Preferences of the French Population Regarding Access to Genetic Information: A Discrete Choice Experiment

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Abstract – This study analyses the preferences of the French population with regard to the genetic information that is potentially accessible thanks to genomic medicine. More specifically, it is a question of knowing whether or not the French population *(i)* is in favour of knowing all possible results with regard to genetic predispositions; *(ii)* has preferences with regard to the person or the method that would decide upon the list of accessible results; *(iii)* is in favour of researchers having access to patients' genetic data. This study makes use of the discrete choice method, with an online survey, conducted in France with a representative sample of 2,501 respondents. The choice data were analyzed in a mixed logit model, to explore the variability of preferences. The results show a preference for autonomy in choosing the information disclosed, to access the most comprehensive genetic results possible and for a contribution to research through the provision of genetic data.

JEL Classification: C25, I1, O33.
Keywords: genomic medicine, access to information, stated preferences, discrete choice experiment

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Genomic medicine is based on the use of information contained within the entire genome of individuals for the purposes of diagnosis or making therapeutic decisions. The development of genomic medicine is accelerating in OECD countries healthcare systems thanks to a fall in the price of sequencing combined with public policies supporting the dissemination of this innovation. Large-scale projects are being set up in many countries; some examples of these are the Precision Medicine Initiative (Reardon, 2015) in the USA, the Melbourne Genomics Health Alliance (Stark *et al*., 2019) in Australia, the 100,000 Genomes Project by the National Health Service (Turnbull *et al.*, 2018) in the United Kingdom and the China Precision Medicine Initiative in China (Liu *et al.*, 2019). The aim of these projects is to integrate genome sequencing into routine clinical practice, with a particular focus on care pathways linked to cancer and rare diseases for the time being. The regulatory bodies hope to use genomic medicine to improve the effectiveness and efficiency of healthcare. In France, the *Plan France Médecine Génomique* 2025 (the French initiative for genomic medicine, hereafter PFMG), was launched in 2016 (Aviesan, 2016), shares similar the same objectives: to rapidly develop access to high-throughput sequencing on the national territory and to improve the international competitiveness of France in this industrial sector. Two sequencing platforms were installed in 2017 in the cities of Paris and Lyon with the aim of establishing this development and accessibility.

The present study analyses the preferences of the French population with regard to genetic information. More specifically, it is a question of knowing whether or not the French population *(i)* is in favour of accessing all possible results; *(ii)* has preferences with regard to the person or the method that would define the list of accessible results; *(iii)* is in favour of researchers having access to personal genetic data. In order to answer these questions, we use a stated preferences method, known as the discrete choice experiment (DCE), which to our knowledge has seldom been used to study the preferences of the French population with regard to genomic medicine.

The remaining of this article is divided into four sections. Section 1 consists in a review of the problems and challenges surrounding access to genetic information. Section 2 describes the designing of the discrete choice experiment and the recruitment method. The results are presented in Section 3. The implications of the study results are discussed in Section 4 before addressing the limitations of this study, together with the opportunities that it presents.

1. Issues and Challenges for the Population of Access to Genetic Information

Genomic medicine raises numerous questions, which link back to the usual problems associated with genetic information, as well as specific questions regarding new-generation tests, since these tests make it technically and financially possible to sequence all of an individual's genes and therefore to broaden the range of possible results.

1.1. Complex Information

The genetic dimension of a diagnosis is difficult for a non-specialist to understand, and then the main difficulty lies in the limited patients' knowledge of genetics. Indeed, some results determine the genetic origin of a pathology with certainty, whereas others, where the results are uncertain, only provide a risk. Some results may relate to a pathology for which clinical symptoms are present, whereas others indicate a predisposition for a future, as yet asymptomatic disease. The consequences of all of these results may then extend to relatives, ascendants, descendants or unborn children. Genetic information has an personal and familial dimension, it faces concepts of fate or destiny and for that reason can be sought out by some individuals and feared by others. Genomic medicine will be faced with even greater difficulties with the development of its accessibility (Clayes & Vialatte, 2014).

1.2. Specific Informational Challenges Associated with the Sequencing of Genomes

Genomic medicine also faces specific problems relating, to the results that can be accessed *via* genome sequencing and, to the use of the genomic data (Berg *et al*., 2011; INSERM, 2008; Joly & Knoppers, 2014). Whilst "traditional" genetic tests only target a small number of genes, *a priori* linked to the diagnosis being sought, WGS generates much more genomic information not necessarily related to the pathology for which the test has been prescribed. This wealth of information makes it difficult to determine the information that will be transmitted and that will require greater attention when it comes to patient support (Ormond *et al.*, 2010; INSERM, 2016).

With next-generation whole genome sequencing, additional information may become available

(Houdayer *et al.,* 2019). This additional information, which is unrelated to the pathology for which the sequencing was carried out, is referred to as "incidental data" where it is discovered fortuitously during the reading of the sequences, or as "secondary data" where it is sought out voluntarily. Such data make it possible to assess the degree to which the patient is predisposed to other pathologies that may or may not arise in the future, not just for them, but also for their relatives and their unborn children. Such pathologies may be curable or incurable and they may or may not be able to be managed by means of preventive behaviour. For example, without having explicitly sought the information out, the results will indicate with certainty the future occurrence of a pathology such as Huntington's disease or will show an increased risk of cardiovascular disease, diabetes or certain cancers (Green *et al.*, 2013). Additional data may also concern pharmacogenetics and could therefore specify the patient's response to drug treatments. For this reason, genetic medicine is classified as predictive and preventive medicine (Hood & Friend, 2011). At present, secondary data are only observed in a relatively small proportion of diagnostic procedures involving high-throughput sequencing. This is currently estimated to involve 2% of these procedures. However, this figure could increase as technology and knowledge develops. Such data still raise significant questions for practitioners (Parker, 2008; Héron & Gargiulo, 2009; van El *et al.*, 2013). They force a re-examination of the already tricky issue of patient access to genetic test results (Nzale *et al.*, 2020; Plan National Maladies Rares 3, 2018 [the French national plan for rare diseases]). The fact that the technology exists, that it is becoming increasingly efficient and financially viable, and that it provides the geneticist with a promising range of information, does not necessarily mean that all possible results are communicated to the patient, nor does it mean that the patient wants that.

A second problem, that is more specific to genomic medicine, concerns the use of biological samples and patients' genetic data for research purposes. Advances in genomics require the use of very large databases, which are constantly being fed with new individual data, and the creation of biobanks. The PFMG, for example, expects to be producing several tens of petabytes of data per year by 2021 (Aviesan, 2016). These databases must be compliant with confidentiality rules, since the genomic sequence of an individual, which is often supplemented with phenotypic and clinical data, can be identifying. These biobanks will only be able to generate knowledge if they are widely shared, thereby increasing the possibility of interpreting rare genetic events. These data will be accessible, not only for current research projects but also for future projects that are not yet precisely defined.

1.3. National Recommendations and Regulations

Whether it concerns the dissemination of results or the use of genetic data, each country has developed its own set of rules and procedures to define patient consent and its scope. Since 2013, the American College of Medical Genetics and Genomics (ACMG) has been recommending that all genome sequencing should look for pathogenic variations contained in a predetermined list of genes, unless the patient objects to this (Green *et al*., 2013). Fifty-nine genes that are not directly related to the original indication are now being examined (Kalia *et al.*, 2017); they are considered to be medically "actionable", in other words, their pathogenic variations lead to an increased risk of a disease, but one that can be prevented or treated.

In France, practices for disclosing additional results remain heterogeneous. The Law of 27 May 2013 defines the best-practice guidelines applicable to the examination of a person's genetic characteristics for medical purposes (see Appendix 1). In terms of the results that are to be communicated by the geneticist, the patient may express their wish to not receive the diagnosis and, as regards the additional data. The legislation is not favourable for the transmission of any information other than that initially sought and for which the patient has consented to the examination being carried out. Recently, a working group at the *Agence de la Biomédecine* (the Biomedicine Agency) spoke out against the systematic analysis of secondary data from a pre-determined list of genes unrelated to the initial indication (Isidor *et al.*, 2019) and recommended that the communication of incidental data be judged in a diagnostic multidisciplinary consultation meeting, with clinical utility as a criterion. From an operational point of view, the legislation stands, the two high or very high speed sequencing platforms already installed will not transmit incidental or secondary data during the initial phase of their implementation.

In France, researchers must obtain consent from patients in order to use their data for defined

research projects and must check that they do not object to such in the event that there is a change to the project. The latter provision relaxes the obligations incumbent on researchers who use biobanks. However, having been informed of the projects to which their data are contributing, patients are free to withdraw from a research project at any time and without having to provide any reason for this (Noiville, 2019). Conversely, in UK, consent to the use of genomic data is given once and for all.

Looking at the health, scientific and economic objectives of the PFMG, the current legal rules, and the heterogeneity of practices in perspective, it is not surprising that the public authorities are searching for possibilities to develop the genomic medicine while preserving the public interest and protecting individual rights. The complexity of the challenges posed by genomics should not be left out of the public debate: the development of this "new" branch of medicine should remain in line with the values favoured by the population.

1.4. Better Understanding the Expectations of Potential Users

Summaries of published studies and future research (Berger & Olson, 2013; Rogowski *et al*., 2015) identify avenues that economists should pursue to better contribute to the evaluation of genomic medicine and to the issues it raises for its beneficiaries, promoters and regulators. One of these avenues is to assess the preferences and expectations of patients/citizens. Having a greater understanding of their preferences with regard to the results that they are expecting, or knowing whether they are willing to contribute to the establishment of vital biobanks would allow us to better measure the specific contribution made by development strategies such as the PFMG and the possibility of advancing knowledge through the provision of patients' genetic data.

Some economists have already looked into patients' preferences when it comes to genetic test results. Their research is either qualitative (interviews, focus groups) or quantitative (questionnaire-based surveys, revealed preference methods). They provide mean values regarding attitudes towards genetic testing among the general population (Henneman *et al.*, 2013), or for certain types of patient: pregnant women (Ormond *et al.*, 2009), patients with different levels of risk (Bränström *et al.*, 2012), parents awaiting a diagnosis for their child (Townsend *et al.*, 2012). The findings of this research point to a generally favourable attitude towards genetic testing, positive expectations of results and the desire to be fully involved in choices regarding access to tests or results. In research that looks more specifically at genomic testing, the focus is often on the decision as to whether or not to access unsolicited data. The results very consistently show a clear majority in favour of the dissemination of unsolicited data, and a slightly smaller but persistent majority where the unsolicited data concern incurable pathologies (Shahmirzadi *et al*., 2014; Fernandez *et al*., 2014; Gray *et al.*, 2016).

While most of these studies addressed the preferences of patients already undergoing genetic treatment, some studies have looked into the preferences of the general population (Henneman *et al.*, 2013; Marshall *et al.*, 2016; Facio *et al.*, 2016; Regier *et al.*, 2019). The characteristics of national health systems, values and societal preferences mean that the acceptability of genomics and its implications are not necessarily the same in all countries. Nevertheless, the preferences of French population for genomic medicine remain largely unknown: the first economic evaluations of genomic care are starting to be published (Marino *et al.*, 2018) or are currently under way, but there are no studies that address the issue of demand and preferences among the French population with regard to the genetic information that can potentially be accessed. There are a few publications that focus on the preferences of French patients already receiving genomics-based care (e.g. Peyron *et al.*, 2018), but these do not allow for a broader reflection on the expectations and acceptability of this information among the general population.

2. Discrete Choices to Reveal Preferences Regarding Access to Genetic Information

The preferences of the French population regarding access to genetic information are explored here within the scope of an online survey, conducted with a polling institute (CSA) among a representative sample.

The survey asks a series of questions on a range of the respondent's characteristics and a part corresponding to a discrete choice experiment. This experiment is conducted within the context of medical care: the respondents are asked to imagine that they are undergoing medical treatment, part of which involves a genetic test to diagnose the pathology that they are suffering from; however, there are several different tests

available and they must choose which would be the most suitable for them.

The discrete choice method (Box 1) is widely used in health economics in order to study individual preferences (Clark *et al.*, 2014), but, to the best of our knowledge, has not yet been used to study the preferences of the French population with regard to genomic medicine. In order to construct this discrete choice experiment, define the attributes of the proposed tests and their value, establish scenarios and decide upon the design of the experiment, we followed current methodological recommendations (Bridges *et al*., 2011; Johnson *et al*., 2013; Kløjgaard *et al*., 2012; Louvière & Lancsar, 2009).

2.1. Selection of Attributes and Their Levels

Although there are not really any clear rules regarding the selection of the number of attributes and their levels, this step is recognised as being crucial to the validity of the experiment (Kløjgaard *et al.*, 2012). According to the multi-attribute utility theory, each attribute must be of importance to the respondents to enable them to make compensatory trade-offs between the value of the various attributes (Lancsar & Louviere, 2008). The attributes should cover all relevant dimensions of what is being proposed, but they should remain limited in number: indeed, the choice experiment can be complex from a cognitive point of view, and this complexity increases with the number of attributes.[1] Appropriate levels must then be determined for each attribute. They must correspond to relevant values and must present differences that are large enough to allow choices to be made, but not so large that one level would be *a priori* dominant (Lancsar & Louviere, 2008). Finally, the wording or explanations of the attributes must ensure that the respondents have a clear and unambiguous understanding of their content. This is a general constraint for any self-completed questionnaire, but one that is much more important here: indeed, the values proposed in a discrete choice experiment (or the context for the choices) are hypothetical and not necessarily related to the respondent's knowledge or experience.

Recent recommendations emphasise the need for a qualitative approach, as well as for pre-testing to confirm the choice of attributes and their values (Coast *et al.*, 2012; Drummond *et al.,* 2015). With this in mind, we started by identifying the possible attributes, together with their various possible levels, based on a comprehensive review of the literature concerning current issues in genetics, the ethical and legal questions currently being raised, questions raised by professionals regarding the dissemination of results and the perception of genetic information by patients and the general public. The attributes and their levels were then examined and discussed by a group of experts in the field of genomics, made up of two geneticists, one biologist, one public health physician and one health sociologist. They were also submitted to the respondents during the pre-test phase of the survey and were detailed in the section describing the questionnaire and its structure.

Four attributes were selected (Table 1):

- *Decision* (the person who will be able to decide upon the results that could be communicated): the identity of the person who decides refers back to

1. Marshall et al. *(2010) estimate that 70% of discrete choice experiments include between 3 and 7 attributes, most commonly between 4 and 6 attributes.*

Box 1 – **The Discrete Choice Experiment**

The Discrete Choice Experiment (DCE) is a method used to reveal preferences based on the concept of hypothetical choices. It was developed during the 1970s through the work of Daniel McFadden (McFadden, 1974). In particular, McFadden applied a mathematical formulation to the random utility maximisation (RUM) model (Manski, 1977). RUM is a behavioural model describing how agents are supposed to make choices from among a finite and countable number of options (discrete choices). It is based on three theories: *(1)* The random utility theory, according to which the utility an agent derives from the consumption of a good cannot be fully observed (Böckenholt, 2006); *(2)* the multi-attribute utility theory, according to which the utility is derived from the characteristics of the good rather than the quantity of the good itself (Lancaster, 1966); *(3)* the revealed preference theory, according to which the agents choose the option that provides them with the greatest level of utility (Samuelson, 1938; 1948).

The DCE consists of presenting chosen hypothetical situations from among several options that combine a number of characteristics (or attributes), from which participants indicate which one they prefer. For example, the decision to consult a doctor could be influenced by the waiting time for an appointment, the amount of time spent in the waiting room or the cost of the consultation. Different values or levels are assigned to each of these characteristics. Using the experimental design methodology, these various values are combined to form choice tasks. The first test could be made up of an option A for a consultation in 3 days' time that costs 20 euros with a 45 minute waiting time and an option B for a same-day consultation that costs 30 euros and has a 60-minute waiting time. Since the options differ in their composition, the participants have to make trade-offs between time, cost and waiting time during the successive tests. These trade-offs provide the information needed to model preferences (i.e., utility gained from marginal changes in the attributes).

the debate in genomics as to the patient's capacity to make decisions and whether such decisions should be transferred to the expert, i.e. the geneticist (with behaviours that can range from shared decision-making to *a priori* benevolent paternalism), as well as the possible existence of collective rules that would be imposed, identically or not, on all patients. We have chosen four possibilities that illustrate this debate: the doctor makes the decision alone following a discussion with the patient; the patient makes the decision alone following a discussion with the doctor; collective rules, which are enshrined in law, define the results to be delivered; local and specific decisions for each patient determine what he or she will receive.

- *Results* (the scope of these results): as we have already mentioned above, genetic information is complex and high-speed sequencing can reveal genetic mutations that cause or will cause pathologies other than those for which the test has been prescribed and that are currently asymptomatic. We have deliberately limited the choice by concentrating on the option of whether or not the patient wants to know their predispositions with regard to actionable or non-actionable pathologies (we have therefore removed the wording that states that the results may also concern relatives and that there could be a greater or lesser degree of certainty regarding the link between mutation and pathology given the current state of knowledge).

- *RAC* (for *reste à charge*, the cost for the patient): the amount that the patient must pay allows for an understanding of the sensitive nature of a hypothetical payment. This attribute is necessary to allow for the subsequent calculation of the willingness to pay. The upper limit is an approximation of the cost of the test, currently borne by genetic centres but not invoiced to the patients. The lower limit is almost free of charge, reflecting the current situation associated with a prescription in a hospital genetics department.

- *Sample* (the way in which the biological sample taken for the test is used): the management of the sample provides for its destruction; its subsequent re-analysis, but only for the purposes of the patient's care; its being made available solely to researchers; or its simultaneous reuse for both the patient and for research.

2.2. Designing of the Discrete Choice Experiment

The discrete choice method also requires the experimental designing of choice tasks, or in other words, alternative options that combine the possible levels of the attributes, which will be submitted to the respondent in pairs. In order to achieve this, an orthogonal main effects plan design was obtained with the Ngene software (ChoiceMetrics Pty Ltd, New South Wales, Australia), which resulted in 16 pairs of scenarios.

Table 1 – **The attributes and their levels**

Attributes	Levels of the attributes	Abbreviation
Decision "Who should decide upon the results received?"		
	A. My doctor decides, having discussed this with me	'My doctor'
	B. I decide, having discussed this with my doctor	'Me'
	C. The law decides and the same rules are applied to everybody	'The law'
	D. A local ethics committee (made up of doctors, lawyers, philosophers, patient representatives, etc.) decides after examining my results	'Committee'
Results "What results should I receive?"		
	A. Only the results that concern my current disease	'Disease'
	B. The results that concern my current disease + my predisposition to all treatable or preventable diseases	'Actionable'
	C. The results that concern my current disease + my predisposition to certain treatable or preventable diseases included on a list that has been determined nationally by geneticists	'List'
	D. The results that concern my current disease + my predisposition to all treatable or preventable diseases + my predisposition to diseases that are currently untreatable	'All
RAC (out of pocket cost) "How much should I have to pay?" (in euros)		
	1, 40, 90, 160	
Sample "What will happen to my blood sample?"		
	A. My sample will be reanalysed for me (new results may be possible following developments in knowledge) and used anonymously for medical research	'For me and research'
	B. My sample will be used anonymously for medical research	'For research'
	C. My sample will be reanalysed for me (new results may be possible following developments in knowledge)	'For me'
	D. No use after my test, my sample is not stored	'None

Notes: The levels marked as A are the reference values for the choices associated with qualitative variables. Costs for patients are a continuous variable.

In order to limit the number of tasks given to each respondent, these 16 scenarios were randomly split into two different versions of the questionnaire (each therefore containing eight tasks). Choices needed to be made between two non-labelled options referred to as "Test A" and "Test B".[2] An example of a choice task is shown in Figure I.

For the online questionnaire, the formatting and wording of the choice tasks aimed to provide adequate information regarding the genetic tests and what is at stake for a potential beneficiary and to facilitate the cognitive challenge presented by a discrete choice experiment. It should be noted that the questionnaire underwent two rounds of pre-testing in the form of semi-structured interviews, which were held once the questionnaire had been filled in independently under survey conditions (Box 2).

2. We did not offer an opt-out option for this experiment. On the one hand, the hypothetical context that we are asking the respondents to place themselves in is that of medical care during which they are required to undergo a genetic test, and their choice relates only to the characteristics of that test. It can therefore be assumed that the implication if they do not choose these characteristics is that the decision will be left to someone else, which corresponds to the options proposed. On the other hand, in a discrete choice experiment, giving respondents the option to not make a choice only brings about small differences in the estimates (Fiebig et al.*, 2005), while forcing them to make a choice can result in better thought out responses and better quality data (Veldwijk* et al.*, 2014).*

Figure I – **Example of the choice tasks**

	Test A	Test B
Who should decide upon the results received?	**My doctor** decides, having discussed this with me	A **local ethics committee** (of doctors, lawyers, philosophers, patient representatives, etc.) decides after examining my results
What results should I receive?	The results that concern my current disease + **my predisposition to all treatable or preventable diseases**	**Only the results that concern my current disease**
How much should I have to pay?	**1 €**	**40 €**
What will happen to my blood sample?	My sample will be **used anonymously for medical research**	My sample will be **reanalysed for me** (new results may be possible following developments in knowledge) **and used anonymously for medical research**
I prefer test Click the corresponding box	☐	☐

Box 2 – **The Questionnaire and its Structure**

The questionnaire is made up of four parts:

- The first relates to the individual characteristics that allowed the sample to be stratified according to six criteria: gender, age group, socio-professional category, region of residence, size of urban area and size of household;

- The second part introduces the subject of genetics with questions that allow the respondent to be provided with information about genetics, the concept of predisposition and possible outcomes of a genetic test;

- The third part of the questionnaire (the results of which are presented in the remainder of this article) corresponds to the discrete choice experiment. Having asked the respondent to imagine being in a healthcare setting where they had to undergo a genetic test, but were able to choose the test, they are offered eight successive choice tests, each between two different configurations of the test;

- The fourth and final part of the questionnaire deals with the respondent's experience of the discrete choice experiment that they have just completed (interest, difficulty, preferred item), their general attitude towards healthcare and therapeutic innovations and their knowledge of genetics.

The questionnaire was pre-tested among 21 people for the first pre-test and 14 for the second. The sample of pre-testers was an empirical sample recruited in order to cover the 18-49 and 50-70 age groups, as well as education levels ranging from no qualification to higher education. During these two pre-tests that we carried out ourselves, the respondents completed the survey online and then the completion thereof was discussed in an interview grid. We looked in particular at the amount of time taken to complete the questionnaire, the overall acceptability of the survey, the ease of completing the online questionnaire, the comprehension of the questions and the provision of explanations regarding genetics and the attributes and choices being requested, which could be accessed by clicking on the links in the questionnaire. The first pre-test led in particular to us rewording the questionnaire, both to explain the context in which the hypothetical choices were to be made by the respondents (*i.e.*, within the scope of a test that was to be carried out for the purposes of medical treatment), to ensure that the attributes are clearly differentiated from one another and to ensure that the links were actually helpful. The second pre-test allowed us to verify that the rewordings resulting from the first pre-test did not raise any further issues.

2.3. Preference Modelling

The analysis of the data from the discrete choice experiment is based on the *random utility maximisation* model. According to the random utility hypothesis, the utility U that an individual n derives from the option j comprises an observable component V and an unobservable component ε. According to the multi-attribute utility hypothesis, the observable component is a function of the characteristics of the option X_{jk} in the individual preferences for these characteristics β_{nk}. Due to the unobservable component, the modelling focuses on the probability P of the option being chosen, $P_{nj} = exp\left(V_{nj}\right) / \sum_{nj} exp\left(V_{nj}\right)$. In practice, V is frequently assumed to be additive in terms of its arguments and linear in terms of its parameters ($V_{nj} = \sum_k \beta_{nk} X_{njk}$) and ε is assumed to be distributed independently and identically as a type I extreme value ($\varepsilon_{nj} \sim iid\ EV1$). This specification therefore leads to a multinomial logistic regression model (Train, 2009). The interest in this econometric modelling lies in its ability to analyse the variability of the impact of attributes and their values within the sample. This objective responds to an assumption of heterogeneity of preferences with respect to the values of the attributes.

The inter-individual variability of the preference parameters is captured with a normal distribution (see Hauber *et al.*, 2016) whose mean μ and variance σ² are to be estimated. The model includes a constant, β_0, which is associated with the scenario presented on the left in the choice tasks. This is to measure systematic bias in decision making.

2.3.1. Estimation of the Preferences

In our experiment, the deterministic component V is assumed to be linear in terms of its parameters and additive in terms of its arguments. The formula is as follows:

$$\begin{aligned} V_n = {} & \beta_0 + \beta_{n1} * Results\_\text{Actionable} \\ & + \beta_{n2} * Results\_\text{List} + \beta_{n3} * Results\_\text{All} \\ & + \beta_{n4} * Decision\_\text{Me} + \beta_{n5} * Decision\_\text{The law} \\ & + \beta_{n6} * Decision\_\text{Committee} \\ & + \beta_{n7} * Sample\_\text{For research} \\ & + \beta_{n8} * Sample\_\text{For me} \\ & + \beta_{n9} * Sample\_\text{None} + \beta_{n10} * RAC \end{aligned}$$

With the exception of the monetary attribute *RAC*, which is included as a continuous variable, all of the variables were dummy coded (and the reference level is excluded from the model). The reference values, are therefore: *Results*-None, *Decision*-My doctor, *Sample*-For me and for research.

The preference parameters (β_{n1}, …, β_{n9}) are assumed to be distributed normally with a diagonal variance-covariance matrix ($\beta_{nk} \sim N(\mu_k, \sigma_k)$). The cost preferences are assumed to follow a log-normal distribution in order to force all individuals to have non-positive preferences for a cost increase.

The log-likelihood (LL) function of the model is as follows:

$$\text{SLL} = \sum_n \sum_j d_{nj} \ln\left(\frac{1}{R}\sum_r P_{nj|\beta_n^r}\right)$$

where $d_{nj} = 1$ where individual n chooses option j and 0 otherwise. This LL function needs to be simulated (hence simulated log-likelihood, SLL). For the purposes of this study, 1,000 Halton draws were used (R = 1,000), and the optimisation process was initiated with 20 different sets of starting values to test the robustness of the results.

2.3.2. Calculation of the Willingness to Pay

The inclusion of a monetary attribute (*RAC*) in our utility function allows us to calculate willingness to pay (WTP) for changes in the other attributes. In the case of an additive linear utility function, the WTP for attribute k is obtained as a ratio of preference parameters.

$$\text{WTP}_\text{k} = \frac{\partial V / \partial X_k}{\partial V / \partial RAC} = \frac{\beta_{nk}}{\beta_{n10}}$$

The ratio between a parameter and the attribute *RAC*'s coefficient can therefore be interpreted as a marginal willingness to pay, i.e. as the maximum amount that individuals would be prepared to pay in order to improve an attribute by one unit.

The estimated parameters are interpreted as the change in utility associated with moving from the reference value of an attribute to the considered value of that same attribute. The preferences will be heterogeneous with respect to a level of an attribute where the standard error of the coefficient associated with that value differs significantly from zero.

Once the parameters for the distribution of preferences have been estimated, it is possible to provide a visual representation of the heterogeneity of preferences by simulating the distribution of preferences (in this case, the number of samples was equivalent to the number of respondents) and to represent the distribution using Kernel density curves.

3. The Choices Collected and Estimation of Preferences

3.1. The Sample and its Perception of the Discrete Choice Experiment

The survey was sent out (between 28 September and 13 October 2017) in the form of a web link to a CSA panel. The recruitment of respondents needed to result in a representative sample of the French population, stratified by gender, age, socio-professional category, household size and location. 4,380 individuals clicked on this web link. 1,011 of them were not included in the sample as they were out of quota, and 868 individuals did not complete the questionnaire; the majority (61%) of them stopped at the beginning of the questionnaire, and then a further 28% stopped at the start of the section devoted to the discrete choice experiment. The final sample comprises 2,501 individuals aged between 18 and 70 and is representative of the French population (their characteristics are given in Appendix 2, Table A2-1).

Regarding the discrete choice tasks, 60.8% of the respondents find the choices they had to make always or mostly difficult. However, when asked to apply a qualifier to the choice of the hypothetical situation, the respondents found this: "surprising" (15.2%), "complicated" (24.2%), but "interesting" (44.4%). They also largely responded to the logic involved in the discrete choice method, which requires that all the attributes can be subject of a trade-off by the respondent. If an attribute or a value dominates all of the others, the multi-attribute utility function is itself meaningless, 66% of respondents stated that none of the four attributes determined their choice alone. For the others, the attribute that was dominant was only systematically so for 24.5% of them, and that dominant attribute differed depending on the individual (*Decision* for 38.2%, *Results* for 28.8% and *RAC* for 24.9%). Where the respondents stated that they had ignored an attribute in order to make their choices, this was "rare" for 58.8% of them and "always" for 41.2%. The attributes that apparently had the least influence over choices were the *RAC* (47%) and the use of the *Sample* (25.5%), followed by the identity of the *Decision*-maker (15.5%) and the *Results* (11.9%). These results are detailed in Appendix 2 (Table A2-2).

3.2. Preferences that are Sometimes Heterogeneous, but in Favour of Access to Genetic Information

The results obtained by estimating the utility function are presented in Table 2.

All of the mean effects are significant at the 1% level, which indicates that the four test attributes were taken into account by the participants when they chose their preferred test. For each qualitative attribute, moving from the reference value to another option always changes the utility.

The coefficients associated with the different levels of the qualitative attributes are not all random. The assumption of heterogeneity in preferences was rejected for the following effects: *Results* attribute, 'Committee' level of the *Decision* attribute, 'For me' level of the *Sample* attribute. However, for the other attribute levels (the 'Me' and 'The law' levels of the *Decision* attribute, and all levels of the *Sample* and *RAC* attributes), it is preferable to assume the heterogeneity of preferences. A visual representation of the dispersion of each of the random coefficients within the sample is provided by means of density curves (Figure II).

For the *Results* attribute, the coefficients are positive and significant for all three levels: accessing results other than those that are specifically related to the initial pathology systematically increases the utility of the genetic test. However, the scope of the additional results reported has an impact on the increase in utility. As a result, the greatest increase occurs when all of the predispositions are communicated, whether actionable or not. Where the additional data are only available regarding pathologies that are actionable or on the predefined list, the utility also increases for all respondents, but to a slightly lesser degree.

For the *Decision* attribute, the shift from a decision made by the doctor (after discussion with the patient) to a decision made by the patient (after discussion with the doctor) increases the well-being of the individual. Conversely, the shift to a delimitation of results that is the same for everyone and enshrined in law, or the shift to a specific delimitation for each patient, but which is delegated to an ethics committee, results in a decrease in satisfaction. The impacts on utility of a decision that would be made by the patient (after discussion with the doctor) or that would be delimited by the law also vary within the sample and, unlike the previous attribute, the impact is not always the same for all respondents. On average, the shift to a patient-led decision is viewed positively; however, for 13.5% of respondents, this would bring about disutility when compared with the final decision being made by a doctor. Having a law that defines the results that are accessible is viewed negatively on average; however, 30.3% of respondents saw this as a positive. A decision

Table 2 – **Results of estimations (mixed Logit)**

	Parameters for the distribution of preferences			Willingness to pay (in euros)		
	μ (SE)	σ (SE)	% respondents with a negative preference	Mean	95% confidence interval	
Constant	0.235*** (0.021)					
Results - Only concerning my current disease (*Ref.*)						
Ref. + my predisposition to actionable diseases	0.812*** (0.043)	0.000 (0.093)	0	26.24	22.85	29.63
Ref. + my predisposition to a fixed list of diseases	0.759*** (0.045)	0.012 (0.124)	0	24.52	23.13	27.91
Ref. + all my predispositions	0.881*** (0.040)	0.154 (0.208)	0	28.47	25.05	31.88
Decision - My doctor *(Ref.)*						
Me	0.547*** (0.040)	0.497*** (0.094)	13.5	17.67	14.14	21.20
The law	-0.509*** (0.046)	0.988*** (0.058)	69.7	-16.44	-20.35	-12.54
An ethics committee	-0.770*** (0.041)	0.261 (0.182)	100	-24.87	-28.31	-21.43
Sample - For me and research (*Ref.*)						
For research	-0.479*** (0.041)	0.791*** (0.062)	72.7	-15.47	-19.21	-11.75
For me	-0.279*** (0.045)	-0.030 (0.087)	100	-9.020	-12.41	-5.63
None	-0.655*** (0.045)	1.014*** (0.055)	74.1	-21.17	-25.1	-17.23
RAC	-5.319*** (0.080)	1.920*** (0.089)	100			
Observations	20,008	Log-likelihood (model): -11106				
Respondents	2,501	Bayesian Information Criterion (BIC): 22420				
Parameters	20					

*** significant at 1%. μ stands for mean, σ for standard error and SE for error type.
Notes: The willingness to pay (WTP) is given as a mean value and with a 95% confidence interval. A plus symbol next to the willingness to pay indicates that respondents would be willing to pay that amount in order to benefit from the level of that attribute and to preserve the same level of utility, and a minus symbol indicates the amount that they would need to be paid to persuade them to tolerate that level of the attribute without lowering the utility. The confidence intervals for the WTP were calculated using the Delta method following the procedure explained in Bliemer & Rose (2013).

made by a local ethics committee having reviewed the patient's record had the greatest negative impact on utility for all respondents.

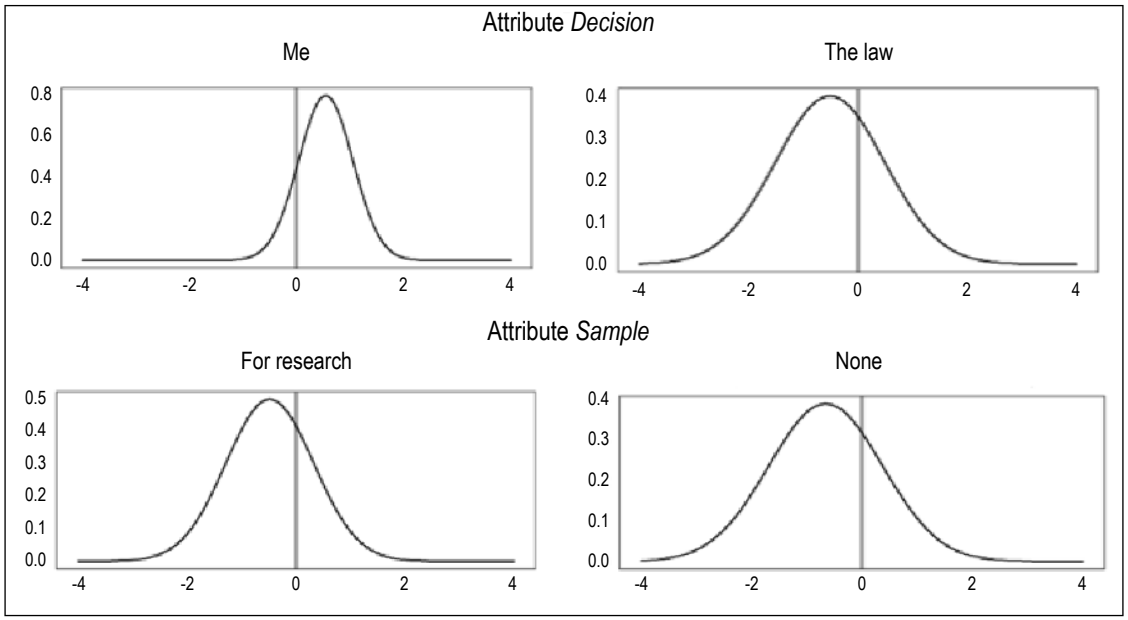
As regards the *Sample* attribute, the coefficients associated with all levels of this attribute are negative and significant. By way of a reminder, the reference level is a reanalysis of the sample for the patient and making the sample available for research. Shifting from this option to no other use, i.e. no reanalysis for me or for research, is the change that, on average, brought about the greatest degree of disutility. However, 25.9% of respondents would prefer that their sample be for immediate use only. Moving from the reference option to use for research only would, on average, bring about a greater decrease in utility than subsequent use for the patient only. However, the impact of limiting use to research remains positive for 27.3% of respondents. Finally, shifting from use for me and for research to purely personal use is also negative, but can be considered as a constant within the sample.

Finally, the coefficient associated with the attribute *RAC* is significant, negative and of variable magnitude. All else being equal, and not surprisingly, the increase in the cost to be borne by the patient reduces the utility associated with the test.

3.3. Willingness to Pay to Change the Options for Accessing Genetic Information

The results regarding the willingness to pay (cf. Table 2) demonstrate that the respondents are prepared to pay, on average, between 24.52 and 28.47 euros to gain access to additional results. They are willing to pay 17.67 euros to be able to choose for themselves which results

Figure II – **Random coefficient density curves from the mixed logit estimation**



Notes: On the vertical axis, density. On the horizontal axis, the coefficients resulting from the mixed logit estimation.

they will be able to access rather than letting their doctor decide what they can be told about. In order for it to be acceptable for the delimitation of the results to be determined by the law or an ethics committee, they would need to be paid a compensatory amount of 16.44 or 24.87 euros, respectively. Finally, in order to waive any further use of their sample, whether it be for themselves or for research, they would need to be paid 21.17 euros, and 9.02 euros if the subsequent use excludes research while maintaining the benefit of reuse for themselves.

4. Initial Results and Prospects for Research on Genomics in France

Our results show, that the French population has a preference for tests that would allow to look beyond the results targeting the pathology for which the test was prescribed, with that preference increasing in line with the scope of that additional data. The desire to have information, all of the information possible when it is presented as being potentially available, may seem like it has not been properly thought out when linked to a hypothetical situation. However, the same results have previously been obtained by other studies, in other countries and among specific populations (Gray *et al.*, 2016, among colorectal and lung cancer patients in the UK; Peyron *et al.*, 2018, among French families with a child suffering from a rare developmental disorder with no known aetiological diagnosis), or among the general public (Daack-Hirsh *et al.*, 2013 in the USA; Facio *et al.*, 2013 in the USA; Fernandez *et al.*, 2015 in Canada; Hishiyama *et al*., 2019 in Japan; Marshall *et al.*, 2016 in the USA). The fact that the patient may experience disappointment or anxiety when faced with the results of sequencing or additional data (Chassagne *et al*., 2019) must not result in this initial positive attitude towards the additional information being discounted. For professionals and public authorities alike, it is therefore a question of knowing how to support this strong demand, or to find a way to justify and explain why such access, while technically possible, is not yet authorised in France. It is also possible that the announcements made in the PFMG 2025 and the dissemination of information on the opportunities associated with genomic medicine will further increase these expectations over time.

Our respondents value access to all predispositions even more than they value access to just those pathologies that are actionable; this result differs from that found by Marshall *et al.* (2016) in the USA. Furthermore, in our study, the utility of expanding the results beyond those concerning the current pathology is identical for all individuals, whereas other research has shown heterogeneity in this preference for more results: Marshall *et al.* (2016) show that in the USA, some of the respondents have no interest in genetic information in general; Regier *et al.* (2015) show heterogeneity in the utility of genetic information (however, they did specify the severity of the diseases in the choice of results to be accessible, which we have not done here). The heterogeneity in the utility attributed to the additional data may depend on

the provisions of a more explicit presentation of the risks associated with the pathologies within the attributes. The different attitudes to risk would then be reflected in varying preferences.

In line with this first analysis, and also in accordance with the literature (Daack-Hirsh *et al.*, 2013; Regier *et al.*, 2015; Marshall *et al.*, 2016), our respondents prefer a decision with upstream support from a doctor, but that is ultimately made by themselves (Moumjid *et al*. 2017). In addition to this desire for autonomy, there is real opposition to decisions that would be made in reference to a list of accessible results set out in the law, and in particular to decisions that would be made by a local ethics committee, with none of the respondents wanting that option. The respondents want decisions that are personalised within the scope of their individual relationship with their doctor; general regulation by law would not guarantee that degree of personalisation. While it could be more attentive to individual situations, a local ethics committee that would make a decision after examining the medical records appears to be perceived as being both restrictive in terms of the autonomy of the patient outside a chosen relationship of trust and, unlike the law, offers little guarantee of equality.

Not being able to reanalyse one's own sample for the purposes of one's own treatment is indeed seen as a disadvantage; respondents appear to have taken on board the rapid development of genetic knowledge and the opportunity to benefit from it. Our results regarding the use of samples are also of interest for assessing the acceptability in France of the construction of genomic biobanks and databases. The disutility associated with samples that will no longer be available for research clearly shows, albeit indirectly, that contributing to biobanks is valued in itself by individuals. The research appears positive here, and the obstacles that could be raised by questions regarding management, ownership and anonymity are not highlighted here.

The heterogeneity of preferences, as reflected in the random distribution of certain parameters, particularly those linked to the nature of the decision-maker, demonstrate that the importance attached to the different characteristics of the test is not always the same for each individual. Beyond the average level of preferences, it is therefore possible to highlight characteristics that are either seen as unanimously positive, such as access to all results, or unanimously negative, such as the role of a local ethics committee in accessing results. These convergences or variabilities in preferences can present a source of reflection for a public decision-maker.

From a methodological point of view, the relevance of a discrete choice survey lies in its ability to look beyond the points of view that could be gathered by means of a traditional questionnaire. The results prove this interest. By way of an example, although 47% of respondents reported that cost had little influence over their decisions, estimates show that this characteristic is clearly significant for the level of utility, even if the importance of cost varies within the sample.

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Our results allow us to characterise the methods of access to genetic information that are most in line with the *a priori* expectations of the French population, and to compare them with current practices or debates on the dissemination of genomic tests. However, our study was not without its limitations. The first is inherent in any discrete choice experiment that places the respondent in a hypothetical situation, in this case that of having a disease and needing to undergo genetic testing and having to choose a test that most closely matches their preferences. There is no guarantee that the trade-offs and wishes would result in the same choices in the real world. The second possible limitation is that the complexity of the concepts and the range of issues associated with accessing a genomic test and the additional data may have made the choices made here "superficial". Nevertheless, the responses that we received from the survey with regard to its difficulty, as well as its interest, and the fact that none of the attributes were spontaneously declared dominant by a majority of the respondents, tend to support the use of this method. The qualitative approach undertaken in order to establish our choice experiment resulted in elements of choice that all appear significant in the estimates. This is also a reassuring sign, although it does not rule out the possibility that some decisive elements may be missing.

In order to build our choice scenarios, we made use of an orthogonal design that assumes that all parameters carry the same weight. An alternative strategy, which is currently quite widespread, is to use an efficient configuration, which takes account of the *a priori* information on the preferences to be estimated and which would increase the accuracy of the estimates. Looking beyond the debates on the comparative contribution of

these approaches (Olsen & Meyerhoff, 2017; Yao *et al.*, 2015), we decided that it would be preferable to not integrate results from studies carried out within populations other than the French population (which could have provided us with *a priori* distributions of preferences within our field of study), especially since the relatively large size of our sample is able to counterbalance any possible loss of precision in our estimates. However, our results can be used in efficient configurations for other discrete choice surveys concerning genetic information and the French population.

Indeed, we believe it is necessary to continue developing research on access to tests and genomic medicine. At present, access to genomic medicine in France remains limited and primarily concerns the fields of cancer and rare diseases, to which the high-speed sequencing platforms are currently dedicated. As regards the possibility of accessing additional results, this is not widespread and is the subject of heated debate among health professionals (Delanne *et al.*, 2019). However, the Société Française de Médecine Prédictive et Personnalisée [French society for predictive and personalised medicine] recommends that a list of 36 medically actionable genes associated with cancer be communicated to patients (Pujol *et al.*, 2018). Specific studies, which are still ongoing, should allow for a better understanding of the demand for additional results in France. The FIND study, for example, which was financed by the Ministry of Health and Social Affairs (awarded the PREPS 2016 funding) and conducted within the Dijon, Lyon and La Pitié-Salpêtrière APHP university hospitals, explored the demand for additional results among the families of children suffering from rare developmental abnormalities offered genomic testing, as well as the repercussions that the communication of these data would have on their quality of life and their behaviours in terms of seeking treatment. It is essential that these issues are investigated within a context where access to genomic medicine is likely to increase and be rolled out more widely to more medical indications – in line with the ambitions set out in the PFMG 2025.

By focusing on the ways in which information is accessed when access to genomic medicine is supposedly already effective, we have examined the expectations or the intensity of the demand that the French population might have for these new treatments and associated tests. This decision was motivated by the current situation in France: access to this new medicine can only be provided within the scope of specific medical care, which, as we have highlighted, already raises many questions for patients, practitioners and the regulator. Nevertheless, with the spread of this field of medicine, it is reasonable to assume that, in the medium to long term, the question regarding the level of demand for genomic testing within the population will be more pressing: do French people want to undergo such testing? Would this be on prescription from a health professional (GP, specialist, geneticist) or freely available on the market? If this demand were to increase, this would require even greater attention to be paid to the nature of the results communicated and the use of the samples, particularly when it comes to uses outside of the medical sphere.

As we can see, there are many questions and avenues of research in the field of genomic medicine. We have been able to produce an initial assessment of the expectations of French people when it comes to the ways in which genetic tests are accessed. These initial results should already be able to fuel the debate among the professionals who would need to guide patients towards truly informed consent and, beyond that, towards informed decision-making for those who wish to access the results and, on the other hand, among public policy decision-makers, to ensure that these technologies are rolled out in a way that is respectful of societal preferences and at the very least with a constructive discussion regarding citizens' preferences. □

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APPENDIX 1

EXTRACTS FROM THE DECREE OF 27 MAY 2013 DEFINING THE BEST-PRACTICE GUIDELINES APPLICABLE TO THE EXAMINATION OF A PERSON'S GENETIC CHARACTERISTICS FOR MEDICAL PURPOSES

The genetic characteristics of a person may only be examined for medical or scientific research purposes. The express written consent of the person involved must be obtained prior to the examination taking place and after he or she has been duly informed of its nature and purpose. The consent shall state the purpose of the examination. It may be withdrawn at any time and without formalities.

The results of a genetic examination should not be communicated directly to the patient by the medical biology laboratory, but by the prescriber [...]. The methods by which these results are communicated must be defined in advance, in particular during the consultation giving rise to the prescription. The person shall be free to express, in writing, their wish to not be informed of a diagnosis.

The question as to whether the results are to be returned to the patient arises when the genetic examination leads to the incidental discovery of information other than that being sought. In order to protect the patient from information that is not of use, that is likely to cause concern or that he or she does not wish to know, the applicable law (Article 16-10 of the French Civil Code and Article R. 1131-4 of the French Public Health Code) is not favourable for the transmission of any information other than that initially sought and for which the patient has consented to the examination being carried out.

Under these conditions, it is up to the doctor to determine the appropriate course of action on a case-by-case basis and in the context of the individual consultation with their patient. He or she is advised to contact a doctor working within a multidisciplinary team, bringing together clinical and genetic competences, as mentioned in Article R. 1131-5 of the French Public Health Code.

Original Text of the Decree

L'examen des caractéristiques génétiques d'une personne ne peut être entrepris qu'à des fins médicales ou de recherche scientifique. Le consentement exprès de la personne doit être recueilli par écrit préalablement à la réalisation de l'examen, après qu'elle a été dûment informée de sa nature et de sa finalité. Le consentement mentionne la finalité de l'examen. Il est révocable sans forme et à tout moment.

Le résultat d'un examen génétique ne doit pas être directement communiqué au patient par le laboratoire de biologie médicale mais par le prescripteur (…). Les modalités de communication de ce résultat doivent être préalablement définies, notamment au cours de la consultation qui a donné lieu à la prescription. La personne peut exprimer, par écrit, sa volonté d'être tenue dans l'ignorance d'un diagnostic.

La question du rendu des résultats au patient se pose lorsque l'examen génétique conduit à révéler fortuitement d'autres informations que celles recherchées. Le droit en vigueur (art. 16-10 du code civil et art. R. 1131-4 du code de la santé publique), pour protéger le patient d'informations inutiles, angoissantes ou dont la révélation n'est pas désirée, n'est pas en faveur de la transmission d'informations autres que celle initialement recherchée et pour laquelle le patient a consenti à la réalisation de l'examen.

Dans ces conditions, il appartient au médecin de déterminer au cas par cas et dans le cadre du colloque singulier avec son patient la conduite à tenir. Il lui est conseillé de prendre l'attache d'un médecin œuvrant au sein d'une équipe pluridisciplinaire rassemblant des compétences cliniques et génétiques telle que mentionnée à l'article R. 1131-5 du code de la santé publique.

APPENDIX 2

Table A2-1 – **Characteristics in the sample and in the general population (in %)**

	Sample	General population
Gender		
Male	48.4	48.8
Female	51.6	51.1
Age		
18-24	11.0	12.3
25-34	19.3	18.6
35-49	30.9	30.7
50-59	20.4	20.0
60-70	18.4	18.4
Profession		
Farmers, farm workers	1.2	1.1
Craftspeople, traders, company managers	4.0	4.3
Managers, senior intellectual workers	11.2	11.4
Intermediate professions	18.8	17.7
Employees	22.0	20.4
Labourers	13.2	15.9
Retired	16.6	16.0
Other, no professional activity	13.0	13.2
CSP		
CSP+	35.2	34.5
CSP-	35.2	36.3
Unemployed	29.6	29.2
Distribution by region		
Paris region	18.8	19.3
North	6.3	6.4
East	8.9	8.6
East Paris Basin	7.6	7.7
West Paris Basin	8.8	9.1
West	13.9	13.4
South-West	11.0	11.0
South-East	13.1	12.2
Mediterranean	11.7	12.5
Number of persons within the household		
1 person	17.6	16.8
2 people	35.0	33.5
3 people	21.1	20.6
4 people	18.5	18.6
5 or more people	7.7	10.6
Size of urban area		
Fewer than 2,000 inhabitants	21.2	22.7
From 2,000 to fewer than 20,000 inhabitants	16.6	16.9
From 20,000 to fewer than 100,000 inhabitants	13.8	13.1
More than 100,000 inhabitants	31.5	30.1
Paris region	17.0	17.2

Table A2-2 – **Perception of the survey (number of observations and percentages)**

We placed you in a hypothetical situation. Did you find this:		
Complicated	605	24.2 %
Surprising	380	15.2 %
Boring	128	5.1 %
Pleasant	131	5.2 %
Unpleasant	147	5.9 %
Interesting	1,110	44.4 %
Total	2,501	100.0 %
The choices that you just made were:		
Always difficult	163	6.5 %
Mostly difficult	1,359	54.3 %
Mostly easy	919	36.7 %
Always easy	60	2.4 %
Total	2,501	100.0 %
Did you base your choices on only one of these four characteristics?		
Yes	850	34.0 %
No	1,651	66.0 %
Total	2,501	100.0 %
Which one?		
Who will decide what results are returned to you?	325	38.2 %
What results in addition to those concerning your current disease?	245	28.8 %
How much should you have to pay for this test?	212	24.9 %
What will happen to your blood sample once the test is complete?	68	8.0 %
Total	850	100.0 %
Would you say that this characteristic influenced your choices:		
Most of the time	642	75.5 %
All of the time	208	24.5 %
Total	850	100.0 %
Did you disregard one of the four characteristics when making your choices?		
Yes	1,319	52.7 %
No	1,182	47.3 %
Total	2,501	100.0 %
Which one?		
Who will decide what results are returned to you?	205	15.5 %
What results in addition to those concerning your current disease?	157	11.9 %
How much should you have to pay for this test?	620	47.0 %
What will happen to your blood sample once the test is complete?	337	25.5 %
Total	1,319	100.0 %
To what extent would you say that this characteristic influenced your choices?		
Not at all	543	41.2 %
Very little	776	58.8 %
Total	1,319	100.0 %