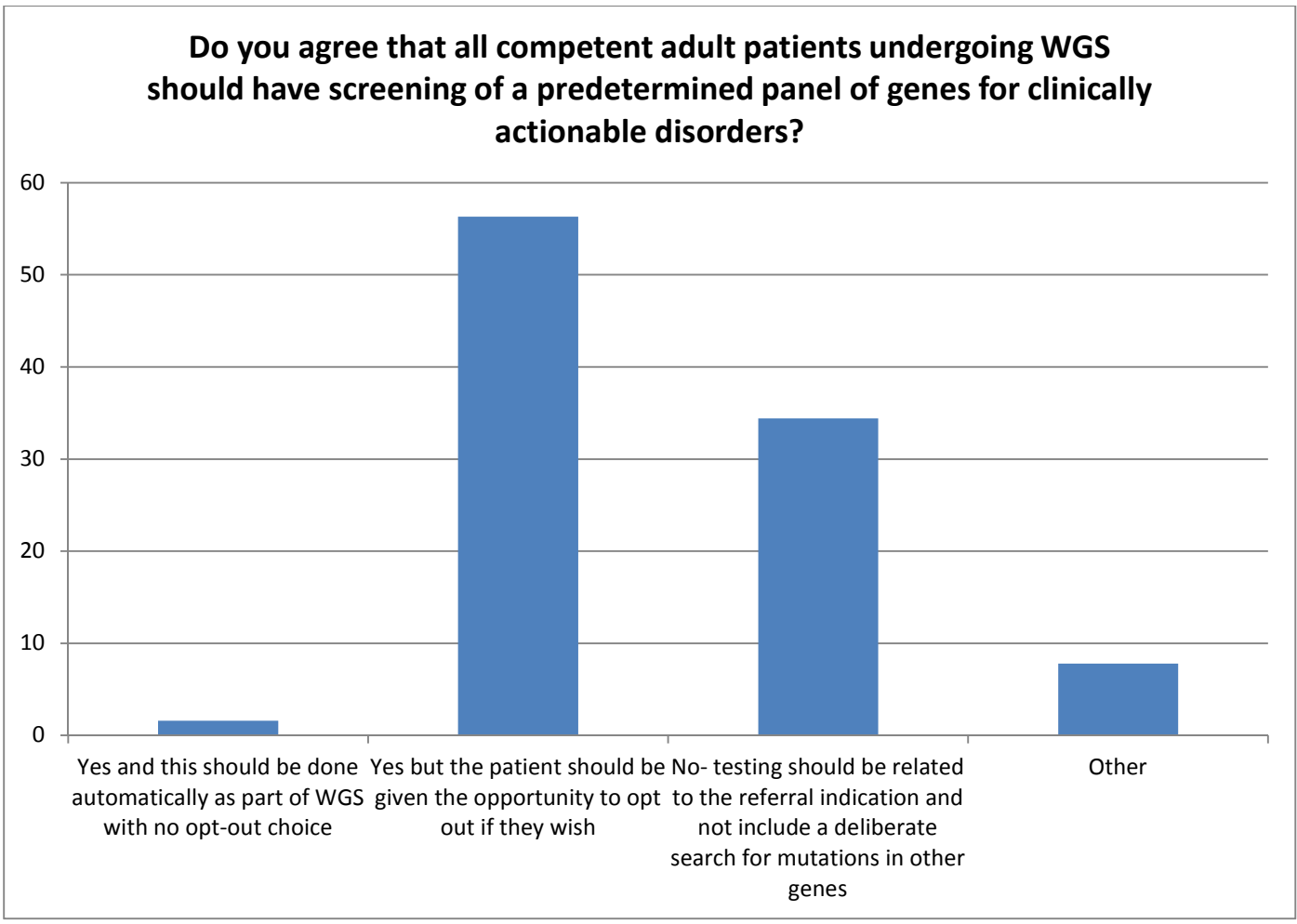
This was another area of high concordance, with 85.9% of participants indicating their belief that a more in-depth consent procedure is required for WGS in comparison with other genetic tests such as array-CGH. Most (89%) felt that this should be by way of a longer explanation of the possible results and 63% thought that a more detailed consent form would be helpful. Relatively few (29.6%) thought that more than one counselling session prior to obtaining consent or a web-based tool (36.1%) would be desirable.

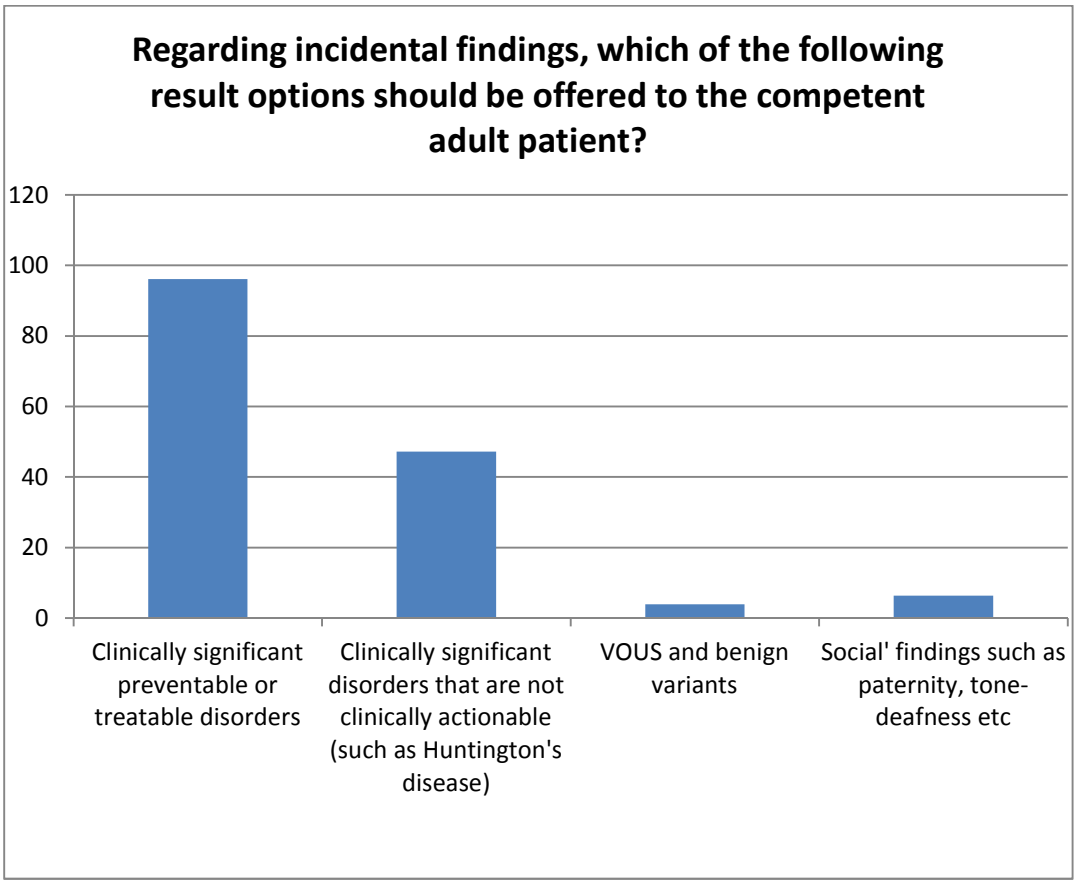
Re-contact:

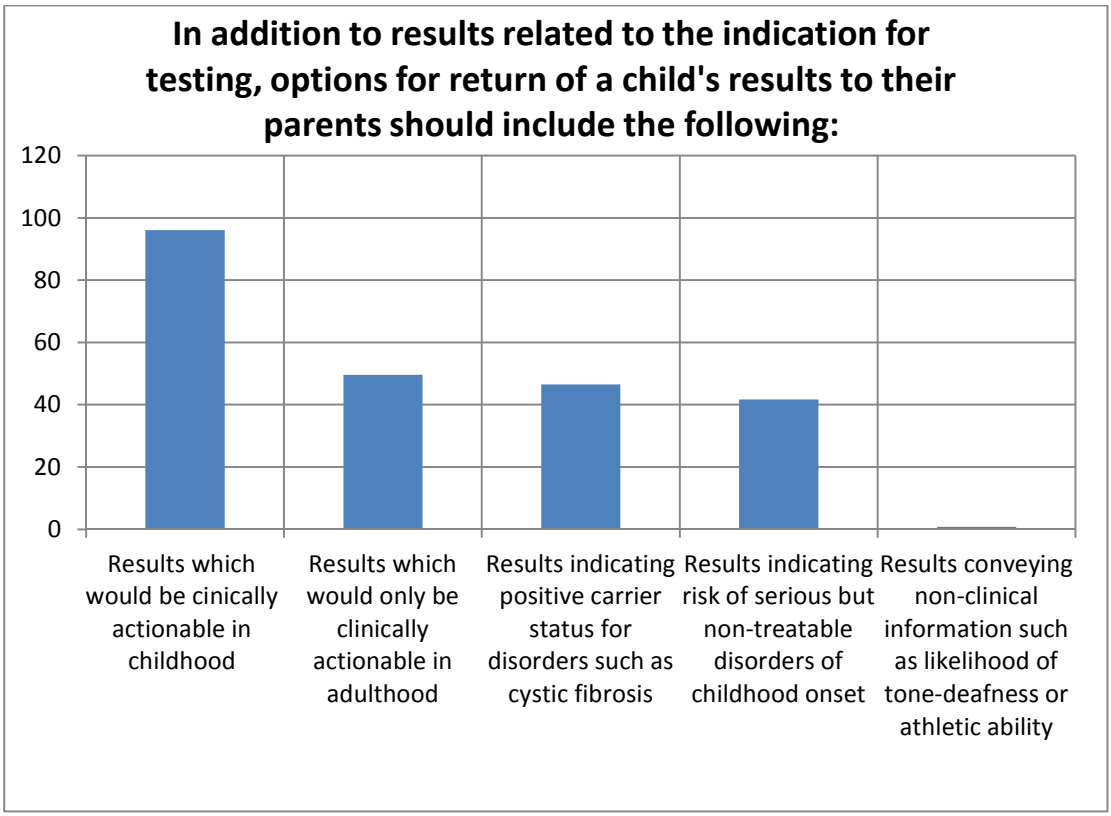
58. 6% of participants felt that the clinical service ordering WGS had a duty to review previous results in light of new information and to re-contact patients (assuming consent has been obtained). 24% felt that they was no such duty, and 17.2% said that re-contact should be undertaken in certain circumstances, for example if an “automatic alert” could be set up.

Survey data

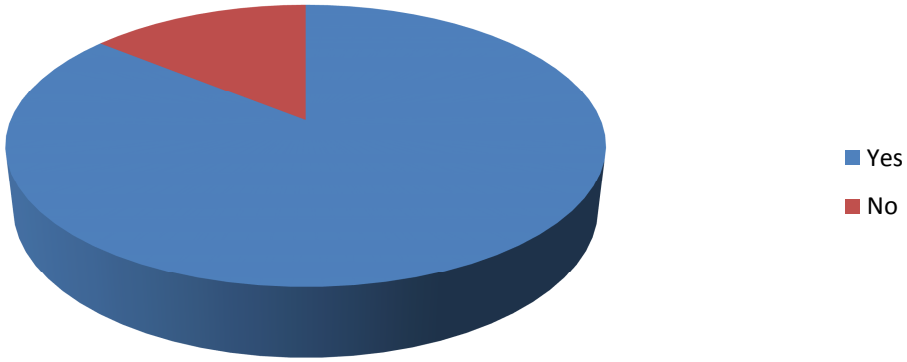

Participants' countries of work
30
25
20
15
10
5
0
Austria
Belgium
Cyprus
Czech republic
Denmark
UK
Finland
France
Greece
Germany
Iceland
Ireland
Italy
Lithuania
Malta
Netherlands
Norway
Poland
Portugal
Slovenia
Spain
Sweden
Switzerland


Do you agree that all competent adult patients undergoing WGS should have screening of a predetermined panel of genes for clinically actionable disorders?
60
50
40
30
20
10
0
Yes and this should be done automatically as part of WGS with no opt-out choice
Yes but the patient should be given the opportunity to opt out if they wish
No- testing should be related to the referral indication and not include a deliberate search for mutations in other genes
Other

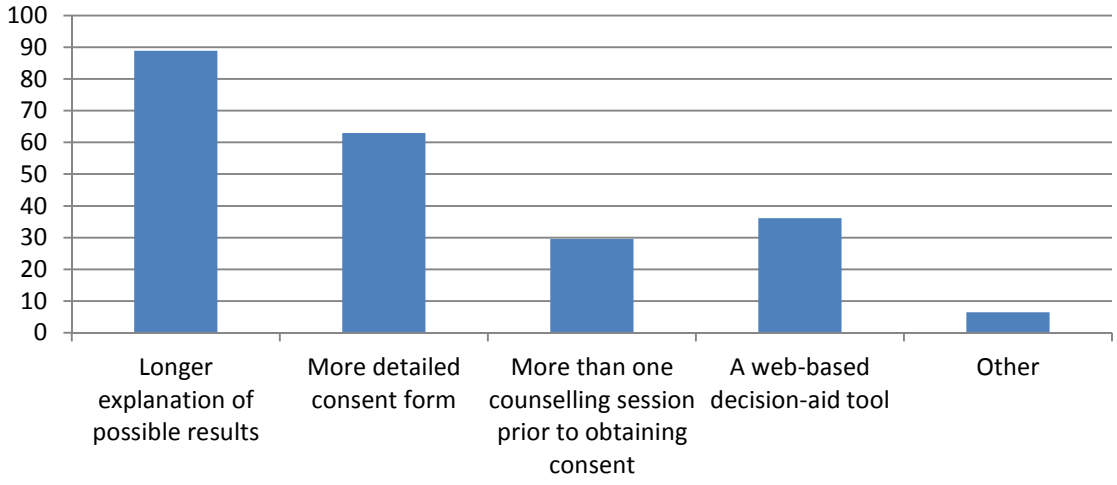

Regarding incidental findings, which of the following result options should be offered to the competent adult patient?
120
100
80
60
40
20
0
Clinically significant preventable or treatable disorders
Clinically significant disorders that are not clinically actionable (such as Huntington's disease)
VOUS and benign variants
Social' findings such as paternity, tone-deafness etc

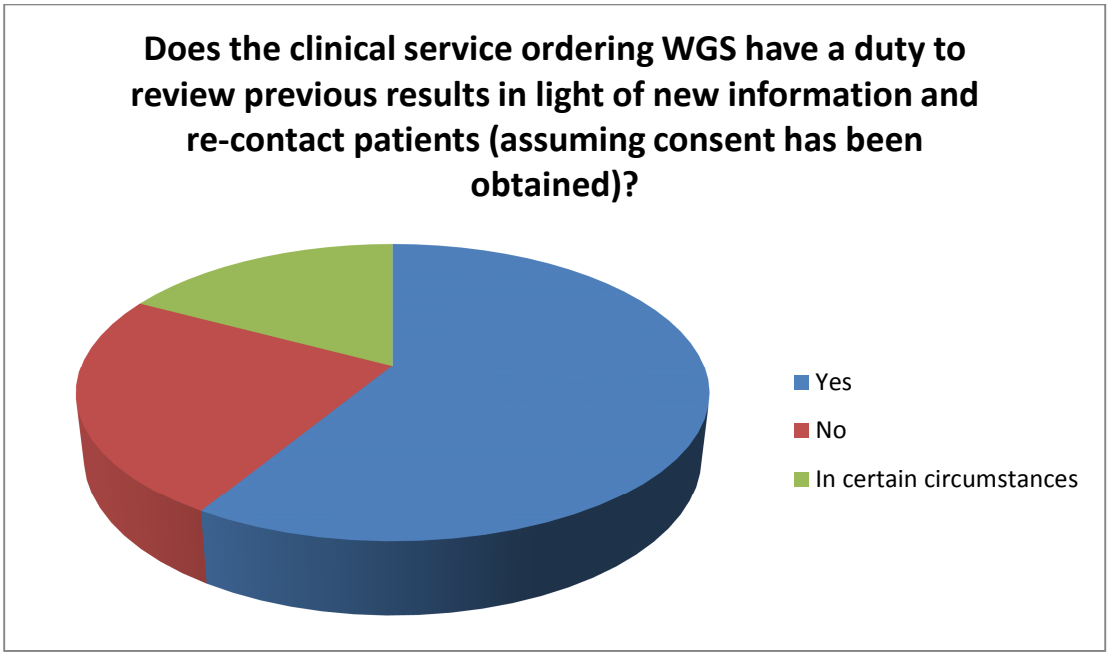

In addition to results related to the indication for testing, options for return of a child's results to their parents should include the following:
120
100
80
60
40
20
0
Results which would be cinically actionable in childhood
Results which would only be clinically actionable in adulthood
Results indicating positive carrier status for disorders such as cystic fibrosis
Results indicating risk of serious but non-treatable disorders of childhood onset
Results conveying non-clinical information such as likelihood of tone-deafness or athletic ability

Do you think that WGS in the clinic requires a more in-depth consent procedure than array-CGH (for example a more in-depth explanation of potential results, a longer consent form or more than one consultation to obtain consent?



If you answered yes to the previous question, which of the following would you consider incorporating into your consent procedure for clinical WGS?





Choice and patient expectations

Studies of patient preferences regarding the clinical use of whole genome sequencing have so far been limited. One study, by Tabor et al interviewed participants from 2 families with a genetic condition who were being offered WGS as part of a research project. Participants were offered the option of different categories of results to be returned; a "summary of overall variation", "variants considered to be potentially harmful" and "variants associated with common diseases, drug response, non-medical and personality traits and ancestry" (Tabor et al 2012, p. 1312). Participants had mixed feelings about the return of results, and described having difficulty anticipating their reaction to different types of results and so in deciding which categories of results to receive. However they emphasised the importance to them of being given options regarding return of results. The researchers concluded that web-based tools might facilitate patient-led management of results. They also noted that the consent process that they had used, which was 2-3 hours long, was viewed unfavourably by all participants.

A study performed as part of the TECHGENE project looked at participant views on the use of next generation sequencing technologies in general. The technologies were viewed positively, with some concerns expressed regarding their use in the prenatal setting, as participants felt

that certain results should not be returned, as they might lead to the kind of discrimination which they did not feel was appropriate within their society (A Soulier, unpublished data).

As part of the 3Gb-TEST project a questionnaire was sent out to 20 patient associations in the UK, France, Belgium and Switzerland, asking whether WGS had been discussed by the association committee and whether any members had contacted the association enquiring about WGS. Three associations responded. An umbrella group for associations of patients with genetic disorders based in the UK are currently conducting a study of patient attitudes towards WGS which will be published in the next few months, and it is hoped that collaboration can be established prior to the next deliverable. A retinitis pigmentosa support group in the UK and and autism support group in Switzerland responded and stated that WGS had not been discussed at an organisational level nor had any patients enquired about this technology.

It appears that at present WGS may not yet have entered the awareness of patient groups, and if this is the case, it may be that public awareness of the approaching availability of this technology and the potential ethical issues related to it is limited also, as patient groups are in general highly motivated to keep up to date with developments in genetics which may potentially benefit their members.

Discussion

Although initial publications regarding ethical issues in whole genome sequencing suggested a high degree of divergence, it seems that in many areas there is a trend towards finding common ground, and this common ground centres around maximising the benefits of whole genome sequencing whilst respecting the preferences of the patient as far as possible. Areas of consensus include the return of incidental findings which would be clinically actionable to competent adults, and return of incidental findings which are actionable in childhood to children. In addition in the survey conducted for this report, there was agreement that a different consent procedure is needed for WGS than for other forms of genetic testing such as array CGH. A further area of consensus involves the need for respect for patient preferences, and involvement of the patient in decision-making.

One major area of divergence include the use of diagnostic WGS as a tool for opportunistic screening. Some feel that this would be an acceptable option, but that it should not be a

condition of undergoing WGS for diagnostic purposes. However there is a significant body of professional stakeholders who feel that testing should be limited to the presenting complaint of the patient. There was further dissent surrounding the issue of which results should be offered to patients, with some feeling that non-actionable results should not be offered. Regarding the return of paediatric results to parents, there was divergence on the issue of whether adult-onset results should be returned. It may be that the idea of 'no testing children for adult-onset conditions' has so permeated the consciousness of geneticists that this is more an automatic response than a reasoned consideration. Evans (2013) makes a compelling case for considering incidental findings in a different light to the planned testing for a familial disorder. Return of IFs relating to a non-treatable condition in childhood is a further area of contention. There has been much less discussion on this topic, and it warrants further consideration in any future guidelines.

Finally there are indications, however slight, that patient and thus likely public awareness of WGS and the issues surrounding this technology may be limited. Education and public awareness regarding WGS is thus something that needs focussed attention as we move closer to widespread introduction of this technology in the diagnostic setting.

Conclusion

Whole genome sequencing is a complex technology, and this complexity is reflected in the difficulty of establishing clear ethical guidance. Issues that compound this complexity include lack of experience with the technology, and lack of understanding of the results. Over time certain matters will become clearer, but guideline formulation cannot wait. There are indications that at least part of the dissent is artefactual, created by small committees whose conclusions have not reflected the voice of their membership. Some of the dissent may be created by applying traditional ethical thinking regarding genetic technology to this new domain without fully reflecting on the issues.

In the next deliverable an attempt will be made to conduct such reflective consideration of the issues, in the hope of unravelling some of the complexity and,using the conclusions of this deliverable along with those of deliverable 5.1, coming to conclusions that are acceptable to a wider range of stakeholders.

References

Bowdin S, Ray PN, Cohn RD, Meyn MS. 2014. The genome clinic: a multidisciplinary approach to assessing the opportunities and challenges of integrating genomic analysis into clinical care. Human Mutation 35(5):513-519.

Evans

Jamal S, Yu J-H, Chong J, Dent K, Conta J, Tabor H, Bamshad M. (2013) Practices and Policies of Clinical Exome Sequencing Providers: Analysis and Implications. *American Journal of Medical Genetics* 935-950.

Kullo IJ, Haddad R, Prows CA, Holm I, Sanderson SC, Garrison NA et al. 2014. Return of results in the genomic medicine projects of the eMERGE network. Frontiers in Genetics (5): 1-8.

Lemke A, Bick D, Dimmock D, Simpson P, Veith R. (2013). Perspectives of clinical genetics professionals toward genome sequencing and incidental findings: a survey study. *Clinical Genetics* 84: 230-236.

Lohn Z, Adam S, Birch P, Townsend A, Friedman J. (2012). Genetics professionals' perspectives on reporting incidental findings from clinical genome-wide sequencing. *Am J Med Genet* Part A 161A:542-549.

Tabor HK, Stock J, Brazg,T, McMillin MJ, et al. 2012. Informed consent for whole genome sequencing: a qualitative analysis of participant expectations and perceptions of risks, benefits, harms. American Journal of Medical Genetics Part A 158A: 1310-1319.

Van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV et al. (2013a) Whole Genome Sequencing in Health Care. Recommendations of the European Society of Human Genetics. *European Journalof Human Genetics* 21: 580-584.

Van El CG, Dondorp W, De Wert G, Cornel M. (2013b) Call for Prudence in Whole-Genome Testing. *Science* 341: 958-959.

Zawati MH, Parry D, Thorogood A, Nguyen MT, Boycott, KM et al. 2013. Reporting results from whole-genome sequencing in clinical practice: A proposal for Canada? Journal of Medical Genetics: 68-70.