Test preferences of the Dutch public regarding the preconception expanded carrier test

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Summary

Background

Expanded carrier screening (ECS) is a relatively new technique using next generation sequencing that can determine whether individuals are carriers of genetic disorders. Two couple members who are both carrier of the same autosomal recessive or X-linked genetic condition have a 25% chance for every pregnancy that the child will be affected by this disease. In the Netherlands, ECS has been offered for several years now on a small scale. Suboptimal test characteristics could compromise the access to or the uptake of the test. The aim of this thesis is therefore to study which preferences couples with a child-wish who are open to preconception ECS have regarding the test characteristics of preconception ECS.

Methods

Subjects between the age of 18 and 40 with a child-wish within 10 years were included in the study. Only respondents who were open to ECS were asked to participate in the discrete choice experiment. Each respondent answered 14 choice tasks in which they had to choose between two test options and the opt-out. The test options were varied by the selected levels of the following attributes: the price of the test, accuracy, provider, type of information provision and the type of genes tested. A mixed logit analysis and multivariate mixed logit analysis were conducted to analyse the DCE results.

Results

The survey was completed by 537 respondents, of whom 481 were open to ECS and answered the choice tasks. Being open to ECS was associated with being non-religious, having a higher educational level and using or considering other forms of prenatal screening. The price of a test, accuracy, type of information provision and provider had a significant impact on the respondents' preferences. Price and accuracy were most influential on respondent's decisions to choose a specific test. The test with the highest test acceptance would be one with a low price, high accuracy, provision by midwife or general practitioner (GP) and information provision by counselling. Significant preference heterogeneity was observed. Several respondent characteristics showed to be associated with specific preferences. The most important characteristics being the educational level of the respondents, whether they had prior knowledge of ECS and whether they already had children or not.

Conclusion

The majority of Dutch inhabitants between 18-40 years old are interested in taking an ECS test. A low price, high accuracy, provision by midwife or GP and information provision by counselling increase the possibility of test acceptance. The characteristics of individuals influence their test preferences, and therefore these characteristics should be considered to offer different test options. Future research is necessary to further specify the implementation of the test; however, the first steps are taken in reaching a high participation rate.

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1. Introduction

Every year many children are born with severe, genetic, non-curable diseases. (1–6) Serious autosomal recessive (AR) conditions account for 20% of infant mortality and 10% of paediatric hospitalizations. (7) This causes suffering to the children and burdens the parents. Additionally, these diseases are associated with high healthcare costs. (8–11) Expanded carrier screening (ECS) is a relatively new technique using next generation sequencing (NGS) that can determine whether people are carriers of these AR disorders.(12) Two couple members that are both carrier of the same autosomal recessive or X-linked genetic condition have a 25% chance for every pregnancy that the child will be affected by this disease. (13,14) Mostly these carriers do not experience any health effects themselves. (15) ECS can be conducted among couples before conception or during pregnancy. When couples are aware of their mutual carrier status they can take this into account in their family planning by e.g. pre-implementation embryo selection, adoption, prenatal diagnostics, preparing for having an ill child or, when the test is performed antenatally, an abortion. (16) Clearly, there are more options preconceptionally than antenatally. ECS could impact many couples as approximately one in 600 pregnancies is affected by the diseases included in the test. (7,12)

The societal aim of ECS can be viewed from two perspectives: the ethical and prevention perspective. The prevention perspective sees ECS as a possibility to prevent children with severe diseases from being born, reduce disability and reduce healthcare costs for society. From the ethical perspective, the main aim of ECS is to increase reproductive autonomy, which means that couples have the power to autonomously make well-considered reproductive decisions. (17) Regardless of the perspective chosen, it is important that the aspects of the ECS test are compatible with people's preferences and their norms and values (which are expected to be the fundament of these preferences). Firstly, seen from the prevention perspective, availability of an ECS test and a higher test uptake will create more prevention possibilities. Suboptimal test characteristics could compromise the access to or the uptake of the test. (18) Secondly, the compatibility with couples' preferences is also important from the ethical point of view, because reproductive autonomy also includes a couple member's consideration of taking the test, based on couples' values and opinions, and not just on the test characteristics. (17) Thus, given the composition of the test and the genetic diagnostic technology used, they should be optimal for couples to consider the test.

In recent years, knowledge about and availability of preconception ECS has been increasing massively, but several aspects ECS have not been studied yet. Earlier research showed that the Dutch population has a positive attitude towards preconception ECS and that provision of the test by general practitioners is feasible. (7,13,14,19) In addition, various studies explored the public's preferences for test characteristics, showing that these are not completely consistent across the various studies. Plantinga et al. (7) concluded that most people did not object to a couple-result, whilst Nijmeijer et al. (14) contradictorily found that most people preferred to receive both an individual and couple-based result. Both studies found that the general practitioner was the most preferred provider of the test, but Nijmeijer et al. (14) concluded that the medical specialist was the second-best choice, whilst no clear second-best alternative was by Plantinga (7). The preferences of the population concerning the test characteristics are thus not completely clear and so far, only qualitative studies (7,20) have explored the relative importance that individuals assign to these characteristics. Lastly, Nijmeijer et al. (14) found that various socio-demographic characteristics influence people's attitude towards ECS, but whether these characteristics also influence test preferences has not been investigated.

1.1 Objective and research questions

To improve the reproductive autonomy of the population and/or prevent children with severe diseases from being born, the ECS test needs to have characteristics that are compatible with people's preferences. **The aim of this thesis is therefore to study which preferences couples with a child-wish who are open to preconception ECS have regarding the test characteristics of preconception ECS.** This aim will be reached by answering the following sub-questions:

1. Which test characteristics (attributes) are most important to this population? Does the importance assigned differ when tested in a direct or indirect way?
2. For this population, what is the ideal combination of test characteristics (attributes) measured by a discrete choice experiment?
3. To what degree do patient characteristics influence their test preferences measured by a discrete choice experiment?

1.2 Outline

This thesis consists of multiple parts. In chapter 2, the background of the topic of this thesis will be discussed. More information will be provided about expanded carrier screening, the history of reproductive screening and the national and international expanded carrier screening programs will be discussed. In chapter 3 the methods of this research will be discussed. Firstly, discrete choice experiments and their validity will be discussed. After that, the study design (data collection, survey structure and DCE design) and statistical methods used will be explained. Then, in chapter 4 the results of the conducted analysis will be presented per research question. In addition, the results of the sensitivity analysis will be portrayed. Lastly, in chapter 5, the discussion, the findings will be placed in a wider context, and the strengths and weaknesses of this research will be discussed. Also, the final conclusion will be drawn. The reference list and appendices can be found at the end of the thesis document.

2. Background

2.1 Background of expanded carrier screening

Chromosomes, genes and mutations

Inside each cell nucleus of the human body, chromosomes reside which contain genetic information. Chromosomes consist of many genes, which in their turn consist of introns and exons (Figure 1). Exons are the parts of the gene that code for proteins. Since a gene consists of multiple exons, it thus codes for a collection of proteins. The proteins coded for in genes make up the entire human body. Each gene codes for specific proteins, these can be proteins needed e.g. for muscles to function, but genes can also determine eye colour and other characteristics that vary between people. Humans have two copies of each gene, one inherited from the mother, and one inherited from the father. A mutation in genes can cause a protein to stop functioning properly, which can lead to disease which can lead to illness in the affected person or his or her offspring. Mutations can occur from many different causes, for example, errors made in copying genes, toxic influences, or inadequate repair mechanisms. (21)

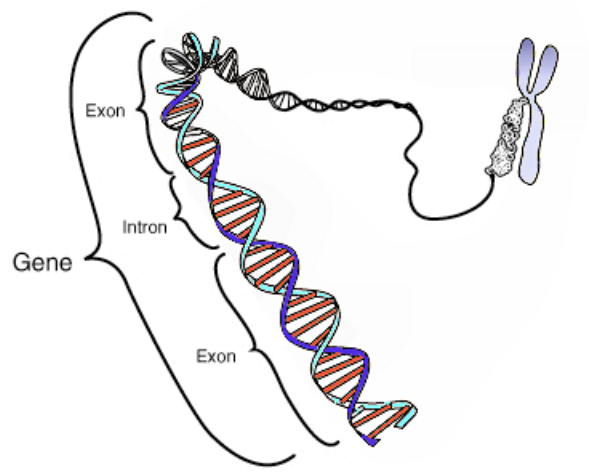

Figure 1
Gene with introns and exons. From: National Human Genome Research Institute (2014) (22)

Inheritance patterns

Monogenic diseases are those caused by a mutation in only one gene. Monogenic diseases can be caused by mutations in genes located on autosomes (non-sex chromosomes) or sex chromosomes. In addition, monogenic disorders can be dominant or recessive. When a condition is dominant, it means that a mutation in only one of two gene copies leads to disease (Figure 2, left). When a disorder is recessive, both genes must be mutated for the disease to manifest itself (Figure 2, right). Monogenic diseases can also be bound specifically to the X chromosome (i.e. the mutated gene is located on the X chromosome) and be recessive or dominant. Figure 3 shows the inheritance pattern of these X-

linked recessive diseases. In the case of recessive diseases, when a person has only one mutated gene, this person is a carrier of the disease but will be healthy. When both couple members are carriers of the same genetic disease, they have a 25% chance that their child is affected by this disease in each pregnancy. (23)

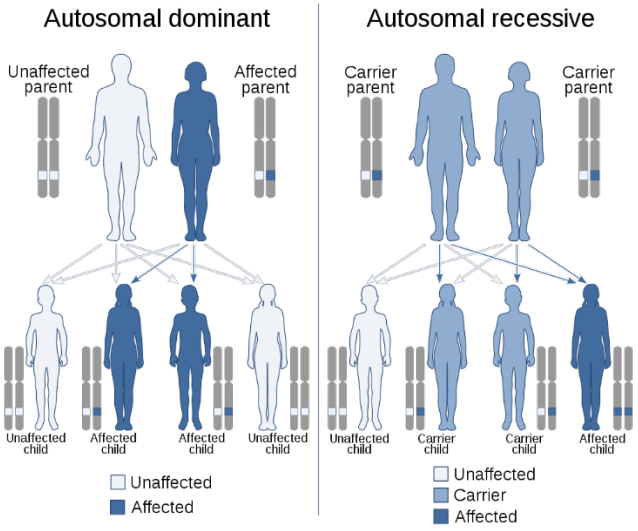

Figure 2
Autosomal dominant/recessive heritage pattern
From: Domaina, Kashmiri (2020) (24)

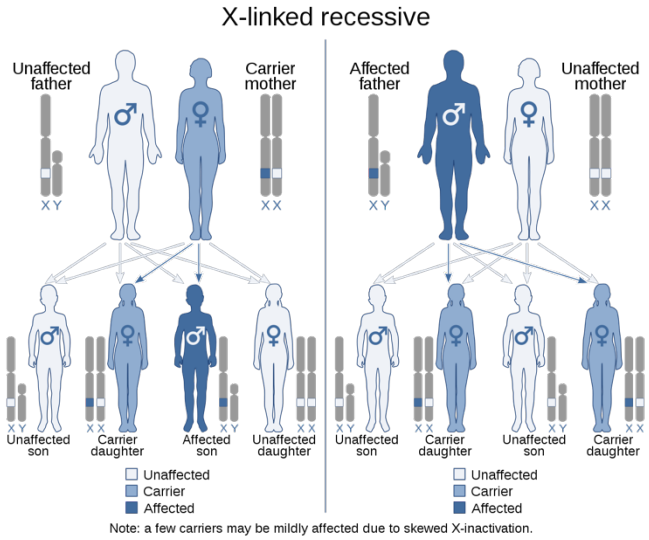

Figure 3
X-linked recessive heritage patterns
From: Domaina, Kashmiri (2020) (25)

Testing techniques

Carrier screening aims to identify which diseases an individual couple member is carrier of. The diseases that are included in a particular test are selected in advance. Next generation sequencing (NGS) is used to sequence the genes. The exons of these genes and the twenty surrounding introns of the selected genes are sequenced.(26) Then, analysis of these sequences can be conducted in roughly two ways: targeted gene panel analysis and sequence analysis. In targeted gene panel analysis, the sequence found is tested for known pathogenic mutations. (27) The Infinium Global Screening Array (GSA) is a well-known panel that screens for carriership in this manner. (28)This panel is used, for example, by commercial direct-to-consumer genetic testing companies such as 23andMe. (29) In the second technique, sequence analysis, the sequence found is compared to a reference sequence. (27) In this way, a large number of mutations can be identified in only one sequence analysis, which are not yet known to be pathogenic, but which, given the size and expected effect of the mutation, would likely lead to disease. These can also be considered pathogenic or likely pathogenic. Medical centres that offer ECS mostly use sequence analysis as their testing technique. (12,26)

Accuracy of carrier screening

In general, sensitivity and specificity are used to describe the accuracy of a test. The sensitivity is the probability of the test result being positive when the disease is present. The specificity is the probability of the test result being negative when the disease is absent. (30) Two features of carrier screening make it difficult to determine the accuracy of ECS tests. Firstly, it is difficult to exactly determine whether disease (would have) occurred in the unborn child or not. This is because a positive test often leads to the use of pre-implementation genetic diagnosis (selecting a healthy embryo during IVF), use of a sperm/egg donor or abortion. Also, there is only a 25% probability of a child with the condition/disease. When a couple receives a positive ECS test result, it is thus difficult to determine whether they are actually carriers of the disease as this could only be proven the birth of a child with the genetic condition, but often, due to the reasons mentioned, this is prevented or does not occur. Secondly, the accuracy depends on the definition that is used. The first definition used is that accuracy is the percentage of couples that receive a positive/negative result (of both being carrier of a genetic disease) and are actually a carrier of a genetic disease. The second definition used is how accurate a certain test is in identifying whether a couple is carrier of a specific genetic mutation. (31) The first definition thus focusses on disease, whilst the second focusses on specific genetic mutations. For example, when reading about the test offered by the company 23andMe, they claim to have a test with an accuracy of 99%. (32) However, close reading reveals that 23andMe claims that when testing on specific genetic mutations, in 99% of the cases a carriership yes/no result is similar to the golden standard result they use: sequencing. However, the probability that a couple that received a negative test result is also not a carrier of any of the genetic diseases included in the test will only be around 50%. This is because only a selection of known pathogenic mutations are included in the 23andMe test. A couple member could be carrying a new large mutation, that would likely lead to disease, but this would be missed because the test only includes the known pathogenic mutations. (27,33)

2.2 Historical developments reproductive screening

Reproductive screening includes all screening possibilities in the context of reproduction. (34) It can be conducted before the pregnancy, i.e. preconceptionally, or during the pregnancy, i.e. prenatally. (17) During the last decades, several developments have taken place worldwide that have contributed to the current reproductive screening programs.

In the mid-1970s, the concept of prenatal screening was introduced with the establishment of the maternal serum α-fetoprotein (AFP) test. By analysing the blood of a pregnant woman in the second trimester open neural tube defects (NTDs) could be detected in the unborn child. (35) Later, in the 1980s screening on trisomies (like Down syndrome, Edwards syndrome and Patau syndrome) with serum tests and ultrasound techniques became more frequent.

In contrast to the ECS test, the first carrier screening tests performed were not based on testing for genetic mutations in the DNA. In fact, in the 1970s the first carrier tests were performed, and these tests analysed for example red blood cell characteristics to determine carriership for hemoglobinopathies. Later on, from the late 1980s onwards, genetic testing did start to be used to determine carriership of certain diseases. Single genes were analysed and tested for known pathogenic mutations. The number of autosomal recessive conditions that could be tested on was expanded over the years but remained limited due to the high costs of testing. Another reason for this amount being limited at first, was that not as many pathogenic mutations had been identified at that time. (36) It this time, the test was offered to high-risk populations, for example screening on hemoglobinopathies was available to people from African and Asian regions. (37,38)

In 2004 a program was initiated to decrease the cost of human genome sequencing to 1000 dollars in 10 years. In the following years, several NGS techniques entered the market. (39) Due to these techniques it became possible to code many pieces of DNA simultaneously, instead of gene by gene. (40) These largely impacted the possibilities of carrier screening: it enabled fast and low-cost analysis of large numbers of genes. Carrier screening for large numbers of conditions at the same time is defined as expanded carrier screening (ECS). Compared to ancestry-based carrier screening programs, ECS has several advantages. The first one is that it makes carrier screening available to all people, regardless of their ethnic background. This removes the need to specify an individual's background (which can sometimes be difficult) and decreases stigmatization of ethnic groups. Secondly, the price of ECS is comparable to single-gene screening, which makes ECS more cost-effective. Thirdly, it provides more people with more information on their reproductive risks and, assuming they want that information, therefore increasing reproductive autonomy. (37,38,41)

Over the years, the perspective on the goals of reproductive screening changed. In the starting period, prevention was seen as the primary aim of reproductive screening. What is meant by prevention in this context, is that by reproductive screening, the number of children born with diseases can be reduced, therefore preventing disease. (17) This viewpoint, however, quickly started to cause moral challenges. The first concern is that because screening is referred to as the prevention of disease, couples no longer feel that they have a free choice of action when the test-result is positive. Secondly, seeing this type of screening as prevention would discriminate against people living with the conditions included in the screening. Due to these concerns, the focus shifted from prevention to reproductive autonomy as the aim of reproductive screening. (17) In the Dutch guideline, the goal of preconception carrier screening is clearly described as the increase of reproductive autonomy, and not as the increase of health gains by reducing the number of ill children being born. (34)

2.3 Preconception carrier screening in the Netherlands

In the Netherlands reproductive carrier screening started in the 1970s and many developments have been taking place since then. The first type of screening was the screening on hemoglobinopathies. Later on, multiple studies were conducted on cystic fibrosis screening, which was eventually made available to Dutch inhabitants from 2010-2016. (37,42)

The next development in this field took place in 2012 when an outpatient genetic screening clinic was opened in Volendam. Volendam is characterized by a high degree of genetic isolation, thus couples have a higher chance of both being carrier of the same diseases. In the outpatient clinic, couple members that both originated from the Volendam community were offered a targeted carrier test for four diseases that were highly prevalent in the community. During the study period, a high prevalence of carrier couples was detected. (43) Today, the outpatient clinic and its corresponding program are still active. (44,45)

Since 2016, an expanded carrier test including 50 AR and X-linked diseases is provided by the Amsterdam University Medical Centres. This test is available to the general population for a price of 650 euros per person. The test is reimbursed by the health insurer for high-risk groups. (26) People are in the high-risk group in case of consanguinity, and/or family history of disease included in the carrier test. In addition, certain ethnic groups are also identified as high-risk groups (like the people from Volendam, Ashkenazi Jewish people, and individuals from African or Mediterranean origin). (46)

In the North of the Netherlands, an implementation study of preconception ECS was conducted in 2016 by University Medical Centre in Groningen. The test used in this pilot study included 50 AR diseases and was provided by trained general practitioners in the region for free to couples who wish to conceive. (13,19) The pilot showed that provision of the test by general practitioners was feasible and that 90% of the couples that attended pre-test consultation participated in the ECS. (13,19) After the implementation study, the ECS test continued to be offered by six general practitioners in the North of the Netherlands. (12) The testing package has been expanded, the current test includes 90 genes, which are linked to approximately 70 autosomal recessive and X-linked diseases. (12) The test costs 475 euros per person for individuals in the general population, the test is covered by health insurance under the same conditions as mentioned above in Amsterdam, i.e. only to couples from the high-risk groups. (47)

2.4 Preferences of Dutch population regarding preconception ECS

Overview of previous literature

Several studies into the preferences of the Dutch public regarding ECS have been published in the previous years.

Plantinga et al. (7) and Nijmeijer et al.(14) found an overall positive attitude towards the test: approximately 1/3 of the population of reproductive age (18-40 years) would take the test if it was offered to them for free. Demographic characteristics of respondents were seen to influence the likelihood to accept the test offer, however, findings about this are not completely consistent. Plantinga et al. (7) found that respondents that were non-religious and older were more likely to accept the offer. Nijmeijer et al. (14) found that non-religious people and people with a wish to conceive a child in the future, and people with a higher educational level were more likely to accept the offer. Schuurmans et al. (13) found that people with a higher education level, no children or a satisfying relationship were more likely to take the test. However, in contrast to other research, they found no significant difference in age and religion between those who accepted and declined the test-offer. (13)

Not only the attitude, but also the preferences of individuals regarding the characteristics of the preconceptions ECS test have been studied in quantitative studies. Regarding the diseases that should be included in the test, the respondents did not have a clear preference between only severe diseases that were not treatable, diseases that were to some extent treatable or early-onset or late-onset diseases. However, they did show disapproval of tests in which non-health-related characteristics were included. (7) Regarding the provider of the test, Plantinga et al. (7) found that the public had a very clear preference towards the test being provided by the general practitioner (no clear second preference). Partly in contrast to this, Nijmeijer et al.(14) also found that people preferred the GP as provider mostly but found the hospital as a clear second preference. Regarding the price of the test, it was found that most people were willing to pay around 50-100 euros for the test, and most people believe that it should be (partly) reimbursed by health insurance. (7,14) Regarding the test result, Plantinga et al. (7) found that 70% of the respondents did not object to a couple-based result. However, Nijmeijer et al. (14) found that 60% of the respondents would mostly prefer to receive an individual as well as couple result. Another important test characteristic is the method of information provision. It was found that people most preferred a personal consultation with the provider of the test, with a brochure as the second preference. (7)

In addition, qualitative interviews have been used to find out what the preferences of people are regarding preconception ECS test characteristics, and how important these characteristics are compared to each other. Bijsterbosch (20) conducted interviews with couples with a child-wish and found that the accuracy, guidance by care professionals before and after the test, price and type of

diseases tested are the most important factors for people to decide whether they will or will not participate in preconception ECS. Experiences with genetic of chronic diseases (work or family related), religion and educational level were found to influence the test preferences of the respondents.

Concluding remarks

Previously, several studies have been conducted to obtain information about the preferences of the Dutch public regarding preconception ECS, however, there are contradictions and gaps in the knowledge gathered. From quantitative studies can be concluded that many Dutch people are interested in doing the preconception ECS test and whether people are interested or not depends on their demographic characteristics (such as religion, education level, age). Different studies draw different conclusions about which characteristics this concerns. The testing preferences that Dutch citizens have for the ECS test have also been examined in previous quantitative literature. Questionnaires examined people's preferences regarding the types of diseases included in the test, the provider, the provision of information, and the type of result. The conclusions of different studies were at some points consistent and inconsistent at other points. Test preferences have not been explored with an indirect preference eliciting method, in addition, the order of the importance of the different characteristics of the test have not been assessed in a quantitative study. One qualitative study explored which test characteristics are most influential in deciding which test to choose. In addition, it was found that test preferences are associated with certain characteristics of respondents. To conclude, knowledge about the preference of people regarding preconception ECS is there, but it is often inconsistent, not gathered by quantitive research, and preference data is only gathered by using direct preference eliciting methods.

2.5 Preconception expanded carrier screening worldwide

Worldwide multiple expanded carrier screening programs have been implemented. These programs differ in their characteristics. In the paragraphs below the current preconception ECS programs that have been implemented will be described. In addition, the situation in the neighbouring countries of the Netherlands is summarized (regardless of whether they have implemented expanded carrier screening or not).

Countries where expanded carrier screening has been implemented

Australia

In Australia, there are currently two main programs that offer expanded carrier screening. Firstly, the Victorian Clinical Genetics Services (VCGS) program offers ECS for cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS) and is available to all couples from the general population before or in early pregnancy. The test is provided by trained GPs and community midwives. The test costs 285 Australian Dollars per individual and is fully covered by health insurance. Secondly, the Mackenzie's Mission project has been established in 2019. This project is a government-funded trial to test the feasibility of a national, government-funded ECS program. The pilot test includes 750 severe recessive and X-linked diseases and will be offered to 10,000 couples in Australia. The test is provided by the GP before pregnancy or in early pregnancy. The pilot will end when the recruitment of the participants has been completed, which is expected at the end of 2021. In addition to the feasibility of the screening (health economic effects, outcomes), the ethical aspects and psychological impact of the test on couples will be evaluated. (20,37,48)

Israel

The Israeli population lives in a large number of separate subgroups, which makes the prevalence of autosomal recessive conditions in Israel particularly high. This enhances the priority of screening on these conditions, which has thus been done already for many decades in Israel. Since 2013 Israel has introduced a free and nationwide screening program including diseases that have a disease frequency of more than 1 in 15,000 live births, and a carrier frequency of more than 1 in 60. For the general population, the test consists of SMA, CF and FXS but depending on the couple's ethnicity, other diseases are included in the test. The test is provided by genetic counsellors or trained personnel under the supervision of a clinical geneticist. Usual practice is that the female couple member is tested first; the male couple member will be tested only if the test result female couple member is positive. The test is funded by the government for the specific diseases with frequencies mentioned above in the specific populations. Costs for couples who wish to have additional testing can be covered by supplementary health insurance. In addition to the general program, the Dor

Yeshorim program is available. Ultra-orthodox Jews can participate in this program. It is intended to be used before an arranged marriage to find out whether the future spouses are not carriers of the same genetic conditions. If this is the case, the arranged marriage will be cancelled. (20,37,49)

Saudi Arabia

Saudi Arabia is the country with the highest rate of autosomal recessive disorders per capita. Since 2004 there has been a mandatory premarital screening program for everyone, focussed on sickle cell disease and thalassemia. Research has identified thousands of founder mutations that are responsible for the majority of the genetic disorders in Saudi Arabia. A pilot is currently conducted with an expanded version of the premarital screening program. After the pilot, it is expected that an expanded carrier screening program will become available to everyone. (37,50)

Neighbouring countries

Belgium

In Belgium, eight clinical genetics centres jointly offer one type of ECS test. The test is available to all couples from the general population with a child wish, not only high-risk couples. The test comprises more than 1000 genes that are associated with autosomal recessive and X-linked recessive diseases. The test is a couple-based test, which means that one test-result per pair is provided; individual test-results are not available nor disclosed. Only for the seven most frequent diseases, an individual result is also reported. (15) The test costs 1400 euros per couple and is not covered by health insurance. (20)

France

There is no nationwide preconception ECS program in France, currently. For high-risk couples (consanguineous, autosomal disease in the family) carrier screening can be carried out for a limited number of diseases. The “Comité Consultatif National d’Éthique”, a national committee of Ethics on Health and Life sciences, proposed in 2018 to offer carrier screening to all couples with a child wish in the childbearing age who are interested in genetic counselling. (51) Bonneau et al. (51) studied the opinion of the general public in France towards preconception screening. They found that most participants had a positive attitude towards the implementation of preconception screening in France. In addition, most respondents believed that the test should be conducted on medical prescription and that information should be provided by health professionals. Concerning costs, the public thought that health insurance should (partly) cover these.

Germany

In Germany, several private clinics and offer preconception carrier screening. The tests offered at these clinics cover around 600 genes. (52,53) An example of one of these clinics is “Das Genetikum”. This private clinic with various locations around Germany and offers testing on known and new pathogenic mutations. (54) In addition, commercial companies worldwide offer their services to the German population. (55)

The overall attitude of the government and public towards preconception ECS in Germany is positive. A 2016 article states that the “Gemeinsame Bundesausschuss des Gesundheitswesens”, a federal joint committee on healthcare, was going to do a method evaluation of the test, thereby trying to accomplish health insurance coverage of the test. (56) In addition, Jung et al. (57) studied the attitude of the German population towards carrier screening on cystic fibrosis in 1994. They found that the uptake of this screening was high and that the idea is accepted by the population.

<u>Commercially available expanded carrier screening</u>

Several commercial companies offer direct-to-consumer expanded carrier screening tests. Many of these companies offer worldwide service, and thus couples worldwide can access these tests, which cost around 175 euros per person. In general, the tests screen for a large number of genes and diseases. The consumer collects DNA material itself with a test kit derived at home (often saliva) and sends it to the lab of the commercial provider for analysis. Customers can find information about the test and the interpretation of the results on the website of the provider. The commercial companies thus do not provide genetic counselling themselves but do advise customers to seek this counselling in their national healthcare system. (37,58,59)

3. Research methods

3.1 Background information discrete choice experiment

3.1.1 Eliciting preferences

In this thesis, preferences of participants regarding the ECS test will be estimated by conducting a DCE. Preferences can be defined as: “Preferences refer to certain characteristics any consumer wants to have in a good or service to make it preferable to him.” (60) There are two distinct ways of exploring preferences: by conducting revealed and stated preference studies. In stated preference studies researchers state the alternatives and the attributes of each of the alternatives, and participants choose one alternative, the most preferred one. (61) In revealed preference studies, the choices people make are observed, and from this, conclusions are deducted about their preferences. (61) Whilst revealed preference studies need to be performed in real-life situations, stated preference studies are particularly suitable for researching products that are not available on the market (yet), or of which no variations exist. (62) From both stated and revealed preference data, choice models can be designed. One method to gather stated preference data is by conducting a discrete choice experiment (DCE). In a DCE, participants perform choice tasks: they are asked to repeatedly choose 1 option of two (or more) different hypothetical goods (or services) with different characteristics (attributes). Every choice task contains different alternatives, that are created by varying the attributes of the goods (levels). A simple example of a choice task is displayed in Figure 4. By statistically analysing the choices participants make, the (relative) importance participants assign to the attributes and the trade-offs they would make between these are derived. (63) In addition, positive or negative utility values can be assigned to all levels. One of the economic theories that DCEs are based on, the theory of demand, assumes that by valuing all the parts that together form the good, the value of the complete good can be estimated. (64,65) This means that by adding up all the negative or positive utilities that are assigned to the levels of a specific good, the value of the complete good can be estimated. However, another underlying theory of DCEs, the random utility theory (RUT), states that another factor should be considered in the calculation of the total utility of the good. The RUT states that the utility of the respondent consists of a systemic element and a random element, which is related to unmeasured preference variation. (66) Therefore, the systemic element, gathered by adding up the utilities of the levels, is be combined with the random element.

DCE studies have several underlying assumptions: respondents act rationally, understand all information provided to them, perform the choice tests actively and are expected to behave according to 4 axioms: monotonicity, continuity, completeness, transitivity. Firstly, the are expected to prefer more attractive levels over less attractive levels (for example prefer the lower price when compared to a higher price), the monotonicity axiom. Secondly, respondents are expected to behave according to the continuity axiom, this means taking into consideration all attributes and making trade-offs between those when choosing between the choice options. Thirdly, respondents are expected to make consistent choices (if they get the same choice task twice, they choose the same option these two times), the completeness axiom. The last axiom, transitivity, encompasses a broader form of choice consistency. If there are three alternatives A, B and C, the respondents are expected that when they choose A over B and B over C, they also would choose A over C. (67) All of the described assumptions form the basis of DCE methodology.

	Test 1	Test 2	No test
Provider	Midwife	Commercial company	I would not undergo either test
Price	€1000	€500	
	o Select	o Select	o Select

Figure 4
Example choice task
In this example choice task, provider and price are the attributes. Midwife and commercial company are examples of levels within the provider attribute.

3.1.2 Statistical models used to analyse DCE data

To analyse choice data gathered by DCE experiments, literature describes different models that can be utilized. These models differ from each other in certain characteristics or assumptions, as outlined below.

Conditional logit model

One of the models described in literature to use for DCE analysis is the conditional logit model. Using the conditional logit model, the utility function for an alternative is described as:

$$U_j = (X_j \beta_,) + \varepsilon_{j,} \qquad Equation\ 1$$

Based on the theories above, the utility of alternative j (U_j) is the combination of the utilities of the explained part ($X_j\beta_,$) and the error term ($\varepsilon_{j,}$). X_j are the characteristics of choice j. $\beta_,$ are the preferences for the observed choice characteristics (coefficients). The idiosyncratic preferences for choices are described by ε, these can be product and consumer-specific. For example, unobserved characteristics of the product, random preferences of the consumer, optimization mistakes, or misspecification of the utility function.

In the conditional logit model, homogenous error variance is assumed. Therefore, this model is suitable to identify the general valuation structure of a good but cannot identify group or individual preference heterogeneity. (68,69)

Latent class model

In contradiction to the conditional logit model, the latent class model is a model used to analyse DCE results that is suitable to identify heterogeneity. The latent class model can be used to find out whether certain characteristics of respondents are associated with certain preferences. This model assumes that (1) the total group of respondents consists of several subgroups; and (2) all respondents within the same group, named a class, are identical and that the differences between the classes are as large as possible. A latent class analysis fits a separate conditional logit model for each class. In equation 2 the utility functions are described for an example in which there are 3 classes. (70)

$$U_{j1} = X^j\beta_1 + \varepsilon_{j1} \qquad U_{j2} = X^j\beta_2 + \varepsilon_{j2} \qquad U_{j3} = X^j\beta_3 + \varepsilon_{j1} \qquad Equation\ 2$$

$Uj_{1:}$ Utility of alternative J in class 1

X_j: Characteristics of choice j

B_1: Preferences of respondents in class 1 for the choice characteristics

E_{j1}: Error term in class 1

Mixed logit model

Another model to analyse DCE data that can identify respondent heterogeneity is the mixed logit model. This model assumes that all respondents differ from each other in terms of both preferences and choice consistency (error term is different for every respondent). In addition, it assumes that all these preferences are normally distributed around the mean. The mean is thus the average preference, expressed in terms of a coefficient, and the standard deviation around it is the amount of heterogeneity that exists in the respondent group. Equation 3 describes the utility function for alternative j, specific for respondent i. (71)

$$U_{ji} = X^j\beta_i + \varepsilon \qquad Equation\ 3$$

$U_{ji:}$ Utility of alternative J for respondent i

X_j: Characteristics of choice j

B_i: Preferences of respondent i for the choice characteristics

E_{j1}: Error term of respondent i

3.1.3 Validity and reliability of discrete choice experiments

An often-stated bias that can occur in DCE studies is hypothetical bias, which means that people behave differently when real-world choices have to be made compared to what they state when filling in the questionnaire (hypothetical choices). (72) Before DCEs were conducted to elicit patient preferences, they were used as well in other fields of study. (61,73) In the transportation field, the conclusions from revealed preference studies were roughly in accordance with that of stated preference studies. (61) Studies regarding the validity of DCEs in the field of environmental goods found that not all respondents' choices were in accordance with monotonicity, continuity, completeness and transitivity axioms. (73) Also in the healthcare-related DCEs behaviour of respondents does not always comply with these axioms. One of the reasons for this is that healthcare-related DCEs often include complicated information, which might be difficult to understand for the respondents. This can decrease the validity of the test results. (67) In addition, it is difficult to assess external validity, since revealed preference data is scarce in healthcare because choices are often (partially) made by physicians instead of solely by patients (shared decision making) and patients often are not financially responsible for the (total) healthcare costs (due to insurance coverage). Although these discussed conditions make it difficult to assess whether there is hypothetical bias, a meta-analysis concluded that DCEs can predict real-world health-related choices reasonably. (72) Skjoldborg, Lauridsen and Junker (74) studied the reliability of a DCE concerning rheumatoid arthritis. They studied two types of reliability: at the input level (how consistent were the answers of the respondents over time) and at the output level (consistency of the attribute weights and WTP). Both the results at the input and output levels were found to be consistent. The percentage of consistently answered choices between the surveys was 76% and 87%, implying a good correspondence. The confidence levels of the WTP were overlapping, indicating that the DCE was reliable.

3.2 Study design

3.2.1 Data collection

To answer the research questions, a DCE was conducted among 481 participants between 18-40 years old that had a child-wish and were open to preconception ECS. (7,19) The goal was to approach 1000 people to reach the amount of 300 complete responses, based on an expected response rate of around 30%. (18,75–77) The first part of respondent recruitment was done by sending the survey to friends, family and distributing it via social media. Also, messages were placed in specific Facebook groups and on forums (for people with a child wish, young parent groups). SurveySwap was also used to recruit respondents. The rest of the respondents were recruited by Dynata, a professional bureau for recruiting respondents.

3.2.2 Survey structure and development

The data was gathered by an online survey. The survey was designed and conducted using Lighthouse Studio from Sawtooth Software. (78)

After the first version of the survey had been developed, a pilot was conducted. There were 30 complete responses to the pilot. Of those 5 were filled in during think-aloud sessions. During these sessions, one of the researchers was present by video calling whilst the respondent was filling in the questionnaire. Several adaptations were made to the questionnaire (clarifications, spelling mistakes) after the pilot. These were based on participants' feedback in response to the survey during the think-aloud session, on the findings of the researchers during the think-aloud sessions, and on the written comments given by respondents after participating in the pilot independently.

The survey that was designed consisted of several parts, which will be elaborated on in the following paragraphs. A complete overview of the survey can be found in Appendix A.

1. Informed consent

Before the start of the questionnaire, respondents had to give informed consent. Figure 5 displays the statements participants had to agree to before continuing to the survey. To participate, they had to check the box and go to the next page.

I understand that…

...Participation in this study is voluntary.

...My responses will be handled anonymously for a research report.

...Individual answers will not be named in the survey report.

...there is no fee for participation in this questionnaire.

...this questionnaire is aimed at individuals between 18 and 40 who think or wish to have (more) children within 10 years.

...By participating in the study, I am making an important contribution to science.

- o I understand this and agree to participate.

Figure 5
Informed consent

2. Respondent characteristics

Informed consent was followed by collection of information on respondents' characteristics. Respondents were asked about their gender, age, place of residence, educational level, income, religion, whether they are in a relationship, country of birth of them and their parents, number of children, use/consideration of prenatal diagnostics and child-wish. These characteristics were selected because they were expected to be associated with being or not being open to ECS, or because they were expected to influence preferences for the characteristics of the ECS test. These expectations were based on earlier literature and hypothesis. After the informative text about preconception ECS, respondents were asked whether they would consider this test. Only the people that would consider the test were selected to participate in the DCE. This in order to make sure that if the opt-out was chosen in the choice tasks, this is most likely because the respondent thinks both tests (with their characteristics) are not favourable, and not because they are not interested in the ECS test in general. After the informative text about genetic disorders, people were asked whether they knew people with genetic disorders. This question was included as earlier literature described having experience with people having a genetic or chronic disorder influences preferences for the characteristics of the ECS test.

3. Introduction and information

Because preconception ECS screening is a relatively new topic in the Netherlands, many people have no prior knowledge. Also, previous interview studies revealed the complexity of the topic. Therefore, informative pages were added to the questionnaire. On one of the informative pages, preconception ECS was explained (also using a short clip). On the other informative page, genetic diseases were explained, and examples were given of the various categories (severe, mild, non-health-related).

4. Introduction choice tasks and rationality question

In this part of the questionnaire, all attributes were introduced one by one. For each attribute there was an explanation of how it is specified, and what the possible levels within the attribute are. Every time an attribute had been introduced, an example choice task had to be filled in by the participant. In this manner, the choice tasks are practised with each time an increasing number of attributes. After the introduction of the choice tasks, the respondents were asked the rationality question, which is displayed in figure 6. Test 1 costs less and is more accurate than test 2, which makes it the dominant test option. Choosing test 2 over test 1 would indicate that people did not understand the explanation or the principle of the choice tasks. When respondents did choose test 2, they were led to a new page where they were asked if they would really choose a test that is more expensive and less accurate.

	Test 1	Test 2	No test
Accuracy	99 out of 100 tests correct result	95 out of 100 tests correct result	I would not undergo either test
Price	€50	€1000	
	o Select	o Select	o Select

Figure 6
Rationality question

5. Choice tasks

Respondents have to answer 14 choice tasks in total: 12 different choice tasks, 1 duplicate choice task and 1 extra choice task. Every choice task consists of two mutually exclusive alternatives and an opt-out option. There are two possible opt-out designs possible within DCEs: a dual-response and a regular none-option. A dual-response non-option is often used if a high opt-out choosing rate is expected, in order to still gather enough information of trade-offs people would make when not having an opt-out option. The disadvantage of dual-response non-options is that is increases the lengthiness of the questionnaire and might cause people to not seriously weigh between the choice

options if they already know the opt-out is their preference. (79) In this study only people who are open to the ECS test are participating in the choice tasks. Therefore, it is expected that the opt-out is only chosen when the characteristics of the other two alternatives were not valued favourable enough to the participant (the characteristics were so unattractive that, even if someone is open to the test, someone would rather have no test than the tests with the characteristics listed). Since it was not expected that the opt-out would not be chosen often, the regular none-option was included, as enough information can be gathered in this manner and the disadvantages of the dual-response non-option can be avoided. Figure 7 is an example of a choice task from the questionnaire (in Dutch).

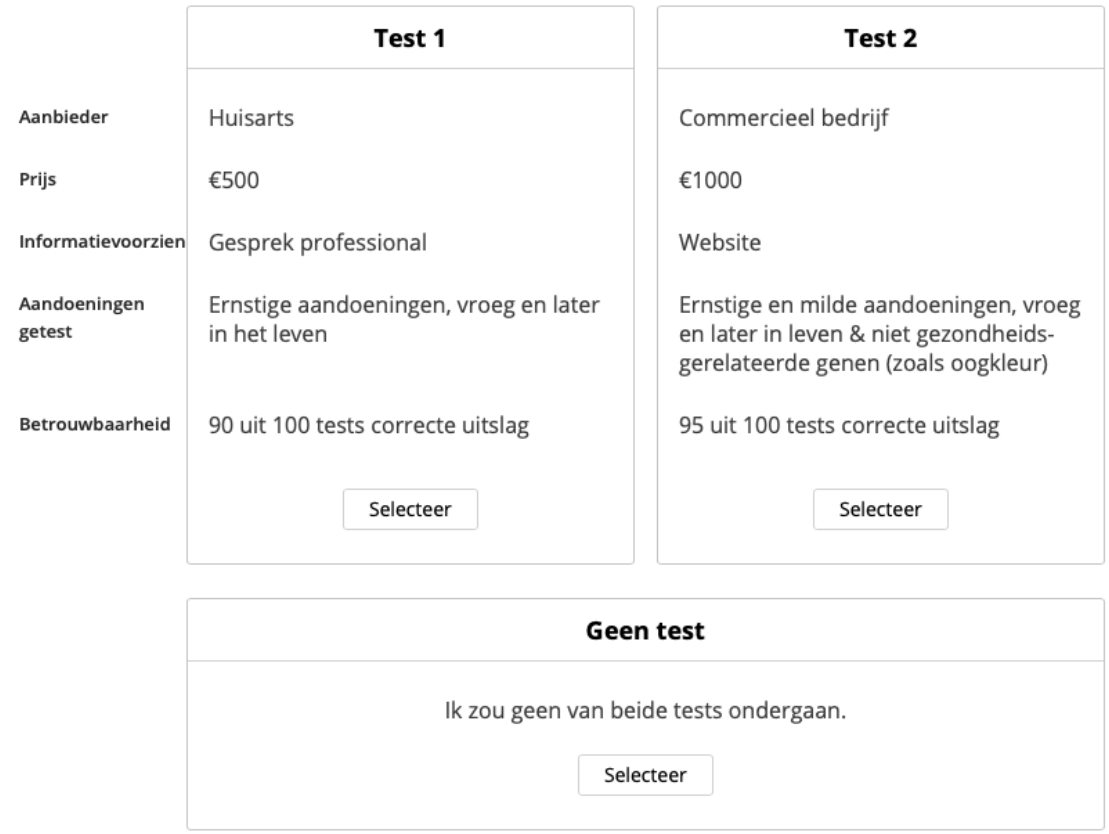

Figure 7
Example choice task

5. Evaluation questions

At the end of the questionnaire, the respondents were asked to fill in several evaluation questions. They were amongst others asked whether they based their decision on all attributes, whether the instructions in the questionnaire were clear, whether it was easy to choose between the different choice options and whether they missed certain attributes.

Questionnaire technique

The questionnaire was online, which allowed to include some automated responses to some answers that the respondents filled in. Firstly, the people that did not meet the inclusion criteria (age, child-wish, considering ECS) were not be asked to fill in the choice tasks. Secondly, people that did not have a relationship, were given information about that they should imagine themselves in a point in their life where they would want to have children with their current partner, when filling in the questionnaire. Thirdly, when people choose the non-dominant option in the dominance question, they will be given an additional explanation.

3.2.3 DCE design

3.2.3.1 Attributes and levels

The first step of designing the DCE was defining the attributes and levels that were included. This step is essential, as the selected attributes and levels define the options that are included in the experiment. Together, the attributes chosen must contain the full utility of the good. (76) In figure 8 the attribute selection process is displayed.

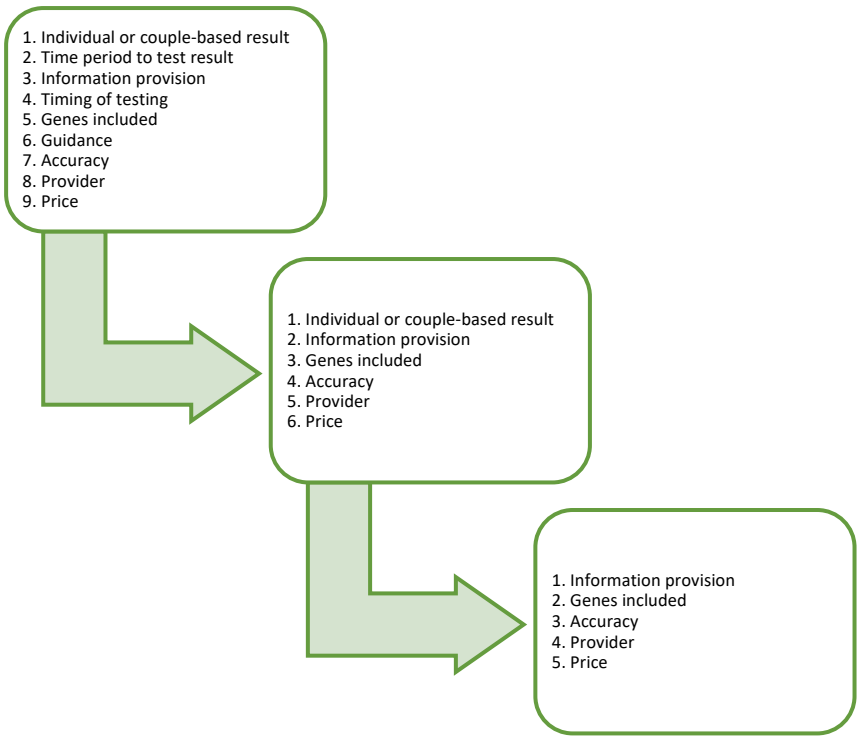

Figure 8
Attribute selection process

First, based on a literature study including several qualitative and quantitative studies on preferences of people concerning ECS and prenatal screening a list of 9 possible attributes was composed.

Secondly, based on the literature, discussion with ECS experts and keeping in mind the study objectives the six most important characteristics were selected. Firstly, the proposed attribute guidance was dropped. There were two main reasons for this, the first one being that couples are always counselled by a clinical geneticist after a positive ECS test. Variation was only possible in the guidance prior to the test, and this possible variation was included in the levels of the information provision attribute (with a counselling option) and the provider attribute (with 4 options in providers). Secondly, the proposed attribute time to test result was dropped based on earlier research. A conduced DCE concerning the prenatal testing (NIPT) found that women find the time of results the least important attribute of 6. (80) Bijsterbosch (20) (qualitative study regarding test preferences ECS) found that time of results was not one of the most important test characteristics of ECS. Thirdly, the attribute timing of testing was dropped. This attribute would have addressed whether the test should be performed before or during pregnancy. When they find out they are a carrier, there are more options for couples preconceptionally than antenatally. Also, the options preconceptionally are less emotionally burdening. Therefore, ECS is mostly performed preconceptionally, and also in the Netherlands, this is the common standard. (12,26) Learning more about people's preferences regarding this attribute was not considered highly relevant for this reason.

The selection at that time consisted of 6 attributes. A review conducted by Marshall et al. (81) in 2007 concluded that in 70% of de DCEs 3-7 attributes are used, with most using 6. Literature also describes that including too many attributes increases task complexity resulting in increased error variance and attribute non-attendance. This results in decreased validity and reliability of the results. (82) Thus, when the number of attributes is selected, a trade-off must be made between including all attributes to include the entire utility of the good, and the task complexity. When the concept choice tasks were designed containing the six selected attributes, it became clear that the choice tasks became very complex. Making trade-offs between six attributes is difficult in general, but in this research the subject is also complex, and some of the levels are as well (e.g. accuracy). Therefore, it was decided to drop one more attribute: “couple or individual result”. This decision is based, firstly, on the fact that a couple-based outcome is mostly chosen worldwide, and so there does not seem to be much variation in opinion on this topic. In the centres that offer ECS in the Netherlands, but also in Belgium, Australia (Mackenzie’s Mission), Germany and France couple-based results are used. (15,48,51,52) Secondly, as concluded by Bijsterbosch (20)this is an attribute that is not likely to be

important in the decision to take the test or not. In addition, it is a characteristic of the test that can be altered more easily than the others. Changing the way people are informed about their carriership is less radical than e.g. changing the provider of the test. Therefore, it is less relevant to gain more knowledge about people's preferences regarding this attribute.

In the following paragraphs a description will be given of the selected attributes. In addition, the chosen levels will be explained, and the changes that were made to these levels based on the results of the pilot. An overview of the levels used for the pilot, and the levels used for the final data gathering can be found in table 1.

Table 1
Levels pilot and post-pilot

Attribute	**Levels pilot**	**Levels post-pilot**
Accuracy	- 90 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result	- 91 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result
Price (per couple)	- €50 - €200 - €500 - €1000	- €200 - €500 - €1000
Type of diseases tested on	- Package 1: Serious, early-onset - Package 2: Serious, early & late-onset - Package 3: Serious & mild, early & late-onset - Package 4: Serious & mild, early & late-onset and non-health-related genes	- Package 1: severe diseases - Package 2: severe & mild diseases - Package 3: severe, mild diseases and non-health-related genes
Type of information provision	- Counselling - Brochure - Website	- Counselling - Brochure - Website
Provider	- Commercial company - Midwife - Medical specialist - General practitioner	- Commercial company - Midwife - Medical specialist - General practitioner

Accuracy

The proportion of tests that have a correct result (carriership of the couple correctly determined)

For every screening test, accuracy of the test-result is a relevant characteristic. Literature (18,20,63,80,83) emphasizes that this is often an important characteristic for people in screening tests, therefore it was also included in this DCE. This was also pointed out by the pilot results, which showed that accuracy was even the most important characteristic for respondents. The levels were based on the sequence technique (*see background*). For the pilot, the levels chosen were 90%, 95% and 99%. For the final DCE, the levels were altered slightly: 91%, 95% and 99%. This was done to make the differences between the levels constant (4%).

Price

The amount of money a couple has to pay (out-of-pocket) for the ECS test

Price was included as an attribute because it is important to discover what people are willing to pay (WTP) for the ECS test and whether they are willing to trade off the price with other levels of attributes. In addition, an earlier DCE regarding prenatal testing (NIPT) and a qualitative research regarding ECS showed that price is an important characteristic for people when deciding whether or not to have a specific test. (20,63) Also, earlier research shows that people are willing to pay less than the cost price of the test. (13,84) For the pilot, the levels 50-200-500-1000 euros were included. These levels were selected because the current prices for ECS are between 0 (when it is covered by health insurance) and around 1000 euros.(26,58,59) However, from the results of the pilot, it became clear that respondents did not differentiate between 50-200 (and to calculate WTP respondents must have different preferences for all of the levels). In addition, the NIPT test costs 175 euros so it would not be realistic to offer the ECS test for 50 euros. (85) Therefore, the levels 200-500-1000 were included in the final DCE.

Type of genes tested on

The severity of diseases that are detected with the test

One of the characteristics of the ECS that can be varied is the number and type of included genes to be tested. The centres that offer ECS in the Netherlands at this moment offer screening on 50-75 severe recessive and X-linked conditions. However, for example in the Mackenzie's mission ECS programme, far more conditions are included. (12,26,86) Variation is thus possible in the number and type of diseases that is screened for, from a few genes that code for very serious diseases, to thousands of genes, also including non-health-related characteristics. It is important to know the Dutch's public preferences on this; would they have the preference to include more mild diseases than are currently are, or even genes that code for non-health related characteristics? Therefore, this

was included as an attribute. In addition, previous literature also found that the public has a clear opinion on this; it is an important attribute of the test. (7,20) The selection of the levels was based on the study by Plantinga et al.(7) In the pilot the following levels were included:

- Package 1: Early-onset, severe diseases
- Package 2: Early and late-onset, severe diseases
- Package 3: Early and late-onset, mild and severe diseases
- Package 4: Early and late-onset, mild and severe diseases and additionally non-health-related genes

In the ranking assignment of the pilot, the respondents ranked the type of diseases included as the most important attribute. However, the conditional logit analysis of the pilot data showed no significant difference between the utility assigned to these four packages. When asked directly, respondents indicated that they thought the type of illness was very important, while the DCE result showed that they did not think it was important at all. During the thinking aloud sessions of the pilot, and in the open feedback of the pilot, respondents indicated that the explanation about the diseases did not include enough examples, and that the distinction between the levels was not clear. Therefore, the number of levels was reduced and simplified. These are the final levels that were included in the DCE:

- Package 1: Early and late onset severe diseases
- Package 2: Early and late onset mild and severe diseases
- Package 3: Early and late onset mild and severe diseases and non-health related genes

<u>Type of information provision</u>

The manner in which people are informed about the test before taking it

In the event of a positive result (post-test counselling), couples will always be counselled by a medical specialist. However, it is also valuable to find out what type of information provision the Dutch public would prefer prior to testing. Earlier research also showed that respondents found this an important test characteristic. (20) The levels included are the options that exist: a website, brochure or counselling with the provider of the test. The attribute thus focusses on the manner in which people are informed about the preconception ECS, and not what information they will be provided with.

Provider

The person or agency that executes the blood test and provides results of the test

In the Netherlands, there are multiple potential providers of the ECS test. Previous literature was inconsistent about the most preferred provider; thus, it is interesting to examine that quantitatively within this study. (7,14) It was also identified before as an important characteristic of the test. (20) The selected levels are: commercial company, general practitioner, medical specialist, midwife. These are the realistic potential providers of the test at the national-level. At this time in the Netherlands, the test is offered by the first three of the named providers. In other countries the midwife is sometimes the provider of the ECS test, and therefore it is interesting what the preference of the Dutch public regarding this would be.

3.2.3.2 Design choice tasks

Pilot choice task design

First, a pilot was conducted. The choice tasks of the pilot and designed using Ngene Software from Choice Metrics. (87) The Ngene script for the pilot was written using small uniform priors for the 13 parameters that needed to be estimated. The estimated priors for the pilot can be found in table 2. To have level balance in the choice tasks, 24 choice tasks were designed. However, literature shows that respondents generally only manage to execute a maximum of 16 choice tasks before they lose their focus (average of choice sets in DCE's is 11). (88,89) Due to the complexity of the choice tasks in the DCE, the decision was made to divide the 24 choice tasks in 2 blocs, resulting in every respondent being asked to answer 12 choice tasks. Using Ngene, a D-efficient design was created, to guarantee that respondents get the optimal set of choice tasks to obtain information from. A double choice task was included in both blocks to determine the test-retest reliability. In addition, a dominant choice task was added to determine whether respondents understood the choice-task concept. This resulted in a total number of 14 choice tasks per respondent.

There were 30 complete responses to the pilot. Table 3 shows the results of the conditional logit analysis of the pilot data.

Table 2
Pilot priors

Attribute	Levels	Uniform priors (pilot study)	
		Lower range	Upper range
Accuracy	- 90 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result	- 0.1 0.2	- 0.2 0.3
Price (per couple)	- €50 - €200 - €500 - €1000	- -0.08 -0.14 -0.2	- -0.000001 -0.08 -0.14
Type of diseases tested on	- Package 1 - Package 2 - Package 3 - Package 4	- -0.1 -0.1 -0.25	- 0.1 0.1 -0.15
Type of information provision	- Counselling - Brochure - Website	- -0.15 -0.15	- -0.05 -0.05
Provider	- Commercial company - Midwife - Medical specialist - General practitioner	- -0.1 0.1 0.175	- 0.1 0.175 0.25

Table 3
Results of Conditional logit analysis of pilot study (n=30)

Attribute	Level	Mean
Accuracy	90 in 100 tests correct result	
	95 in 100 tests correct result	1.16***
	99 in 100 tests correct result	1.77***
Price (per couple)	€50	
	€200	-0.28
	€500	-0.85**
	€1000	-1.33***
Type of genes tested	Package 1: Serious, early-onset	
	Package 2: Serious, early & late-onset	0.37
	Package 3: Serious & mild, early & late-onset	0.33
	Package 4: Serious & mild, early & late-onset and Non-health-related genes	-0.37
Type of information provision	Counselling	
	Brochure	-0.62*
	Website	-0.62*
Provider	Commercial company	
	Midwife	1.11***
	Medical specialist	0.99***
	General practitioner	1.54***
Opt-out		0.25

*p<0.05 **p<0.01 ***p<0.001

Final choice task design

The choice tasks of the final study were also designed using Ngene Software from Choice Metrics. (87) The results from the pilot were also used to update the priors and levels of the Ngene script (see table 4). (90,91) Some of the levels were altered. Firstly, the accuracy level 90%, was changed into 91%. Secondly, for the price attribute, the 50-euro level was dropped. Lastly, the number of levels of the attribute "type of genes tested" were reduced to three, and the differentiation between late and early onset diseases was removed. Due to the change in levels, the number of parameters that needed to be estimated decreased to 11. To ensure level balance, the number of choice tasks was still set at 24. Again, a division into two blocks of 12 choice tasks was made and the consistency question was added. In addition, one extra choice task was included to test whether people would be interested in the GSA-panel screening (see background). In this choice task, option 1 was a test with a 50% accuracy and 100-euro costs, option 2 a test with 99% accuracy and 1000 costs and option 3 the opt-out.

Table 4
Post-pilot priors

Attribute	**Levels**	**Uniform/ Normal distribution post-pilot priors**		
			Mean (normal)/ Lower range (uniform)	**SD (normal)/ Upper range (uniform)**
Accuracy	- 91 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result	- Normal Normal	- 1.1 1.6	- 0.24244307 0.24
Price (per couple)	- €200 - €500 - €1000	- Normal Normal	- -0.6825074 -1.130126	- 0.1803627 0.2677
Type of genes tested on	- Package 1 - Package 2 - Package 3	- Uniform Normal	- 0.1 -0.5503995	- 0.4 0.3293
Type of informatio n provision	- Counseling - Brochure - Website	- Normal Normal	- -0.6221769 -0.6460257	- 0.2372494 0.2314
Provider	- Commercial company - Midwife - Medical specialist - General practitioner	- Normal Normal Normal	- 1.08059 1.0528 1.54968	- 0.270874 0.28162 0.3347

3.3 Data analysis

3.3.1 Descriptive statistics

Figure 9 shows the selection process of respondents during the questionnaire in a flow diagram. The responses to the survey were classified into several categories. The first group are the respondents that dropped out somewhere along the course of the survey. Either they only opened the survey, were open to ECS but did not complete the DCE, stopped the survey during the demographic questions etc. The second option is that respondents are excluded based on the inclusion criteria age and child wish within 10 years, this group of responses are called the excluded respondents. The third group of responders are the "short complete responses". The respondents that filled in these responses, filled in the questions about their demographic characteristics but were excluded from the DCE because they were not open to expanded carrier screening. The last group, the fourth, are the "long complete responses". These are complete DCE responses.

Data was collected from participants on several characteristics. These characteristics and the categories the answers are subdivided into are listed in table 11 (Appendix B). To answer the question whether certain patient characteristics are associated with being/not being open for ECS, the Pearson chi-square test and two-sample t-test were performed using Stata/MP 16. (92) Associations with a p-value of <0.05 were assessed as being significant.

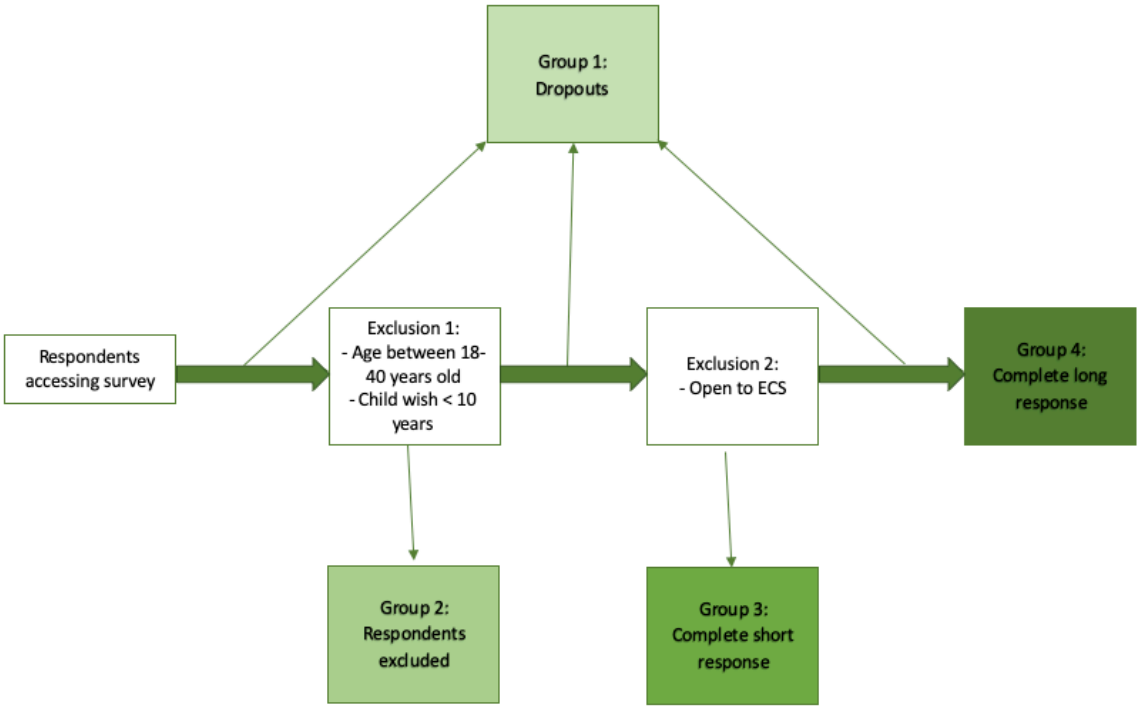

Figure 9
Flow diagram response types

3.3.2 Analysis discrete choice experiment data

Utility functions
Utility functions are used to calculate the utility for test alternatives and the opt-out, these are described below:

Utility function for alternative A and B:

$$V(altA) = V(altB) = \beta1 * accuracy_{95} + \beta2 * accuracy_{99} + \beta3 * price_{500} + \beta4 * price_{1000} + \beta5 * genes_2 + \beta6 * genes_3 + \beta7 * information_{brochure} + \beta8 * information_{website} + \beta9 * provider_{midwife} + \beta10 * provider_{MS} + \beta11 * provider_{GP}$$

$Equation\ 4$

Utility function for the opt-out:

$$\mathrm{V(optout)} = \beta0 \qquad Equation\ 5$$

$V = Utility$
$\beta0 = Opt - out\ coeffiecent$

Model evaluation
As stated earlier, several models can be used to analyse the DCE data. All analyses were performed using Stata/MP 16. (92) To retrieve the pilot coefficients, a conditional logit analysis was conducted. As one of the sub-questions was related to respondent heterogeneity, a mixed logit model and latent class model were conducted to analyse the final data (as these models can identify heterogeneity, paragraph 3.1.2). (93–96) Based on these results, eventually the mixed logit model was used to determine the final results. The mixed logit model had a better model fit and was more suited to answer the research questions. Two analyses were conducted, one simple mixed model analysis, and another multivariate mixed logit analysis. In both models, first, all variables were included as random parameters, and after evaluation the model, the variables with non-significant standard deviations (SDs) were included as fixed parameters. The number of Halton draws was increased until the found coefficient were stable.

In the following paragraphs, a description per sub-question is given of the methods used to answer that sub-question.

Sub question 1: *Which test characteristics (attributes) are most important to this population? Does the importance assigned differ when tested in a direct or indirect way?*

The indirect choice eliciting method used in this research are the choice tasks. The direct choice eliciting method ranking assignment.

The DCE results were evaluated by performing a mixed logit analysis. This resulted in a coefficient for every attribute and level. To determine each attribute's importance relative to one another, the attribute importance score was calculated. The range of each attribute, meaning the difference between the coefficient of the most positive, and the coefficient of the most negative coefficient, was calculated. By dividing the range of one attribute by the total of all the ranges of the attributes added together, the importance score of the attribute is calculated. The attribute with the highest importance score is the attribute that is most influential in the respondent's decision to choose a specific test or not.

The ranking assignment was analysed using two methods. Firstly, per attribute the percentage of respondents was calculated that chose this attribute as most important. Secondly, the complete ranking respondents gave was evaluated. This was done by giving the number 1 ranked attribute 5 points, the number 2 ranked 4 points etc. Each attribute ended up with a total amount of points, and lastly, the percentage of the total score was calculated for each attribute.

Sub question 2*: For this population, what is the ideal combination of test characteristics (levels) measured by a discrete choice experiment?*

The mixed logit analysis was used to answer this research question. The interpretation of the levels in this model is as follows: the base case level has a value of 0 and the other levels' coefficient has a relative value to the base case. The coefficient of the level is positive if this level is preferred over the base case. The coefficient of the level is negative if the base case is preferred over the level. The more positive/negative the coefficient, the more the level is/is not preferred over the base case. In this way, the most and least preferred level for each attribute can be identified.

To be able to make the results more insightful, choice predictions were calculated using the following formula:

$$\text{Prob}(\text{Y} = \text{j}) = \frac{\exp\,(\text{V}_\text{i})}{\sum_{k=1}^{j} \exp\,(V_k)} \qquad Equation\ 6$$

Prob(Y=j) = probability that choice option j is chosen over option k

Vj/k = utility choice option j/k

Sub question 3: *To what degree do patient characteristics influence their test preferences measured by a discrete choice experiment?*

To answer this research, question a multivariate mixed logit analysis (MLA) was performed. Several steps were taken to design this model. Firstly, a multivariate mixed logit model was designed for the opt-out and all attributes separately, including interaction terms for all levels of the attribute interacting with the patient characteristics (6 models in total). From these models, the significant interactions were selected into a combined model (19 interaction terms). Then this model was reduced step-by-step, removing the non-significant associations (p>0.05). The final model included 11 interaction terms. The last step was including the variables that did not have significant SD as fixed variables instead of random variables.

Significance

Coefficients with a p-value of <0.01 were assessed as being significant.

3.3.3 Sensitivity analysis

Stata was used to perform a sensitivity analysis to determine whether removing specific groups of participants influenced the final DCE analysis results. To evaluate the effect of removing specific groups of respondents, the effect on the conditional logit model output was evaluated. The following paragraphs discuss the considerations made for each component.

Rationality test

There were two questions to test the rationality of respondents. First, people were asked to choose between three options:

1. A test for 50 euros and 99% accuracy
2. A test for 1000 euros and 95% accuracy
3. No test

This question will be referred to as the first rationality question. If they choose the second option, which is a test with a higher price and lower accuracy, people were asked a follow-up question. This follow-up question is referred to as the second rationality question. In this follow-up question a short explanation was given of the choice they made, and they were asked whether they were sure of this choice. If they still would choose the clearly least preferable option, they failed the rationality test. The respondents that failed the rationality test were included in the sensitivity analysis.

Non-attendance

Non-attendance is defined as choosing the same choice option in all choice tasks. However, choosing the opt-out in all choice tasks was excluded from this definition.

In the questionnaire, respondents that choose the opt-out in more than 3 choice tasks were given an extra question, asking them to give a reason for choosing the opt-out so often. To this question, several respondents answered that they would for example never pay more than 200 euros for a test or had other reasons that indicated the test offer was not preferable enough for them. However, also several respondents indicated, although they answered positively to the screening question, that they would actually not be interested in the test. Unfortunately, not all respondents clearly explained their reason for choosing the opt-out often. Therefore, it was not possible to make a differentiation between respondents that chose the opt-out because they were actually not open to ECS and the respondents that did not think the characteristics of the test were attractive enough. For that reason, non-attendance was defined as filling in option 1 or 2 in every choice task. These respondents were included in the sensitivity analysis.

Time spent on the questionnaire

The time respondents spent to complete the survey was analysed. Taking different cut-off values, the effect on the conditional logit results was evaluated. When 4 minutes was taken as a cut-off point, a significant effect on the conditional logit output was observed. Therefore, respondents that finished the survey in less than 4 minutes were selected to be included in the sensitivity analysis.

4. Results

4.1 Respondents

As figure 10 shows, the survey was accessed 1611 times, 604 of these responses were complete responses. 293 respondents were excluded based on age and/or child-wish exclusion criteria. 714 incomplete responses occurred due to technical issues (respondents not being able to move on to the next page, interrupted internet connection) and unknown reasons. 56 respondents were excluded from filling in the DCE because they would not be open to ECS and are included in the analysis as short completes. There were 548 complete responses to the DCE. 67 respondents were excluded from the analysis as a result of the sensitivity analysis (more information on this can be found in section 4.4.4). This results in 481 DCE responses that were included in the analysis as long completes.

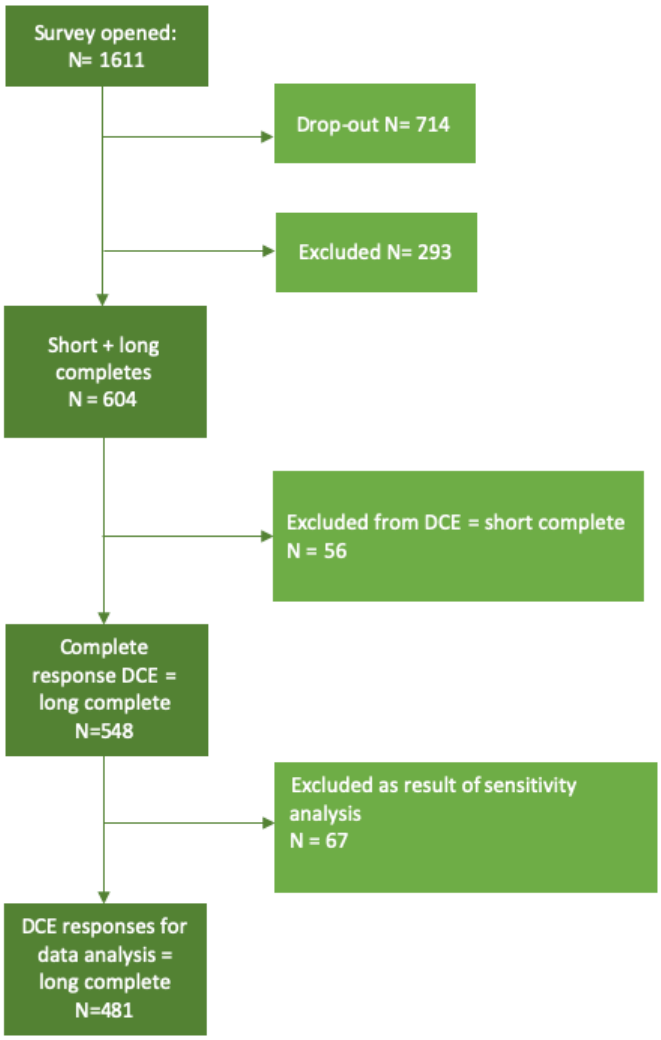

Figure 10
Flow diagram displaying the different respondents' types to this survey.
- Drop out: due to technical problems or unknown reasons
- Exclusion: age <18 and >40, not having a child wish within 10 years
- Short response: not being open to ECS, completing socio-demographic details
- Long response: completing the DCE and socio- demographic details

Respondents

Table 5 displays the characteristics of the 537 respondents that were included in the final analysis. Most of the respondents were female (70%) and the mean age of the respondent group was 29.5 years. Most of the respondents had an education level of higher vocational education. However, only 25% of the respondents had a modal income. Only 30% of people with an HBO or WO education earned a modal or more than modal income (≥3000 euros per month). The majority of respondents were in a relationship and did not have children yet. Most of the respondents did not have a migration background and were not religious. Half of the respondents had heard of ECS before participating in the survey.

When comparing the characteristics of respondents to characteristics of the general public (Appendix C, Table 12 & 13), an important difference is the distribution of man/women that filled in the survey. In the general population between 18-40 years old, 51% is male, 49% female. In the study sample, 70% was female, and 30% male. Moreover, the respondents to this survey are more highly educated than the average general population. Almost 60% studies/has graduated at WO or HBO level, whilst this is only 35% in the general population (15-75 years). The income of the respondents is, however, lower than average population (20-39 years). Only 25% of respondents have a modal or above modal income (>3000 euros per month). As for the other characteristics, the respondent group roughly corresponds with the general population. 87% of the pregnant women got the 20-weeks ultrasound scan. (97) Almost 70% of the respondents in this study would be interested in preconception screening.

Respondent characteristics associated with being more/less open to ESC

During the survey, the respondents had to answer the question whether they would be open to ECS and were given the options “yes”,” maybe” and “no”. 90% of the respondents were open to ECS (answered yes or maybe), and 10% was not. When comparing the group of respondents that were open to ECS to the respondents who were not open to ECS, characteristics were found that differ significantly between the groups. Table 5 shows the comparison between the two groups and the corresponding p-values. Important findings are that respondents open to ECS were less likely to be religious (22% vs. 34% religious, p-value 0.02). In addition, being open to ECS is associated with considering/having participated in prenatal screening ($p<0.001$) and having a higher educational level (p-value 0.01).

Table 5

Baseline characteristics

	All respondents (n = 537)	**Long completes (n = 481)**	**Short completes (n=56)**	**p-value[1]**
Gender				0.17
Male	160 (30%)	142 (30%)	18 (32%)	
Female	375 (70%)	338 (70%)	37 (66%)	
Different	2 (0%)	1 (0%)	1 (2%)	
Mean age, years ± SD	29.5 ± 5.9	28.9 ± 5.8	29.5 ± 6.2	0.50
Province[2]				0.96
Zuid-Holland	130 (24%)	114 (24%)	16 (29%)	
Noord-Holland	84 (16%)	78 (16%)	6 (11%)	
Noord-Brabant	81 (15%)	73 (15%)	8 (14%)	
Gelderland	72 (13%)	65 (14%)	7 (13%)	
Other provinces	170 (32%)	151 (31%)	19 (33%)	
Educational level				0.01
Primary	3 (1%)	2 (0%)	1 (2%)	
VMBO	15 (3%)	13 (3%)	2 (4%)	
Havo	22 (4%)	18 (4%)	4 (7%)	
VWO	18 (3%)	18 (4%)	0 (0%)	
MBO	158 (30%)	132 (27%)	26 (46%)	
HBO	195 (36%)	178 (37%)	17 (30%)	
WO	126 (23%)	120 (24%)	6 (10%)	
Income (Euros)[3]				0.95
0-1000	86 (16%)	77 (16%)	9 (16%)	
1001-2000	133 (25%)	116 (24%)	17 (30%)	
2001-3000	184 (34%)	165 (34%)	19 (34%)	
3001-4000	63 (12%)	60 (13%)	5 (9%)	
4001-5000	3 (5%)	32 (7%)	3 (5%)	
5001-7500	1 (2%)	18 (4%)	1 (2%)	
7501-10,000	7 (1%)	6 (1%)	1 (2%)	
> 10,000	8 (1%)	7 (1%)	1 (2%)	
Religion				0.02
Yes	126 (23%)	107 (22%)	19 (34%)	
No	380 (70%)	349 (73%)	31 (55%)	
Prefer not to say	31 (6%)	25 (5%)	6 (11%)	
Partner				0.97
Yes	394 (73%)	356 (74%)	38 (68%)	
No	143 (27%)	125 (26%)	18 (32%)	
Mean duration relationship, years ± SD[4]	7.6 ± 7.1	7.0 ± 7.3	6.7 ± 4.3	0.81
Ethnicity[5]				0.49
No migration background	440 (82%)	396 (82%)	44 (79%)	
First generation migration background	36 (7%)	31 (6%)	5 (9%)	0.48
Second generation migration background	61 (11%)	54 (11%)	7 (13%)	0.78

Children				0.57
None	340 (63%)	311 (65%)	29 (52%)	
1	111 (21%)	95 (20%)	16 (29%)	
2	64 (12%)	56 (12%)	8 (14%)	
3	13 (2%)	11 (2%)	2 (5%)	
>3	9 (2%)	8 (2%)	1 (2%)	
Prenatal diagnostics				p<0.001
Yes	372 (69%)	361 (75%)	11 (20%)	
No	165 (31%)	120 (25%)	45 (80%)	
When children				0.53
Within 1 year	122 (23%)	112 (23%)	10 (18%)	
Within 1-5 years	272 (51%)	241 (50%)	31 (55%)	
Within 5-10 years	133 (25%)	118 (25%)	15 (27%)	
Other	10 (2%)	10 (2%)	0 (0%)	
Previous knowledge ECS				0.54
Yes	270 (50%)	244 (51%)	26 (46%)	
No	276 (50%)	237 (49%)	30 (54%)	
Know someone with genetic disease				0.09
Yes	231 (43%)	212 (44%)	19 (34%)	
No	265 (49%)	230 (48%)	35 (63%)	
Don’t know	41 (8%)	39 (8%)	2 (4%)	

[1] P-value for the comparison of long and short completes. For categorical variables the Pearsons’s chi-square test was used, for continuous variables the two independent sample T-test.
[2] Provinces that the most respondents were from are listed independently. "Other provinces" include: Drenthe, Flevoland, Friesland, Groningen, Limburg, Overijssel, Utrecht, Zeeland.
[3] Personal net income per month
[4] Of people who have a partner
[5]No migration background: respondent and parents born in the Netherlands.
First generation migration background: respondent was born outside of the Netherlands.
Second generation migration background: parent(s) of the respondent born outside of the Netherlands. (98)

4.2 Discrete choice experiment results

4.2.2. *Sub-question 1: Which test characteristics (attributes) are most important to this population? Does the importance assigned differ when tested in a direct or indirect way?*

First the attribute importance measured indirectly will be discussed, then the attribute importance measured directly, and lastly, the two will be compared.

Attribute importance measured indirectly

Table 8 on page 49 shows the mixed logit results. All attributes, except for the types of genes included, had a significant impact on the choice of test. Figure 11 displays the attribute importance measured by the DCE. On the X-axis the attributes and levels are presented, and on the Y-axis the corresponding coefficients based on the mixed logit model. The attribute price had the greatest impact on the choice of people for a certain test. It accounted for 53% of the decision making. The second most important attribute is accuracy of the ECS test, which had an importance score of 27%. Provider and information ranked 3rd and 4th, respectively, which importance scores of 8 and 7%. The type of genes included in the test were the least important attribute based on the DCE results (importance score 5%). The opt-out has a negative coefficient, which means that when choosing between a test option with the base case level of each attribute and the opt-out, people would prefer the base case test. In table 8 (page 49) p-values and standard deviations of the coefficients can be found.

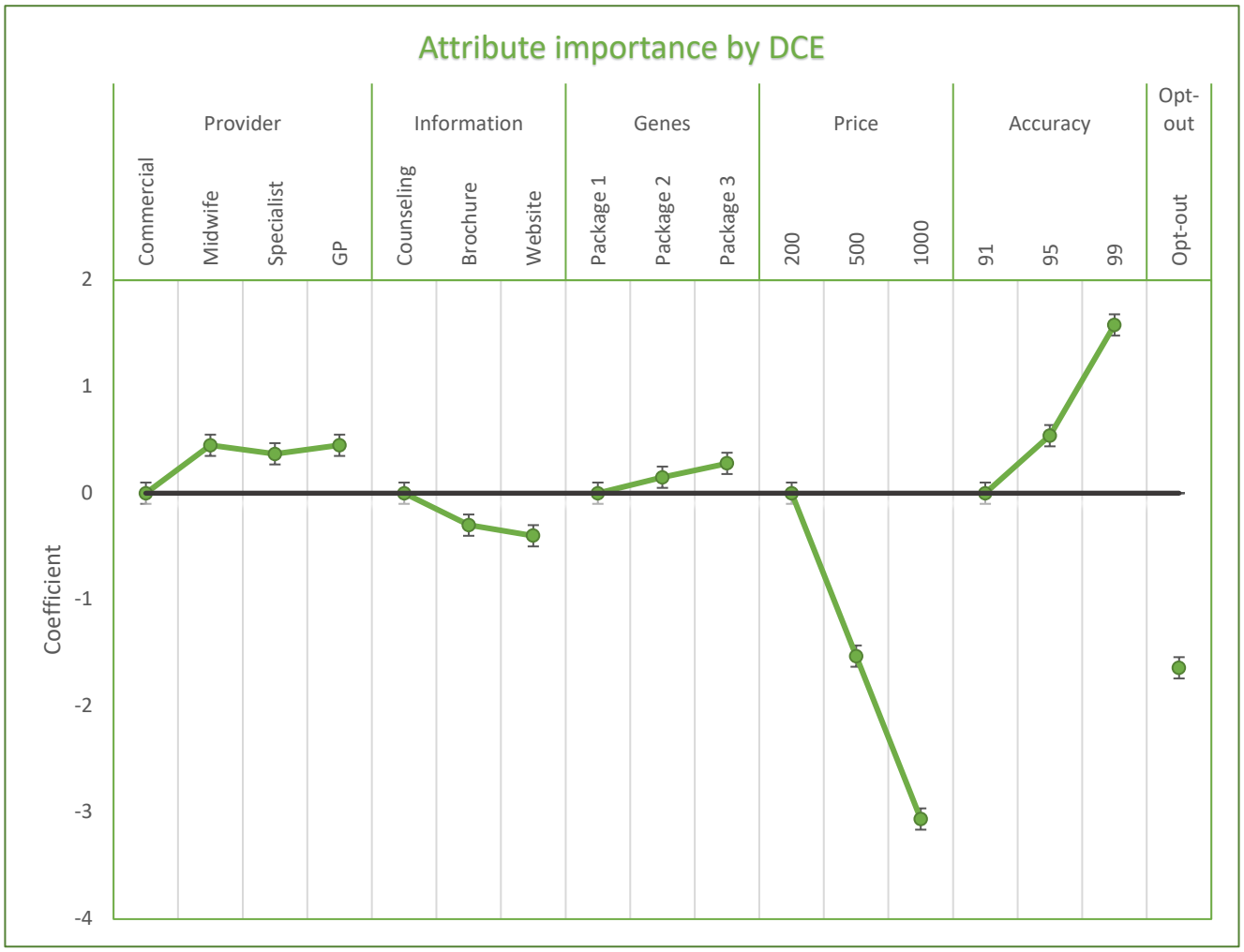

Figure 11
Preferences of respondents regarding the characteristics of the ECS test based on the outcomes of the mixed logit model. The higher the range of a certain attribute (e.g. the range of the attribute price is between 0 and -3.06), the more important the attribute is in the decision to take an ECS test with certain characteristics. The negative coefficient of the opt-out indicated that respondents choose the base-case ECS test over not taking a test.

Attribute importance measured directly

The respondents were also asked to directly rate/rank the attributes which they found most and least influential in their decision for a specific test. This ranking assignment was analysed in two ways. Firstly, figure 12 displays the % of the total score that a specific attribute was rated with. As can be seen in the figure accuracy is being ranked as the most important attribute, with 26% of the total score. After that, the genes attribute is rated as most important, followed by price and provider attributes. The type of Information provision is rated as the least influential in de decision to choose a specific test. The attributes were all given between 15-26% of the total score, which shows that there quite a bit of variation in the rankings of the respondents.

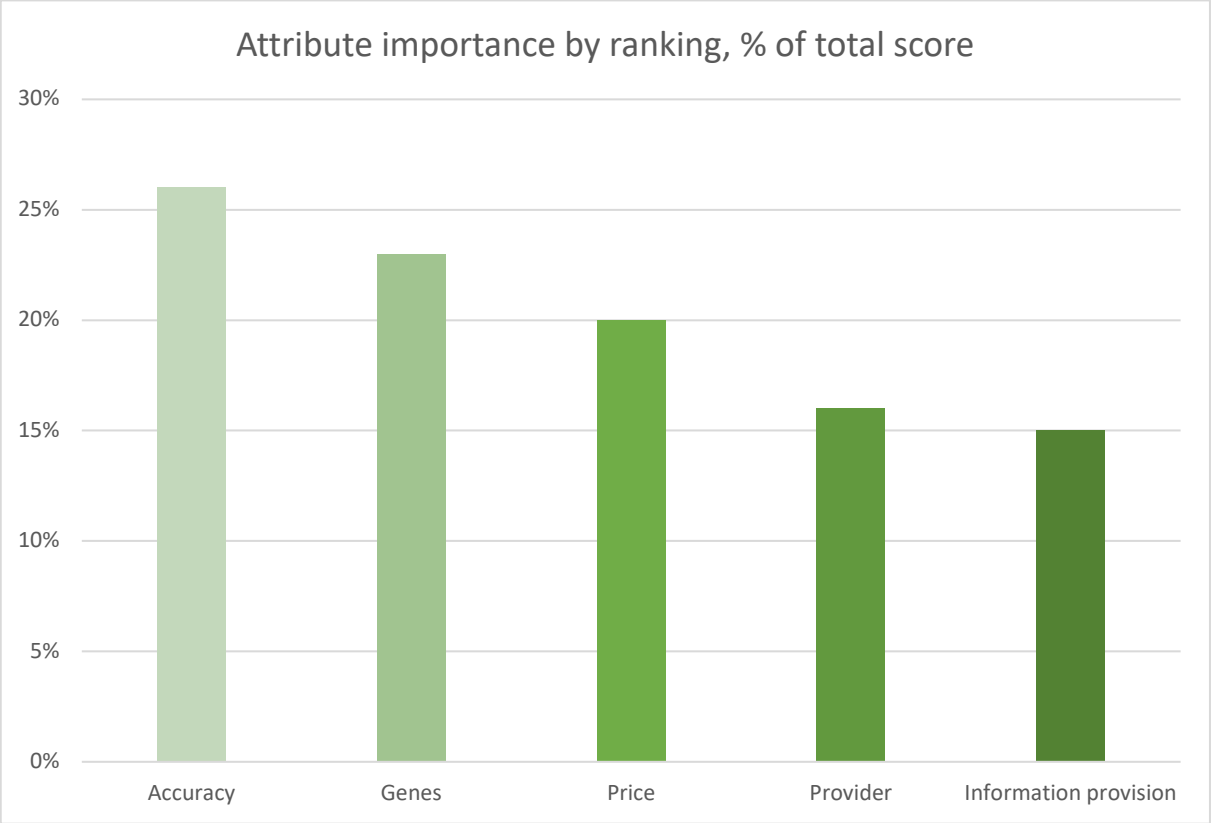

Figure 12
This figure shows the average rank score assigned by respondents. On the X-axis, the attributes are plotted. On the Y-axis the attribute ranking given by the respondents as a percentage of the total score is displayed. Every time an attribute is rated as most important by a respondent, this attribute receives 5 points. For 2nd most important 4 points, etc. In this figure the % of the total number of points per attribute is shown, rated by 479 respondents.

To gain more insight in the variation of the rankings given by respondents, figure 13 displays the % of respondents that gave a specific attribute a specific ranking. Accuracy was ranked most important by 40% of all the respondents. There is a big difference with the runner up, the types of genes included in the test, which was ranked as most important by 21% of the respondents. Almost the same percentage of respondents (20%) ranked price as the most important attribute in their decision. The type of provider and the information provision were ranked first by the least amount of respondents, 12% and 7% respectively.

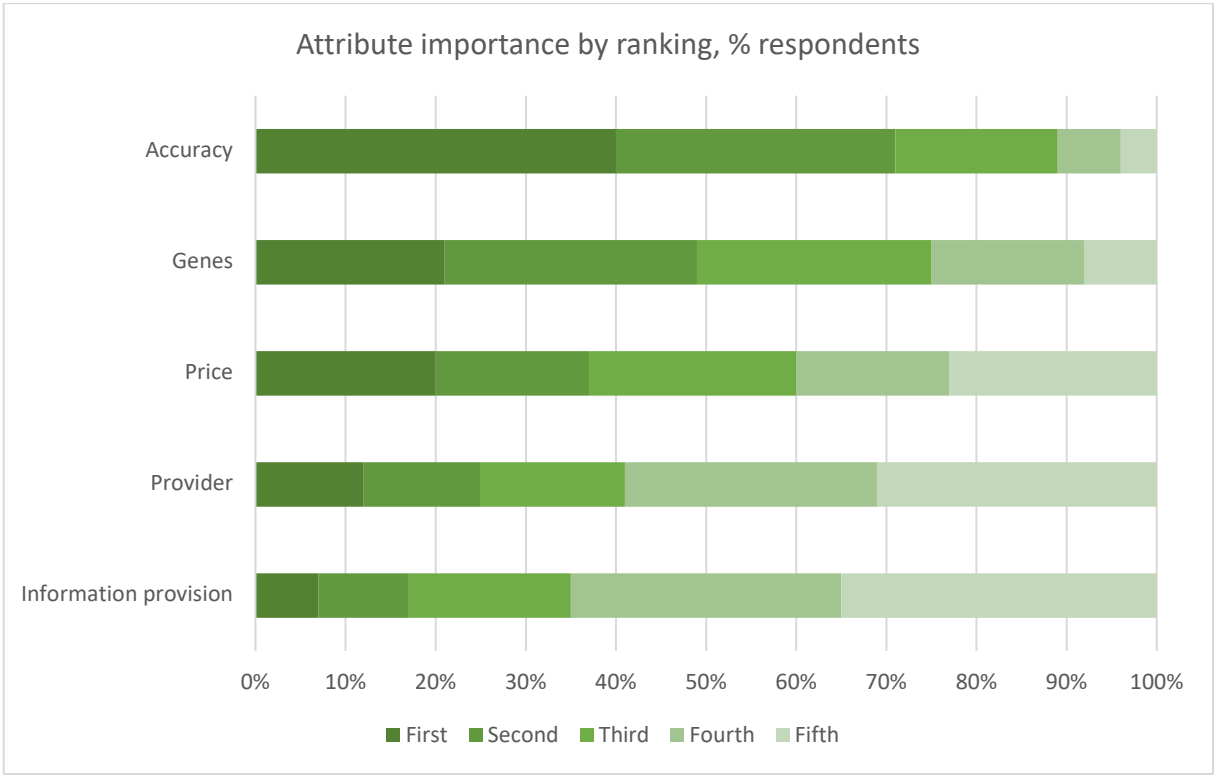

Figure 13
This figure shows how the attributes were rated by the respondents (n=479). 40% of the respondents rated accuracy as the most important attribute, 21% genes rated as most important, 20% price, 12% provider and 7% information provision. 30% rated accuracy as the second most important attribute, 18% as the third, 7% as the fourth and 4% as the fifth most important.

Comparison direct and indirect importance

Table 6 displays an overview of the earlier discussed importance scores that were calculated. Table 7 displays the ranking of attributes that result from this. When qualitatively comparing the importance scores the rankings seem to be associated, however there are some big differences. What is particularly striking is that there is a big difference in the importance that is granted to the types of genes included in the test. Based on DCE, this is the least important attribute (score 5%), based on the ranking assignment, this is the second most important attribute (score 21%). Another attribute where there is a large difference between the importance score given is price (53% vs. 20%). For the other attributes, the importance scores are pretty similar.

Table 6
Overview of importance scores resulting from different strategies of calculation

	DCE: Importance score	Ranking: % of respondents #1
Provider	0.08	0.12
Price	0.53	0.20
Information	0.07	0.07
Genes	0.05	0.21
Accuracy	0.27	0.40
Total	1	1

Table 7
Importance of attributes rated from 1-5 based on DCE results/the ranking assignment

	DCE	Ranking assignment
Provider	3	4
Price	1	3
Information	4	5
Genes	5	2
Accuracy	2	1

4.2.3. Sub-question 2: For this population, what is the ideal combination of test attributes measured by a discrete choice experiment?

Table 8 shows the estimated coefficients from the mixed analysis. From the estimated coefficients it can be concluded that the most preferred test would be a test with an accuracy of 99%, for a 200-euro price, including gene package 3, provided by a midwife or GP with pre-test information offered by counselling.

Table 8

Mixed logit results. The base case level has a value of 0 (e.g. commercial provider). The other levels have a positive coefficient when they are preferred over the base case level, and a negative coefficient when the base case level is preferred over that level. The higher the coefficient, the more the level is preferred.

Attribute	**Levels**		
		Coefficient (S.E.)	**SD**
Accuracy	- 91 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result	- 0.54 (0.08) *** 1.58 (0.13) ***	- n/a 1.68***
Price (per couple)	1 euro	-0.003 (0.00) ***	0.004***
Type of genes tested on	- Package 1 - Package 2 - Package 3	- 0.15 (0.07) * 0.28 (0.11)**	- 0.67*** 1.64***
Type of information provision	- Counselling - Brochure - Website	- -0.30 (0.07) *** -0.40 (0.07) ***	- n/a n/a
Provider	- Commercial company - Midwife - Medical specialist - General practitioner	- 0.45 (0.09) *** 0.37 (0.10) *** 0.45 (0.11) ***	- n/a 0.87*** 0.67***
Opt-out		-1.64 (0.19) ***	3.17***

*p≤0.05 **p≤0.01 ***p≤0.001. S.E.: standard error
SD n/a: variable was included as a fixed variable in the final mixed logit model, as the SD was not significant in the mixed logit model with all variables included as random
Log likelihood: -4666.4225

Figure 14 shows choice prediction based on mixed logit analysis. Table 9 lists the test characteristics of the tests described in this text and in Figure 14. When two tests are offered, the base case test (for free) and the opt-out, 84% of the respondents would chose the base case test. There is only a 13% choice probability that the worst possible test is chosen over the opt-out. When comparing the current tests that are available in the Netherlands to the opt-out, the vast majority of respondents choose the current test over the opt-out. When choosing between the test provided by UMCG and AMC, 66% chooses the test provided by UMCG. When the characteristics of the UMCG and AMC test are compared, the observation is be made that the preference of respondents for the UMCG test is caused by the lower price of the test and the provision of the test by the GP instead of a medical specialist. When the UMCG would change the type of information provision of their test from counselling to a website, only 40% of the people would choose it over the opt-out (otherwise 90%).

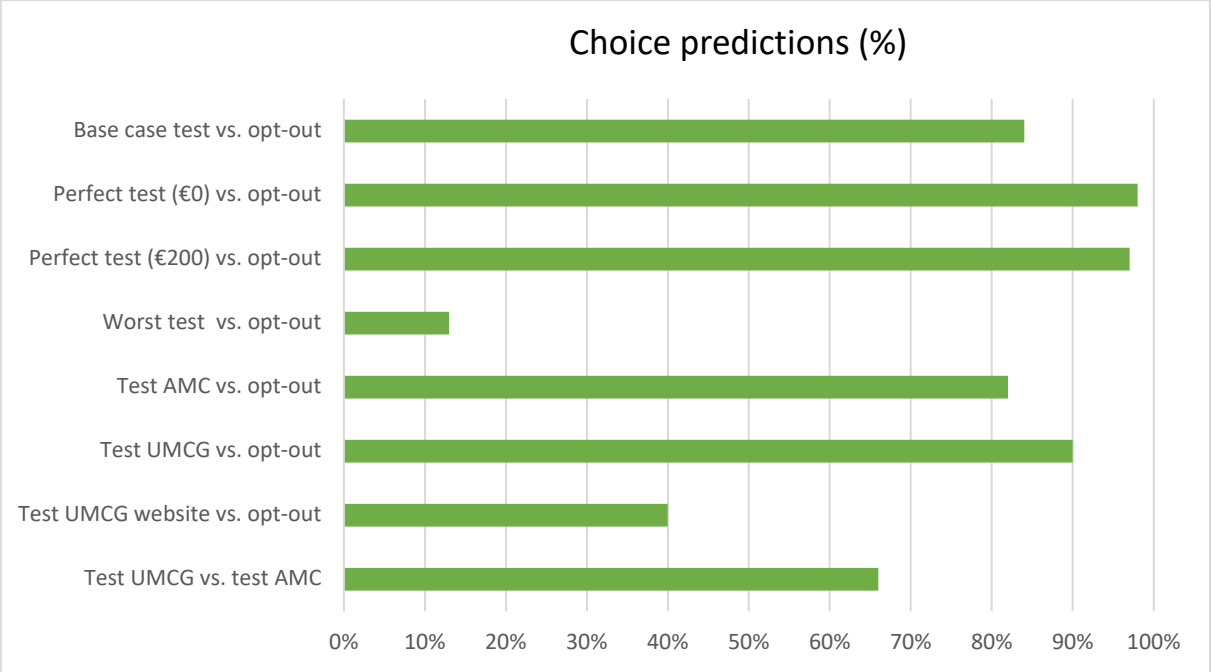

Figure 14
Choice prediction calculated based on the mixed logit model. The % is the percentage of respondents that would choose test X over test Y. Test characteristics are listed in table 9.

Table 9
Overview of the composition of the different tests.
The table shows the composition of the different tests that the choice predictions were calculated for. The base case test is a test with all the base case levels as test characteristics. The perfect and worst test are composed off all the levels that gained the highest and respectively lowest utility scores. The AMC and UMCG test characteristics are based on the characteristics of the test as it is currently available at these centers.

	Accuracy	Price	Genes	Information provision	Provider
Base case	91%	€0	Package 1	Counselling	Commercial company
Perfect test	99%	€200	Package 3	Counselling	GP/Midwife
Worst test	91%	€1000	Package 1	Website	Commercial company
Test AMC	99%	€650	Package 1	Counselling	Medical specialist
Test UMCG	99%	€475	Package 1	Counselling	GP

4.2.4 Sub-question 3: To what degree do respondent characteristics influence their test preferences measured by a discrete choice experiment?

Respondent heterogeneity

In figure 15 the standard deviation around the coefficients of every level is shown. There is a significant variation in preferences. This is seen by the high and significant ($p<0.001$) SD of the opt-out, accuracy 99%, price, gene packages, and provider specialist and GP. A multivariate mixed logit analysis was performed to try to identify which respondent characteristics might explain this heterogeneity.

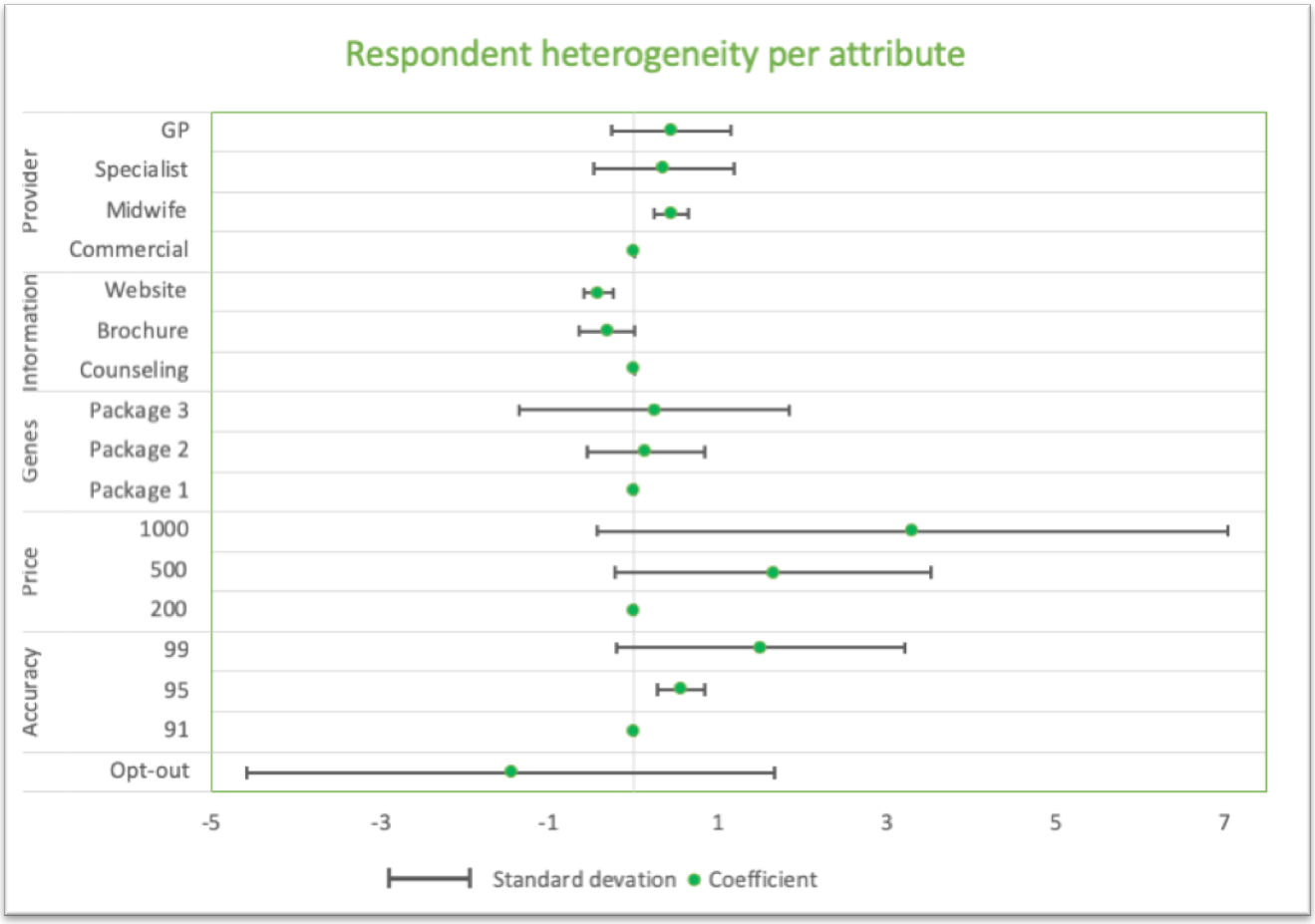

Figure 15
Respondent heterogeneity per level.

Respondent characteristics associated with specific test preferences

Figure 15 displays the results of the multivariate mixed logit analysis (see Appendix D) for the interactions of dummy variables that were significant ($p<0.001$). Several respondent characteristics were found to be associated with certain preferences, in the following paragraphs these interactions will be explained.

Firstly, the time frame at which people want children affects the preferences that are for the test. Although people with a child wish within 1 year would prefer the test to be administered by a medical specialist rather than a commercial company, this preference is less strong than in the group of people with a child wish within 1-10 years.

In addition, educational level has an effect on the respondent's preferences for the composition of the test. First, people with a higher educational level attach more utility to the reliability of the test compared to people with a lower education. In addition, people with a higher educational level, have a stronger aversion towards paying a higher price, than people with a lower education: they are willing to pay approximately half of the price that people with a lower education are willing to pay. Finally, educational level and the way respondents prefer to obtain information about the test is associated. All respondents prefer to obtain their information through counselling, however, people with a lower level of education have a stronger aversion towards receiving information through a brochure or website than people with a higher level of education.

Another factor that plays into respondents' preferences is whether or not they knew about ECS before participating in the study. In fact, people who had heard of ECS before would be willing to pay 2.2 times more for a test than people who had never heard of ECS before. In addition, respondents on average preferred to have the base case test over the opt-out, and this aversion towards the opt-out was even stronger in the group of people who were already familiar with ECS.

Another characteristic of respondents that influences their preferences is whether or not they were in a relationship at the time of completing the questionnaire. People without a relationship were more likely to opt out of the test than those in a relationship.

Another factor that had an effect on what preference people have for the opt-out is whether people already had children. People who already had children have a weaker aversion to the opt-out. In addition, they have a weaker preference for test taking by a midwife versus a commercial company than people without children.

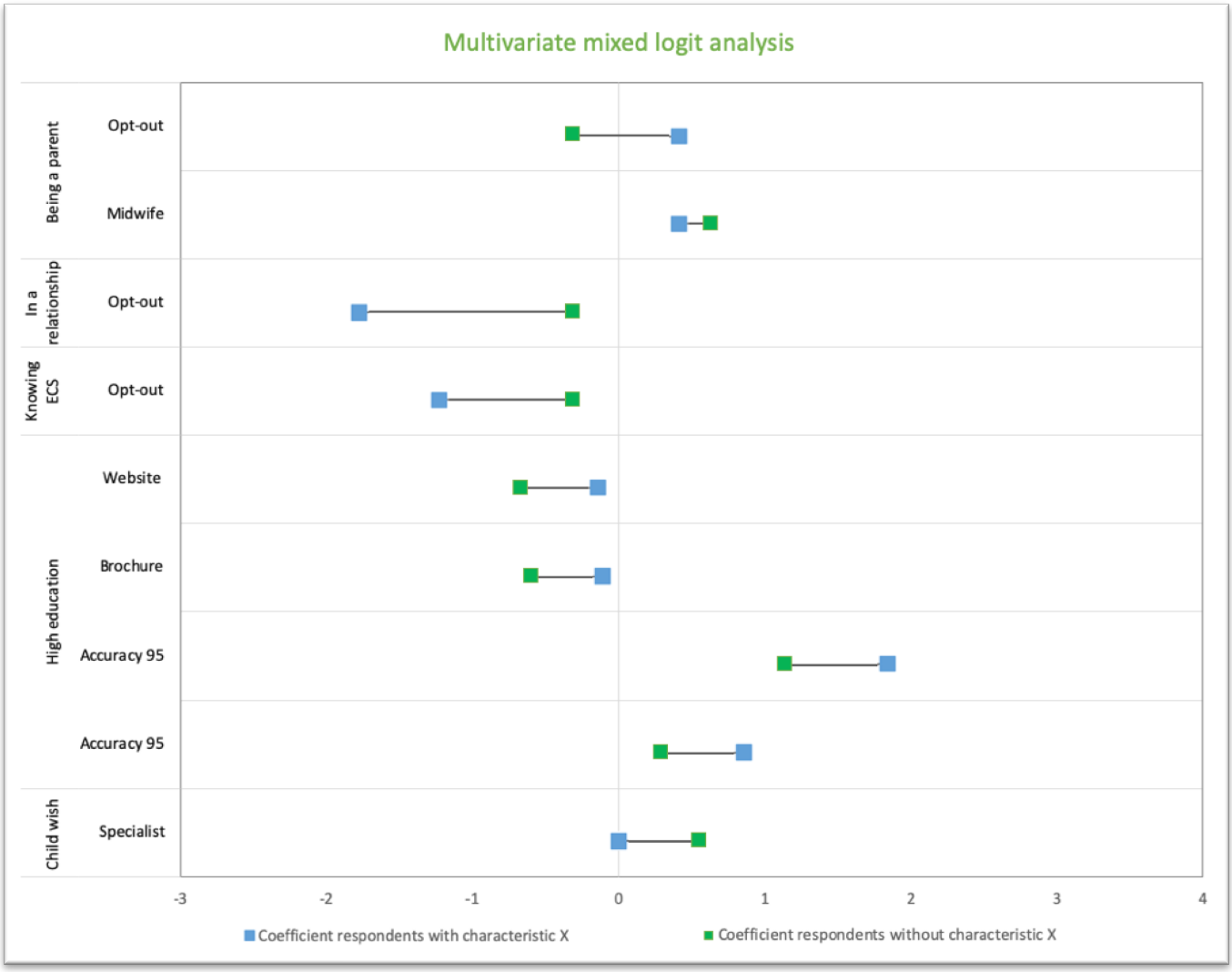

Figure 16
Graphic depiction of the multivariate mixed logit analysis results (full table: Appendix D). On the Y-axis the respondent characteristics and their interaction with a certain level are plotted. On the X-axis the coefficient of for the respondents with or without a specific characteristic is presented. For example, the upper characteristic is "being a parent". The interaction with the level opt-out and midwife are presented in this graph. On the x-axis can be seen that the blue marker shows that the coefficient for parents is 0.36, whilst the coefficient for respondents that are not parents yet is -0.31.

4.3 Extra choice task

In the extra choice task people were asked to show their preference, choosing between three options:

1. Test with 99% accuracy for 1000 euros
2. Test with 50% accuracy for 100 euros
3. Opt-out

The first option has the test characteristics of targeted gene panel analysis (50% accuracy, 100 euros) and the second option of sequence analysis (99%, 1000 euros).

The respondents strongly preferred the sequence analysis test over the other two options (figure 17). 54% of the respondents choose the first option, compared to 39% choosing the opt-out and only 7% choosing the second option.

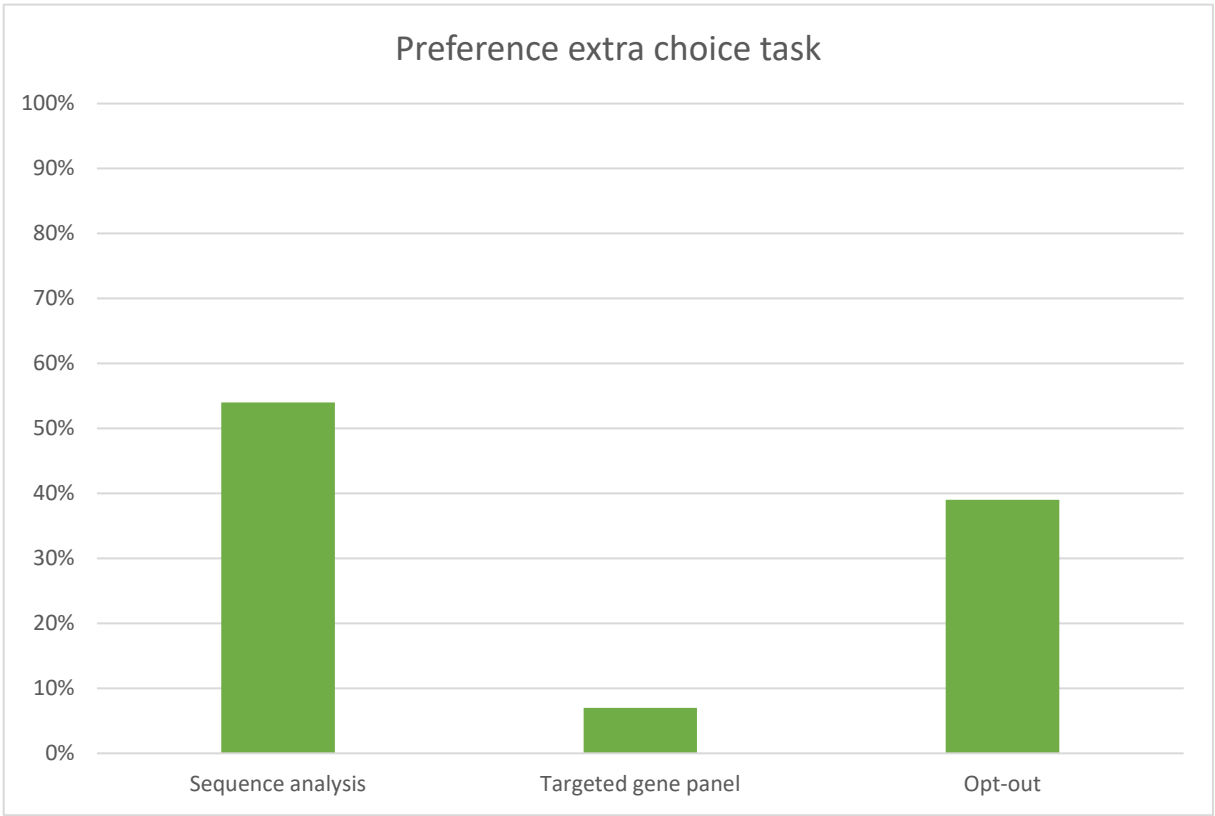

Figure 17

% of people that choose a certain option.

Which respondent characteristics were associated with choosing targeted gene panel or opt-out over sequence analysis can be found in appendix E Table 16.

Firstly, respondents with a younger age more often choose option 1 than respondents of an older age ($p<0.001$). 70% of the respondents under 25 years selects option 1, whilst of the respondents older than 25 years only 49% choses this option, and they more often prefer the opt-out or option 2.

Secondly, having heard from ECS before the questionnaire is associated with choosing the opt-out less often ($p<0.001$). People who indicate they have heard of ECS before are significantly more likely to select option 1, than those who have never heard of it before (62% vs. 46%). The opt-out is therefore chosen much more often by people who have never heard of ECS before. The second options are preferred equally often by both groups (7% and 8%).

Thirdly, people who indicate that they know someone or have a genetic disorder themselves more often prefer the first option than people who do not know anyone with a genetic disorder (61% vs. 49%). The second option is chosen exactly as often in both groups, which means that the opt-out is selected more often in the group of people who do not know anyone with a genetic disorder ($p<0.05$).

Lastly, already being a parent of one or more children was associated with choosing the opt-out more often ($p<0.01$). People who already have children are more likely to select the opt-out within this choice task, than people who do not yet have children (45% vs. 35%). They also prefer option 2 more often (10% vs. 6%). And thus, less often choose option 1 (45% vs. 59%).

4.4 Survey evaluation and sensitivity analysis

4.4.3 Survey evaluation

In total, 6 253 choice tasks were completed by 481 respondents. 2 respondents completed the DCE choice tasks but did not finish the ranking assignment and evaluation questions. The median time people took to finish the survey was approximately 10 minutes (interquartile range 9 minutes). 78% of the respondents filled in the same answer twice in the double choice task.

Respondents were also asked questions to evaluate the survey. 91% of the respondents indicated that the instructions of the survey were clear, 8% thought they were somewhat clear, and one the respondents had the opinion that the instructions were unclear. Figure 18 displays the responses of the respondents to the Likert scale evaluation questions. Figure 18 indicates that the respondents in general had a positive opinion about the survey, as only 4% would not participate in a similar study again. 68% of the respondents agreed or strongly agreed to the statement that stated that they had considered all the characteristics when deciding between the different choice options. Only 10% found it difficult to choose between the different choice options. 72% of the respondents reacted positively to the statement that the survey helped gain a better understanding of their preferences for the characteristics of the carrier test.

When the respondents were asked whether any particular characteristics of a carrier test were missing in the current research, the majority of respondents (83%) indicated that they did not miss any characteristics. The respondents that did miss certain characteristics, named the following: guidance during the process and after the result, turn-around time of the result, type/invasiveness of the test, and confidentiality of results.

The respondents were also free to give a written evaluation of the questionnaire. Many respondents stated here that they found the questionnaire interesting and well explained, some mentioned learning a lot and gaining more insight into the preferences. Others opined that the questionnaire was too long and thought the information texts were too complicated. On the other hand, other respondents indicated that they would have wanted more information.

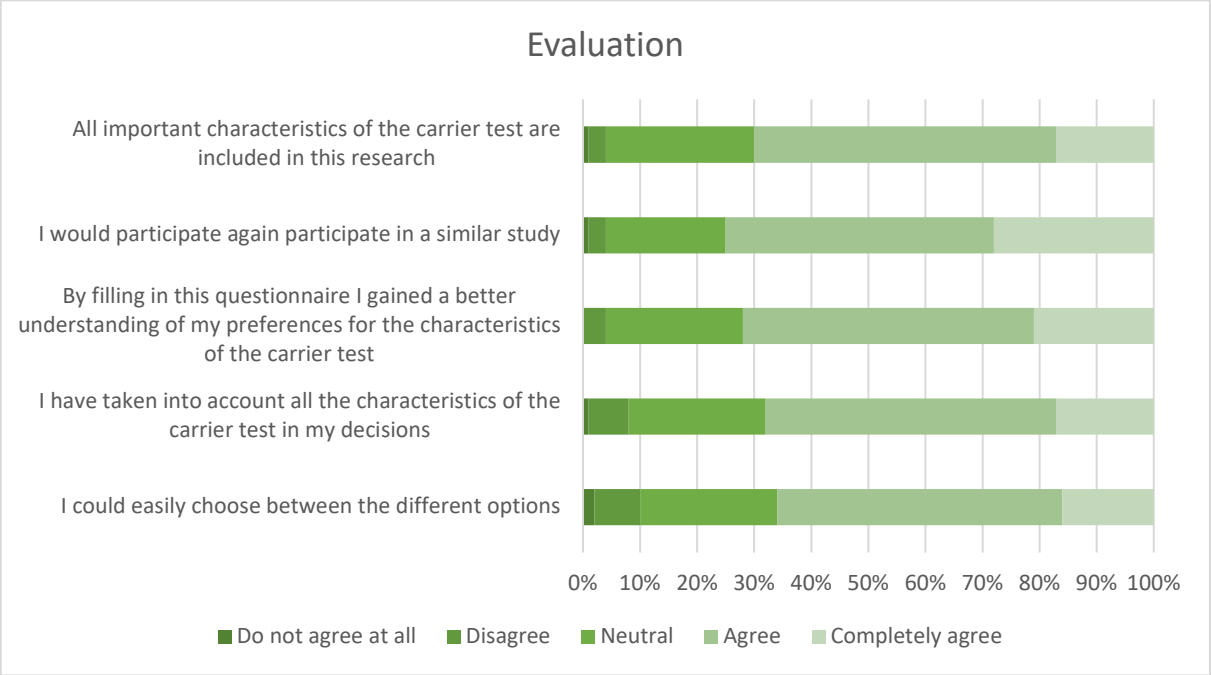

Figure 18
Survey evaluation by respondents

4.4.4 Sensitivity analysis

As mentioned in section 4.1, 67 respondents were removed from the final analysis as a result of the sensitivity analysis. Further explanation on the methods of the sensitivity analysis can be found in section 3.3.3. In this paragraph the results of the sensitivity analysis will be discussed.

Rationality questions in the survey checked whether respondents understood the comprehended the explanation about the test. 56 respondents (10%) failed the first rationality test. Of those people, 38 also failed the second rationality test. 8 respondents displayed nonattendance by choosing the most left choice option in all the choice tasks. 30 respondents finished the questionnaire in less than four minutes. A sensitivity analysis was conducted removing the respondents that failed the rationality test, displayed nonattendance and/or spent less than 4 minutes on completing the whole survey. This concerned 67 respondents in total, as some of the respondents qualified for more than one of the criteria. These respondents together are now called: “sensitivity analysis group”. A conditional logit analysis was conducted to analyse the results of the total group of respondents (including the sensitivity analysis group) and an analysis was made based on the data of only the “sensitivity analysis group” (appendix F). The results of only the “sensitivity analysis group” showed only a significant coefficient for the opt-out coefficient. In addition, the found coefficients differed greatly from the coefficients that were found in the total group of respondents. Therefore, the “sensitivity analysis group” respondents were not included in the final analysis.

4.4.5 Opt-out

43 respondents chose the opt-out option in all of the choice tasks. These respondents were asked to give a reason for this. The majority of respondents stated that had something to do with the test characteristics (for example they would never pay 200 euros for the test). However, some indicated reasons that revealed they were actually not open to ECS, although they answered the selection question affirmative.

5. Discussion

5. Discussion and conclusion

5.1 Discussion

Key findings

The purpose of this study was to identify the preferences of members of the Dutch public who are open to the carrier test, regarding the characteristics of this test. To start with, the characteristics of people that would consider taking an ECS test were compared with the characteristics of people that would not. People open to ECS are more often highly educated, open to prenatal screening, and not religious than people who are not open to ECS.

Secondly, the preferences of the respondents open to ECS, for the characteristics of the test were investigated with a MLA. The opt-out had a negative utility value, indicating that respondents would choose the base-case test over the opt-out. The decision to accept a specific test or not was influenced by the accuracy of the test, the price, the provider, and the way of information provision ($p<0.01$). The genes included in the test (differentiation between packages 1-3) did not significantly influence the decision of respondents that were open to ECS ($p = 0.05$). The DCE results showed price was the most influential on the utility of the test (importance score 53%). Respondents preferred the lowest possible price and the highest possible accuracy of a test. In addition, they preferred counselling to be informed about the test over a website or brochure. Respondents had an aversion towards a commercial company being the provider of the test and would most prefer it to be provided by the GP or midwife. A clear differentiation between the packages of genes included in the test was not made, but there was a probable preference for including the broadest package (also including mild and non-health-related genes) ($p = 0.05$).

Respondent preferences and respondent characteristics were associated. Respondents strongly preferred the characteristics of a sequence analysis test over the characteristics of a targeted gene panel. Respondents that have heard from ECS before, know someone with a genetic condition, or do not have children yet, have chosen the opt-out less than sequence analysis than respondents without these characteristics. Below these findings will be interpreted, compared with earlier research, and discussed in terms of validity and reliability.

Interpretation of findings

When placing the found results in the context of earlier work, there are many overlaps. In accordance with earlier studies, also in this one a positive attitude of the public towards ECS is found. (7,14) 90% of respondents would be open to the test. The characteristics associated with being open to ECS were greatly consistent with earlier research, which also found that respondents being religious or having a higher educational level made them more likely to be open to ECS. In this study, an association between being willing to participate in ECS with age or already having children, like in earlier studies, was not found. (7,13,14)

This thesis was the first research that evaluated the relative importance of the attributes in the decision-making process. Although the relative importance was not assessed before, Bijsterbosch (20) did identify the most important attributes that influence the decision. The conclusions of this study and the current study correspond to one another, except for the attribute “the type of genes tested”. In the current study, the type of genes included did not significantly influence the choice of respondents for a specific test. The respondents did not clearly differentiate between the packages but seemed to slightly prefer the package also including non-health related genes. This contradicts earlier conclusions by Plantinga et. al (7) who used a psychological questionnaire to study preferences. Respondents in our study did not differentiate between early-onset and late-onset diseases but did indicate that they least preferred non-health related genes to be included in the test. This contradiction could be explained by the difference in method between these two studies.

Both the current study and Plantinga et al. (7) concluded that respondents least preferred a commercial company as the provider of the test and most preferred counselling as the type of information provision and the lowest possible price and highest accuracy for the test.

Respondent heterogeneity was not studied before. In the MLA, most respondent heterogeneity was present in the coefficient of the opt-out and the multivariate MLA showed this could be explained by specific respondent characteristics. Respondents that are in a relationship, have heard from ECS or have no children yet are more averse of the opt-out and respondents than respondents that do not have these characteristics. The latter could be explained by couples that already have a healthy child, assess the risk of having a child with a genetic disorder smaller, and therefore have less interest in participating in the test than couples who do not have a child yet.

As was also found by Bijsterbosch (20) respondents with a high educational level have other preferences compared to people with a lower educational level: they would pay less for a test, attach

more importance to the accuracy of the test and have a less strong preference towards being informed by a brochure or website compared to by counselling than subjects with a lower educational level. Respondents having heard of ECS before this study would be willing to pay more for the test, and less often chose the opt-out than people who have not heard of the test before. This indicates that people with more knowledge, assign higher value to the test.

Strengths and limitations

Strengths

The first asset of this thesis is that the method used to elicit preferences. A DCE has not been conducted before in this field, and DCEs can predict real-word health-related choices reasonably. (72) In addition, it enabled including existing and not-yet-existing test possibilities and the relative importance of test characteristics could be estimated using this method. Another strength of this study is the high number of respondents that was reached. The required number was around 300 to reach good power, but eventually 481 were included for the models. (75–77) The group was selected to be a good sample of people that would be eligible for the test. The fourth asset of this study was the high quality of the survey. The respondents were informed about ECS, genetic conditions and the attributes and levels step by step. In addition, questions checked whether they also understood the given information. Another strength of this study is that a multivariate analysis was performed. This allowed to not only reveal people's preferences for the attributes and levels, but also the characteristics that caused heterogeneity. This results in many possibilities to improve the ECS test.

Limitations

The first limitation of this study is related to its method: the DCE. When conducting a DCE, attributes and levels have to be selected and this dictates the possible results that are found. (99) In this study attribute selection was done diligently based on quantitative research, qualitative research and a pilot study in accordance with the report of the ISPOR Good Research Practices for Conjoint Analysis. (76) When the number of attributes is selected, a trade-off must be made between including all attributes to include the entire utility of the good, and the feasibility and task complexity. Five attributes were included in this study, and it is possible that therefore not the entire utility of the ECS screen offer is included in the selected attribute. However, when more attributes would have been included this would have probably decreased the validity and reliability of the results.

The second limitation of the DCE method is that hypothetical bias could have occurred, which means that individuals made different choices in the hypothetical survey setting than they would have made in real-life situations. (100) This can influence all the utility values found, however the expectation is

that this mostly influences the utility of the opt-out and price. When making the decision in real-life respondents possibly would opt-earlier at lower price levels, because it is real money they have to spend.

Thirdly, selective non-response could have influenced the results of this study. Respondents were recruited by social media, forums about pregnancy and through a professional bureau. People who were recruited always could choose voluntarily to participate or not participate. Therefore, it could be possible that the non-responders had different characteristics than the responders. For example, people that have more affinity with the topic are possibly more likely to fill in the survey, and therefore the % of people open to ECS could be an overestimation. Specific details of non-responders are difficult to gather when gathering participants online. Recruiting respondents personally would enable also gathering details about non-responders. This would however be very time-consuming.

Another limitation of using DCE to find out about preferences, is that although people's preferences are researched, it remains obscure exactly what the people's reasoning behind these preferences is. To reveal this, questions could be added to a DCE about this topic. However, qualitative research methods are more suitable for revealing respondents' rationales.

Validity and reliability

An overview of the incorporated methods to test reliability and validity is displayed in Appendix G.

Reliability

A conducted study has a high reliability, if, when the study would be performed again according to the described methods, the found results will very likely be similar. (101) The survey evaluation showed that the quality of the survey instructions was good, as 91% of the respondents assessed the instructions to be clear. The dominance test was only filled in incorrectly by 7% of the respondents, showing that people understood the principle of the DCE and the explanation that was given about ECS. This resulted in a high test-retest of 78%. This means that the respondents had a high choice consistency, and thus a low error variance. 68% of the respondents indicated considering all characteristics when deciding. This indicated that simplified heuristics were probably not often used by respondents. In addition to the respondents understanding the questions and explanation well, and therefore giving reliable answers, also the analysis was conducted in a way that ensures reliability. There were clear in- and exclusion criteria, incomplete survey responses were removed, and an analysis were performed diligently and deliberate, and were described in detail. Therefore this study is expected to have a high reliability.

Validity

A DCE is performed to form a model, which is never exactly similar to reality. By assessing the validity, an estimation is made of how close the model is to reality. It is important to assess the internal and external validity.

When comparing the sample of this study to the general Dutch population (age group 18-40 years old), this sample included more women than the distribution in the normal Dutch population. There was no expectation, nor evidence, that this influenced the results, because men did not have different preferences than women in our sample. Besides the male-female distribution being different, the respondents in our sample were more often highly educated (vs. age group 15-75 years old) and had a lower income than people in the general population (age group 20-29 years old). This is probably caused by a large proportion of the sample being students. This hypothesis cannot be tested, because the respondents were not asked during the questionnaire whether they were students. The MLA showed that highly educated people have different preferences than lower educated people. Because our sample largely exists of highly educated people, the preferences of highly educated people can also be more prominent in the overall mixed logit analysis. As highly educated respondents assigned higher importance scores to the accuracy and price attributes, this could result in lower importance scores of these attributes when the proportion of highly educated people would lower (like in the general population). In addition, for information provision counselling would still be the preferred level, but less utility difference would be observed with information provision by a brochure or website.

External validity is about assessing whether the study results would apply to other situations. (102) This study was conducted with the main goal to inform Dutch policy makers and healthcare. Therefore, only Dutch participants were included, and levels were chosen mostly based on the Dutch current situation. For example, the GP is one of the possible providers. In the Netherlands, GPs have a central role in the health care system. However, there are many other countries or health systems where there is no GP or no developed primary care. In that case, specific conclusions are not applicable to other situations. However, in countries where inhabitants broadly have similar ethical believes and healthcare systems, the less specific conclusions are applicable. For example, if the same DCE would be conducted in Germany, price and accuracy would still be assessed the most influential attributes. The utility assigned to other attributes may be different.
Next, face validity and convergent validity will be discussed. Firstly, the face validity for this research is high regarding the price and accuracy attribute. The utilities of these attributes have the expected sign, and an increase in the value of the levels, is associated with a further increase/decrease of the

utility. This also is a sign of high construct validity. Secondly, convergent validity will be assessed comparing the results of the DCE with the results of the ranking assignment. A striking difference when comparing these, is the ranking of the "type of genes included" attribute. According to the DCE, it is the least importance attribute, whilst according to the ranking assignment it is the second most important. This difference can be explained by the difference in method that was used. In the choice tasks, respondent's trade-off the specific gene packages, with the other attribute levels. The variation in gene packages might have been too small to have a large influence on the trade-off. Another factor that could play a role, is that respondents might reason that although they do not need information on for example non-health related genes, they don't might it being tested, because they always have the option of not using the information. Another attribute that was clearly rated differently in the ranking assignment and DCE, was the price of the test. The price was the most important attribute according to the DCE but was the third most important according to the ranking assignment. When having to make trade-offs, respondents thus assign more importance to the price of the product, than when making a rational ranking. The rest of the rankings given by both methods were largely consistent. In conclusion, the convergent validity is moderate when assessing the DCE importance ranking compared to the ranking assignment. However, this can be better explained by the difference in method than the validity of the DCE results.

Finally, it is important to discuss two other points in the context of the validity of the study. First, as discussed in section 4.4.5, it appears that not all people who indicated they were open to ECS actually were. For that reason, some respondents chose the opt-out option repeatedly because they were not open to the test, not because they did not like the test characteristics. This would mean that the opt-out would probably have an even more negative utility if these people were not included. The effect of this is not expected to be large, as the screening question did screen-out most respondents that are not interested in ECS. In a future study, a multiple-choice option should be included at the end of the choice tasks, which also has a multiple-choice option to indicate that a respondent is not open to ECS and therefore chose the opt-out in every choice task. Secondly, the MLA that was conducted in this study increases the validity. This enabled the discovering of reasons for heterogeneity in the study sample.

Recommendations

Policy recommendations

When working on the possible nationwide introduction of ECS, it is important to take the preferences of the future test-takes into consideration. Suboptimal test characteristics could compromise the access to or the uptake of the test. This study showed that people are most influenced by the price and accuracy when deciding to take the test or not. A higher price and a lower accuracy increased the choice for the opt-out test. Therefore, the highest possible accuracy should be pursued, and the lowest possible price. The price of the test should be placed at a level that makes it evenly accessible to higher and lower income people. Also sequence analysis should be offered, and not a targeted gene panel analysis, the accuracy is too low for respondents to be interested in this test (even at a low price). The respondents had an aversion towards the test provider being a commercial company but did not have a very clear preference for either the GP, midwife or specialist providing the test. Therefore, the costs of the test could be reduced, and feasibility of provision to the whole population could be increased by choosing the cheapest and most available provider.

When differentiating between three different gene packages, the respondents did not have a strong preference for a specific package. There was only a slight preference for the more extensive gene packages. This is thus a characteristic that is not expected to have much influence on the chance of people accepting the test offer. The selection of the most suitable gene package can therefore be best made by professionals based on ethical, technical and feasibility arguments.

The respondents strongly preferred the information being provided by counselling compared to a brochure or website. This preference was less strong in highly educated people. Therefore, it would be a possibility to inform all couples by a website/brochure, and provide an pretest counselling appointment for the couples that would prefer it.

In this research, prior knowledge of ECS showed to improve the WTP of the test and decreased the chance of choosing the opt-out. Therefore, it is important that the overall knowledge of the Dutch general public about ECS is increased. A national campaign would be a good way to achieve this.

Recommendations for further research

The current study added a lot of knowledge to what is already known about ECS in the Netherlands and worldwide. However, more research should be done before introducing a nation-wide ECS program in the Netherlands. And, when possibly conducting another DCE concerning this topic, some changes could be made to improve the validity of the study. Therefore, there are several possible recommendations for future research.

Firstly, as mentioned earlier, this study was very specific for the Dutch healthcare system and results are most specific for the Dutch population. A study comparing preferences in different countries would be interesting to find out whether these differ between countries. In addition, despite them being in the same age range, it is important to differentiate between students and already working people in the reproductive ages. They could have different preferences as high education students often do not have a current income currently, but often expect to have this in the future at the moment they want to have children.

Before nation-wide introduction of ECS in the Netherlands it is important to study some aspects of the test. Firstly, the current study showed that the midwife would also be a possible provider of the test as far as respondents are concerned. Until now, only GPs and medical specialists provide the test in the Netherlands. Therefore, the possibility of provision by a midwife compared to a GP should be explored. In addition, to reduce costs, the possibility of first only testing one person of a couple could be investigated. If this person is not a carrier, there is no risk of having a child with a recessive disease. If this person is a carrier, the other member of the couple will also be tested. In this manner, a lot of costs could be saved.

Concerning information provision, the specific preferences of the public should be explored: what do people want to know about the test? When is the information clear? Also, more extensive cost-effectiveness studies should be conducted, specific for the Dutch healthcare system to be able to support the implementation. Further research on the ethical concerns regarding this topic is also important as ECS is a controversial method to prevent disease and is currently being performed.

5.2 Conclusion

In conclusion, the majority of Dutch inhabitants between 18-40 years old are interesting in taking an ECS test. A low price, high accuracy, provision by midwife or GP and information provision by counselling increase the possibility of test acceptance. The characteristics of individuals influence their test preferences, and therefore these should be considered e.g. by offering different options of information provision. Respondents with prior knowledge of ECS are more often open for the test and are willing to pay more for it. Therefore, prior to expanding the availability of the test, a nationwide information campaign is important. Future research is necessary to further specify the implementation of the test. With the results of this study steps can be taken to design an ECS test with the most optimal test characteristics, ultimately with the goal of achieving a high degree of reproductive autonomy.

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Appendix A: Overview of the questionnaire

In table 10 an overview is given of all the components of the online survey. Also, a description of every component is given.

Table 9
Questionnaire overview

Survey component	Description
Introduction	Dear Participant, Thank you in advance for your interest and participation in this survey. The purpose of this survey is to get a better idea of the preferences of potential users of the carrier test. In this way, these preferences can be considered when making choices for the introduction of the test. The carrier status test is a test that can be done by couples who wish to have children done prior to pregnancy. It can be used to determine whether they are both carriers of the same genetic disorder, and therefore have an increased chance of having a child with increased risk of having a child with a genetic disorder. Further down in the questionnaire you will receive detailed information about this test. This study is being conducted by two students Health Economics (Policy and Law) of the Erasmus University Rotterdam. Completing this survey takes about 15 minutes and is completely anonymous. If you have any questions or comments about this questionnaire, please contact us at dragerschapsonderzoek@gmail.com
Informed consent	*Respondents had to agree with the following statements (check the box) to be able to participate in the survey.* I understand that… ...Participation in this study is voluntary. ...My responses will be handled anonymously for a research report. ...Individual answers will not be named in the survey report. ...there is no fee for participation in this questionnaire. ...this questionnaire is aimed at individuals between 18 and 40 who think or wish to have (more) children within 10 years. ...By participating in the study, I am making an important contribution to science. o I understand this and agree to participate
Exclusion questions – Part 1	*Respondents were asked to fill in:* - Age - Child wish within 10 years (yes/no)
Demographic questions	*Respondents were asked to answer questions about:* - Sex - Province - Educational level - Income - Religion - Partner - Ethnicity - Children currently
Prenatal diagnostics	*Respondents were provided with a short informational text about prenatal diagnostics, followed by a question:*

	Prenatal diagnosis involves checking before the birth of a child whether the child has certain disorders. This can be done, for example, by testing the mother's blood, by testing the amniotic fluid, or by doing an extensive ultrasound scan. During possible previous pregnancies, have you used prenatal diagnosis / In the future, would you consider using prenatal diagnostics during a possible pregnancy?
ECS Information	*Respondents were provided with an information text + video about ECS and were asked whether they had heard of ECS before:* The carrier test and purpose of the current study Most children in the Netherlands are born healthy. However, there are also born sick children or children who become ill later in life, for example because they have an inherited disorder. Even if you are are healthy, you can also have a child with an inherited disorder. Within your genes is information stored where your hereditary characteristics laid down. This information determines to a large extent what you look like and ensures that your body works properly. works. For each gene (for example the gene that determines your eye color), there are several variations. For each characteristic a person has two variations, which determine the characteristic. Sometimes one of the two genes that determine a particular characteristic of a person is different from normal. Such a deviation is called a mutation. Carriers of a genetic disease have a fault in one of the two same genes. Therefore they have no health problems, because in addition to the 'wrong' gene they have a 'good' gene. But if the partner of a carrier is also a carrier of the same the same 'faulty' gene, there is a 1 in 4 chance that your future child will be born with two mutations and therefore two mutations and will therefore have a genetic disorder. With a preconception carrier test you can determine whether you are a carrier of such a recessive such a recessive hereditary disease before there is a pregnancy. For the test, blood only needs to be taken from both partners. The purpose of a carrier test is to give future parents information about the health risks of their future parents about the health risks of their future child and to help them make choices about having children. When future parents know that there is a chance of having a child with a recessive genetic disorder, there are several choices the couple can make. First, the couple can prepare for the possible arrival of a child with a serious condition. Second, they can choose to undergo IVF (IVF stands for in vitro fertilization. In this technique, eggs are fertilized with sperm cells in the lab fertilized with sperm cells. Together, this forms an embryo and will then be transferred to the woman into the uterus) and during this process have an embryo without a genetic disorder selected. Also, couples can choose to adopt a child, a sperm or egg donor or they can choose not to have children (with the current partner). Prior to pregnancy, a couple has the most choices. Watch the video below to learn more about the carrier test: VIDEO When the preconception carrier test is used to test for 50 serious diseases that develop early in life, about 1 out of 150 couples will have a positive test. Since there is then a 25% chance of having a sick child, this means that in approximately 1 out of 600 pregnancies in the Netherlands there is of one of those 50 genetic diseases tested. The purpose of the questionnaire is to find out what individuals with a wish to have children who are open to a carrier test important characteristics of the test. Based on the preferences of the potential user, the the preconception carrier test can be designed in

	a way that the user's wishes as much as possible. Here, the costs of the test, the provider costs of the test, the provider, the reliability, the way in which information is information provision and which diseases are tested for. Question: Prior to this questionnaire, have you heard of the carrier test for couples with a desire to have children?
Exclusion questions – Part 2	*Respondents were asked the following question to differentiate between people that were open/not open to ECS:* Question: Imagine being offered a free, completely reliable carrier test, where you have the choice of what hereditary diseases to be tested for, would you consider it? Answer options: yes/maybe/no
Genetic conditions	*Respondents were provided with an informational text about genetic conditions, followed by questions:* Genetic Disorders There are many different types of autosomal recessive genetic disorders, which differ in age of manifestation, severity, and whether treatment is possible or not. A distinction can be made between diseases that most people consider to be severe and those that most people consider mild. Serious diseases Most people consider a disease to be a serious genetic disease if it is untreatable and is accompanied by a lot of pain and/or a severe physical disability and/or a severe mental disability and/or premature death. In this definition, it does not matter whether the disease manifests itself early or later in life. Examples of severe conditions: - Pontocerebellar hypoplasia: because of the genetic defect, certain parts of the brain do not develop properly. As a result, children with this disease usually cannot talk, walk, sit, and have difficulty eating and drinking. Most children with this condition die at a young age. - Parkinson's disease: Abnormalities in certain genes can lead to the develop into an inherited form of Parkinson's disease. The disease of Parkinson's usually develops later in life, when people are between 40 and 60 years of age. Parkinson's disease can present with many different types of symptoms can occur. For example, there may be depression, dementia, twitching limbs, difficulty starting and executing movements and stiff muscles. Often, ultimate and admission to a nursing home is necessary and people with Parkinson's disease die prematurely. Mild diseases Most people consider a disease to be a mild genetic disease if it is accompanied by mild physical disability or intellectual disability or is treatable. Examples of mild diseases are: - Deafness: certain forms of deafness are caused by an autosomal inherited disease. - Miyoshi muscular dystrophy: an abnormality in certain specific genes causes symptoms of the muscles to develop. This usually begins in young adulthood age with weakness of the calf muscles, which can cause problems with climbing stairs, running and jumping. Over the years, the disease can spread to the rest of the legs and upper arms. In some cases, it eventually requires a wheelchair. After this respondents were asked whether they knew anybody with a congenital genetic disorder. If they answered in the affirmative to that question, they were asked whether it involved themselves or a family member.

Introduction choice tasks	*Respondents were provided with information about every attribute and its levels. After the explanation, an example choice task was given that included the attributes that had just been explained.* - Provider & price - Information provision - Genetic conditions tested - Accuracy
Understand information	Did you understand the explanation correctly? Answer options: yes/no
Rationality question	We are curious about your preference: which of the three options would you choose? **Test 1** Price: €50 Euro Accuracy: 99 out of 100 tests are correct **Test 2** Price: €1000 Euro Accuracy: 95 out of 100 tests correct **No test**
Extra explanation rationality question	If people choose option 2, they were asked the following: you have chosen a test where you pay more, while the reliability of the test is lower. Would you actually be willing to pay more for a less reliable test? Answer options: yes/no
Fixed characteristics	The fixed characteristics of the preconception ECS test were also summarised in the questionnaire before the start of the choice tasks. These are the following: - The ECS test is conducted prior to the pregnancy - A blood sample is taken to be able to conduct the test - Couples can decide for themselves what to do with their carriership information - A positive test is always followed up by an appointment with the clinical geneticist
Choice tasks 1-7	*Respondents were asked to choose between the three choice options*
Evaluation question 1	*Respondents were asked to answer the following question:* You are half way through the choice tasks, what do you think of the questionnaire so far? Respondents could choose different options (Informative, Interesting, Enjoyable, Long, None of the possible answers)
Choice tasks 8-13	*Respondents were asked to choose between the three choice options*
Extra choice task	*Respondents were asked to fill in one more choice task, this time containing less attributes and different levels than earlier.* This is the final choice task. The options are slightly different than the options in the previous selection tasks. In this choice task, you only need to pay attention to the price and the accuracy of the test (the other characteristics are the same for both tests). In this choice task, option 1 was a test with a 50% accuracy and 100 euro costs, option 2 a test with 99% accuracy and 1000 costs and option 3 the opt-out.
Ranking question	*Respondents were asked to rank the attributes from most to least important in their choice for a specific test.*

Extra question if people choose > 3 times opt-out	*Respondents that choose the opt-out >3 times during the choice tasks, were asked the following extra question:* You chose "No test" in more than three choice tasks. What was your reason for this? - Price too high in both options - Reliability too low in both options - Different, being:
Likert scale evaluation	*Respondents were asked to rate the following statements on a scale of 1-5:* - I could easily choose between the different options - I have taken into account all the characteristics of the carrier test in my decisions - By filling in this questionnaire I gained a better understanding of my preferences for the characteristics of the carrier test - I would participate again participate in a similar study - All important characteristics of the carrier test are included in this research
All characteristics – Which not?	*Respondents were asked whether they think other attributes should have been included as well:* Are there any particular characteristics of a carrier test that, in your opinion, should be included in this study (and are not currently been included)? If yes: which?
Clear explanation? What not?	*Respondents were asked whether they thought the instructions were clear and how this could be improved if they were not.*
Open evaluation	*Respondents were asked if they had any remarks about the questionnaire*

Appendix B: Respondent characteristics

Table 10
Data were collected from participants on the following characteristics. The categories made for each characteristic are listed in the table.

Characteristic	Categories
Age	Two groups: • < 25 years old • >25 years old
Sex	Three groups: • Man • Woman • Different
Educational level	Two groups: • Lower educated: primary school, VMBO, havo, VWO, MBO • Higher educated: WO & HBO
Income	Two groups: • Below modal income: income 0-3000 per month • Above modal income: income 3001-more than 10.000 per month
Religion	Two groups: • Religious • Non-religious
In a relationship	Two groups: • I a relationship • Not in a relationship
Migration background(98)	Three groups: • No migration background: respondent and parents born in the Netherlands. • First generation migration background: respondent was born outside of the Netherlands. • Second generation migration background: parent(s) of the respondent born outside of the Netherlands.
Being a parent	Two groups: • Respondent does not have children • Respondent has 1 or more children
Prenatal diagnostics	Two groups: Used prenatal diagnostics during previous pregnancies / would consider using prenatal diagnostics during a possible pregnancy in the future: • Yes • No
Child wish within 1 year	Two groups: • Respondent wishes to have a child within 1 year • Respondent wishes to have a child within 2-10 years
Knowing ECS	Respondent has heard of carrier testing for couples with a desire to have children prior to the questionnaire: • Yes • No

Knowing someone with genetic condition	Imagine being offered a free, completely reliable carrier test, where you have the choice of which hereditary diseases to test for, would you consider it? Two groups: • Respondents that answer YES or MAYBE to this question • Respondents that answer NO to this question

Appendix C: Additional information respondent section

Table 11
Characteristics of the Dutch population between 18-40 years old and the Dutch general population.

	Dutch population 18-40 years[1]	**Dutch general population 15-75**
Gender		
Male	51%	
Female	49%	
Age (years) (SD/Median)	29	
Province		
Gelderland	11%	
Noord-Brabant	14%	
Noord-Holland	18%	
Zuid-Holland	22%	
Other	35%	
Ethnicity[2]		
Dutch	68%	
First generation migration background	18%	
Second generation migration background	14%	
Education level[X]		
Low-educated		27%
Medium level of education		38%
Highly educated		35%

[1] Data was provided by the CBS (103,104), percentages were calculated using Stata/MP 16. (92) Percentages were calculated based on the data from the following tables.
[2] No migration background: respondent and parents born in the Netherlands. First generation migration background: respondent was born outside of the Netherlands. Second generation migration background: parent(s) of the respondent born outside of the Netherlands.(98)
[X]Low-educated: VMBO, basisschool, MBO completed partly, HBO/WO completed first years
Medium level of education: MBO, upper school havo/vwo
Highly educated: HBO/WO
Data provided by Ministerie van Onderwijs, Cultuur en Wetenschap (105).

Table 12
Modal income and average income per age group and level of education.(106,107)

Modal income	€ 3.042 per month
Income per age group	
20-24 years	€ 1300 per month
25-29	€ 2333 per month
30-34	€ 2.550 per month
35-39	€ 3225 per month
Income per education level	
Low-educated	€ 2158
Medium level of education	€3092
Highly educated	€5100

Table 13
Association educational level and income. Pearson chi-square test was performed: p value 0.000

	Not highly educated	**Highly educated**	Total	
Income < modal income	181	222	403	
	45%	55%		*Row percentage*
	84%	69%		*Column percentage*
Income > modal income	35	99	134	
	26%	74%		*Row percentage*
	16%	31%		*Column percentage*
Total	216	321	537	

Appendix D: Multivariate mixed logit model

Table 14:
Multivariate mixed logit model with price linear variable. The coefficients should be interpreted as follows: e.g.: coefficient medical specialist = 0.55 for the group of respondents that do not wish to have a child in less than a year. The coefficient for people that do want to have a child in less than one year = 0.55-0.49 = 0.06. They thus have a less strong preference for the medical specialist as a provider compared to a commercial company.

Attribute	**Levels**	**β**	**S.E.**	**Sig**	**SD**	**S.E.**	**Sig**
Accuracy	- 91 in 100 tests correct result - 95 in 100 tests correct result - 99 in 100 tests correct result	- 0.29 1.14	- 0.10 0.15	 0.006 <0.001	- n/a 1.24	- n/a 0.14	- n/a <0.001
Price (per couple)	1 euro	-0.002	0.0002	<0.001	n/a	n/a	n/a
Type of genes tested on	- Package 1 - Package 2 - Package 3	- 0.21 0.20	- 0.07 0.10	- 0.002 0.043	- 0.69 1.51	- 0.09 0.10	 <0.001 <0.001
Type of information provision	- Counselling - Brochure - Website	- -0.60 -0.67	- 0.12 0.10	- <0.001 <0.001	- n/a n/a	- n/a n/a	- n/a n/a
Provider	- Commercial company - Midwife - Medical specialist - General practitioner	- 0.63 0.55 0.64	- 0.09 0.09 0.10	- <0.001 <0.001 <0.001	- n/a n/a n/a	- n/a n/a n/a	- n/a n/a n/a
Opt-out		-0.31	0.33	0.349	2.72	0.16	<0.001
Respondent characteristic							
Child wish < 1 year	Child1yearXspecialist	-0.49	0.14	0.001	n/a	n/a	n/a
High education	High_educationXaccuracy95	0.51	0.13	<0.001	n/a	n/a	n/a
	High_educationXaccuracy99	0.65	0.20	0.001	1.08	0.24	<0.001
	High_educationXprice	-0.002	0.00	<0.001	0.003	0.0002	<0.001
	High_educationXbrochure	0.44	0.12	<0.001	n/a	n/a	n/a
	High_educationXwebsite	0.47	0.13	<0.001	n/a	n/a	n/a
Knowing ECS	Knowing_ECSXopt_out	-0.86	0.31	0.005	n/a	n/a	n/a
	Knowing_ECSXprice	0.001	0.00	<0.001	n/a	n/a	n/a
In a relationship	Partner_yesXopt_out	-1.41	0.35	<0.001	n/a	n/a	n/a
Being a parent	Number_of_childrenXmidwife	-0.16	0.06	0.005	n/a	n/a	n/a
	Number_of_children Xopt_out	0.67	0.16	<0.001	1.88	0.22	<0.001

SD n/a: variable was included as a fixed variable in the final mixed logit model, as the SD was insignificant in the mixed logit model with all variables included as random

Log likelihood: -4675.4085

Appendix E: Extra choice task associations with respondent characteristics

Table 15
Outcome Pearson's chi-square test association between respondent characteristics and choice in the extra choice task.

Respondent characteristic	**p-value***
Sex	0.580
Age	<0.001
Educational level	0.116
Income	0.317
Religion	0.914
In a relationship	0.460
Migration background	0.617
Being a parent	0.006
Prenatal diagnostics	0.645
Child wish within 1 year	0.283
Knowing ECS	<0.001
Knowing someone with genetic condition	0.017

* Pearson's chi-squared test

Table 16
Preference for the extra choice task in different age groups

	Choice extra choice task			Total
Respondent characteristic	**Option 1**	**Option 2**	**Option 3**	
Age > 25 years	173	31	161	355
	49%	8%	43%	
Age < 25 years	88	4	34	126
	70%	3%	27%	
Total				481

Table 17
Preference for the extra choice task of respondents who heard from ECS before the questionnaire and did not hear from ECS before the questionnaire.

	Choice extra choice task			Total
Respondent characteristic	**Option 1**	**Option 2**	**Option 3**	
Have not heard from ECS	109	16	112	237
	46%	7%	47%	
Have heard from ECS	152	19	73	244
	62%	8%	30%	
Total				481

Table 18
Preference for the extra choice task of respondents who know anyone with a genetic condition and do not know anyone with a medical condition.

	Choice extra choice task			Total
Respondent characteristic	**Option 1**	**Option 2**	**Option 3**	
Does not know anyone with genetic condition	131	20	118	269
	49%	7%	44%	
Does know someone with genetic condition	130	15	67	212
	61%	7%	32%	
Total				481

Table 19
Preference for the extra choice task of respondents who already have children and who do not have children yet.

	Choice extra choice task			Total
Respondent characteristic	**Option 1**	**Option 2**	**Option 3**	
Not having children already	185	18	108	311
	59%	6%	35%	
Having children already	76	17	77	170
	45%	10%	45%	
Total				481

Appendix F: Sensitivity analysis results

Table 20
Conditional logit results based on all long completes (complete DCE responses) (n=548)

Attribute	Level	Coefficient
Accuracy	91 in 100 tests correct result	0
	95 in 100 tests correct result	0.27***
	99 in 100 tests correct result	0.74***
Price (per couple)	€200	0
	€500	-0.38***
	€1000	-0.80***
Type of genes tested	Package 1:	0
	Package 2:	0.13**
	Package 3:	0.19***
Type of information provision	Counselling	0
	Brochure	-0.13**
	Website	-0.12**
Provider	Commercial company	0
	Midwife	0.21***
	Medical specialist	0.20**
	General practitioner	0.29***
Opt-out		-0.12

*p<0.05 **p<0.01 ***p<0.001

Table 21
Conditional logit results based on "sensitivity analysis group" responses (n=67). Respondents were selected into the sensitivity analysis if they failed the rationality test, displayed nonattendance and/or spent less than 4 minutes on completing the whole survey.

Attribute	Level	Coefficient
Accuracy	91 in 100 tests correct result	0
	95 in 100 tests correct result	-0.02
	99 in 100 tests correct result	0.03
Price (per couple)	€200	0
	€500	-0.05
	€1000	-0.04
Type of genes tested	Package 1	0
	Package 2	0.05
	Package 3	-0.04
Type of information provision	Counselling	0
	Brochure	-0.03
	Website	-0.09
Provider	Commercial company	0
	Midwife	0.06
	Medical specialist	0.22
	General practitioner	0.29
Opt-out		-1.38***

*p<0.05 **p<0.01 ***p<0.001

Appendix G: Validity and reliability table

Table 22
Validity and reliability in this thesis. Based on article by Janssen et al. (101)

Category	Explanation	Incorporation in thesis
Face validity	Are results consistent with expectations before the experiment?	Draw up the hypothesis based on previous research, compare this with results.
Convergent validity	Are results consistent with other results, obtained through a different test?	Compare results obtained from DCE with results obtained from ranking assignment.
External validity	Can the findings in the study be generalized to other situations?	Not possible, no revealed preference studies conducted.
Test-retest reliability	Are the results the same when the test is performed twice by the same participant?	Same choice task twice in DCE
Version consistency reliability	Do different versions of the same DCE result in similar preference estimates?	This can be tested by adding fixed-choice-tasks make small survey changes across the different surveys. This however also has disadvantages and will therefore not be incorporated in this thesis.