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Whole genome sequencing and analysis and the challenges for health care professionals: recommendations of the European Society of Human Genetics.

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Introduction

In recent years the cost of generating genome information has shown a rapid decline (Service 2006). High throughput technology makes it possible to sequence the whole exome or genome of a person at a price that is affordable for some health care systems. Thus, services based on this technology are becoming available for patients at an increasing pace. There is, therefore, a need to discuss how best to structure the offer of these services logistically and determine clinical utility of genetic testing so that patients can receive appropriate advice and genetic testing. The Public and Professional Policy Committee (PPPC) and the Quality Committee (QC) of the European Society of Human Genetics (ESHG) have discussed these challenges at a joint workshop in Gothenburg, Sweden, in 2010 (Hastings et al. 2012), and several workshops in 2011 (PPPC January 2011 in collaboration with the EU-funded project TechGene; and PPC January 2012; QC June 2011). A report for the Netherlands Health Council has served as Background Document for the PPC's reflections (Dondorp & De Wert 2010). Focusing on the clinical diagnostics setting, this paper with recommendations for health care professionals, is intended to contribute to the discussion and the development of guidelines in this fast moving field. The paper and recommendations are posted on the ESHG website from June 20 to August 1, 2012, and the membership is invited to comments. The final version will be sent to the ESHG Board for approval.

Considerations

The changing landscape of diagnostic genetic testing in health care

Until recently, a diagnostic genetic test tended to focus on one specific question. In case of clinical suspicion of a monogenic condition, DNA analysis of one or a few specific genes was performed, while in cytogenetics the whole genome was analysed at a relatively low resolution of 5-10Mb to answer a defined clinical question. Increasingly, however, diagnostic tests may now look at a large panel of genes (e.g. breast cancer genes, or genes implied in cardiovascular events) via targeted DNA sequencing or microarrays. In addition, high resolution next generation sequencing techniques that may detect mutations throughout the genome, are being introduced diagnostically. Whole genome or exome sequencing (WGS, WES) generates an enormous amount of raw data that needs complex bioinformatic analyses to generate useful information. Depending on the aim of the test, the analysis may focus on the entire genome (whole genome analysis, WGA), the exome (whole exome analysis, WEA), a selection of genes, the quantitative comparison between copies of different chromosomes, or other selected analyses. Expectations and experiences of the recent changes in DNA-laboratory methods with targeted DNA sequencing or microarrays might be used to improve

the understanding of the challenges for professionals as WGS and WES are introduced into health care.

WES is already in use in several labs in a diagnostic setting (Durbin 2010). As far as WGS is concerned, several groups have sequenced individual genomes (Wheeler 2008), or are conducting research, such as in the Personal Genome Project (Lunshof et al 2010). A proof of principle regarding the clinical utility of WGS followed by WGA has been reported (Ashley 2010; Lupski 2010). Moreover, expectations of personalized medicine appear to become more likely by the use of whole genome technologies. In the Ashley paper (2010), pharmacogenomic variants were found that could guide therapy; the detection of carrier status of cystic fibrosis in this analysis could possibly lead to testing of the partner and in case of a carrier couple, this could affect reproductive options. Furthermore, the detection of the mutations associated with sudden death may lead to cardiologic consultation with management implications. In an example from cancer research findings of distinct genetic mutations in the tumours of a patient (Gerlinger 2012) may lead to targeted therapeutic strategies. Initial successes in diagnosing hitherto unknown causes and/or predictors of disease have raised expectations on the wider use of WES and WGS (Vissers 2010). The different settings where whole genome techniques might be applied (research, pharmacogenomics, diagnosis in patients with symptoms, presymptomatic testing, population screening programs) raise different questions. The focus of this paper will be on the challenges presently encountered in the diagnostic setting, and their relevance for these other settings.

The advantages and challenges of whole genome sequencing and analysis

An obvious advantage of next generation sequencing techniques is the greater potential to find the genetic component of health problems, and probably, in the near future, at a lower cost than that of currently used techniques (Heger 2011). The sheer mass of data generated can reveal disease-causing alleles that could not be detected otherwise. Moreover, cheap technology generating more and more genomic information may be expected to contribute to improved health care.

In the clinical context, the challenges of handling vast amounts of information, most of which will not be relevant for the patient, has prompted some groups to focus or target their analysis using filters. However if the focus is narrowed too soon in the analysis or too restrictively, potential disease-causing alleles or regions may be missed. This could mean that the use of filters would hinder the diagnostic process. WGA or WEA could be applicable to a range of different disorders, and new variants could more easily be added to the interpretation (Heger 2011). Drawbacks of this approach are that the analysis may be too time-consuming and that a larger number of unsolicited findings will burden the diagnostic process and strain informed consent procedures. In the different context of population screening, targeted programs such as prenatal screening for Down syndrome, may profit from the high sensitivity and specificity reached by massive parallel sequencing, where the analysis focuses on a very specific analysis: the numerical comparison of fetal DNA fragments in maternal blood (Chiu et al. 2011).

Challenges at the interface of health care and research

In establishing a diagnosis it is crucial to know whether or not a mutation can be interpreted as a causal variant for a specific disorder. Known causal variants of genes with proven clinical validity may therefore be the focus of initial analyses. If a causal variant cannot be detected, then wider or in depth analyses need to be considered. In a diagnostic context it has been argued that a high sensitivity is needed to reduce the number of false negatives and to avoid missing potential disease-causing variants (Berg et al. 2011). Whereas genes of uncertain

clinical validity would have been disregarded in the first instance, it is unclear what status they should have in the second instance. It is debatable whether variants of uncertain clinical validity should be communicated to a patient or family members and included in a person's medical file. The number of variants are likely to increase as more genetic regions are scanned. However, for research purposes it certainly is important to document these genes and variants and make the information available to other researchers. Protocols need to be established as to whether and how whole genome information should be documented, shared and stored and for how long. Given the pace of discoveries, it is paramount that accessible biobanks and databases are created with up-to-date genotype and phenotype information on variants and patients.

In this way, as patients almost automatically become included in scientific research activities, there is a risk that their individual interests are subordinated to the research aims of their doctors. For instance, a new and not yet understood finding may help to develop knowledge and thus be highly important from a research perspective, while in the clinic it may be an irrelevant positive finding, difficult to explain to the individual, leading to stress and uncertainty for parents or patients, or even to inappropriate patient management. Current ethical and legal norms require that doctors give priority to the interests of their patients so that patients are not turned into research subjects without their informed consent. However, as diagnostic testing for the purposes of health care and biobank research (Meulenkamp 2010) tend to become intertwined activities, relevant normative frameworks including consent procedures for diagnosis, research, disclosure and storage need to be reconsidered and if necessary adapted to the challenges of the new situation. For instance, many research protocols state that no information about test results will be given to individual participants because the research findings may need to be confirmed in long lasting follow-up studies. However, as WGA may lead to the identification of variants with known clinical relevance, many people argue that individual feedback should be given if the possibility of an individual health benefit is realistic (Wright 2011, Bredenoord 2011). There is a necessity to teach and train healthcare practitioners to follow, digest and properly interpret this genomic tsunami. As science progresses, knowledge on validity is constantly evolving. Evidence can only be established while doing research, which calls for a flexible service provision. Thus the question emerges on how and when a patient should be recontacted as new information becomes available on potentially relevant genetic variants. A general duty to recontact cannot be maintained given the impossibility to delimit its scope. However, balancing pros and cons may require recontacting when findings have a potentially high information value, for example therapeutic options might emerge for some disorders. New ways of communicating via web sites, forums and social media may be explored to give patients or participants access to their data or to actively recontact them. Patient interest groups could be consulted for advice regarding this issue. With this in mind, counsellors must prepare patients and their general practitioners to deal with uncertainty, and should explain the possibility that variants of unknown significance may be found before the analysis is undertaken.

Unsolicited findings

The issue of incidental findings as a challenge for diagnostic testing is not new. For instance, karyotyping for mental retardation and multiple congenital anomalies may identify mutations that were not initially considered. Certainly array techniques, such as array comparative genomic hybridisation (CGH) have increased the scale of this challenge. For example, when looking for the cause of mental retardation, an increased cancer risk may be identified (Schwarzbraun 2009). In the case of WGA 'unsolicited findings' seems a more appropriate term than 'incidental findings' hitherto used, since the nature of the technique is such that in principle a mass of data will be generated that is not related to the initial diagnostic question.

It can be argued that, at this point, the classical distinction between diagnostic testing on the one hand and screening on the other (where screening is defined as the offer of medical testing to persons without symptoms or other indications that would make such testing clinically necessary; see next section) loses much of its sharpness (Dondorp & De Wert 2010). From an ethical point of view, this observation underscores the need for a separate justification in terms of the proportionality of using whole genome techniques in a diagnostic setting: do the advantages outweigh the disadvantages? As we have argued, the importance of clarifying a severe health problem may outweigh the potential drawbacks of testing that can be expected to lead to unsolicited findings. Whether it does should be decided by the health professionals before the test is offered and discussed with the patient (or the parents) as part of pre-test counselling. As for other presymptomatic genetic testing, patients may change their opinion after having the blood taken to the test and should be allowed to exert their rights of autonomy.

Distinguishing between general categories of possible findings may be helpful to facilitate consent for testing without overburdening patients with information, and to direct professional decision making with regard to what findings should, in principle, be retained or returned (Berg 2011). This approach would also allow patients to indicate any specific information needs or preferences, including possible claims to a 'right not to know'. However, such claims do not automatically override professional responsibilities in cases where the health interests of children or family members are at stake (Dondorp & De Wert, 2012).

To contribute to the need for guidance, clinicians should share their experiences and establish best practices with regard to counselling and informed consent procedures and the handling of unsolicited findings. As these unsolicited findings could also emerge as a clinical issue a long time after testing, the question as to how this new information should be handled and communicated to the patient should also be addressed.

Population screening

Unsolicited findings and outcomes of unclear significance are a well-known problem also in the context of population screening (Al-Shahi 2007). In screening (as defined in the previous section), the use of genomic information calls for a different standard regarding evidence thresholds for clinical validity and utility than in a diagnostic setting. Screening requires high specificity in order to reduce the number of false positives. The use of filters to select regions and variants of clinical relevance may enable WGS-based targeted screening, which as such need not differ much from current approaches. However, there is an important difference in how the scope of such screening is defined. The question is no longer which target diseases should be included in the test-panel, but which should be excluded by selective analysis of WGS-data. The challenge will be to avoid a broader scope in the test that would not be based on a rigorous evaluation of clinical utility and other screening criteria.

One area where this challenge will have to be met is preconception carrier screening, allowing reproductive options in case both partners are carrier of mutations for the same autosomal recessive disorder(s). Commercial companies already offer screening packages in which carrier status for more than a hundred of such disorders are simultaneously tested. The risk to be avoided here is that couples make important reproductive choices based on test results that are still insufficiently understood.

Neonatal screening is another area where the introduction of WGS may lead to widening the scope of testing beyond what can be justified in terms of the current classical screening criteria (Goldenberg & Sharp 2012). Some have argued that these criteria need to be modified in order to allow for WGA-based testing becoming instrumental in personalized medicine. Although this reality is not for the near future, some have suggested that neonatal screening

would be the best setting for analysing the genomes of individuals, who might then profit from personalized prevention and treatment during the full length of their lives (Collins, 2010). Another problem with this approach is that it may lead to information that only becomes relevant later in life. Revealing this information may undermine the child's right to decide him- or herself, once mature enough to do so, about what to know or not to know about his own health prospects.

This problem of undermining the child's future autonomy rights also arises when WGA is used in the context of prenatal testing (e.g. as follow-up to an abnormal ultrasound) or perhaps in the future also in that of routine prenatal screening (De Jong et al. 2010; Kitzman 2012). Although in both contexts WGA information may be relevant to a decision by the woman or the couple about whether or not to carry the pregnancy to term, it should be acknowledged that this may also lead to the birth of children known to be at risk for severe late onset disorders. Clearly, this outcome is at odds with PPC recommendations concerning genetic testing of minors (ESHG 2009). Moreover, there may be a tension between the aim of reproductive screening (enhancing autonomy by providing meaningful reproductive options) and the fact that widening the scope of testing will make counselling and decision-making only more difficult.

Informational privacy and family relations

Further exploration is needed regarding the ethical, legal and social (ELSI) implications of generating genomic data and information in the context of diagnostics or population screening, in view of questions related to informational privacy. For instance: should the raw data obtained through WGS be stored and if so under what conditions? It may well be that when prices drop, it will become cheaper and also more practical from an ethical and legal point of view to perform a new WGS procedure whenever required for clinical diagnostics or screening.

Other issues that require further guidance are how to deal with information that patients or parents have indicated they would not want to receive, but that may still be important for their own health, for that of their children, or the health or reproductive interests of any close relatives. And how to deal with outcomes that may be clinically relevant but will or may only affect the child in its adult life (Hens et al 2012)? For instance, if diagnostic testing aimed at finding the cause of a hitherto unexplained disease (other than severe intellectual disability), finds that a girl is at risk of hereditary breast and ovarian cancer, difficult questions arise as to how to best respect her future autonomy rights without depriving her of what may be life-saving information, while also taking account of the possible health or reproductive interests of family members.

Commercial applications

Whereas in some countries criteria including clinical utility, a positive risk-benefit ratio for participants and meaningful options in case of a positive result, must all be fulfilled in order for a screening programme to be responsibly introduced in health care (Wright 2011), a different perspective is taken by providers and consumers of genomic tests that can be purchased directly from companies without the intervention of a health care professional. From the perspective of the individual's right to information about his or her genome, limiting regulations are regarded as unnecessarily paternalistic and interfering. Ideally, independent information about the pros and cons of WGS should be available to the public, based on expert judgements from professionals explaining the stakes (Health Council of the Netherlands 2008).

Previously, the PPC has discussed genetic testing for common complex disorders, as well as genetic testing in commercial settings (Borry 2010; van El 2011). These earlier statements on

the importance of clinical utility as the central criterion to assess testing and screening possibilities certainly also apply to whole genome techniques. Whole genome testing for common disorders would often not satisfy the criteria nowadays used to evaluate screening strategies, because of limited clinical utility (Roberts et al 2012; van El 2011). It may be hard for the public as well as many physicians to distinguish between useful and less useful offers, and concerns regarding suboptimal counselling and quality control are real (Borry, 2010).

Conclusion

Many of the issues mentioned in this paper are not entirely new, but the scale of the challenges certainly is. For instance the number of unsolicited findings and the amount of information becoming available surpass our current experiences. Since our frameworks and guidelines for offering good clinical services and sound screening are based on these experiences, the question arises whether these frameworks should limit new developments, or whether those developments require the existing frameworks to be reconsidered and adapted. This need not mean that the technology is allowed to determine what will be offered in health care, the so called “technological imperative”. There is a clear need for professionals from various disciplinary backgrounds to contribute to sustainable new frameworks that allow building new health care practices in a responsible way (Wright 2011). In addition patient and public experiences can be used to discuss and learn as societies how to incorporate new genomic technologies in our daily lives

Recommendations:

- 1) Whenever in a clinical setting targeted analysis of genome data is possible, it is preferable to use this targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic variants of limited clinical utility should be filtered out and not reported.
- 2) Always expect the unexpected. Whenever the use of array CGH or WGA is considered, a protocol has to be ready to guide the return of unsolicited findings.
- 3) As testing for health care and biobank research tend to become intertwined activities, relevant normative frameworks including consent procedures for diagnosis, research, disclosure and storage need to be reconsidered and if necessary adapted to the challenges of the new situation.
- 4) If individual health benefit is realistic, it should be possible to report genetic variants indicative of serious health problems.
- 5) Best practices should be discussed among professionals to establish guidelines for informed consent regarding diagnostic testing. Patients’ or parents’ claims to a right not to know do not automatically override professional responsibilities when the health interests of children or family members are at stake. Patient groups could provide important input into this.
- 6) In case of new information arising some time after a diagnostic question was dealt with, the possibility of recontacting participants in case of clinically relevant findings should be considered. A guideline should be established detailing how and when this should be done.
- 7) In case of testing minors, guidelines need to be established on what information may be disclosed, to balance the autonomy of the child and the parent’s right to information that may be in the interest of their (future) family.
- 8) To facilitate the interpretation of genome data, international collaboration is needed to build databases on genotypic and phenotypic information of variants / patients.

- 9) A sustained effort at genetic education of health care professionals is required at various levels: in primary care to adequately inform and refer people, in specialized care to counsel or refer patients and to discuss and interpret genetic test results.
- 10) Genetic experts should engage in discussing new developments in genetics and explain the pros and cons of genetic testing and screening in commercial and clinical settings to inform the public and raise public awareness.
- 11) Enhancing genetic literacy in patients and lay public might help to involve the public in this debate.

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