3Gb-TEST

A Map Of Issues And Their Existing Framework For Translation Of WGS Into Clinical Practice

Deliverable 5.1

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I. Introduction

Whole genome sequencing, although a "new" technology, is far from being a new concept. Since the sequencing of the entire human genome over a decade ago, it has been clear to researchers and clinicians alike that this technology would eventually find its way into the clinic. The attractiveness of this technology is twofold – firstly the traditional approach to genetic diagnosis remains, in many cases, difficult and lengthy, and secondly, there are still many diseases for which knowledge of the pathophysiology is limited, and it is hoped that more detailed knowledge of the genetic changes underpinning the disease may help not only in diagnosis but also eventually in treatment and ultimately prevention. The current technologies have allowed much progress along the path to understanding the basis of many human diseases, but there is still much work to be done, and an increasing recognition of the limits of current knowledge, particularly with regard to epigenetic factors. The recognition that 15% of pathogenic genetic change arises from outside exonic sequence (Raffan and Semple) makes whole-genome analysis not only interesting from a scientific point of view, but a clinical necessity if a more complete understanding of the pathogenesis of genetic disease is sought.

There have been many intermediate steps along the path to whole genome sequencing – individual gene analysis, panels of genes of interest, karyotyping and array CGH have all helped to highlight both the benefits and the potential harms of more detailed and less targeted genetic analysis. Whole genome sequencing is, in a way, the natural end-point of this progression and has been described as the "ultimate genetic test"(Drmanac). The excitement and promise surrounding WGS make useful ethical analysis difficult. Ethical analysis is often charged with being too negative(Biesecker et al, Wilfond et al), of considering potential consequences too early in the development process, or conversely of developing the analysis too late (Chadwick). On the one hand it is important to recognize and circumvent where possible the potential dangers of this powerful technology, but this must be balanced with an appreciation of the potential for benefits, both in the short and long term. One of the critical difficulties which has faced the various committees who have worked on guidelines in this area is the phenomenon of what can be called 'evidentiary lag-time'. In order to produce relevant high-quality guidelines, our evidence-based medicine culture requires that pronouncements be based on reliable evidence. However, when a new technology is introduced, there is little evidence about the impact that introducing it will have on patients. It is not considered to be good practice to offer a new technology without guidelines for its use, and so guidelines and recommendations are created which are often vague and mainly refer to the need to collect

evidence in order to conduct sound medical care, and therefore are less helpful for practitioners, or the guidelines take a strong line but are subsequently criticized for lack of evidence.

This deliverable will consider the currently available guidelines concerning whole-genome sequencing, and consider the critiques that have been leveled at them to date. The second part of the deliverable describes a review of the literature looking at issues regarding whole genome sequencing and identifies urgent considerations in the development and refinement of preliminary recommendations for the clinical use of new genetic technologies.

I. Review Methodology

In order to identify published recommendations, guidelines and policies, systematic literature review was carried out. The aim of the literature search was to identify documents containing or commenting on guidelines, recommendations or policies pertaining to whole genome sequencing. A search was carried out using Ovid SP using the databases EMBASE, Medline, The Philosopher's Index, PsychInfo and CAB abstracts. All years and citation databases were covered. The search string was: whole genome sequencing plus policy OR recommendation OR guideline. This search returned 35 articles. The abstracts of the articles were then read for relevance. From this 32 articles were included, as the abstracts indicated that they either contained guidelines, recommendations or policies, or discussed issues relevant to these. In addition a web search was carried out, using Google to identify groups which might have published guidelines or recommendations. The search "whole genome sequencing recommendations or guidelines" was entered leading to identification of 2 further groups. Finally the documents were read to identify other sources. From this a further 2 sources of recommendations were identified. The 32 documents were then read in full. Further articles, guidelines and recommendations were found using the snowball technique. They will be discussed below in three groups: recommendations, commentaries on the recommendations and discussion of the ethical issues identified in the recommendations and commentaries in the reviewed literature.

II. International and national recommendations and published commentaries

a. Recommendations

i. ACMG recommendations for Clinical Exome and Genome Sequencing

The ACMG has produced guidelines related to management of incidental findings in whole genome and exome sequencing, documenting suspected consanguinity as an incidental finding, and informed consent. In 2013 the ACMG produced the document "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing." Prior to this point, the term "incidental findings" had been mainly used to refer to findings of potential clinical significance which had been discovered unintentionally during the process of genetic testing for the diagnosis of a medical condition and which were believed to be unrelated to that medical condition. The ACMG recommendations overturned this definition by recommending that far from being 'unwanted' results that unfortunately were an inevitable inconvenience of untargeted testing, diagnostic laboratories should actively seek 'incidental findings' in a list of 57 genes (later reduced to 56) (hereafter referred to as the IF genes) that they had developed following a "year-long consensus process" (ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing). Although these have now been rescinded, the argumentation merits consideration as it highlights important issues in the clinical implementation of WGS.

The ACMG aimed to include genes fulfilling the following criteria:

1. Confirmatory approaches for medical diagnosis are available
2. Preventative measures and/ or treatments are available
3. Individuals with pathogenic mutations might be asymptomatic for long periods of time
4. The mutation met criteria for reporting as pathogenic
5. There is evidence of clinical utility and validity

However they acknowledge that evidence was not available for clinical utility and validity for all of the variants listed, and in those cases it "drew upon the clinical judgment of its members". Additionally the membership were acknowledged to have disagreed about certain conditions, and to have had incomplete knowledge of some of the conditions listed. They admitted that for some

conditions there were no confirmatory diagnostic approaches available, and that in some cases the variables listed did not meet the criteria for reporting as pathogenic.
The recommendations were aimed at all genome and exome analyses performed clinically for all individuals except fetuses. The recommendations deviate from traditional ethical practice in two significant respects:

1. They endorse the deliberate testing of children for adult-onset conditions. The pre-existing recommendation against testing children for adult-onset conditions before they attain majority has been endorsed by numerous organizations, ethicists and practitioners world-wide, including the ACMG (Friedman Ross et al)
2. They advocate against respecting the preferences of patients with regard to receiving incidental findings results. This is counter to general recommendations in medical ethics which support patient autonomy and in particular patient choice.

Other potential problems with the recommendations which were acknowledged by the ACMG included the fact that the analysis leading to the generation of incidental findings results might not be of the same quality as sequencing for a primary indication, and that a negative report might be misunderstood as proof of absence of a pathogenic mutation in the IF genes reported.

The ACMG's arguments in support of these controversial recommendations are based around a concern that patients and their families should be given the opportunity to benefit from the new enhanced capacity of diagnostic genetic testing to detect mutations across a number of genes, thus providing them with the opportunity to access prevention or treatment in a timely manner. The ACMG argued that without the recommendations, this opportunity would be wasted. They claim that the duty of healthcare professionals to warn patients and their families about these incidental findings "supersedes concerns about autonomy, just as it does in the reporting of incidental findings elsewhere in medical practice" (p. 11).

They also justified their recommendations on the basis that:

1. It would be more onerous for laboratories to mask incidental findings than to detect and report them.
2. It would be burdensome and impractical to explain each condition that was being screened for to patients, and to obtain their informed consent for each one.

In terms of testing children for adult-onset disorders, this was justified by stating that the principle of respecting children's future autonomy by not imposing genetic testing for adult onset conditions was discordant with the respect accorded by society for parental decision-making and that at present, screening a child for variants in these 57 genes might represent the sole opportunity that a parent would have to find out about their own genetic risk factors.

ii. ACMG incidental findings in clinical genomics: a clarification

Following a number of commentaries, the ACMG published an article entitled "Incidental findings in clinical genomics: a clarification". In this article they address, among other things, concerns raised by other authors regarding autonomy and protection of children:

- Autonomy – the ACMG states that the clinician is expected to 'contextualise findings' to, among other things, patient preference, and that this is in line with shared decision-making in other areas. In addition they state that any complicated medical test involves the risk of unexpected results, and that information about this possibility forms part of the informed consent procedure. They underline their position that it is unethical to fail to report 'a laboratory test result conveying the near certainty of an adverse yet potentially preventable medical outcome'. (ACMG clarification p.664)
- Incidental findings in children –testing of children for adult onset conditions is in fact in the best interests of the child because if they carry a pathogenic mutation for an adult-onset condition, then it is likely that one of their parents also carries it, and preventing the disease in the parent is in the child's best interests. Also the general principle of not testing children for adult-onset conditions is designed for conditions that are identified in the family, and so for which the child will be offered testing later, during adulthood. However children undergoing genomic screening for other conditions are unlikely to be re-offered testing in adulthood and so will lose this opportunity to know their status later on. The risk of creating parenting difficulties related to knowing the future health of the child is said to be outweighed by the benefits of conveying medically useful information to the child. Finally they add that their recommendation about not conducting predictive testing for adult onset disorders in children does not apply in the case of WGS because reporting an incidental finding is not the same as a diagnostic test for an adult onset condition and therefore is not covered by the recommendations.

After a number of publications arguing against these recommendations, in conjunction with internal and external debate and a member survey, the ACMG announced in April 2014 that it would be changing its recommendations to propose that patients be given the option to opt-out of certain categories of results prior to having the test (ACMG news 2014).

iii. ACMG recommendations regarding reporting of suspected consanguinity

A further form of potential IF in the course of WGS is the discovery of likely consanguinity between the parents of the individual being tested. This type of IF was discussed in a separate ACMG document which contained the following recommendations: If the results of WGS are indicative of a first or second degree relationship between the parents of the individual tested, both the **result** (in terms of % of homozygosity) and the **interpretation** that there is a possibility of a first or second degree relationship should be clearly stated. For lower levels of homozygosity, only the result without an inference about the relationship between the parents should be given. The recommendations are based on the need for the clinician to be alerted to the increased likelihood of recessive disease, the lack of access of the laboratory to detailed family information, in particularly the presence or absence of multiple consanguinity within the family, and the need to alert clinicians to the possibility of abuse, particularly in the case of young and/ or intellectually disabled mothers. (ACMG standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing).

iv. ACMG guidelines on informed consent

Patients undergoing whole-genome sequencing should be informed of the possibility of incidental findings and the potential meanings of such findings, the categories of result which will be returned, and those which will not be reported, the limitations, benefits and risks of WGS and the potential implications for relatives, and what alternatives to WGS are available. Patients also have to be told whether data which is individually identifiable will be used in a database, and they should be given the opportunity to opt out of this if they so choose. The intention to re-contact or not should also be communicated. (ACMG: Points to consider for informed consent for genome/ exome sequencing).

v. Presidential commission for the study of bioethical issues

The US Presidential commission guidelines list 17 recommendations pertaining to medical testing and research, including but not limited to whole genome sequencing, 10 of which relate to clinical use of testing. They state the need to inform patients about the potential for incidental findings, the plan to communicate and manage these findings, and which types of findings will be returned and which will not be disclosed. They recommend the development of guidelines to classify and manage these findings. They emphasize the need for further research on the impact of incidental findings, alongside education for healthcare professionals and the public about incidental findings and the associated legal, ethical and practical considerations. They highlight the need for support from the healthcare system to allow time for discussion of incidental findings prior to conducting genomic tests, as well as access to care to act on findings where appropriate. The statement regarding patient preferences and incidental findings is somewhat ambiguous – it states that patient preference not to know incidental findings should be respected 'to the extent consistent with the clinician's fiduciary duty'. The importance of attempting to ensure patient comprehension of risk is emphasized, and the recommendations include a suggestion that clinicians should think about the use of supports to decision-making such as pictures and formal decision-aids. Risks should be given as absolute risk, using population-based evidence. The importance of tailoring tests to the needs of the patient is emphasized. Finally the recommendations call for the development of evidence-based standards for planned screening programs that consider the management of incidental findings.

vi. ESHG: Whole genome sequencing in health care

The ESHG recommends that whole genome sequencing should not be used where targeted sequencing would be effective, and that use of WGS requires justification in terms of an assessment of potential risks and benefits for each patient. If in the course of analysis for a clinical indication incidental findings are uncovered which indicate serious health problems for the patient or their family for which treatment or prevention would be available, these should be reported by the healthcare professional. The recommendations state that a patients' right not to know does not "automatically over-ride professional responsibilities if the patient's own health or that of his or her close relatives are at stake" (van El CG et al 2013a p. 582). In terms of testing children, the recommendations state that guidelines are needed to establish what results should be shared in order to balance autonomy, and needs of the child and parents to know or avoid knowing information that could also have implications for future offspring or other family members. There are

general recommendations calling for sharing of knowledge through specially-developed structures, the development guidelines for informed consent (which incorporate the potential for involvement in biobanks and research) and of guidelines for re-contacting patients, education of healthcare professionals, raising public awareness and building databases to facilitate interpretation of results. The recommendations acknowledge the need for further consideration before producing fixed guidelines. However they are vague on the topic of incidental findings – they recommend filtering out genetic variants that are known to be of little or no clinical utility but they do not suggest actively looking for variations in genes other than those thought to be related to the clinical problem. In a subsequent article published by some of the authors of the ESHG recommendations, they clarified that they did not see opportunistic screening as a justifiable use of WGS, and that obliging patients to accept the extra screening in order to get an answer to their clinical problem violates their right to autonomy (van El et al). They also state that the child's best interests may be more important than the right of the parents to have access to genetic information or to avoid receiving results, but that this is an area that requires further consideration. The authors evoke the blurring caused by clinical implementation of WGS not just between research and clinic, but between the clinical activity of diagnosis and the public health activity of screening.

vii. The Danish Council of Ethics

The Danish council of ethics recommendations are very clear on the subject of incidental findings. The patient should be able to decide if they wish to receive incidental findings, and the types of findings they want to be informed about. They acknowledge that the requirement in Denmark to record all relevant health information that the doctor receives creates difficulties as untargeted testing is likely to generate such results, and patients may come across these accidentally whilst accessing their electronic records.

The council reported difficulty coming to a consensus on the issue of limiting testing in minors, with some having the view that parents should be able to request genome testing for their children or access direct-to-consumer testing, whilst others were in favour of restricting such tests to situations in which there were strong medical arguments for doing so.

viii. Health Council of the Netherlands

This report which also considers the ethical and social issues arising from the increasing availability of WGS points out that the majority of health-relevant information which will be generated by WGS, even if used solely in the medical context and not for example as a direct-to-consumer product, will be about potential health problems other than that which was the indication for the test. Therefore, they suggest, the normative frameworks developed for screening may be relevant. They point to situations such as prenatal WGS, in which much information about a child who has not even been born will be generated. No recommendations are issued, but rather a call for guideline development, especially with regard to the management of incidental findings.

ix. PHG Foundation UK

The UK Public Health Genomics foundation has also published an extensive report examining ethical and social issues surrounding WGS. They recommend the introduction of WGS into clinical practice, but that its use should be limited, so that only 'variants of relevance to the specific condition are analysed and shared with patients('Next steps in the sequence' p. 155). They recommend the urgent development of bioinformatics expertise and infrastructure, in conjunction with the development of an evidence base consisting of standardized databases of normal and pathogenic variation, with 'linked analytical tools to facilitate clinical use' (p. 156).

In terms of genomic screening, the PHG calls for policy research to look into the implications of a more general use of WGS screening, either as opportunistic screening in those undergoing WGS for clinical indications or as a population screening tool. They highlight the relevance of established criteria for screening tests with their emphasis on strong evidence of clinical validity and utility, evaluation of risks and benefits and the ability of the healthcare system to provide appropriate follow-up care.

The remaining recommendations are for the development of best practice guidelines, education, transparent commissioning pathways and economic health modeling of the impact of genomic testing in the NHS (National Health Service), and for the establishment of a limited number of 'sequencing hubs' – specialist laboratories who would carry out the initial data generation and analysis to concentrate expertise and to provide a high quality service across the country.

Table 1: Overview of recommendations and guidelines for clinical use of WGS

Organisation/ Body	Opportunistic screening	Patient preferences	Testing of children	Database participation	Research and development requirements
ACMG	In favor but now support option to opt out	Not taken into account in 2013 version; pre-test opt out possible in 2014 version	Children should be treated no differently from adults	Patients should have right to opt out of databases	
Presidential Committee for the study of bioethical issues	Tests should be tailored to needs of patient	Ambiguous – preference not to know should be respected if it is consistent with fiduciary duty of physician			Impact of IFs, use of supports for decision-making
ESHG	Against – use targeted sequencing where possible	Taken into account (but right to know doesn't necessarily trump professional responsibilities)	Calls for guideline development	Sharing of knowledge to be supported	Informed consent guidelines, recontact guidelines, creation of databases to aid interpretation of results, public and professional education
Danish Council of Ethics	Not justified	Patient preference important	Council split		
Health Council of the Netherlands					No recommendations – call for guideline development
PHG Foundation	Not justified at present– only variants relevant to specific condition should be analysed. Need to look into implications of population screening use.				Need for bioinformatics expertise and infrastructure, standardized databases of variants, best practice guidelines, economic modeling and education. Development and use of specialist hubs for analysis.

The move towards clinical use of WGS has generated a strong response from clinicians, ethicists and other interested parties leading to a number of articles in this domain. The arguments raised in those articles will be considered in the next section.

b. Commentaries

The main target for commentaries was, perhaps unsurprisingly, the ACMG recommendations. This is unsurprising not solely because of the content of the guidelines, but also because the ACMG released specific recommendations for practice rather than recommendations for gathering more evidence about practice, in order to make practice recommendations.

i. Guideline development

Friedman Ross et al looked at the way in which the original ACMG recommendations were developed. Citing guidelines published by the Institute of Medicine in 2011 setting standards for 'objective, scientifically valid and consistent practice guidelines' (Freidman Ross p. 523),Friedman Ross et al state that the ACMG have failed to meet several of these standards, including failure to consult a sufficient cross-section of stakeholders, lack of quality of evidence on which to base guidelines, the presence of numerous conflicts of interests among the guideline developers, and lack of consideration of the consequences of implementing the recommendations (failure to consider coordination and cost of follow-up and re-contact). The authors point out that a set of recommendations issued by a group of recognized experts will potentially be used as a legal standard of care, with the result that healthcare professionals will be compelled to follow them in order to avoid legal action, even if they are in disagreement (a further reason to involve a good cross-section of stakeholders – naturally any set of guidelines is likely to meet disagreement from some of those who are expected to follow it, but a solid weight of agreement across the community of individuals and groups concerned is likely to make the guidelines more universally acceptable).

ii. Incidental findings

Arguments against the ACMG's recommendation for active screening for 56 genes include the fact that it ignores established criteria for conducting screening tests, and does not take account of previous experience with rolling out testing to asymptomatic individuals, where the penetrance is likely to be lower than in a group selected on the basis of phenotype (Friedman Ross et al). The principal way in which it violates established criteria for screening tests is that there is little or no evidence for most of the IF genes regarding 'predictive value of testing, genotype penetrance, spectrum of phenotypes and efficacy of interventions in unselected populations' (Burke et al p. 854). Burke et al point out that for the 56 genes, most of the patients who are undergoing WGS for a clinical indication will not have any suggestive symptoms. They argue that mutations in the 56 genes that have been identified as being pathogenic have previously been ascertained through looking at samples from symptomatic patients. There may therefore be a number of asymptomatic people or people with less severe symptoms who have not been identified, giving an exaggerated picture of the pathogenicity of the mutation.

The ACMG compare incidental findings in WGS to incidental findings in other areas of medicine, including radiological examinations. They argue that a tumour identified incidentally on MRI would be reported without first obtaining patient consent to give them that information, so why should WGS be any different? Burke et al argue that the difference is that the image that is generated in order to answer the clinical question in radiology also generates the incidental finding, and that the radiographer looking at the image cannot avoid seeing the incidental finding. However in WGS although the dataset generated includes the 56 genes recommended for analysis by the ACMG, the analysis is not usually performed for the whole dataset, but only for the areas of interest. The 56 gene set represents additional analysis that would not otherwise be performed (unless one of these genes was relevant to the patient's condition) (Burke et al). In addition Allyse and Michie claim that there is a qualitative difference between reporting on a physical abnormality detected on a scan, such as a tumor for which an operation may be available, and reporting a future risk of disease.

iii. Opportunistic screening?

The ACMG states that the deliberate search for mutations in the 56 gene panel is akin to other opportunistic screening that takes place in medicine, for example the routine assessment of blood pressure when attending a clinic for (for example) a chest infection. Burke et al emphasise the lack of evidence of improved health outcome that would be considered essential for other proposed

screening tests. They point to the rationale for this requirement for evidence of benefit, citing the tendency of screening to produce 'ambiguous results, unnecessary work-up, iatrogenic harm and false reassurance' (Burke et al p. 856). In a powerful illustration of this point, they cite the example of the recommendation of the US Preventative Services Task Force not to refer asymptomatic women in the general population for BRCA testing, a recommendation based on a systematic review of the harms and benefits (Burke et al). Furthermore, it is one of the primary lessons in basic statistics training that positive and negative predictive values of tests vary with the incidence of the disorder in the population being tested, and so a test is likely to perform differently in an unselected population than it would in a clinically affected one (Burke et al).

iv. Informed consent – should beneficence override autonomy?

The recommendation of the ACMG that IF results should be communicated on the basis that they could provide health benefit even if the patient does not want them has been labeled as 'honoring beneficence' at the expense of autonomy (Allyse and Michie). Criticisms of the ACMG's approach to denying patient preference in refusing information about incidental findings are directed to the justifications provided by the ACMG for what they acknowledge is a break from traditionally accepted ethical norms (Burke et al, Friedman Ross et al). It is argued that the rationale that it is difficult to provide adequate pre-test counseling to allow expression of patient preference is no excuse for not doing it (Friedman Ross). Allyse et al point to the lack of logic in arguing that obtaining informed consent (an established ethical norm) would be too burdensome, whilst at the same time not acknowledging the large burden that is likely to be placed on laboratories, healthcare professionals and patients if this screening is carried out. The ACMG claims that the lack of access of the general public to sequencing justifies screening those undergoing clinical testing against their wishes. This is refuted by stating that it is a. against normal ethical practice to force patients to receive medical information against their wishes, and b. there is no risk-benefit analysis available to help to justify going against current practice (Friedman Ross). Burke et al point to the 'virtually unlimited' right of patients to refuse even lifesaving treatment, and state that the requirement for all patients undergoing WGS testing for a clinical indication to agree to this testing is unacceptable because omitting the 56 gene screen would not alter the clinical efficacy of the test. In addition, such a policy could lead to patients refusing to have the WGS test, thus interfering with their clinical management (Burke et al). Allyse et al argue that it is very close to coercion if, in order to access a

'potentially life-saving' test for a medical condition, one is obliged to accept information about other conditions that one may develop in the future (Allyse et al p.440).

v. Testing children for adult-onset conditions

Friedman Ross et al object to the ACMG's recommendation that screening should also be performed on children undergoing WGS for clinical indications (including screening for adult-onset conditions), on the basis that it goes against the professional standard of acting in the best interests of the child. This principle of best interests for the child has been supported by a number of national and international guidelines, including the ACMG themselves. The argument advanced by the ACMG that genomic screening that provides useful information for the health of parents is in the child's best interests is criticized both by Burke et al and Friedman Ross et al as unethical because it uses a child as a means to provide health benefit for the parent (Burke, Friedman Ross et al). Interestingly Wade et al point to the experiences with neonatal screening which highlight the utility of involving parents in screening decisions for children (Wade et al). They suggest that research around children's reactions to information from WGS and from living with risk information be gathered and taken into account (Wade et al).

vi. Other issues

Experts point to a number of other problems with the ACMG recommendations. Firstly, many of the ethical arguments used to justify the recommendations have as part of their basis the fact that WGS provides easy access to a large amount of useful data (the 'incidental findings'), and that avoiding generation of this data would in fact impose a burden on the laboratory. However there is evidence that looking for, checking and reporting these variants in fact represents a significant expenditure of resources (Burke et al). Secondly, tests ordered by a range of doctors from non-genetics specialties will end up generating more patients for clinical geneticists, as diseases are uncovered which are out of the domain of expertise of the requesting doctor (Friedman Ross). As there is already a shortage of clinical geneticists, it is not realistic to expect that this increased demand can be met. Friedman Ross et al highlight the danger that the recommendations will end up being applied to all domains in which WGS will eventually replace other forms of genetic testing, and thus introduce screening that does not fulfill standard criteria into a number of areas such as neonatal screening. Burke et al

emphasize a need for consideration of the potential harms of WGS as a screening tool, including medicalising healthy people and generating unnecessary expenditure for the healthcare system (Burke et al).

III. Literature review – issues in the clinical application of whole-genome sequencing

a. Incidental findings

The occurrence of incidental findings, despite being acknowledged as an inevitable corollary to the practice of clinical investigations generally, has incited intense and wide-ranging debate. Even the term itself has been the subject of some controversy, as some argue that the frequency of such findings (500 per patient in one author's experience (Majewski et al)) means that they should be seen as an inevitable part of the process rather than an occasional 'side-effect' of testing (Lyon, Majewski et al). Although IFs in WGS have been compared to IFs in radiology, there are reasons for considering WGS differently. The variety of potential findings and the possibility of evolving interpretation mean that a finding which is not deemed relevant to the presenting complaint at the time of original analysis may be so considered in the future. In the new paradigm of genetic testing that is WGS, the term 'incidental findings' may itself present a barrier to effective use and understanding of this technology (Parens et al). Defining 'potentially actionable results' may be complicated by the circumstances of the patient – for example a result may not be clinically actionable, but may impact on the reproductive decisions of a couple (Christenhusz et al). Categorisation of results into 'actionable' or 'non-actionable' may therefore be an oversimplification (Christenhusz et al). Opinions vary as to how much access to results is desirable.

Lohn et al carried out a study of 210 genetics professionals in Canada – which showed that 84% of genetic counselors and 79% of geneticists felt that families should be offered a choice about which IFs are returned to them. The majority were in favour of returning results related to 'serious treatable conditions' (Lohn et al p. 547), and were generally more restrictive in the categories of IF results that they would be willing to return for a pediatric patient. Lemke et al's study in the USA asked clinical genetics professionals which types of IFs they personally would want to know about in themselves. Virtually all expressed a desire to know about 'clinically actionable' findings in themselves or their children, and three quarters wanted to know about an adult onset clinically

actionable disorder or a childhood onset non-actionable disorder in their child. Virtually the same proportion of healthcare professionals were in favour of disclosing results to patients for each category.

Christenhusz et al undertook a systematic review of ethical reasons for and against disclosing IFS Most authors recommend that IFs with known clinical utility and the possibility of prevention or treatment should be shared, but Christenhusz et al raise the question of what exactly should count, as reproductive decisions could potentially count as preventions etc. Christenhusz et al also ask whether informed consent could be used to consent to others making many of the decisions about IFs e.g. that they not be analyzed at all. They state that this would be in conflict with autonomy and privacy but may be most effective way of promoting beneficence. They point out that many people scarcely know what genes are or how they work, and it is thus impractical and unreasonable to expect them to make complex decisions about whether or not IFs should be returned to them. The authors recommend automated filtering systems that obviate the need for consideration of unwanted IFs. Christenhusz et al noted that the majority of the articles referred to research situations and less than a third of them had a clinician as a contributing author.

Crawford et al made the point that in order to know whether an incidental finding has clinical significance or not it may well be necessary to do family studies to determine information such as whether the variation is de novo or inherited. Without this information it may be impossible to determine pathogenicity. They argue that disclosure or not may become a moot point in this situation, and underline the potential implications of a process that may lead to testing and perhaps screening of healthy individuals. Significantly they argue that the impact of uncertain incidental findings may in fact be greater than when the findings show a definite risk of disease. The ACMG has highlighted the fact that consanguinity is a potential 'incidental finding' when using WGS. They discuss the importance of this finding in the consideration of recessive mechanisms for disease, but also as a marker of potential abuse, particularly when the mother is a minor or otherwise vulnerable (ACMG standards and guidelines for documenting suspected consanguinity). Bunnick et al state that they are not in favor of a 'one-size-fits-all' offer of testing where decisions are made for the patient as to which types of results will be returned, nor of giving patients complete control as that could compromise the autonomy of others (eg children). They suggest instead offering a selection of options from which the patient can choose that which best answers their personal needs. This selection of results categories has already been instigated in some departments (Dimmock). Yu et al suggest a different model of results return. Citing the difference between traditional genetic test

results, which often involve a single positive or negative response to a clinical question, and for which the meaning of the results is stable and unlikely to change drastically over time, and WGS results which are numerous and evolving, they call for an altogether different approach. Their idea is to view WGS results as a 'dynamic resource of information from which results should be 'managed' over a lifetime' (Yu et al p. 684). They point to a lack of empirical evidence about harmful consequences of learning one's genetic status and state that a paternalistic approach to results return is therefore untenable. Their model sees patients having complete control over the use and sharing of their results, consistent with the principle of respecting autonomy, maximizing benefit and minimizing harm. They also feel that this approach could bring greater access to WGS across cultures as its flexibility allows for adaptation to cultural values. They also feel that a traditional approach to returning results places unrealizable demands on healthcare resources; particularly in terms of personnel and that their model will overcome this difficulty.

b. Informed consent

From the reviewed literature two main viewpoints emerged regarding the approach to informed consent. Some authors used the traditional model of informed consent, generating lists of the types of information that should be conveyed. Such lists included the types of information which could be obtained, who would be given access to the data, plans for storage and protection and the potential harms of authorized and unauthorized access (Thompson et al, Bunnik et al). A requirement for such detailed information giving is difficult in practice, and may not meet the aims of promoting autonomy and detailed decision-making (Dondorp and de Wert, Thorogood et al, Sijmons et al, Bunnik et al). Tabor et al studied the views of patients on the benefits and potential harms of WGS. They studied 2 families and found that their participants were largely unconcerned about issues related to privacy and data sharing, but had strong views on the need for flexibility in the return of results. The authors commented that the context of these two families (families with known rare genetic conditions) gave them a particular view about the risks of privacy and data sharing versus the potential benefits of genetic information. They noted that the wide range of preference regarding results sharing indicated a need for responsiveness to patient requests and that a web-based tool which allowed patients to manage their results may be beneficial. The paper was written from the perspective that the patients were research participants, but the details of the case given made it clear that this was one of the large number of genetics cases which crosses the line between research and clinic. Of note the consent form was 9 pages long and the consent information-giving session lasted 2-3 hours.

A second approach called for developing new models of consent, aimed not at giving exhaustive amounts of information but rather focused on promoting autonomous decision-making (29, 32). As Majewski et al and Parens et al have pointed out, informed consent rose to prominence in medical ethical practice originally as a means of protecting vulnerable people against unscrupulous medical researchers, and so the model that arose from such a protective process may not be the best tool for WGS, where patients are often eager to use this tool to empower them to gain information about their health (Majewski et al). The main areas to address under this type of model would not be infinite detail on every possible result, but rather more general issues such as identifiability of data and the uncertainties around management of data of evolving significance. (Majewski et al). Bunnik et al describe this way of respecting autonomy as a compromise between giving the greatest amount of choice and retaining comprehensibility of information.

c. Testing children

Discussion of the use of WGS in children primarily centres around management of incidental findings, and in particular which results should be shared with the child's parents. Wade et al note that there is very little empirical research on the topic of WGS in children but that related research on the impact of genetic risk information for single gene disorders shows no psychosocial harms from single gene testing in children . The authors pointed to concerns with the designs of these studies and cautioned against extending this evidence to deduce a lack of negative impact from WGS. They highlight the anticipated burden on the healthcare system due to non-genetic specialists ordering tests and not being able to manage the results, thus increasing demand on specialist genetic services. Wade et al argue that WGS testing should not be restricted on the basis that it may reveal adult-onset disorders that the child could have decided about knowing about later. They argue that this is consistent with other examples where parental authority is accorded a high value unless there is 'serious and demonstrable risk to the child' (Wade p. 546). Donley et al caution that the issue is more complex than simply a question of which results should be shared. The fact that the healthcare professional must make a decision about sharing or not sharing information may in itself lead to conflict and alterations in the healthcare-professional relationship. A particularly problematic area is the tension between safeguarding the future autonomy of the child, and sharing information with the family which might have an impact on their health. Benefit for the child may also come in the form of reduced parental distress, or improved parental health (May et al, Yurkiewicz et al, Dimmock). A further concern with WGS testing of children is that incidental findings such as factors

influencing intelligence or sporting ability may influence child-rearing decisions in an inappropriate and potentially harmful way (Dondorp and de Wert).

d. Prenatal testing

Prenatal testing raises interesting challenges. On the one hand, it has been argued that parents have the right to access information which would influence their reproductive choices, and that information generated by WGS may fit into this category (Yurkiewicz et al). In addition, as with performing WGS testing on children, information may be generated which has health implications for other family members. However, some authors have pointed out that performing WGS would lead to a situation in which many more pregnant women were confronted with decisions about whether or not to continue based on genetic test results as nearly every result would include some questionable findings (Dondorp and de Wert). The idea of a 'normal healthy baby' would be altered as most fetuses in whomWGS was performed would show some genetic variants of varying significance (Donley et al). Other concerns include the fact that if the test exists, there may be pressure (overt or otherwise) on parents to accept the offer of testing, and correspondingly the threat of parental liability for failing to act on the results (Donley et al, Sijmons et al). Arguments in favour of fetal WGS include access to health information and early intervention, and from a societal point of view, information about the prevalence and progression of disease (Lyon and Segal, Dondorp and de Wert). If a pregnancy is continued after WGS, the child's future right to decide if he wishes to know his genetic status may be compromised (Chadwick, Robertson).

e. Storage of data and re-contact

As the number of patients undergoing WGS increases, it will rapidly become extremely difficult for clinical departments to go back through patient data and re-contact patients each time a variant is newly discovered to be clinically significant. A number of authors have pointed out that a solution could be to manage this data via automatic computer analysis of stored genomic data, so that a computer alert is generated when new information comes to light that changes the previous interpretation of an individual's data (Drmanac, Pyeritz). Consideration also needs to be given to data which has been generated but that the patient does not currently want, or data from children which is intended for them to be able to access when they reach adulthood. Storage needs to be secure and reliable, and the possibility of accidental sharing needs to be avoided (Dondorp and de Wert). The

issue of data sharing also arises – in order to improve data interpretation capabilities there is a need to share the most complete data possible but this increases the risk of loss of anonymity. Related to data storage is the possibility of re-contacting patients if new information comes to light concerning variants that have been found in the course of their WGS test. One difficulty is that although at the time of testing patients might make a decision about whether or not they would want to be re-contacted in the event of further information coming to light, their circumstances might change in the interim, making such information more or less relevant (Dondorp and de Wert).

Some authors have pointed out the practical challenges involved in any scheme to re-contact patients, including the difficulty of drawing the limits of the physicican's responsibilities in this domain. One author in the Netherlands reported his department's policy of asking patients to recontact the genetics department after 2 years or in the event that there is a new piece of family or personal medical history, or simply if they are at a moment in their life where they feel that WGS information may be of benefit to them (Sijmons et al). Another department arranges annual follow-up for patients to allow them the opportunity to find out more or to clarify previous results given (Dimmock).

f. Solidarity and equity

There has been a relatively recent trend in ethical arguments related to genetic technologies to increase emphasis on 'non-traditional' concepts such as solidarity and equity rather than the individualistic autonomy-focused arguments that have been at the forefront of bioethics discussions in the past (Chadwick). Definitions of solidarity and equity in relation to genomics were given in the 2007 HUGO statement on Pharmacogenetics, Solidarity and Equity:

Solidarity: Because of shared vulnerabilities, people have the common interests and moral responsibilities to each other. Willingness to share information and to participate in research is a praiseworthy contribution to society.

Equity: To reduce health inequalities between different populations, and to work towards equal access to care is an important prerequisite for implementing genomic knowledge for the benefit of society. Chadwick discusses how the internationalization of the genomics endeavor, made necessary by the need to create large databases of variants, requires a shift in ethical thinking and in particular a harmonization of ethical standards. Some authors have suggested that patients should control how much of their information is shared (Sijmons et al, Thompson), leading to the possibility of more openness than might occur if sharing is controlled by healthcare professionals. It may be that consenting to open sharing of genomic data acknowledges a commitment to autonomy (in other

words that if we believe in the right to self-determination this should include the right to decide to waive privacy rights), and that rather than taking potentially futile and progress-limiting steps to ensure data privacy we should instead acknowledge that the most efficient way to advance genomic understanding is to allow genomic data to be shared (Ball et al). This is the approach taken by the Personal Genome Project (www.personalgenomes.org).

On a smaller scale, performing family genomic sequencing rather than just analyzing one isolated individual gives more accurate interpretable results (Drmanac). For WGS to achieve it's full potential as a useful genetic technology, it may be that a paradigm shift in the way that we position the individual in relation to society is needed.

IV. Next steps

The efficient use of genomic data requires a high level of national and international cooperation to quickly develop the expertise to interpret the data. It is urgent therefore that guidelines are developed that allow for the ethical collection, storage and use of data. This poses particular ethical challenges as ethical opinions vary both across and within cultural contexts. In addition the problem of evidentiary lag-time means that there is a void between introduction of the technology into practice and formulation of guidelines during the period of collection of evidence. Other urgent areas for consideration include WGS testing prenatally and in children, especially with regard to return of results to parents, and more generally management of return of results to patients. Whilst it is commendable that recommendations identify a need for further research and development in a number of areas, it is critical that provisional recommendations are made to ensure that regulatory and expert bodies are able to set standards. A way of using relevant past experience in other domains must be found in order to be able to formulate such recommendations in the interim data gathering period.

V. Appendix – List of resources, Recommendations and References

A. List of resources

American College of Medical Genetics and Genomics

https://www.acmg.net/

European network for Public Health Genomics (PHGEN)

http://www.phgen.eu/typo3/index.php

European Society of Human Genetics

https://www.eshg.org/

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

http://www.egappreviews.org/

Danish Council of Ethics

http://www.etiskraad.dk/en.aspx

Nuffield Council on Bioethics

http://www.nuffieldbioethics.org/

Presidential Commission for the Study of Bioethical Issues

http://www.bioethics.gov/

Public Health Genomics (PHG) Foundation UK

http://www.phgfoundation.org/

The Health Council of the Netherlands

http://www.gezondheidsraad.nl/en

The Personal Genome Project

www.personalgenomes.org

EURAT - Ethical and Legal Aspects of Whole Genome Sequencing

http://www.marsilius-kolleg.uni-heidelberg.de/mk_projects/totalsequencing.html

B. List of Recommendations and Policy Documents Reviewed

ACMG Board of Directors (2013) Points to consider for informed consent for genome/ exome sequencing. Genetics in Medicine 15(9): 748-749.

ACMG.ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. (2013). https://www.acmg.net/ACMG/Publications/Policy_Statements/ACMG/Publications/Policy_Statements.aspx?hkey=6b7572b3-d01c-42a5-b59e-c0593347751c, downloaded 26/02/2014

ACMG.Rehder C, David K, Hirsch B, Toriello H, Wilson C, Kearney H. (2013) ACMG standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing. Genetics in Medicine 15(2) 150-152.

EGAPP.Veenstra D, Piper M, Haddow J, Pauker S, Klein R, Richards C et al. (2013) Improving the efficiency and relevance of evidence-based recommendations in the era of whole-genome sequencing: an EGAPP methods update. Genetics in Medicine, 15(1) 14-24.

European Commission/ Public Health Genomics European Network.European Best Practice Guidelinesfor Quality Assurance, Provision and Useof Genome-based Information and Technologies, PART III: European Best Practice Guidelines for Use of Genome-based Information and Technologies (2012)

European Commission.25 Recommendations on the ethical, legal and social implications of genetic testing (2004).European Communities, Luxembourg.

European Society of Human Genetics.(2013). Whole-genome sequencing in health care. European Journal of Human Genetics 21: 580-584.

Nuffield Council on Bioethics.terMeulen R, Newson A, Kennedy M-R, Schofield B. (2011) Genomics, health records, database linkage and privacy. Background paper.http://www.nuffieldbioethics.org/publications accessed on 26/02/2014.

Nuffield Council on Bioethics. Emerging biotechnologies: technology, choice and the public good. http://www.nuffieldbioethics.org/publications, downloaded 27/02/2014

Presidential Commission for the Study of Anticipate and Communicate. Ethical Management of Incidental and Secondary Findings in the Clinical, Research and Direct-to-Consumer Contexts http://bioethics.gov/node/3183, downloaded 25/02/2014

The Danish Council of Ethics.(2013) Genome testing.Ethical dilemmas in relation to diagnostics, research and direct-to-consumer testing.http://www.etiskraad.dk/Udgivelser/BookPage.aspx?bookID={0F84411D-1DD3-49CD-B8ED-679D29419E20}, downloaded on 27/02/2014

B. References

Abdul-Karim R, Berkman BE, WendlerD, Rid A, Khan J, Badgett T.(2013) Hull S.C. Disclosure of incidental findings from next-generation sequencing in pediatric genomic research. *Pediatrics* 131 (3) (pp 564-571).

Allyse M, Michie M. (2013) Not-so-incidental findings: the ACMG recommendations on the reporting of incidental findings in clinical whole genome and whole exome sequencing.*Trends in Biotechnology*31(8):439-41.

Ayuso C., Millan J.M., Mancheno M., Dal-Re R. (2013) Informed consent for whole-genome sequencing studies in the clinical setting.Proposed recommendations on essential content and process.*European Journal of Human Genetics*. 21 (10) (pp 1054-1059).

Ball M, Thakuria J, Zaranek A, Clegg T, Rosenbaum A, Wu X. (2012) A public resource facilitating clinical use of genomes. *PNAS* 109 (30)11920-11927.

Biesecker L, Burke W, Kohane I, Plon S, Zimmern R. (2012) Next-generation sequencing in the clinic: are we ready? *Nature* 13: 818-824.

Bunnik, Eline M. De Jong, Antina. Nijsingh, Niels [et al.] (2013)The New Genetics and Informed Consent: Differentiating Choice to Preserve Autonomy.*Bioethics*. Jl. 27(6), 348-355.

Burke W, Matheny Antommaria A, Bennett R, Botkin J, Wright Clayton E, Henderson G. (2013). Recommendations for returning genomic incidental findings? We need to talk! *Genetics in Medicine* 15(3):854-859.

Caulfield T, Evans J, McGuire A, McCabe C, Bubela T, Cook-Deegan R, et al. (2013) Reflections on the cost of "low-cost" whole genome sequencing: Framing the health policy debate. *PLOS Biology* 11(11): e1001699 accessed 25/02/2014.

Chadwick R. (2011) Personal Genomes: No bad news? *Bioethics* 25(2):62-65.

Christenhusz G, Devriendt K, Dierickx K. (2013). To tell or not to tell?A systematic review of ethical reflections on incidental findings arising in genetics contexts.*European Journal of Human Genetics* 21:248-255.

Clayton E.W., Haga S., Kuszler P., Bane E., Shutske K., Burke W. (2013)Managing incidental genomic findings: Legal obligations of clinicians. *Genetics in Medicine*. 15 (8) (pp 624-629).

Crawford G, Foulds N, Fenwick A, Hallowell N, Lucassen A. (2013)Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. *Genetics in Medicine*15, 896-899.

Christenhusz G.M., Devriendt K., Dierickx K. (2013) To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts.*European Journal of Human Genetics*. 21 (3) (pp 248-255).

Desai A, Jere A. (2012) Next-generation sequencing: ready for the clinics?*Clinical Genetics* 81:503-510.

Dimmock D. (2013) Whole genome sequencing: A considered approach to clinical implementation. *Current Protocols in Human Genetics*.9.22.1-9.22.7 (SUPPL.77).

Dondorp WJ, de Wert GM. (2013) The ‘thousand-dollar genome’: an ethical exploration. *European Journal of Human Genetics* 21: S6-S26.

Donley G, Chandros Hull S, Berkman B. (2012) Prenatal whole genome sequencing. Just because we can, should we? *Hastings Centre Report* 42(4): 28-40.

Dorschner M, Amendola L, Turner E, Robertson P, Shirts B, Gallego C, et al. (2013) Actionable, pathogenic incidental findings in 1,000 participant’s exomes. *Am J Med Genet* 93, 631-640.

Drmanac R. (2012) The ultimate genetic test. *Science* 336 1110-1112.

Dondorp WJ, de Wert GM. (2013) The 'thousand-dollar genome': an ethical exploration. *European Journal of Human Genetics*.21 Suppl 1 (pp S6-26).

Farberov L., Gilam A., Isakov O., Shomron N. (2013).Meeting summary: Ethical aspects of whole exome and whole genome sequencing studies (WES/WGS) in rare diseases, Tel Aviv, Israel, January 2013. *Genetics Research*. 95 (2-3) (pp 53-56).

Friedman Ross L, Rothstein M, Wright Clayton E. (2013) Premature guidance about whole-genome sequencing. *Personalized Medicine* 10(6):523-526.

Hambuch T., Laurent M., Sickler B., Liao A., Cotter P., Jain S., Lyan Y., Bernd J., Daniel J.O., Poggio P., Ross M., Bentley D. Whole genome sequencing in the clinical laboratory. *Journal of Biomolecular Techniques.* Conference: 2011 Annual Meeting of the Association of Biomolecular Resource Facilities, ABRF 2011 San Antonio, TX United States.

Howard H.C., Swinnen E., Douw K., Vondeling H., Cassiman J.-J., Cambon-Thomsen A., Borry P. (2013) The ethical introduction of genome-based information and technologies into public health. *Public Health Genomics*. 16 (3)100-109.

Groisman I, Mathieu G, Godard B. (2012) Use of next generation sequencing technologies in research and beyond: are participants with mental health disorders fully protected? *BMC Medical Ethics* 13: 36.

Gullapalli RR, Ketaki VD, Santana-Santos L, Kant JA, Becich MJ. (2012) Next generation sequencing in clinical medicine: challenges and lessons for pathology and biomedical informatics. *J Pathol Inform* 3: 40.

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.

Lantos J, Artman M, Kingsmore S. (2011) Ethical considerations associated with clinical use of next-generation sequencing in children. *The Journal of Pediatrics*. 159: 879-880.

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.

Lunshof J.E. Whole genomes, small children, big questions.*Personalized Medicine*.9 (7) (pp 667-669), 2012.

Lyon G.J. (2012) There is nothing 'incidental' about unrelated findings. *Personalized Medicine*. 9 (2) (pp 163-166).

Lyon G.J., Segal J.P. (2013).Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape.*Applied and Translational Genomics*. 2 (1) (pp 34-40).

Lysaght T. HUGO statement on next generation genomic sequencing.HUGO Journal 4: 84-85. Conference abstract: 14th Human Genome Meeting 2010, HGM Montpellier France.

May T., Zusevics K.L., Strong K.A. (2013) On the ethics of clinical whole genome sequencing of children.

Pediatrics. 132 (2) (pp 207-209),.

Majewski J, Schwartzentruber J, Lalonde E, Montpetit A, Jabado N. (2011) What can exome sequencing do for you? *J Med Genet* 48:580-589.

McCormick, Jennifer B. (2013) Whole Genome Sequencing.*Lahey Clinic Medical Ethics*.20(1), 1-2.

Miller D.T., Alfares A.A. (2012) Whole-genome sequencing: Ready for prime time?*Clinical Chemistry*. 58 (12) (pp 1729-1730).

Parens E, Appelbaum P, Chung W. (2013) Incidental findings in the era of whole genome sequencing ?*Hastings Centre Report*.17-24.

Pyeritz R. (2011) Duty to re-contact in the genomic age.*Hematology Reports* 3(s2) 38-39.

Raffan E, Semple R. (2011) Next generation sequencing – implications for clinical practice.*British Medical Bulletin* 99: 53-71.

Rehder CW, David KL. Hirsch B, Toriello HV, Wilson CM, Kearney HM. (2013) American College of medical genetics and genomics: Standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing. *Genetics in Medicine*. 15 (2) (pp 150-152).

Robertson JA.(2003) The $1000 genome: ethical and legal issues in whole genome sequencing of individuals.*The American Journal of Bioethics*.3 (3) (pp W-IF1).

Sharp RR.(2011) Downsizing genomic medicine: Approaching the ethical complexity of whole-genome sequencing by starting small. *Genetics in Medicine*. 13 (3) (pp 191-194).

Sijmons RH, van Langen IM, Sijmons JG. (2011) A clinical perspective on ethical issues in genetic testing.*Accountability in Research*. 18 (3) (pp 148-162).

Sullivan W, Newman W, Ramsden S, Scheffer H, Payne K. (2012) Developing National Guidance on Genetic Testing for breast cancer predisposition: The role of economic evidence? *Genetic Testing and Molecular Biomarkers* 16(6):580-591.

Tabor H, Berkman B, Chandros Hull S, Bamshad M. (2011) Genomics really gets personal: How exome and whole genome sequencing challenge the ethical framework of human genetics research. *Am J Med Genet* Part A 155: 2916-2924.

Tabor H, Stock J, Brazg T, McMillin M, Dent K, Yu J-H, Shendure J, Bamshad M. (2012) Informed consent for Whole Genome Sequencing: A qualitative analysis of participant expectations and perceptions of risks, benefits and harms. *Am J Med Genet* Part A 158A:1310-1319.

Tarini BA, Goldenberg AJ. (2012) Ethical issues with newborn screening in the genomics era.*Annual Review of Genomics and Human Genetics*. 13: 381-393.

Thompson R, Drew CJG, Thomas RH. (2012). Next generation sequencing in the clinical domain: Clinical advantages, practical, and ethical challenges. *Advances in Protein Chemistry and Structural Biology*. 89:27-63.

Thorogood A, Knoppers BM, Dondorp WJ, de Wert GMWR.(2012) Whole-genome sequencing and the physician.Clinical Genetics. 81 (6): 511-513.

Yu J-H, Jamal SM, Tabor HK, Bamshad MJ. (2013) Self-guided management of exome and whole-genome sequencing results: Changing the results return model. *Genetics in Medicine*. 15 (9): 684-690.

Yurkiewicz IR, Korf BR, Lehmann LS.(2014). Prenatal whole-genome sequencing - Is the quest to know a fetus's future ethical? *New England Journal of Medicine*.370 (3):195-197.

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.

Wade C, Tarini B, Wilfond B. (2013) Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families and Pediatric Practice. *Annu.Rev.Genomics* Hum.Genet.14:535-55.

Wilfond B. (2012) Predicting our future: lessons from Winnie-the-Pooh. *Hastings Centre Report*: 3.