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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).

You are in a hospital offering test A and test B. Which do you choose?

	TEST A	TEST B
Variants of unknown significance	None	All
Secondary findings	Possible actions	None
Repeat analysis	Never	At my request
Decision-making	An ethics committee	My geneticist
Support	Appointment with geneticist	Meetings with other families
Cost	€600	€900

I choose the test (tick the corresponding box):

A ☐ B ☐

Fig. 1. Example of a choice set.

2.1. Attributes and levels

Choosing attributes and levels is recognized to be a crucial stage for ensuring the validity of a DCE (Coast et al., 2012; Kløjgaard et al., 2012; Louviere and Lancsar, 2009). We followed the process in four steps presented in Pélissier et al. (2016) and described in detail in Supplementary Material A: a review of the literature on WGS and patients' preferences with respect to genetic tests; two focus groups bringing together professionals; a pre-test involving 15 families; and a meeting of all the stakeholder teams. We identified six attributes presented below.

2.1.1. The disclosure of variants of unknown significance (VUS)

The VUS refer to genetic mutations whose connection with the pathology for which the test was prescribed stems from presumptions based on geneticists' experience and knowledge and not on fully confirmed scientific data. The levels chosen for this attribute relate to the two practices found among geneticists: (i) do not reveal any uncertain finding or (ii) reveal only those findings the geneticist judges most probable. The level of the “all VUS” attribute is also proposed in order to ascertain individuals' preferences beyond current medical practice.

2.1.2. The disclosure of secondary findings (SFs)

The SFs refer to genetic mutations that cause or will cause other diseases than the one for which the test was prescribed. Because of their genetic character, such mutations may also concern the patient's relatives. The ACMG recommendations (Green et al., 2013) and the conclusions of the literature and practice of geneticists (Townsend et al., 2012) are to disclose findings for a set of predefined pathologies and for which there are curative or preventive actions (Dorschner et al., 2013; Green et al., 2013; van El et al., 2013). In addition to this possibility, which stems primarily from professional practice, we propose to respondents the disclosure of all SFs or on the contrary none.

2.1.3. Repeat analysis

With the development of knowledge of genetics, a future re-reading of a sequence might lead to the initial findings being amended. Such re-reading may be done automatically, each year for example, or at the patients' request. Alternatively, the data might not be conserved and so never re-examined.

2.1.4. Decision-making

Three possibilities illustrate the debate as to who should decide about VUS or SFs being disclosed – the geneticist alone after speaking with the patient, an ethics committee after the geneticist has presented the patient's medical records, or the patient having been informed beforehand by the geneticist.

2.1.5. Support

It may take a long time for WGS findings to come through (4–18 months) and the wait may be particularly trying for patients. Patients may be offered support in the form of an appointment with the geneticist, the department's psychologist, a nurse or as part of the information and exchange meetings among patients awaiting results.

2.1.6. Cost

The cost to be footed by patients is the final attribute. It indicates respondents' sensitivity to a hypothetical payment (genetic tests are free for these patients in France in the context of hospital care). The upper bound is an approximation of the cost of testing that was currently incurred by genetic centres. The lower bound is the free testing.

2.2. Experimental design

The DCE involved combining the levels of the six attributes into scenarios among which respondents had to pick. An orthogonal main effect plan was designed with Ngene software (ChoiceMetrics Pty Ltd, New South Wales, Australia). It yielded 36 choice sets, randomly blocked into six versions. Each choice set contains two unlabelled alternatives “Test A” and “Test B” (Fig. 1).

We did not leave respondents the possibility of not choosing, in the form of an opt-out. In our pre-test none of them decided to opt-out. This is consistent with our experiment; the respondents are assumed to have accepted genetic testing and must choose the form it takes (or may leave this choice to others as in the “Decision” attribute). Moreover, an opt-out only introduces slight differences into the estimations (Fiebig et al., 2005), whereas the forced choice task may lead to more thoughtful responses and better quality data (Veldwijk et al., 2014). Last, the survey characteristics described in the next subsection are designed to facilitate respondents' choices.

2.3. Survey

The survey was conducted from February to December 2015 in the centres for genetics of Lyon and Dijon university teaching hospitals in France. Respondents were parents of patients with RDs with no aetiological diagnosis, who might benefit from WGS if introduced as a routine diagnosis, who had no difficulty in expressing themselves in French, and who were seen in consultation over the inclusion period. Parents who accepted to take part in the survey were accompanied by a trained interviewer. The interviewer presented guidelines (Supplementary Material B). He specified the context and objective of the study, the meaning of the attributes and their levels and presented an example of a choice set. The respondent then completed a paper questionnaire without any outside assistance. Verbal consent of respondents was required before conducting the survey. All documents about conducting the survey were approved by the ethics committee of Dijon hospital.

The questionnaire had two parts. The first contained six pairs of scenarios for the DCE. The second asked respondents to indicate how they perceived the survey and their level of knowledge of genetics and to complete a few socioeconomic variables.

Table 1
Attributes and levels.

Attributes	Levels
Variants of unknown significance[a]	None[c]
	Most probable factors only
	All
Secondary findings[a]	None[c]
	Possible (curative and/or preventive) actions
	All
Repeat analysis[a]	Never[c]
	Automatically every year
	At my request
Decision-making[a]	Myself
	My geneticist[c]
	An ethics committee
Support[a]	Appointment with:
	- geneticist[c]
	- psychologist
	- nurse
	Meetings with other families
Cost[b]	€1, €300, €600, €900

Notes
[a] Dummy variables.
[b] Continuous variable.
[c] Reference values.

Alongside this, a questionnaire completed by the geneticist characterized the patient's medical background especially the number of genetic tests already performed and the date the department first took on the case.

2.4. Econometric modelling

The discrete choice method is based on random utility theory in which the level of utility associated with a scenario depends, for the deterministic part of the utility, on the levels of the various attributes under this scenario. Assuming a linear utility function (Eq. (1)):

$$U_{ijs} = \beta' X_{ijs} + \varepsilon_{ijs} \quad (1)$$

where U_{ijs} is the level of utility of respondent i for scenario j in the sth choice set proposed (here j = 1, 2; s = 1,..,6), X_{ijs} is the vector of attribute levels in scenario j, β a parameter vector relating attribute values and utility levels and ε_{ijs} the stochastic part of utility. Respondents are asked to choose whichever of the two scenarios has the greater utility.

Apart from "Cost", all the variables describing attribute levels are introduced as dummy variables (reference categories in Table 1). It is relevant to introduce qualitative attributes by effects coding so as to quantify the impact of the reference levels (Bech and Gyrd-Hansen, 2005). However, Hensher et al. (2015) and Daly et al. (2016) show that effects coding and dummy coding ultimately provide the same information. Their articles also specify again how coefficients should be commented on: relative to the value of the level chosen as the base category for dummy coding and relative to the average of the values of all levels for effects coding. To make for easier commentary, we therefore opted for dummy coding with the most obvious or most usual practices as the base category (nevertheless, results with effect coding are presented in Supplementary Material C).

The quality of the various specifications was compared on the basis of the Akaike and Bayesian information criteria (AIC and BIC respectively). The linearity assumption was tested for the monetary attribute. The variable was introduced in the form of dummy variables and non-linearity of cost was thereby highlighted: the probability of choosing a test increases with its cost but decreasingly so. Cost squared was therefore introduced into the model as a supplement to cost level.

We estimated the preferences with two models, a CL and a LC. The CL presupposes that errors are independent and identically distributed following a Gumbel distribution. To allow for the occurrence of repeated choices for each individual, we included an intra-individual correlation for these choices while maintaining inter-individual independence (*cluster option* in Stata). In expression (Eq. (2)), the vector β is identical for all individuals; β_1 is the parameter for the alternative-specific constant (ASC_{TestA} taking the value 1 for alternative "Test A" and 0 for alternative "Test B"), the other parameters reflect the mean impact of the attribute level with respect to the reference value. The model is written:

$$\begin{aligned} U_{ijs} = {} & \beta_1 ASC_{TestA} + \beta_2\, VUS\ (most\ probable)_{ijs} + \beta_3\, VUS\ (all)_{ijs} \\ & + \beta_4\, SFs\ (possible\ actions)_{ijs} + \beta_5\, SFs\ (all)_{ijs} \\ & + \beta_5 Repeat\ (automatic)_{ijs} + \beta_6 Repeat\ (at\ my\ request)_{ijs} \\ & + \beta_7 Decision\ (myself)_{ijs} + \beta_8 Decision\ (ethics\ committee)_{ijs} \\ & + \beta_9 Support\ (psychologist)_{ijs} + \beta_{10} Support\ (nurse)_{ijs} \\ & + \beta_{11} Support\ (meetings)_{ijs} + \beta_{12} Cost_{ijs} + \beta_{13}\, Cost^2_{ijs} + \varepsilon_{ijs} \end{aligned} \quad (2)$$

The LC can be used to study preference heterogeneity by distributing respondents among more homogenous classes in terms of preference patterns (Greene and Hensher, 2003). These preferences are characterized by a vector of coefficient β_c' specific to each class (Eq. (3)). In Eq. (3), $U_{ijs|c}$ is the utility derived by an individual *i*, belonging to class *c*, for alternative *j* proposed in the choice set *s*.

$$\begin{aligned} U_{ijs|c} = {} & \beta_{1|c} ASC_{TestA} + \beta_{2|c}\, VUS\ (most\ probable)_{ijs|c} + \beta_{3|c}\, VUS\ (all)_{ijs|c} \\ & + \beta_{4|c}\, SFs\ (possible\ actions)_{ijs|c} + \beta_{5|c}\, SFs\ (all)_{ijs|c} \\ & + \beta_{5|c} Repeat\ (automatic)_{ijs|c} + \beta_{6|c} Repeat\ (at\ my\ request)_{ijs|c} \\ & + \beta_{7|c} Decision\ (myself)_{ijs|c} + \beta_{8|c} Decision\ (an\ ethics\ committee)_{ijs|c} \\ & + \beta_{9|c} Support\ (psychologist)_{ijs|c} + \beta_{10|c} Support\ (nurse)_{ijs|c} \\ & + \beta_{11|c} Support\ (meetings)_{ijs|c} + \beta_{12|c} Cost_{ijs|c} + \beta_{13|c} Cost^2_{ijs|c} + \varepsilon_{ijs} \end{aligned} \quad (3)$$

Estimation of the LC was supplemented by a model explaining the probability of an individual belonging to one of the classes. Individual and sociodemographic characteristics could be related to a particular preference pattern.

For both CL and LC, the coefficients measure the impact on utility of the transition of the attribute from the reference level to the value under consideration.

To determine the relative importance of the attributes, we calculated the share of the maximum variation in utility associated with each attribute (Determann et al., 2016). This involves dividing for each attribute the absolute value of the highest coefficient by the sum of absolute values of the highest coefficients of each attribute (Hauber et al., 2016). The higher the attribute's share, the more the utility can be varied by modifying the level of that attribute.

3. Results

3.1. Choice characteristics

In all 513 respondents or 97% of the sample made all six choices proposed. The six versions of the questionnaire were evenly distributed among the completed questionnaires (version: 1 (18.91%), 2 (15.20%), 3 (17.93%), 4 (18.52%), 5 (15.98%), 6 (13.45%)). The database contained 6156 observations.

Dominant preferences due to the difficulty in choosing or to lexicographic preferences (Scott, 2002) were tested. In this case, preferences cannot be represented by a multi-attribute utility function (Lancsar and Louviere, 2006). The difficulty in choosing was mastered as far as could be through close attention to the formulation of attributes and their values and through the means of surveying based on a

neutral but helpful support (Pélissier et al., 2016). Following Scott (2002) and Payne et al. (2011), we were able to reject the presence of lexicographic preferences for the "VUS" and "SFs", which were identified by respondents as the most important, and for the "Cost" which was evaluated as the least influential.

3.2. Refusals and sample bias

Over the study period 634 parents met the inclusion criteria. Geneticists did not propose the study to 52 of them, due to oversight or because of their emotional state after the consultation. Of the 582 parents who were invited to participate in the survey, 54 declined mainly saying they did not have time. In all 513 parents fully completed it. Our response rate is 83.3% and our statistical results concern 81% of potential respondents.

3.3. Respondent characteristics

Of the 513 respondents, 48% were surveyed in Lyon and 52% in Dijon. Their characteristics are presented in Supplementary Material D. The respondents are mostly mothers (65%) whose mean age is 37 years (39 for fathers). The age of the children concerned ranged from the foetus up to 33 years old, with a median value of five years old. One fifth of respondents said they had plans for having a child or that a pregnancy was underway. Most families were waiting for a diagnosis: more than half of the respondents had already had between one and three tests prescribed. Lastly, 73% of respondents judged their knowledge of genetics to be poor or very poor. By contrast, the notions of VUS and IF were judged by most to be clear or very clear (more than 70% for both notions), once the interviewers presented them.

Most respondents said they were satisfied with the way the survey was conducted: 47% were "rather satisfied" and 41% "very satisfied".

3.4. Estimation of preferences and their heterogeneity

Table 2 presents the results of the CL. The value of the pseudo-R^2 (0.167) indicates a medium model fit, with an excellent model fit corresponding to a pseudo-R^2 between 0.2 and 0.4.

The levels of attributes are all significant except for support from a psychologist. Shifting from the reference levels to the other attribute levels modifies parents' well-being. For "VUS" and "SFs", having results is invariably preferable to not having any, whatever the nature of the findings disclosed. For "VUS", going from no result to the most probable results raises utility more than going to all results. For "SFs", parents want to know them: their well-being is raised almost as much by having access to all SFs as by having access only to findings predicting curable or preventable pathologies. "Repeat analysis" also increases respondents' utility and slightly less so if it is at the parents' request compared with if it is done automatically. Computation of the relative importance of attributes shows that these three attributes are those whose values can contribute most to varying respondent utility, with in decreasing order: "VUS", "Repeat analysis" and then "SFs". For "Decision-making", the reference level (i.e. the geneticist decides which findings to disclose after discussion with the patient) improves the parents' well-being compared with a decision by the patient alone or by an ethics committee. They also prefer the same geneticist to support them during the waiting period and to discuss the findings with them; dialogue with a nurse or with other families would be less satisfactory for them ("Support"). Lastly, "Cost" and its square are statistically significant at the 10% level, are respectively positive and negative, indicating the relationship between utility and cost is positive up to a certain level and negative beyond that. "Cost" is the attribute that contributes least to varying utility; it has the lowest relative importance.

For estimating choices with LC, we retained a two-class model. We prioritized Corrected AIC (CAIC) and BIC, as it is known that AIC overestimates the number of classes and BIC tends to favour parsimonious model (McLachlan and Peel, 2000). In addition, the rate of correct predictions criterion follows the same direction as CAIC and BIC (Table 3). Respondents fall unequally into the two classes, with 75% in class 1 and therefore 25% in class 2. We estimated the probability of belonging to either class based on different individual characteristics and in different forms, but no factor appears to be a significant determinant of class membership. Results (Table 4) show as clearly different preference structure between the two classes.

For class 1, the significance and signs of the coefficients of the attribute levels are similar to those estimated by the CL: respondents in class 1 have identical preferences to the mean preferences of the entire sample. The only notable difference is that "Cost" and its square of the test are no longer significant. For the relative importance of attributes, the three most operative are unchanged "VUS", "SFs", "Repeat analysis", although their rankings differ. "SFs" (and no longer "VUS") are now the attributes whose level makes utility vary most.

Parents in class 2 have somewhat different preferences from those obtained with the CL and therefore from class 1. The differences relate to the sign or statistical significance of some of the coefficients and to the relative importance of attributes. "SFs" again have the highest relative importance, but the impact is now negative: utility of parents in class 2 declines when they know the SFs. "Cost" becomes significant but "Repeat analysis" is no longer statistically significant. "Support" and "Decision-making" have the same signs and are significant in both classes, but these attributes are comparatively more important in class 2 where they rank 2 and 3 (compared with ranks 4 and 5 in class 1).

4. Discussion

Our results show the contribution of the LC to the perception of the diversity of expectations of WGS by objectivizing the existence of different preference models.

If we look at the average preferences (CL) or the preferences of the more numerous class (LC, class 1: 75% of our sample), these parents of children with RDs would prefer to have access to all findings, whether uncertain or secondary and would prefer their genetic analyses to be reviewed over time. In this we confirm a result already obtained for genetic tests (Townsend et al., 2012) and especially for parents of sick children (Fernandez et al., 2014): an average preference is for access to more information of whatever kind. This wish may be contrary to the position of some practitioners who fear that the disclosure of VUS and SFs may be a source of distress for their patients. However, qualitative surveys show patients attach value to such information in particular as it will enable them to make decisions and adopt new behaviour (Clift et al., 2015; Kleiderman et al., 2013). Some 25% of the respondents, those in class 2 have a different attitude towards tests and their results. These parents would accept to have access to VUS, especially if they are probable, but would not like SFs to be disclosed to them. Reanalysis is not a plus feature for them. These parents seem to fit in with what might be called a "targeted diagnostic approach": a test at the present time, that they are prepared to pay for up to a certain point, just to know the certain or probable findings related to a condition for which they are looking for a diagnosis. In comparison, parents in class 1 appear now to be involved in a "prospective diagnostic approach": all the findings of whatever kind are expected and an automatic reanalysis is valued.

This division of our study population can be cautiously compared with the findings of quantitative studies. In Marshall et al.'s (2017) contingent valuation study, 38% of the respondents did not value obtaining genomic information. Using a ML, Regier et al. (2015) show that between 16 and 24% of their respondents have disutility with access to SFs. The difference in our study is that the 25% of class 2 are not only more reluctant to know about SFs but also generally distinct from those in class 1 in terms of all the attributes proposed.

Parents in both classes agree, however, on the role they accord to

Table 2
Conditional logit.

		β	SE[a]	RI (rank)[b]
ASC_{TestA}[c]		0.075*	0.043	
Variants of unknown significance	*None (ref)*			29.96% **(1)**
	Most probable	0.859***	0.067	
	All	0.776***	0.065	
Secondary findings	*None (ref)*			24.06% **(3)**
	Possible actions	0.665***	0.065	
	All	0.690***	0.067	
Repeat analysis	*Never (ref)*			25.11% **(2)**
	Automatic	0.720***	0.066	
	At my request	0.647***	0.059	
Decision	*Geneticist (ref)*			9.80% **(4)**
	Myself	−0.276***	0.061	
	An ethics committee	−0.281***	0.053	
Support	*Geneticist (ref)*			9.49% **(5)**
	Psychologist	−0.113	0.095	
	Nurse	−0.224***	0.077	
	Meetings	−0.272***	0.075	
Cost[d]		5.14e-03*	0.003	1.59% **(6)**
$Cost^2$		−6.21e-05*	3.29e-05	
Observations = 6156	Pseudo R^2 = 0.1674	Wald chi2(14) = 425.64		
Respondents = 513		Prob > chi2 = 0.000		

Abbreviations: *ref* reference level, ASC_{TestA} alternative-specific constant, *SE* standard errors, *RI* relative importance of the attribute.
***, **, * statistically significant at the 1%, 5% and 10% level, respectively.
Notes
[a] Clustered by respondent.
[b] Percentage variation in utility (attribute ranking).
[c] Only 13 respondents have always chosen Test A.
[d] Cost and $Cost^2$ are rescaled (basis 90 rather than 900). Computations with the cost attribute need to be multiplied by (899/90) to convert base 90 back into base 900. For example, the threshold for the cost attribute (calculated as the derivative of U_{ijs} with respect to cost) is equal to €413.

Table 3
Choice of number of classes.

		LLF	AIC	CAIC	BIC	% correct predictions
CL		−1776.45	3580.89	3594.89	3675.04	71.41
LC	*2*	−1729.59	3517.18	3669.15	3640.15	88.16
	3	−1720.52	3529.05	3759.68	3715.63	76.18
	4	−1685.77	3489.55	3798.72	3739.72	83.73
	5	−1687.22	3522.43	3910.21	3836.21	69.94
	6	−1663.09	3504.19	3970.58	3881.58	65.19

Abbreviations: *CL* Conditional Logit, *LC* Latent Class, *LLF* Log-Likelihood Full model, *AIC* Akaike Information Criterion, *CAIC* Corrected Akaike Information Criterion, *BIC* Bayesian Information Criterion.

their geneticist in choosing which findings should be disclosed and in supporting them. Payne et al. (2011) show that patients prefer a hospital doctor but not a pharmacist to explain the results. However, when the rank of attributes is exploited, they attribute more importance to compliance with their choice as to SFs (rank 1) than to the geneticist's contribution to the test access procedure (rank 3 or 5). This is evidence, then, both of trust in doctors and of a demand to make their own choices.

We find no statistically significant determinants to explain a parent's membership of either class. No sociodemographic characteristics are significant, whether education or knowledge of genetics, or time spent looking for a diagnosis. We find a result that occurs in many studies: socio-demographic factors fail to explain access to tests and results (Facio et al., 2013; Fernandez et al., 2014), nor do variables that describe genetic knowledge or the patient's medical history (Marshall et al., 2016). Patient characteristics introduced as interaction terms are slightly significant in Regier et al. (2015), or significant only for men in Buchanan et al. (2016). Preference structures do not seem to be linked (or only very loosely so) to the personal characteristics of respondents; they might refer, though, to very profound attitudes of individuals towards the future and uncertainty. Models based on random heterogeneity, such as ML or LC are relevant to describe preferences regarding WGS but not to grasp them in depth. The reasons for access choices and the interpretation of the behaviours underlying this heterogeneity would be better explained through a qualitative approach and by in-depth interviews.

Our study has some limitations. The proposed choices could correspond closely to the situation of parents who would sign consent for WGS testing. However, at the time of the study, WGS was not routinely available for diagnosis, the attributes we have proposed were possible but not implemented, for example the cost to the patient is hypothetical. The explanations and discussion with the interviewers gave the respondents a suitable level of understanding for this “hypothetical consent” to be informed consent. As in any DCE, the preferences we have analyzed remain self-reported; there is no guarantee that our parents would have made the same choices about real access to WGS. This is a usual limitation that cannot be exceeded with a DCE. In our DCE we have chosen not to include an opt-out option. As we have stated, this is consistent with the answers obtained in our pre-test and with the design of our experiment. However, this absence can be seen as a limitation, we did not allow parents to refuse the test, we only allowed them to choose the configuration of a test they were supposed to do. Besides, parents of children with DDs without aetiological diagnosis probably have specific characteristics compared with patients turning

Table 4
Latent class model.

		Class 1 "Targeted diagnostic approach"			Class 2 "Prospective diagnostic approach"		
		β	SE	RI (rank)[a]	β	SE	RI (rank)[a]
ASC_{TestA}		0.077	0.073		0.135	0.109	
Variants of unknown significance	*None (ref)*			27.52% **(3)**			18.55% **(4)**
	Most probable only	1.130***	0.107		0.375**	0.162	
	All	1.133***	0.106		0.194	0.163	
Secondary findings	*None (ref)*			29.34% **(1)**			23.29% **(1)**
	Possible actions	1.094***	0.116		−0.231	0.192	
	All	1.208***	0.119		−0.471**	0.218	
Repeat analysis	*Never (ref)*			29.07% **(2)**			–
	Automatic	1.197***	0.109		−0.255	0.192	
	At my request	0.945***	0.099		0.0686	0.175	
Decision-making	*Geneticist (ref)*			6.63% **(5)**			19.73% **(3)**
	Myself	−0.243***	0.093		−0.399**	0.163	
	An ethics committee	−0.273***	0.091		−0.395***	0.151	
Support	*Geneticist (ref)*			7.43% **(4)**			21.07% **(2)**
	Psychologist	−0.000	0.166		−0.292	0.293	
	Nurse	−0.046	0.130		−0.426**	0.212	
	Meetings	−0.306***	0.118		−0.426**	0.212	
Cost[b]		−5.84e-03	0.005	–	0.030***	−0.007	17.36% **(5)**
$Cost^2$		7.33e-05	5.90e-05		−3.73e-04***	−7.82e-05	
Observations = 6156		Respondents = 513			Pseudo R^2 = 0.18896		

Abbreviations: *ref* reference level, ASC_{TestA} alternative-specific constant, *SE* standard errors, *RI* relative importance of the attribute.
***, **, * statistically significant at the 1%, 5% and 10% level, respectively.

Notes
[a] Percentage variation in utility (attribute ranking).
[b] Cost and $Cost^2$ are rescaled (basis 90).

to WGS for themselves. Before being taken in charge by the genetics department, they have often searched around for a diagnosis, particularly when the DDs are caused by RDs. Disclosure of VUS may then be valued more highly: a hint at a response, even if provisional, would be a step forward for them. The fact that the respondents are parents and the non-negligible percentage with plans for having children (about 20% of respondents) may also contribute to a greater perception of the value of SFs and reanalysis. Lastly, we chose our attributes at the end of a qualitative study specific to our respondents. For other population, attributes specifying the characteristics of the pathologies discovered, the time to obtain results, or the reliability of testing might be better. Our results lead to a preference structure whose non-complexity (two classes) is not necessarily generalizable.

Although our results are related in part to the context of the survey, they have implications for health care and for public policy. They draw attention to different attitudes and overall positions with respect to WGS. Regardless of the objective clinical utility of the findings, respecting patient choice may mean allowing a minority of patients not to know any of them, but also agreeing to disclose non-actionable findings for patients with a strong preference for genetic information. In both cases, the professional must evaluate the information to be provided to allow an informed and autonomous decision for each type of patient. The divergence in the personal utilities should be integrated to assess the merits of the development of these technologies in terms of collective well-being. Preference profiles are then key elements to feed a public debate on our expectations and the desirable conditions of this dissemination. They can also be points of support for designing and then evaluating public policies concerned with collective progress and respectful of individual choices.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.socscimed.2018.08.015.

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