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Preference heterogeneity with respect to whole genome sequencing. A discrete choice experiment among parents of children with rare genetic diseases

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ABSTRACT

The information to which whole genome sequencing (WGS) provides access raises questions about its disclosure to patients. The literature focused on the nature of findings, shows patients share the same expectations while evoking possible heterogeneity. Our objective is to test this hypothesis of preference heterogeneity with respect to the disclosure of results from WGS by means of a discrete choice experiment (DCE).

Our DCE includes six attributes for studying preferences with respect to (1) variants of unknown significance and (2) secondary findings, and more innovatively with respect to (3) repeat analysis of the tests, (4) the decision-making process, (5) patient support and (6) the cost of testing. The survey was conducted at two genetic centres in France from February to December 2015 and included 528 parents of patients with development disorders with no aetiological diagnosis. By using a latent class model, it was possible to identify two preference profiles with parents opting for either a prospective (75% of sample) or a targeted (25%) diagnostic approach. The former valued the exhaustive and diverse genetic information the test can provide, even when the information is uncertain or not directly related to their child's illness; the latter valued only the least uncertain information relating to their child's illness. Understanding patients' preference patterns can help professionals to better accommodate and support patients and enables policy-makers to measure the diversity of expectations in the face of current developments in genomic medicine.

1. Introduction

Whole genome sequencing (WGS) could soon become a first-line strategy for diagnostic testing in genetic medicine with the routine use of next-generation sequencing. While improving diagnostic performance is promoting the spread of WGS (Ashley et al., 2010; Retterer et al., 2016; Yang et al., 2014), there are still obstacles. These are broadly related to questions about the use made of the data obtained, their clinical utility and the disclosure of results to patients.

Disclosure of the results of genetic testing runs into general difficulties: patients often have limited knowledge of genetics, which hampers their understanding of the results announced in terms of risk or predisposition. The disclosure of WGS results also entails specific issues that require increased attention to patient support (Ormond et al., 2010). Secondary findings (SFs) are more likely with WGS: pathogenic variants may be detected that predispose patients to pathologies other than the one for which the test was prescribed. These pathologies will or may occur in the future, or in children living or to be born, and they may be curable or incurable, manageable or unmanageable by preventive behaviour. For example, the results will indicate with certainty the future occurrence of a pathology like Huntington's disease or a high risk of cardiovascular disease, diabetes or certain cancers (Berg et al., 2011).

Although SFs only occur in a fairly small proportion of diagnostic approaches using WGS (reportedly 5%), they do raise major questions for practitioners (Green et al., 2013; Parker, 2008). The fact that the technology exists, performs well, is financially acceptable and that it provides the geneticist with a promising array of information does not necessarily mean that all findings should be disclosed to patients or even tested for.

The patients' choice through their informed consent should be decisive on this issue, but the way in which patients are informed and supported in their choice is a subject of debate among professionals (Thorogood et al., 2012; Yu et al., 2014). For example, the ACMG (American College of Medical Genetics and Genomics) 2013 recommendations about SFs have opened a lively debate on patient

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autonomy, shared decision-making and the paternalism of physicians (Green et al., 2013; McCormick et al., 2014; Townsend et al., 2012; Vayena and Tasioulas, 2013). It is quite systematically shown there is a gap between the preferences of health professionals and of patients as to the desirable characteristics of a test and to the information it yields (Gray et al., 2016; Levenseller et al., 2014; Payne et al., 2011; Severin et al., 2015; Townsend et al., 2012). While health-care professionals often value clinical utility, these studies show that patients value the personal utility of sequencing results and considerably value any and all information.

Research in recent years has made it possible to better determine patients' preferences with respect to access to genetic testing and its results among the general population (Henneman et al., 2013; Marshall et al., 2016; Regier et al., 2015; Townsend et al., 2012) or among certain types of patients: pregnant women (Ormond et al., 2009), persons with increased risk (Bränström et al., 2012), cancer patients (Buchanan et al., 2016; Gray et al., 2016), families of children with idiopathic developmental disability (Regier et al., 2009b), patients or their family members engaged in the process of utilizing exome sequencing (Clift et al., 2015; Facio et al., 2013; Fernandez et al., 2014; Shahmirzadi et al., 2014). Overall, studies show there is a generally favourable attitude towards genetic tests and that patients want to be fully active in choosing to have access to the tests or to their results. In the specific research on WGS, attention is often focused on the decision to have access to SFs. Studies very systematically show a majority in favour of the diffusion of SFs even if they are for incurable diseases (Gray et al., 2016; Fernandez et al., 2014, 2015; Shahmirzadi et al., 2014).

While these preferences are favourable on average, they may conceal disparities. Wang et al. (2004) conclude that not everyone wants to have the same genetic information and they recommend this diversity should be a priority for future research. Quantitative and qualitative research has sought to reveal preference heterogeneity with respect to access to testing and to the nature of the results and the procedures for disclosing them. Heterogeneity may then depend on the pathologies detected (Neumann et al., 2012), on their severity (Hall et al., 2006; Severin et al., 2015) and on the possibility of treating them (Regier et al., 2015). Heterogeneity may also be inter-individual. It will be worth investigating whether preferences for the same test or the same result depend on objective characteristics such as age, sex, income (Buchanan et al., 2016; Regier et al., 2009a, 2009b), personal or family history, including in terms of plans for having children (Hall et al., 2006), medical history (Herbild et al., 2009; Payne et al., 2011), knowledge of genetics (Henneman et al., 2013) or stated attitudes to health and risk. In a systematic review of 115 empirical studies on predictors of genetic testing decisions, Sweeny et al. (2014) conclude that while the impact of test-related predictors (perceived benefits of and barriers to testing, risks of the test procedure, and attitudes toward testing) broadly converges across studies, the characteristics of the pathologies in question (risk, possibility of prevention and management of the disorder, severity, etc.) and above all respondent characteristics (family and personal health history, general health motivation, sociodemographic variables) have extremely variable impacts from one study to another.

It would seem then that individual preference heterogeneity results from personal positions that cannot be readily associated with a particular context or with objective characteristics. Hall et al. (2006) show that preference variability is not related to differences in terms of risk or to cultural or sociodemographic differences. The existence of different types of attitude towards genetic information is also evoked by Ormond et al. (2009) and Regier et al. (2009b). Lastly, Clift et al. (2015) conclude on the basis of 55 in-depth interviews that patients' points of view are diverse and there is no general rule defining preferences toward access to findings. Our article aims to further this hypothesis about preference heterogeneity, by highlighting different structures of preference towards genetic testing that might place the heterogeneity observed in a different light.

We use a discrete choice experiment (DCE), now widely used – especially in health economics (Clark et al., 2014) – to reveal and measure preferences. In the field of genetics, DCEs have already been used to study participation in genetic testing programmes (Hall et al., 2006), to estimate willingness-to-pay for pharmacogenetic testing (Herbild et al., 2009) or for diagnostic testing (Regier et al., 2009a, 2009b), to evaluate the desired characteristics of a genetic test (Severin et al., 2015), to assess the preferences for SFs (Regier et al., 2015) or for pre-treatment genetic and genomic testing (Buchanan et al., 2016), and to determine whether a person wants to act on the WGS information received (Marshall et al., 2017).

In our study, respondents are French parents of children with rare diseases (RDs) and development disorders (DDs) and who could benefit from WGS if it was proposed as a routine diagnosis. A disease is rare when it affects less than 1 in every 2000 persons. The range of RDs is large (6000–8000 are documented) and 75% of them are present from birth or before two years old. In France, the prevalence of RDs is almost 4–6%. DDs concern 3% of births and are overwhelmingly secondary to gene or chromosomal anomalies. RDs with DDs represent two-thirds of the known genetic diseases and their cause is not known in 1 case in 2. WGS may lead to a significant increase in diagnosed cases from 50% to 80% (Willemsen and Kleefstra, 2014) but it is not yet used in France in routine diagnosis. The preferences we study are therefore parents' preferences with respect to WGS prior to actual inclusion in a WGS diagnostic protocol and our objective is to examine possible heterogeneity of their preferences.

To assess preferences DCE involves submitting a set of scenarios of possible configurations of a good or service to respondents' choice. Each scenario describes the good via the values of a set of pre-defined attributes. By drawing on Lancaster's value theory (Lancaster, 1966) and random utility models (McFadden, 1974), the impact of the value of an attribute on the level of respondents' well-being can be measured by observing their choices. In our study, each scenario is associated with a hypothetical WGS test described by the nature of the findings disclosed, of patient support offered, by the identity of whoever defines access to the findings and by the cost of the test.

To look at inter-individual preference heterogeneity, different econometric modelling could be considered. Interaction variables (attribute levels x socio-demographic characteristics) can be integrated in the conditional logit (CL) in order to test whether respondents' predefined characteristics alter the mean preference associated with attribute values. But, this strategy does not allow us to relax the assumptions of independence of irrelevant alternatives (IIA) and of the error terms (*iid* errors are assumed), and to investigate heterogeneity based on unobservable factors (Hole, 2008). Mixed Logit (ML) or Latent Class (LC) methods can handle such issues. The choice between these two models critically depends on expectations about the variation of preferences (Greene and Hensher, 2003; Hole, 2008). If researchers expect preferences to vary greatly between individuals and want information about how heterogeneity is distributed relative to each attribute, the ML is preferred. If individuals are thought to be grouped in a homogeneous preferences pattern, the LC is preferred and will inform about heterogeneity among latent subgroups. Our hypothesis here is that, beyond diversity in the utility attributed to any particular value of each attribute, there are different overall attitudes with respect to WGS. We have therefore chosen a LC model to seek for preference heterogeneity among our respondents.

2. Method

For each step in the DCE – choice of attributes and levels, questionnaire design and completion, econometric analysis – we followed the most recent good practice guidelines (Bridges et al., 2011; Hauber et al., 2016; Johnson et al., 2013; Louviere and Lancsar, 2009).