Genetic Counsellors' Preferences for Preimplantation Genetic Diagnosis: A Discrete Choice Experiment

by

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Abstract

Preimplantation genetic diagnosis (PGD) is a way of testing for a genetically affected embryo. Provincial PGD coverage differences along with ambiguity around scope of testing and patient inclusion criteria create a lack of clarity for public coverage options. A discrete choice experiment was undertaken with Canadian genetic counsellors (GC) to quantify their stated preferences for public PGD coverage, considering the following attributes: PGD indication, risk of the condition, fertility status, family history and number of cycles covered. The completed response rate was 41% with 126 GC completing the survey. Multinomial logit regression was used to estimate part-worth utilities. Key demographic and practice characteristics were considered as preference influences. Risk of the condition was the most important attribute. Overall, GC preferred scope of testing criteria over patient inclusion criteria. This is the first study to quantify GC preferences for PGD coverage and provides insight to help promote discussion about PGD policy.

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List of Abbreviations

ART	Assisted Reproductive Technology
BWS	Best-worst scaling
BORN	Better Outcomes Registry and Network
CAGC	Canadian Association of Genetic Counsellors
CARTR	Canadian Assisted Reproductive Technologies Register
CVS	Chorionic Villus Sampling
DCE	Discrete Choice Experiment
ESHRE	European Society of Human Reproduction and Embryology
GC	Genetic Counsellors
HLA	Human Leukocyte Antigen
IVF	*In-vitro* Fertilization
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
PD	Prenatal Diagnosis
PGD	Preimplantation Genetic Diagnosis
PGS	Preimplantation Genetic Screening
SET	Single Embryo Transfer

1 Introduction

1.1 Chapter Overview

Preimplantation genetic diagnosis (PGD) allows couples at a high risk of having children with a genetic disorder to test for the condition prior to implantation. Only unaffected embryos are implanted in order to avoid having an affected child. While the procedure is effective, it is also highly expensive. Couples who may benefit from PGD must use in-vitro fertilization (IVF), which can cost over $15,000 per cycle in addition to the estimated $3,500 to $8,000 for PGD alone [1]. Public coverage of PGD or IVF is limited internationally and also in Canada. Quebec publicly subsidized both PGD and IVF until 2015 and then Ontario has recently moved to subsidize IVF [2-5]. Outside of these contexts, couples typically pay out-of-pocket for these services, creating significant socioeconomic disparities in access. Differences in coverage across jurisdictions in Canada are further complicated by two broad policy issues: ambiguity in the scope of testing that can be offered and in the inclusion criteria for public coverage. These key policy issues create a lack of clarity in the policy options for public coverage of PGD.

Evidence on the preferences of relevant stakeholders can be a useful strategy to inform policy development in complex or contested areas. Among preference elicitation techniques, stated preference studies using a method called discrete choice experiments (DCE) have been used in the social determination of health care resource prioritization [6-7] and in the formulation of criteria for appropriate reproductive genetic tests [8-9]. DCE is now a robust method to ascertain stated preferences in the health care context [10-14].

A DCE with relevant PGD stakeholders allows for preferences to be elicited regarding the conditions for public coverage of PGD. Genetic counsellors (GC) are typically the health care professionals introducing PGD to couples, and thus are relevant PGD stakeholders. As GC are clinical experts, eliciting the preferences of GC for PGD coverage conditions would provide some insight into the conditions under which PGD might be covered or publicly subsidized.

This chapter starts by explaining the current differences in coverage across Canada and identifying the points of ambiguity related to the key policy options. The importance of preferences in policy making will be highlighted. An explanation of the discrete choice method will be provided. The rationale for using genetic counsellors (GC) as respondents will be provided. Research questions and hypotheses will follow after the overall research objective of measuring GC preferences to inform the conditions under which PGD might be publicly covered.

1.2 Policy Issues Related to Public Coverage of Preimplantation Genetic Diagnosis

The policy context for public coverage of preimplantation genetic diagnosis can be broadly categorized as differences in public coverage and ambiguity in policy options related to scope of testing and patient inclusion criteria.

1.2.1 Differences in the State of Public Coverage for Preimplantation Genetic Diagnosis

There are differences both nationally and internationally in regards to public funding for PGD. The differences are complicated by the fact that PGD is bundled with IVF. Arguments for and against public coverage of IVF include consideration of cost, definition of illness and existing services. These arguments contribute to the differences in the state of coverage for PGD.

The state of coverage for PGD is constrained by IVF and cannot be separated from it. IVF is the technique that is needed to obtain genetic material from the embryo to test in PGD. Since PGD is bundled with IVF, examining national and international coverage of IVF and its related implications is relevant to policy. A few provinces in Canada have chosen to provide some public subsidy such as tax credits for IVF, but public coverage defined as payment of the services by the government is generally limited. Currently, New Brunswick provides a rebate for 50% up to $5,000 annually for privately secured IVF services [15-16]. Ontario recently extended IVF coverage for one cycle for all causes of infertility [5]. Manitoba provides tax credits [17] that subsidize consumers of private IVF services. In comparison, PGD had not been covered by any province except Quebec [18] which had covered PGD between 2010 to 2015. A comparison of PGD and IVF coverage in Canada appears in Table 1. No information could be found from websites or literature about coverage for the three territories [19].

Table 1: Comparison of In-vitro fertilization and Preimplantation Genetic Diagnosis Coverage across Canada

Province	IVF Coverage	PGD Coverage	References
Newfoundland and Labrador	None – does not offer service in province	None	[20]
Prince Edward Island	None –does not offer services in province	None	[20]
Nova Scotia	IVF not covered based on a Supreme Court decision	None	[21]
New Brunswick	50% rebate up to $5,000 per year for those who need IVF	None	[15-16]
Quebec	Before 2010 – Refundable tax credit equal to 50% of eligible expenses to a maximum of $10,000/yr Between Aug 2010 – Nov 2015 – Coverage for single embryo transfer; Absence of criteria limiting access to the program meant that women regardless of age, marital status, fertility status and sexual orientation could be covered; no limit on the number of children – after each birth, the couple was eligible for another 3 cycles of IVF After Nov 2015 – tax credit of 20%-80% for IVF depending on income; only for childless couples	PGD irrespective of fertility status only on embryos to identify "serious monogenic diseases and chromosomal abnormalities" (Section 18) up to Nov 2015; Unclear if covered after change in IVF	[2, 22]; [23]; [4, 24-25]
Ontario	Before 1994; paid for all IVF After 1994: 3 cycles of IVF for complete tubal occlusion In 2015, the Liberal Government promised 1 IVF cycle for all causes of infertility per patient per lifetime; started December 21 2015 up to 5000 patients per year	None	[16] [3] [5, 26-27]
Manitoba	Fertility Treatment Tax credit 40% refund up to $8000 for IVF per year without a limit on the number of treatments in one's lifetime	None	[16] [17]
Saskatchewan	None	None	[28]

Alberta	None	None	[29] [30]
British Columbia	None	None	[31-32]

IVF: In-vitro fertilization; PGD: Preimplantation Genetic Diagnosis; CBC: Canadian Broadcasting Corporation

The state of public subsidy globally is also highly varied, ranging from full public coverage of PGD, such as in the United Kingdom [33], to no public coverage, such as in the United States [34]. Similar to some provinces in Canada, some countries preferentially subsidize IVF and not PGD including Australia [35], Germany [36-37] and Italy [38]. There are also some countries which do not cover IVF or PGD [34].

The global differences in public coverage for IVF may be due to similar reasons found by Redmayne and Klein who studied why there were different coverage decisions across six United Kingdom purchasing authorities [39]. These reasons included consideration of cost, definition of illness and existing services.

The high cost of IVF is one reason against public coverage [39]. Since the major expense of PGD is due to IVF [1] and PGD is a bundled technology with IVF, this is one reason why PGD may not be covered. Yet, the policy option of not publicly covering IVF can be expensive as well. Knoppers et al. argue that when there was a lack of public coverage and patients had to pay out-of-pocket, patients tried to maximize their pregnancy success rate by implanting multiple embryos simultaneously [40]. Implanting multiple embryos places the couple at risk of having twins or triplets, which would then increase downstream health care costs for the government in the form of special care nurseries and complications related to multiple births [41]. Quebec had been the only province that publicly covered both IVF and PGD. This allowed the province to use public coverage as an important policy lever to control the practice of single embryo transfer (SET). By limiting publicly subsidized IVF to SET, the multiple birth rate and the downstream health care costs had decreased in Quebec [23]. The ability to set policy levers to control practice and decrease downstream health care costs [42] could be a reason to support public coverage of IVF. The same argument of using public subsidy as a policy lever to control practice could apply for PGD. Thus, consideration of cost affects the coverage decisions across jurisdictions.

In addition to cost, how illness is defined is also relevant to the provision of public coverage for IVF. Differences in illness definition result in differences in coverage policy across jurisdictions. Redmayne and Klein found that one reason against covering IVF was that couples who underwent IVF were not seen as "really ill" [39]. Supporters of coverage argue that IVF is part of the treatment for infertility [43], which is defined by the World Health Organization as a "disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular sexual intercourse" [44]. In previous Canadian studies, infertility was defined as not becoming pregnant within 12 months despite not using birth control [45-46]. For couples who are infertile and are at risk of a genetic disease, public coverage of PGD would treat both "illnesses". However, for couples who are fertile and at risk of transmission of a genetic disease to their offspring, the person affected with the illness would be the offspring rather than the couple. How a country defines illness contributes to the differences in public coverage for IVF and PGD.

A third reason that affects the decision about public coverage is the presence of existing services. Fertile couples who are at risk for a genetic disease in their offspring can use prenatal diagnosis (PD) to avoid transmission of a genetic disease. PD serves an analogous function to PGD as both techniques allow women to test for an affected embryo. The laboratory test for a chromosomal rearrangement or genetic mutation is the same in PGD and PD. The main difference is that PD occurs during pregnancy rather than before implantation. If a fetus is found to be affected via PD, the couple would be faced with a choice of either continuing the pregnancy with an affected child, or pregnancy termination [47]. Unlike PGD, PD is covered across Canada [48] and many countries around the world [34]. PGD provides an alternative to PD for fertile couples who choose not to undergo pregnancy termination due to either personal or religious reasons [49] while also aiding infertile couples who are at risk of having a child with a genetic condition. Proponents argue that if one technology is covered, a similar rationale could be used to cover an analogous technology. Opponents argue that coverage of PGD is different due to the necessary bundling with IVF. The fact that PGD fulfills a similar function as PD and benefits infertile couples, but is not being covered in most jurisdictions, further highlights the difference in public coverage of reproductive technologies.

There are differences both nationally and internationally in public coverage of IVF and PGD, which may be due to considerations of cost, definition of illness and existing services available. Differences in coverage of IVF affect PGD because PGD relies on the use of IVF. The differences in PGD coverage therefore reflect a complex policy context in which to situate the current study.

1.2.2 Ambiguity in Criteria for Public Coverage

Alongside differences across Canada and internationally with respect to public coverage of IVF or PGD, ambiguity regarding the criteria under which public coverage could be provided compounds the policy uncertainty. Ambiguity regarding criteria exists for: 1) the scope of testing and 2) patient inclusion criteria.

First, ambiguity exists in the scope of appropriate PGD testing, specifically related to the types of conditions to be tested for and related concerns about the degree of risk that would warrant testing. Specifically, there is no clear consensus about whether to limit use of public coverage to rare or severe conditions at very high risk of being passed on to the prospective child, or to extend coverage to milder conditions with reduced risk of occurrence. These criteria are important as they have a significant influence on the volume of cases that could be publicly subsidized.

Currently, PGD is clinically indicated for a diverse array of conditions, including single gene disorders, cancer predisposition syndromes, chromosomal abnormalities, repeated pregnancy loss, sex determination for X-linked disease and Human Leukocyte Antigen matching [50-53]. PGD for non-medical sex selection or to select for a disability are also possible, but tend to be ethically contentious [54-55]. However, what is currently possible from a scientific and ethical point of view may not necessarily represent the scope for public subsidy. Certain jurisdictions such as Quebec, Japan and Singapore use phrases such as “severe”, and “serious” in reference to PGD coverage indications, where their definitions are typically left to the discretion of clinicians to interpret [56-59]. In contrast, the United Kingdom is specific about the conditions under which PGD would be accepted for public coverage by providing a list of indications [60-61]. In general, the main policy debate is whether less severe conditions such as adult-onset conditions, predisposition conditions and non-medical sex selection or more ethically contentious indications including Human Leukocyte Antigen (HLA)-matching for a savior sibling, could be publicly subsidized [62-65].

Ambiguity around the scope of coverage is further complicated by the degree of risk for the couple to have an affected child. Each PGD indication is associated with a specific risk of the genetic condition depending on its inheritance pattern. Couples could be at a high risk of having an affected child if the inheritance pattern is autosomal dominant, X-linked or autosomal recessive. Autosomal dominant disorders have a 50% chance of recurrence in future pregnancies if a parent is affected with the condition. X-linked disorders result in an affected male in 50% of sons and an unaffected but carrier female in 50% of the daughters. Autosomal recessive disorders have a 25% chance of recurrence in future pregnancies if each partner is a carrier of the condition. However, couples could be at a lower risk of having an affected child if parents are not found to be affected or to be a carrier of the genetic condition. These couples who are neither affected or carriers have a residue risk for germline mosaicism [66]. *Germline mosaicism* refers to having up to 1% risk of the mutation being passed on to the child because the mutation is carried either in the egg or sperm cell rather than in the blood of either parent. The threshold level of risk to set for a genetic condition to be publicly covered is variable across jurisdictions. Some jurisdictions such as the United Kingdom specify that coverage should be restricted to greater than 10% risk of recurrence [67], while others such as Quebec had not placed restrictions on coverage based on recurrence risk [2]. As with disease severity, policy debate regarding recurrence risk is relevant to the possible expansion of public coverage to include lower risk conditions that may be milder, later onset or more ethically contentious. In turn, the broader the scope is, the greater the volume of cases for public subsidy.

In addition to questions about the scope of testing, policy debate about coverage criteria relate to types of patient populations to be covered, based on fertility status, family history or maternal age. Some of this variation may be based on social norms such as sexual orientation and marital status or what is deemed to be ethically acceptable while others may be based on clinical limitations such as maternal age.

Policy tension exists regarding whether to offer PGD only for those who are infertile versus extending PGD to those who are fertile. Ontario has chosen to offer one cycle of IVF coverage to those who are infertile while declining coverage for fertile couples who would need IVF to undergo PGD [5]. Quebec had covered both infertile couples and fertile couples who were undergoing PGD [18].

The question of family history relates to whether PGD coverage is only for couples who have no children or extending to those who do. In the United Kingdom, couples with unaffected children were excluded from coverage, though coverage was extended to couples where one member had unaffected children from a previous union (L. Mercer, personal communication, August 2014 [68]). In contrast, coverage was not restricted based on family history in Quebec [2] and Ontario announced coverage of one cycle of IVF regardless of sexual orientation, family history, or gender [5]. An Australian study looked at the reproductive and genetic history of 50 women seeking PGD and found that approximately 60% had no children, 30% had unaffected living children, 18% had affected living children and 8% had affected children who died [69]. However, there are no studies examining whether PGD would be recommended for coverage by providers based on the existing family history.

In addition to fertility status and family history of the couple, the issue of maternal age is a much debated inclusion criteria for public coverage. Late maternal age is known to negatively affect the success rate of IVF [70], and to increase the risk of chromosomal abnormalities, which is relevant for PGD [71]. While Ontario has restricted IVF coverage to women under the age of 43 years [5], there was an active policy debate in Quebec regarding the importance of maternal age as a criterion for coverage restriction [72-73]. There had been no restriction of maternal age in Quebec, but legislation proposed in 2014 had attempted to restrict maternal age to 18-42 years, as part of broader efforts to manage the IVF program [72, 74]. Critics were concerned about exceptional cases such as the 16-year-old who might want to preserve her eggs prior to chemotherapy for a blood-related cancer or the 43-year-old who had her eggs frozen at 26 years of age but would not be able to use her eggs through IVF due to her advanced maternal age [72]. When Bill 20 was passed, it allowed for women over the age of 43 to have access to IVF provided it was self-pay [24].

In summary, there are differences in public coverage across jurisdictions, including within Canada, as evidenced by the current changes in public subsidy across the provinces. There is also continued policy ambiguity about criteria for coverage. Ambiguity around the scope of testing and the inclusion of specific patient populations warrants additional study to provide insight into these key policy issues. Data on stakeholder preferences can be important and useful in these contexts.

1.3 Importance of Preferences in Policy Making

Preference refers to a value or utility for a particular good and involves understanding the factors underpinning a choice between alternatives [75]. Using an econometric approach, specific relative weights can be assigned to the factors or attributes of a good based on preference data [76]. A *revealed preference* refers to preferences that are reflected by what is actually chosen based on alternatives that exist in the real world. In contrast, a *stated preference* is a choice made between alternatives that vary in their attributes, but which may not currently exist or where the alternatives may be hypothetical [75]. Researchers can study stated preferences in healthcare by creating hypothetical alternatives. Researchers have addressed the types of clinical and policy questions relevant to this study using stated preference studies, which includes understanding important aspects of health care resources [77-78], determining health care resource prioritization [6-7] and formulating criteria for appropriate reproductive genetic tests [8-9]. Obtaining preferences for PGD to gain insight into conditions under which public coverage could be provided could be useful to inform policy making.

1.3.1 Lack of Health Care Providers' Preferences for Preimplantation Genetic Diagnosis

A variety of studies describes the attitudes and current practices of a variety of PGD providers, and demonstrates that clinical practice varies based on the IVF provider [51, 53]. For example, in a survey of European PGD providers, Geraedts and colleagues (2001) showed that PGD for chromosomal translocations was available in all but one of the 20 centres that responded, compared to monogenic conditions where some conditions were not offered in any centre, while other conditions such as cystic fibrosis was offered in 13 different centres [53]. Speechley and Nisker surveyed Canadian IVF centres in 2010 and showed that chromosomal translocation testing was offered in 4 out of 17 centres that responded while recessive monogenic conditions were offered in 4 out of 17 centres as well. Part of the difficulty was that the embryo biopsy needed for PGD was performed on site only in 6 of the centres while the remainder were sent to another Canadian centre or to the United States [51]. These studies show that while there may be some consistency such as providing PGD for chromosomal translocations in Europe, the clinical practice depends on the individual centres. Furthermore, limitations in regards to some aspect of the technology such as not providing embryo biopsies on site may restrict the testing options within a centre. The lack of consistent clinical practices warrants a study of PGD based on health care provider preferences.

1.3.2 Introduction to Discrete Choice Experiments

This study requires a method that is able to elicit stated preferences based on alternatives representing varying clinical PGD situations, in order to address the policy issues highlighted in Section 1.2. A discrete choice experiment (DCE) is a method that allows for quantitative assessment of trade-offs to assess the relative importance of individual attributes. The following is an explanation about DCE.

A DCE instrument is created by first determining the good of interest and then describing the good based on a set of characteristics known as attributes. For instance in marketing chocolate, the type of chocolate used and whether extra ingredients are added would be two examples of attributes [79]. Main-effects attributes are the attributes that are selected for study after a qualitative phase through literature review, focus groups and pre-testing. The attributes are then categorized into several levels, which could be continuous, such as the cost of the item, or categorical, such as the type of chocolate described as dark, milk and white. A scenario is a description of the good with one level from each attribute presented such as a white chocolate (rather than dark or milk) with peanuts added (rather than no added ingredients). Through experimental survey design, a set of choices that vary based on the attribute levels are created and the respondent is asked to choose between the goods described within each choice set; this is also known as a choice task. A collection of choice tasks in a choice survey allows for the quantification of preferences according to pre-defined attributes and allows for trading-off between levels of the attributes [80-81]. The instrument is usually followed by a demographic and attitude questionnaire that can be used to identify potential subgroups that may make choices differently. This difference may help to explain some of the random components that influence the utility of the good; this is known as a non-main effects interaction. An interaction is when there is a difference in what is observed between combining two or more variables rather than keeping the variables as separate terms. [75]. Interaction models combining main-effects levels and demographic, practice or attitude variables can be created to account for variables within the model that may influence the outcome, which is choice in the case of DCE. The quantitative phase of the DCE would involve administering the survey to multiple respondents and then performing regression analysis to infer the relative importance of each attribute.

A DCE was chosen as the method of choice for this study primarily for two reasons. First, a DCE allows for stated preferences to be elicited based on the respondent's selections given alternative scenarios [82-84]. Trade-offs made between the individual attributes reflected in the choice alternatives allow for insight into stated preferences. Second, with limited resources where health care professionals find difficulty in offering a test which is not covered by a government health plan because of high costs to patients, a DCE can provide information that could help inform a hypothetical situation if a self-pay test were to be publicly covered [80].

DCE is the preferred method in this study as it allows for different sets of scenarios that vary based on the attributes to be compared, similar to what a clinician tends to see in practice, rather than looking at characteristics in isolation like in ranking or rating [81, 85]. Best-worst scaling (BWS) could also have been performed. In a BWS, respondents are asked to determine the most important and least important attribute based on a single profile [86-89]. While one advantage with BWS is that respondents are asked to look at one profile at a time and therefore coefficients could be compared across the attributes on a common scale, it was found in one study about prioritizing genetic testing that BWS was more burdensome and difficult to answer compared to DCE [89]. Whitty et al. also found that the majority of Australian adult respondents (72.6%) preferred DCE over BWS tasks when asked about preferences for funding new health technologies [90]. As well, there is more scientific literature and experience in health care using DCE compared to the newer technique of BWS. Therefore, DCE was chosen as the method of preference elicitation for the study over BWS.

DCE studies have been used from a social perspective, eliciting preferences on services, programs, and policy priority-setting [6, 82, 91-92].For example, Koopmanschap et al. used a

DCE among Dutch healthcare professionals and found that severity of disease, costs per quality-adjusted life-year gained, individual health gain and budget impact were the most important decision criteria for healthcare priority setting by decision-makers [92]. Therefore, DCEs are useful to study stated preferences for clinical or policy related questions. There are guidelines on how DCEs could be conducted based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published checklist for good practices [14], experimental design [13] and statistical analysis [93].

In a DCE, the alternative scenarios are structured based on varying levels of different attributes that describe the preferences of interest. The respondents are asked to make choices between the alternative scenarios and the choice allows for inference of the relative importance of the different attributes. Respondent choices are then modeled as a function of scenario attributes, using regression techniques where the relative importance of each attribute level is ordered based on its part-worth, represented by the regression coefficient associated with the attribute level [94]. The null hypothesis is that the parameter estimate associated with each attribute level is not statistically significantly different from the mean parameter estimate of zero when the attributes are effects coded. If cost is included as an attribute, willingness-to-pay for an attribute can be estimated [83].

The discrete choice method is based on *random utility theory*, which states that a good's utility can be described in terms of its indirect utility related to its attributes as well as an unobservable factor that can also alter its utility. There is a deterministic component and a random component that is used to evaluate the utility of the good [95]. A *good* is a service or product being offered that may have different characteristics. For example, if a maker of chocolate was to determine which chocolate product would be best to market, the preference of chocolate by customers would depend on the deterministic components and also a random component, which may vary based on demographics and behaviour of the individual [79]. There are unobservable factors that make up the random component to explain errors in the dependent variable, where the dependent variable is the stated preference. The relationship is assumed to be a linear additive one with the utility of the good represented as follows:

$$U = V + \varepsilon = \Sigma_i^n \beta_i * A_i + \varepsilon \qquad \textbf{Equation 1}$$

In Equation 1, U represents the utility of the good, V stands for the cumulative utility function described in terms of a summation of the terms $i = (1,\dots n)$ of the coefficients β_i multiplied by the characteristics of the good A_i, and ε stands for random component composed of unobservable factors that influence the utility. By describing the utility of a good in this way, the various characteristics of the good can be quantified and ordered so that the strength of the stated preferences can be elicited [83].

The experimental design of the DCE requires decisions to be made regarding orthogonality, balance and efficiency [13]. An *orthogonal* design refers to one where there is independence of all attribute levels meaning that there is zero statistical correlation between the levels of different attributes [96]. A *balanced* design involves the appearance of the levels of each attribute the same number of times. Finally, *efficiency* seeks to create the smallest variance-covariance matrix [14], where *variance* (σ^2) is the amount of variability that a parameter estimate has around the mean [75] and *covariance* refers to the amount that two random variables vary together [75]. The variance-covariance matrix (Ω) is calculated by using the variance as well as the design matrix, which is a matrix of the attribute codes (X) where rows correspond to the alternatives and columns correspond to the coded attribute variables (Equation 2) [97].

$$\boldsymbol{\Omega = \sigma^2 (X'X)^{-1}} \qquad \textbf{Equation 2}$$

The variance-covariance matrix is then used to calculate the relative D-efficiency, which is one of the most commonly accepted measures for design efficiency for nonlinear statistical models [97]. The relative D-efficiency is calculated as:

$$\textbf{D-efficiency} = \boldsymbol{[|\Omega|^{1/K}]^{-1}} \qquad \textbf{Equation 3}$$

In Equation 3, K refers to the number of parameter estimates. For a D-efficient design, the variance-covariance matrix is minimized [98]. These fundamental considerations will be included in the study design to create a DCE study that helps to quantify preferences for PGD coverage.

1.4 Genetic Counsellors as Study Respondents

Understanding the stated preferences of informative stakeholders for PGD use via a DCE experiment is particularly valuable given the differences in clinical practice both nationally and globally. The stakeholders chosen were health care providers and in particular, genetic counsellors given their role in PGD. While PGD patients would have been a good potential population to target, access to these patients for research would be difficult and the patients do not have the medical background to assess genetic conditions other than their own. Therefore using PGD patients as the study population was deemed to be beyond the scope of the thesis and instead, health care providers were chosen. Currently, geneticists and genetic counsellors (GC) have considerable discretion with regard to how they counsel patients about preimplantation genetic diagnosis [51]. Genetic counsellors usually work in conjunction with a Medical Geneticist in multiple areas including prenatal screening, cancer predisposition syndromes, adult genetics, single gene disorders, and chromosomal abnormalities. The role of GC is to address the benefits and limitations of PGD with potential couples and their recommendations influence access to and utilization of PGD. GC provide risk assessments based on personal and family history, initiate genetic testing under medical directives and provide psychosocial support [99]. Medical Geneticists would have been an appropriate population to study because these are medical doctors who diagnose and counsel patients about genetic conditions and would therefore discuss PGD with patients. However, as a single group, the numbers may have been too small to reach conclusions that were statistically significant. For example, in 2006, there were approximately 80 Medical Geneticists in Canada [100]. Studying GC represents an advantage over studying geneticists, as GC are a relatively homogenous group of health care providers numbering approximately 300 across Canada compared with approximately 80 Canadian geneticists [100]. As GC are a larger homogenous group of health care providers for PGD, they were chosen as the study respondents.

Given that GC are a large group of health care providers who introduce PGD to patients, they provide a clinical perspective about relevant policy options related to ambiguity in scope of testing and inclusion criteria for public coverage of PGD. Preference data in the form of a well-established DCE method could explore the stated preferences of GC regarding the use of PGD.

The trade-offs made by GC between attribute levels using DCE results could provide insight regarding the important conditions under which public coverage could be provided for PGD.

1.5 Research Objective

The research objective was to provide insight regarding the conditions under which public coverage could be provided for PGD by determining and quantifying the stated preferences of the GC population through a structured discrete choice experiment survey. The perspective was of GC as hypothetical members of a policy advisory committee being asked for recommendations regarding PGD coverage across Canada.

1.6 Research Questions and Hypotheses

Insight from GC to address policy ambiguity regarding public coverage for PGD will be ascertained using a DCE to derive the stated preferences of GC. The two research questions are as follows:

1) What are the stated preferences of GC for important attributes of PGD use?

2) How do demographics, regional policy and experience factors associate with the stated preferences of GC regarding PGD use?

The first research question will be addressed through the assessment of main-effect attributes. Despite the differences and ambiguity surrounding policy options, an educated hypothesis based on a clinical point of view could be made about the first research question. As presented in Section 1.2.2, ambiguity about the scope of testing and the patient criteria for coverage exists and serves as the starting point for attribute consideration detailed in Chapter 2. For instance, there is little debate in the genetics community about acceptance of public coverage for an infertile couple presenting with a high risk for an offspring to have a severe, non-treatable, single-gene condition that is life-threatening and of early onset. In other cases, changes in certain characteristics may make decision-making more difficult. When the genetic condition has moderate severity, when coverage or cost may be a factor and when a couple is fertile, the decision to present PGD as an option may become less clear. Issues hypothesized to be important to GC were PGD indications, family history and their fertility status.

The second research question will be addressed by using interaction models. Another set of hypotheses relate to the interaction between the demographics, practice and attitude of GC on their preferences regarding PGD coverage. Although GC are taught to be non-directive [101], GC have their own perspective based on personal history, place of practice, knowledge and experience. Therefore, adding demographic and attitude questions could lead to exploration of associations with the preferences identified through the discrete choice experiment. Variables for exploration include type of practice, years of practice, whether the respondents have children, and household income. Genetic counsellors who have more experience were hypothesized to select higher risk of a genetic condition as they were trained in an earlier and more traditional environment where the recommendation for a procedure would have been based on stricter criteria and thus a preference for higher risk conditions. Less experienced GC have been trained more recently and there may have been liberalization of criteria for testing similar to the observation by Moore and Low about increased elective obstetric interventions in healthy women based on liberalization of indications over time [102-103].GC who have their own children were hypothesized to be more accepting of coverage for PGD regardless of fertility status or family history of the couple. The rationale was that these GC would sympathize more with a desire to parent a healthy child. GC with greater personal household income were hypothesized to recommend less coverage of cycles as financial costs of private PGD may not be weighted as highly by the GC due to their own financial security. Thus, the demographics of the providers and their experience with children were hypothesized to play a role in recommendations for coverage.

1.7 Organization of Thesis

In order to fulfill the research objective of this study, Chapter 1 has introduced key policy issues for coverage and the use of a DCE survey to elicit the stated preferences of GC. Chapter 2 describes the method chosen to fulfill the checklist for good practices in conjoint analysis through a qualitative and quantitative approach as described in Section 1.3.2. Chapter 3 details the results of the national main study of GC and Chapter 4 discusses the results, compares the findings to previous work, explores policy implications and limitations of the study, and suggests future directions for research.

2 Methods

In the current study, the methods were based on a modified version of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) checklist for good practices when using conjoint analysis applications in health [14] (Figure 1). The modifications were twofold: a qualitative phase of focus groups was added in order to validate the attributes and levels that were based on literature review, and pretesting was used to ensure clarity of the instructions and the scenarios used for the pilot and main studies. The study is divided into two phases. The first is the qualitative phase (Phase 1) (boxes 2-7 of Figure 1) involving identification of attributes and levels, conducting focus groups and performing pretesting. The second is the quantitative phase of pilot-testing and conducting the main study survey (Phase 2) (boxes 8-14 of Figure 1). These phases and steps will be used to describe the methods used to elicit preferences of GC regarding PGD public coverage in the following sections.

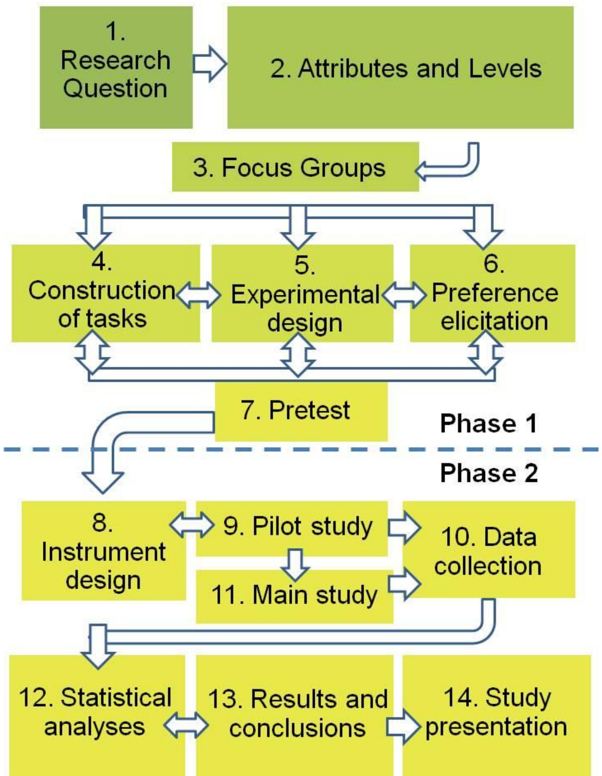


Figure 1: Overview of the methods used in the thesis

Approach modified from "Figure 1 – A checklist for conjoint analysis in health care" in *Value in Health* by International Society for Pharmacoeconomics and Outcomes Research 14(4) *Bridges et al.*, Conjoint Analysis Applications in Health – a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force, *403-413, (2011)* [14] *Reproduced with permission of BLACKWELL PUBLISHING in the format Thesis/Dissertation via Copyright Clearance Center (*Permission for use in Appendix 1*).*

2.1 Target Population

Canadian genetic counsellors were recruited as the target population. The inclusion criteria were broad and included all Canadian GC whether or not they were currently practicing in the field, receiving training in genetic counseling, conducting research, and living or working in Canada, because the goal was to provide a comprehensive sample of the Canadian GC population regardless of their current role. There is an estimated 300 Canadian GC [104]. Operationally, members of the Canadian Association of Genetic Counsellors (CAGC) were invited to participate as a way of sampling from the population of GC in Canada. GC were also included regardless of whether they obtained a Masters in Genetic Counselling or became a genetic counsellor through another route, because their clinical perspective was valued regardless of their educational background. A convenience sample was taken for the focus groups with the goal of 6-8 participants per group and pretesting with approximately 6-8 GC within the Toronto area. The pilot study had a goal of 20 participants. The main survey utilized GC who identified themselves as members of CAGC through the CAGC list-serve, through snowball recruitment and the annual education meeting. GC were excluded from the main study only if they had participated in the pilot study.

2.2 Identifying Attributes and Levels

Identifying attributes is an important task within the DCE development process because attributes that are missing from the study or do not address the main purpose of the study could create bias or misinform policy decisions [105]. In order to address the two research questions as proposed in Section 1.6, important aspects of PGD needed to be identified and validated through literature review, focus groups and pretesting to become attributes for use in the DCE. An iterative process was used to identify attributes and levels for the DCE. Attributes and levels identified through the literature review were expanded upon by the focus groups, were clarified by pretesting and then trialed in the pilot study. This mixed methods approach allowed for extant knowledge to be combined with additional topics of discussion from focus groups not present in the literature, as well as cognitive interviews to help with the wording of attributes, levels and the preamble [105]. As recommended by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, a ranking exercise was used at the end of each focus group once the focus group discussions generated an excess number of possible attributes that would be infeasible to test in the study [14].

2.2.1 A Literature Review of Studies

An initial list of potential attributes was generated through a literature review using published and grey literature. Relevant studies were identified in Embase, Medline, Google Scholar, public infertility/IVF sites and governmental sites with key terms “PGD”, “preferences”, “policy”, and “genetic counsellors”. The ISPOR guidelines were used to inform assessment of which studies were most likely to prove useful to developing the DCE. The guidelines were: “relevance to the research question, relevance to the decision context and whether the attributes are related to one another” [14]. Five relevant studies were found (see Table 2).

The study that was most relevant was by Kalfoglou et al. because service providers and patients were asked about their attitudes and experiences in the use and regulation of PGD. Thirty-two in-depth interviews were conducted including 13 patients and 19 PGD service providers [50]. Five of the 19 service providers were genetic counsellors. There was agreement that PGD was supported for "severe, life-threatening genetic illness" and for HLA-matching and disagreement regarding adult-onset genetic disease [50].

Table 2: Characteristics of Relevant Studies.

Reference	Study Population	Objective	Study Design	Relevant Attributes	Findings
[106]	33 BRCA1/2 mutation carrier patients	Determine attributes and preferences about how PGD information should be delivered in genetic counseling	Tutorial about PGD was presented followed by detailed interviews	Fertility status Characteristics of genetic condition	Differentiates between couples who are able to conceive naturally but needs IVF for PGD Adult-onset cancer syndromes with incomplete penetrance – no consensus between patients and providers
[107]	1500 infertility patients	Determine the preferences and demand for sex selection	Cross-Sectional survey with self-report questionnaires	Family history	Demand for sex selection increased in patients with no children and in those with children of all one sex (and there was a desire for a child of the opposite sex)
[50]	13 patients and 19 PGD	Explore "experiences	In-depth interviews	Characteristics of genetic	Consensus that "severe,

	service providers including 5 genetic counsellors	and attitudes" of the use and regulation of PGD		condition	life-threatening genetic illness" or HLA-matching for sibling was appropriate but debate about adult-onset genetic disease, sex selection and non-medical characteristics
[108]	Not applicable	Highlight clinical challenges related to use of prenatal technologies	Expert opinion; Conference abstract from invited speaker	Fertility Status Cost of PGD	Infertile couples or in-fertile couples who have increased risk of genetic condition PGD has higher costs compared to CVS or amniocentesis
[51]	17 Canadian IVF providing units with medical directors answering	Determine PGD practice patterns in Canada	Internet survey	Characteristics of genetic conditions/PGD indications Cost	Categories for PGD testing included translocations, gender testing for X-linked conditions, recessive monogenic conditions, adult-onset conditions and HLA-matching. Not every centre would offer all categories for testing The most

					ranked reason why patients do not pursue PGD

BRCA: Breast cancer gene 1 and 2; PGD: Preimplantation Genetic Diagnosis; IVF: In-vitro fertilization; HLA: Human Leukocyte Antigen;

Based on the literature review, Table 3 shows five possible attributes for the proposed DCE. All the attributes found in the literature were included in the next phase with the exception of cost. Cost per cycle was not chosen as an attribute as genetic counsellors are not the payers for PGD. For the first attribute “Characteristic of genetic condition”, the levels were grouped into severe life-limiting condition, adult-onset condition and HLA matching to encompass the various characteristics found in the literature. The second attribute “Fertility status of the couple” explores the distinction between an infertile couple who needed IVF for both PGD and infertility and a fertile couple who required IVF only because of PGD which is an active policy debate. The third attribute examines the importance of the existing family history, which is found within the literature. The fourth attribute asks about whether public coverage should be in place. This was done to avoid protest votes regarding coverage [83]. For example, if a respondent strongly believes that public coverage should not be permitted for PGD and the fourth attribute was not present, the individual may protest by ignoring the levels of all other attributes in favour of choosing zero cycles to be funded in the fifth attribute. The fifth attribute refers to the “Amount of coverage” based on number of cycles. This was a hypothetical attribute that was used in lieu of cost to determine the extent of public coverage. The levels used were a modification of the numbers of cycles that have been covered in other jurisdictions. “All cycles” describes all cycles needed until the patient becomes pregnant and it is a hypothetical level to represent unlimited public coverage.

Table 3: Potential Attributes and Levels for use in Discrete Choice Experiment Design Based on Literature Review

Attribute	Description	Levels
Characteristic of genetic condition	Characteristics such as age of onset and severity are varied based on coverage situations globally	a) severe life-limiting condition b) adult-onset condition c) HLA matching
Fertility status of couple	Whether infertility makes PGD more likely as an option	a) Infertile b) Fertile
Family history	Make-up of the family	a) Have children b) No children
Coverage		a) Public coverage of expenses b) No public coverage
Amount of coverage	Level of government or third party contribution	a) none b) 1 cycle c) 3 cycles d) all cycles

HLA: Human Leukocyte Antigen; PGD: Preimplantation Genetic Diagnosis;

2.2.2 Focus Groups

Focus groups were conducted to supplement the literature review regarding potential attributes and levels. Focus groups are one method to augment literature reviews to determine characteristics that are most important to the respondents [109]. There are three distinct advantages of using focus groups for this research: 1) observing group GC interactions in response to the PGD characteristic raised, 2) focusing on common themes across the GC profession rather than opinions of individual clinicians, and 3) triggering discussion of ideas that may otherwise have been missed in order to validate the criteria found in the literature [81].

The primary objective in the two focus groups was to describe attributes and possible levels that could be used to inform a DCE survey. However, the approach differed between the two groups. For the first focus group, the PGD characteristics were brainstormed without prompting from the literature review to ensure that all important characteristics of PGD were captured. In the second focus group, the participants were presented with the generated attributes and levels identified from the literature review as well as those from the first focus group to validate their appropriateness and to create a list of important characteristics of PGD. This format is similar to a “emergent-systematic focus group” design where the variables are explored in the “emergent” focus group and then verified in the “systematic” focus group [110]. The second objective in both focus groups was to optimize the response rate for the main study by exploring recruitment strategies. The third objective of focus group two was to ensure clarity and comprehensiveness of the instructions for the main survey by asking participants to review and comment on the draft version of the question booklet, which included the background, preamble and sample choice question. The background gives an introduction to the survey and the preamble describes the attributes, the levels and the clinical scenario in more detail. The sample choice question provides instructions on how to answer the choice questions.

Focus group participants were recruited via email to all Toronto-area GC and through a recruitment poster at The Hospital for Sick Children. Interested individuals were asked to email or call. They were then assigned to one of two focus groups based on participant availability. Two focus group sessions were conducted in July 2012 at the Hospital for Sick Children in Toronto, Ontario. The first focus group involved 6 GC from the following areas: laboratory (1 participant), pediatric (4), and newborn screening (1). The second focus group participants were 10 GC from the following areas: ocular (1), pediatric (2), pediatric cancer (1), adult cancer (1), adult (1), prenatal (3 GC, one of whom counsels about PGD) and policy (1).

Facilitators with expertise in qualitative methods were used during the session to ensure that all the objectives for each group were addressed within the time allotted. Focus group guides for the moderators were provided (Appendix 2). The agenda for each focus group was emailed to participants in advance of the session. A second document containing additional materials was emailed to the participants prior to focus group two (Appendix 3). The first part of this document had a table of PGD considerations obtained from the reviewed literature and characteristics suggested by participants of focus group one. Blank spaces were included in the table to allow for additional PGD characteristics suggested by focus group two participants. This table was used to facilitate individual participant ranking of the characteristics at the end of focus group two. The second part of the document had a draft version of the question booklet with the background, preamble, and sample choice question in order to address the third objective of the focus groups.

In order to address the primary objective, participants were asked to brainstorm and discuss PGD considerations to help inform possible attributes at the beginning of each session. Participants were then asked to determine extreme situations in order to inform levels that would be needed for the DCE survey. Then individuals were asked to rank the considerations that arose following the focus group discussions. The attributes were ranked individually by participants from *1* being the most important to *N* being the least important. In focus group two, participants read through and commented on the draft version of the question booklet to help address the third objective. Finally, participants from both groups were asked to discuss recruitment preferences and study details relevant to the second objective.

During the focus group, the researcher took field notes about the PGD considerations, possible levels and recruitment strategies via a projected Powerpoint presentation. The field notes were then reviewed after the focus groups to refine categories and determine their applicability to the study. The documentation completed by the individuals in the form of rankings for both groups and comments about the clarity of the question booklet for the second focus group were collected during the focus group and then analyzed after the session. The rankings were analyzed by taking the sum of the ranks and averaging them to get a rank order for each focus group. The averaged rank order was then ordinally ordered from the lowest to the highest to compile a list of the attributes deemed to be the most important within each focus group. The combined ranking which includes data from both focus groups was calculated by taking the sum of the ranks from the participants in both focus groups and then dividing the rank by the number of participants who ranked each PGD characteristic. The resultant average score for each characteristic was ordinally ordered from the lowest to the highest to compile a combined list of important attributes based on the focus groups.

Table 4 illustrates the ranking of PGD considerations after both focus groups. The first column contains the list of all PGD considerations that were considered for ranking. Column 2 demonstrates the ranking of the PGD considerations that were brainstormed by the 6 participants in the first focus group. The results from the second focus group are shown in Column 3. Two of the participants from focus group two did not submit their rankings. PGD considerations not ranked in Column 2 were newly suggested by focus group two participants or obtained from the literature and are highlighted in bold. Column 4 demonstrates the combined rankings from both focus groups with a total of 14 participants, with the PGD considerations ranked in order of most (1) to least (14) important.

Table 4: **Combined Ranking of Preimplantation Genetic Diagnosis Considerations after Both Focus Groups (n=14)**

PGD Considerations	Ranking after 1st Group (n=6)	Ranking after 2nd Group (n=8)	Combined Ranking (n=14)
Certainty of results/Feasibility and accuracy of Results	--	1	1
Characteristics of the genetic condition (Age of onset, severity, life-limiting, treatability, predisposition)	2	2	2
Cost (medical) lifelong versus procedure itself	1	6	3
Mandatory genetic consultation	6	3	4
People's motivation for PGD	4	5	5
Recurrence risk/Germline mosaicism/Threshold	--	4	6
Fertility status of couple (fertile/infertile)	--	7	7
Mother's age	5	9	8
# of cycles covered	3	10	9
Does IVF need to be covered?	--	8	10
Family history of couple (# affected/unaffected children)	7	13	11
Social work assessment	9	12	12
Chromosomal screening	--	11	13
Family income	8	14	14

Notes: "n" refers to the number of participants involved in ranking. "--"refers to PGD considerations that were not ranked in focus group one. PGD considerations in **bold** were newly suggested by focus group 2 participants. PGD: Preimplantation genetic diagnosis; IVF: In-vitro fertilization; # of cycles covered: Number of IVF cycles covered by the government.

Based on the rankings from the focus groups, the attributes from the literature review assigned greater priority included severity, number of cycles covered and existing family history. Each ranked attribute from the combined list was discussed by the researchers and deliberated as to its relevance for study inclusion. Table 5 shows the PGD considerations as determined by the focus groups and the decision of whether to include the consideration as an attribute, to mention the consideration as part of the background preamble or to ask a question related to the consideration within the demographic and opinions section. Brief rationales for inclusion or exclusion of considerations are presented.

The considerations included in the preamble were “Certainty of results / Feasibility and accuracy of results” and “Mandatory genetic consultation” to assure the respondents that the accuracy and certainty of the results were properly provided by a genetics consultation service.

Included considerations within the attributes were “Characteristics of the genetic condition”, “Fertility status of the couple”, “Number of cycles covered” and “Family history” as they appeared to be active policy issues. Since GC are trained in counselling about risks [111], “Recurrence risk / Germline mosaicism / Threshold” was included as an attribute to capitalize on clinical strengths of GC.

Considerations included in the demographic section were “Mother’s age” and “Does IVF need to be covered?”. There is literature stating that “Mother’s age” is important for the success rate of IVF [70, 112]. If this were varied in the study, the chance of a successful pregnancy would also differ within the two choices presented. This confounder may not be explicitly captured in the statistical analysis and may create bias. Therefore it was not included as an attribute but asked as part of the demographic section directly to GC about the importance of maternal age for coverage. “Does IVF need to be covered?” was a good policy question as the government could cover PGD only and not IVF. Therefore this policy question was added to the demographics and attitudes part of the survey.

Several considerations were not included in the study. The consideration of “People’s motivation for PGD” was difficult to assign into levels and hard to define with enough clarity for the respondents to ensure accurate interpretation of the results. The considerations of “Social work assessment” and “Family Income” were not included in the study as these had inherent controversial social value determination. It was difficult to understanding how respondents would react if they were used in the study and how the results could be interpreted. In addition, “Chromosomal screening” was felt to be out-of scope for the study. While “Cost of the genetic condition” was considered an important attribute based on the ranking of importance for the GC, it was thought to be too dominant of an attribute which could bias the estimation of the model [14, 105]. Furthermore, GC are not the ones who would ultimately be funding PGD and would not be able to fully assess opportunity costs similar to a policy maker. Therefore “Cost of the genetic condition” was not included in the study.

Table 5: Inclusion of the Attributes Recommended from the Focus Groups.

PGD Considerations	Preamble	Attribute	Demographic
Certainty of results/Feasibility and accuracy of Results	+	-	-
Characteristics of the genetic condition (Age of Onset, severity, life-limiting, treatability, predisposition)	-	+	-
Cost (medical) lifelong versus procedure itself	-	-	-
Mandatory genetic consultation	+	-	-
People’s motivation for PGD	-	-	-
Recurrence risk/Germline mosaicism/Threshold	-	+	-
Fertility status of couple (fertile/infertile)	-	+	-
Mother’s age	-	-	+
# of cycles covered	-	+	-
Does IVF need to be covered?	-	-	+
Family history of couple (# affected/unaffected children)	-	+	-
Social work assessment	-	-	-
Chromosomal screening	-	-	-
Family income	-	-	-

“+”means that it was included and “-“means that it was not included. PGD: Preimplantation Genetic Diagnosis; # of cycles covered: number of cycles covered; IVF: In-vitro fertilization; # affected: number of affected children

In total, “Characteristics of the genetic condition”, “Recurrence risk”, “Fertility status”, “Number of cycles” and “Family history” were included as attributes for further pretesting. For the “Number of cycles funded” the levels were based on the literature review. Including “zero” funded cycles allowed for the possibility of not funding PGD/IVF at all. The level “all cycles” allowed for unlimited funding up to the point of a successful pregnancy. Since cost was excluded as an attribute, the difficult debate about how to define cost was avoided.

Once the primary objective of the focus group was met, the second objective was to determine the recruitment strategies. Focus group participants agreed with the idea of emailing and mailing via the CAGC list-serve for optimal recruitment. The third objective of the second focus group was to determine the clarity and comprehensiveness of the instructional information in the preamble.

Firstly, the clarity of the preamble framing was discussed as part of the third objective. The DCE was initially framed by using the example of a 35-year-old non-smoking and non-obese female using single embryo transfer. This framing allowed for control of age and obesity which are known to influence the success of pregnancy rates [70, 113]. While the participants felt the scenario was clinically relevant and understood the rationale for specifying “non-smoking” and “non-obese” with a single embryo transfer, a change was made to the age of the female. The age of the patient at 35 years had a connotation with late maternal age so the age was lowered to 30 years to negate this concern and to optimize the chance of IVF success.

Secondly, the comprehensiveness of the preamble was considered. Participants requested more information about empiric risks of IVF, ranges of successful pregnancy rates, labeling of the diseases being presented and the costs per cycle of IVF. Empiric risks of IVF were not included as it was decided that the risks should be known as part of standard clinical practice. Ranges of pregnancy rates would differ based on the scenario and were not included in the attempt to have participants focus on trade-offs of the attributes rather than the pregnancy rates. Labeling of the diseases was thought to restrict the generalizability of the results. Including the costs per cycle of IVF was asking the GC to act as payers of the health care system which they are not. Rather, GC were chosen primarily to act as policy advisors based on their clinical expertise.

Based on the focus group data, 5 possible attributes were selected to include in pretesting, the study recruitment details were proposed and the study guide was modified to reflect the findings. This information was then considered in the construction of tasks, experimental design and preference elicitation (see boxes 4-6 in Figure 1).

2.3 Construction of Tasks

Construction of tasks involves deciding whether to use full or partial profiles, determining the number of scenarios per task, optimizing the number of choice tasks in the DCE questionnaire and choosing whether or not to include opt-out options [80]. The construction of tasks for this study was aided by Sawtooth software (Orem, Utah) which provided tools to design, host and analyze choice-based experiments [114].

Firstly, full or partial profiles refer to whether the respondents are presented with a profile that contains all the attributes (full profile) or a fraction of the attributes (partial profile). While it is desirable to present full profiles, partial profiles could be preferred if there are too many attributes to consider, causing respondents to ignore certain attributes and focus only on a few. A full profile with a reasonable number of attributes as suggested by Sawtooth was chosen in order to be comprehensive and avoid the need for level overlap to oversimplify the tasks [114].

Secondly, forced choice-elicitation format, which is a binary choice, tends to simulate the real world options of clinicians [81]. While presenting three profiles would be more efficient, a two-profile per choice task format was used to present a more simplistic task so that the respondent could focus on trade-offs between the attribute levels as a binary choice rather than consider more than two profiles. Two-profile choice tasks are also more commonly used in health services research [93]. Thirdly, in constructing the tasks, the number of choice tasks in the DCE questionnaire needs to be determined. The ISPOR Conjoint Analysis Checklist recommends between 8-16 up to a maximum of 32 choice tasks [14]. Thus for the purposes of the pilot study, sixteen choice tasks were thought to be a manageable number to complete.

Finally, the use of an opt-out option was debated within the construction of the tasks. An opt-out option is a way to provide respondents with an option not to choose the presented choice sets within a choice task. This allows for the creation of a realistic set of options including a no-coverage policy option. If there were two choice alternatives presented, the opt-out option would present a third option of “prefer neither”. However, when a respondent chooses the opt-out option, it causes lack of data for that choice task because beta-coefficients cannot be estimated [80]. An alternative to the opt-out option for the main choice task is to use a two-stage opt-out option. The use of a two-stage opt-out forces the trade-off but offers a second follow-up question where respondents could prefer to refuse both options. This can give a sense of how many people would have preferred neither option and would still allow for part-worth estimation of all the data while estimating the frequency of opt-out use. However, it would add a second question to each choice task and increase the time for completion of the study. Initially, a zero level coverage was used instead of an opt-out. Selecting the scenario associated with the zero level coverage for cycles would imply that the respondent would rather see both scenarios not funded than to select the alternative scenario at any level of funded cycles. This would act as a surrogate to a third option of opting-out of either option. Therefore, the tasks were constructed with a full profile study showing two profiles per task and 16 choice tasks in total for the pilot study with no opt-out option. Through the course of pretesting, the pilot study and the main study were modified to include a two-stage opt-out option (Please see Section 2.6 for the rationale).

2.4 Experimental Design

Once the tasks are constructed, the next step is to determine the design that would allow for the most unbiased and statistically rich set of data by balancing considerations of respondent efficiency with statistical efficiency [13]. Elements of desirable design include orthogonality, balance and efficiency as described in Section 1.3.2. Pretesting was done to help identify restrictions needed. An orthogonal design could not be used as two restrictions were needed based on the proposed attribute levels that were correlated to each other. The two restrictions were: always presenting HLA-matching with 25% chance of finding an identically matched sibling and HLA-matching for an affected child with having affected children in the "Family history" attribute. The restrictions resulted in an unbalanced design.

Experimental design statistics generated by Sawtooth Software (Sequim, WA) were used to compare relative D-efficiency of designs that differed based on number of choice tasks (16 or 18), inclusion and exclusion of HLA-matching and the restrictions.

A rationality test was built into the design which will be described in more detail in Section 2.5. The survey design was based on main effects attributes only without interactions between the main attributes. Interactions were introduced between the main effects and the demographic and attitude data as outlined in Section 3.3.3.

2.4.1 Blocking and Sample Size

In order to allow for the most unbiased and statistically rich set of data, the experimental design also requires that blocking and sample size be considered. Based on one attribute with two levels and four attributes with three levels, there were 162 ($2^1 \times 3^4 = 162$) possible scenarios in a full factorial design which could be presented over 81 choice tasks. Presenting all 81 choice tasks to each respondent would be a significant time burden unless the study was blocked. Blocking refers to taking the full factorial study and dividing the choice tasks into a certain defined number of smaller more manageable sets of choice tasks known as versions. Assuming that the respondents all complete their version of the study and answer only the choice sets within their block, all the blocks of choices would have collected data and therefore all potential choices and alternatives would be answered [13]. The difference is that instead of one participant answering all 81 choice tasks, the completed data from all the respondents would have data collected from the 81 choice tasks. The 81 choice tasks could be covered in 6 versions of the survey. Since the survey pretest determined that 16 choice sets would allow for a survey to be completed in approximately 20 minutes in total, 16 choice sets were used. In order to encourage well-read and analyzed responses from as many Canadian GC as possible, the "complete enumeration" method through Sawtooth software's design option was used. This procedure takes a subset of the full-choice design and ensures that there is minimal overlap between the levels, the frequency of the levels within the attributes are balanced, and that orthogonality is maximized [13].

Blocking can also affect the minimum sample size needed for the study. In turn, maximizing sample size can decrease the size of the confidence intervals [13]. Calculation of a minimum number of respondents adequate for sampling in a conjoint analysis related to health care depends on the question format, number of choice sets, how precise the desired results are, the degree of variation of the respondents, whether subgroup analyses are desired and whether the respondents are available [115]. Once the number of choice tasks is decided, the following equation,

$$\mathbf{nta / c \geq 500} \qquad \textbf{Equation 4}$$

Equation 4 can be used as a rule of thumb, where n = the smallest possible sample size needed, t = number of choice tasks, a = number of scenarios per choice task and c = the largest number of levels used to define an attribute [116]. If Equation 4 was determined to need 46 individuals, a blocked study with 6 blocks would need 46*6 = 276 respondents. Alternatively, de Bekker-Grob et al. proposed that there were five elements needed to calculate the minimum sample size needed for each coefficient within a DCE. The minimum sample size needed for the study is dependent on the coefficient that is determined to need the largest sample size to find a statistical difference from the reference level for the attribute. The five elements are 1) the significance level (α), 2) statistical power level ($1-\beta$), 3) the statistical analytic model, 4) parameter values from pilot study, and 5) the design of the DCE [117]. The practical guide using the statistical program R (version 2.14.1, 2011) was followed based on the code provided by de Bekker-Grob et al. [117]. The significance level was set at $\alpha = 0.025$ to allow for the estimated parameter to deviate in either direction from zero. The statistical power level was set to 80%. The statistical analytic model was multinomial logit. Based on this method, a minimum sample size of 213 respondents would be needed assuming an $\alpha = 0.025$, at a statistical power of 0.8 to see whether having affected children is statistically different from having all unaffected children which is the reference level for the attribute family history.

2.5 Preference Elicitation

Following construction of tasks and experimental design, preference elicitation was performed (box 6 in Figure 1). Preference elicitation involves using wording to promote completion of the survey and to explain the tasks, choosing the proper type of conjoint analysis and including questions that promote reliability of the responses [80]. Special attention was paid to the wording of the study guide material describing the scenario as well as the attributes and levels to ensure proper motivation and explanation of tasks. The rationale for using a DCE as the type of conjoint analysis for the study was already described in Section 1.3.2. The questions that promote reliability of the responses can be explored using a fixed-choice set.

The use of fixed-choice sets allows for tests of the quality of the responses [14]. Repeating a choice set without including it within the data analysis is thought to be one way to assess whether respondents are consistent with their responses. However, including this internal consistency check would require an additional choice set that did not seem justified. Another check of the quality of responses is to determine whether respondents would consistently identify the alternative that had the best level within the attributes. A favourable scenario allows for testing to see if respondents are rational about their choice. It could be used as a control for internal validity, which is a measure of how accurate the responses within the study are without influence of confounding factors or bias. A dominant option was embedded where all the most desirable attribute levels were present [82]. This rationality check would test to see whether respondents would always pick severe childhood-onset life-limiting condition in a couple who is infertile where there is public funding as the dominant choice above all others as this does not seem to debated in the literature. Using a sensitivity analysis, those who were viewed as “irrational responders” would be included and then excluded in data analysis to see whether there were any effects on the results. Figure 2 depicts the fixed–choice task within the pilot study. The first option was thought to be more desirable compared to the second. Level overlap of the number of cycles was used as it was unknown whether respondents would prefer 3 or 6 cycles to be funded.

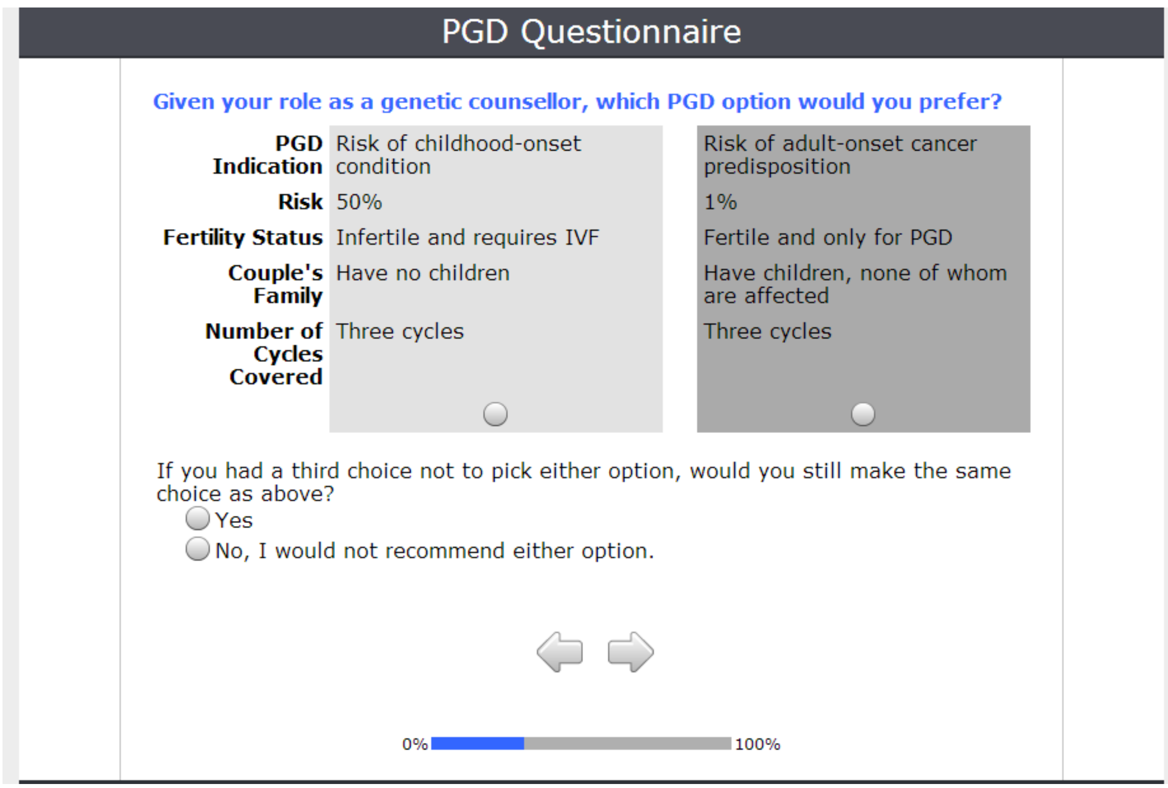


Figure 2: Fixed-choice task.

PGD: Preimplantation Genetic Diagnosis.

The use of the fixed-choice task increased the number of choice tasks to 17 in the pilot study. The addition of one choice task was not felt to increase the survey burden significantly. Therefore a total of 18 choice tasks were used in the pilot study.

2.6 Pretesting

Pretesting involves a participant reading through the questionnaire and answering questions about clarity of wording, and comprehension of directions given. It can also test the demographics portion of the survey, which had questions about the respondent, questions about their practice, questions related to the survey and questions about their attitudes. The demographics and attitude section was used to help address research question 2 as stated in Section 1.6. The goal of pretesting was to have participants give comments about the questionnaire and also give a sense of the time it took to complete the survey based on completing the questionnaire as if they were part of the main study. Individuals contacted for pretesting were from the group of GC who consented to re-contact from the focus groups. A Cognitive Interviewing Protocol was used for pretesting as the protocol allows for a methodical approach to exploring the length of time for completing various portions of the survey, understanding of the instructions and clarity of the wording. The protocol was adapted into the Pretest guide (Appendix 4). The pretest contained three sections: 1) Instructions, background and preamble; 2) Choice questionnaire; and 3) Demographic and attitude questionnaire. During pretesting, the preamble and background were provided in paper form for the participants to read and questions were asked as part of the interview. The choice sets were presented on a laptop for self-completion using the Sawtooth Software SSI Web CAPI module (Computer Aided Personal Interview) available through Sawtooth (Orem, Utah). CAPI allows for surveys to be conducting using a laptop or PC without an internet connection. The demographics and attitudes questionnaire was presented in paper form. Time taken to complete each section was calculated. The data from the CAPI module was not analyzed as it was used multiple times during the session by the same people to help clarify wording after the initial practice run was used to monitor for timing.

Pretesting data were gathered from 7 individual pretest interviews conducted by one interviewer (EG). The genetic counsellors had agreed to be re-contacted based on their consent form from the focus groups. The seven interviews were done between December 2012 and March 2013 with each interview being conducted in the counsellor’s office. All counsellors were located in Toronto, Ontario. The Pretest guide and draft of the preamble and background were changed after the fourth interview in order to test “Characteristics of a genetic condition” as being “childhood-onset, adult-onset or adult-onset cancer predisposition” instead of “severity, life-limiting and treatability”. Respondents completed a draft survey while timed, and answered questions related to the choice set combinations, and clarity of instructions. Alterations to the survey based on pretesting contributed to the instrument design (as shown in box 8 of Figure 1). The mean time for completion of the survey was calculated to be included in the main study. Minor changes were made to the preamble and choice task framing to improve clarity.

The results of the time taken in minutes for each section of the survey and the overall duration for the 7 pretesting participants are shown in Table 6. There were 16 choice sets presented through the CAPI module. The total time for survey completion is a sum of the preamble/background reading time, choice set completion time and demographics questionnaire completion time. The total time for pretesting includes the sections on the Cognitive Interviewing Protocol that asked for feedback about clarity and terminology as seen in Appendix 4.

Table 6: Average Duration of Survey during Pretesting

Pretesting Sections	**Average Time (mins) n=7**	**Standard Deviation (mins)**
Preamble/Background reading	5.1	2.6
Choice-Sets	8.7	2.1
33 Demographics/Attitude questions	6.6	3.2
Total time for survey	20.4	3.7
Total time of pretesting	45.9	10.9

Mins: Minutes

Based on Table 6, the average total time it took to complete the survey for 16 choice sets and the demographics section was 20.4 ± 3.7 minutes, which is within the targeted time as suggested by the focus groups. Most focus group participants agreed that a survey burden of around 20 minutes (range of 15-45 minutes) was reasonable for the study. No participant reported that the completion of the survey was burdensome. An increase in the number of choice sets to increase D-efficiency was thought to be reasonable and would not alter the projected completion time for the total survey. The final survey time would be based on the number of choice sets used which in turn would be based on the design statistics and altered based on pretesting.

Pretesting results were reviewed for their relevance to the survey. Pretesting allowed for participants to highlight the issues of face validity of the survey and the need for restrictions.

Face validity of the survey is required so that when respondents are deliberating the choices, the choices themselves are reasonable. If they were not, there would be respondent inattention where respondents would lose interest in the subject and question the survey's objective and intentions [13]. Based on the pretesting results, restrictions were needed between HLA-matching in combination with "Risk of a condition" and "Family history" as stated in Section 2.4. When restrictions were placed for the last two pretesting participants with HLA-matching coming up with only 25% risk and HLA-matching appearing only with "have children, at least one of who is affected", this made the choices more realistic and increased face validity. However, pretest participant #7 commented that she felt that the option was coming up more often than the others as seen in an unbalanced design [75]. The result was a decrease in D-efficiency (data not shown). Therefore HLA-matching was removed as a level and the "Characteristics of genetic condition" attribute was changed to "PGD indications".

Another pretesting finding was confusion from the "zero coverage" level for the "Number of cycles" attribute. The participants had a difficult time interpreting how to trade off between the choices. One participant stated that if the level was zero, she would always choose the other option so that something would be covered while others felt that it was a way to choose no funding and used it if they did not like the other option. Confusion among the pretest participants created concern that the interpretation of the results would be difficult. Therefore the pilot study tested the use of the two-stage opt-out option as described in Section 2.3. This would allow for part-worth estimation of all the data while estimating the frequency of opt-out use.

Given the results of pretesting, decisions about the attributes and levels for pilot testing and survey design were made. The attributes and levels for pilot testing are found in Table 7. The number of cycles covered was changed to a continuous variable by giving the option of 1 cycle, 3 cycles and 6 cycles instead of allowing for all cycles. The number 6 was chosen because this had been the maximum level of coverage provided by the Government of Quebec [56].

Effects coding was used to measure non-linear effects of attribute levels while allowing the base level to be estimated [75]. It is achieved by creating variables for each attribute being coded such that there is one less variable for the number of levels within each attribute. The base level is made equal to the negative sum of the variables [75]. For example, for PGD indication, the variables Condition1 and Condition2 were created. Childhood-onset condition is represented by Condition1 (x 1) + Condition2 (x 0) = Condition 1. Adult-onset condition is represented by Condition1 (x 0) + Condition2 (x 1) = Condition2. Adult-onset cancer predisposition is represented by Condition1 (x -1) + Condition2 (x -1) = (-Condition1) + (-Condition2).

Table 7: Attributes and Levels for Pilot Testing along with Effects Coding

Attribute	**Levels**	**Effects coding**
PGD indication	•Childhood-onset condition •Adult-onset condition •Adult-onset cancer predisposition	1 0 0 1 -1-1
Risk of genetic condition	•50% •25% •1%	1 0 0 1 -1-1
Fertility status of couple	•Infertile •Fertile	1 -1
Family history	•Have children, some of who are affected •Have children, none of whom are affected •Have no children	1 0 0 1 -1-1
Number of cycles covered	•1 cycle •3 cycles •6 cycles	1 0 0 1 -1-1

PGD: Preimplantation Genetic Diagnosis.

Design statistics were used to determine whether to include main-attribute interactions in the study design. All the statistics were generated via the CBC Test Design Efficiency Test through Sawtooth Software (Orem, UT), which models random respondents to answer the questionnaire based on conditional logit theory. Comparisons between two different designs were made based on the number of prohibitions needed to ensure clinically relevant choice tasks, whether the survey was balanced, the “maximum difference” which refers to the difference in appearance between the most frequently appearing level and the least frequent, and the “maximum standard error” which shows how precise the estimate is. “Strength of the design” is the measurement of the “Information matrix” provided by Sawtooth and is used to compare different designs in order to calculate the relative D-efficiency or the efficiency of one design compared to the other. The “relative D-efficiency” is calculated by dividing the strength of each design to obtain a ratio which becomes the percentage efficiency of one design compared to the other. Some attributes were altered due to their effects on the design based on the design statistics. The above discussions about restrictions needed for HLA-matching and risk, suggested that there may be an interaction between the attributes “PGD indication” (A1 under “# of Levels”) and “Risk of the genetic condition” (A2 under “# of Levels”). Table 8 shows the design statistics related to adding the interaction between PGD indication and the risk of the condition attributes.

Table 8: Design table for Interactions

Design	**# Prohibit.**	**# of Levels**					**Balance**	**Max Diff**	**Max Stan. Error**	**Strength of Design**	**D-efficiency**
		A1	**A2**	**A3**	**A4**	**A5**					
1. No interactions; n=300 opt out 15%; 1 fixed choice task (out of 18)	0	3	3	2	3	3	Y	0	0.022	2656.04	Reference for Design 2
2. Interaction A1xA2 (PGD indication x Risk); n=300, opt out 15%; 1 fixed choice task (out of 18)	0	3	3	2	3	3	Y	0	0.044	1534.43	0.5777

Prohibit = number of restrictions; # of Levels = number of levels within each attribute A1 = PGD indication; A2 = Risk of condition; A3 = Fertility status A4=Family history and A5 = Number of cycles covered. Max Diff = maximum difference of frequencies between the highest frequency and the lowest frequency within an attribute. Max Stan. Error = maximum standard error. PGD: Preimplantation Genetic Diagnosis.

The inclusion of an interaction between PGD indication and risk of the condition conferred a D-efficiency of 57.7% compared to no interaction. There was also an increased standard error and the inability when using interactions to comment on the part-worth utility of individual attributes. Thus, main-effects interactions were not included. Only interactions from the main attributes and the demographics were performed to answer research question 2 (Section 1.6).

2.7 Pilot Testing

The objectives of the pilot testing were to 1) explore the feasibility and comprehension of the DCE design, 2) to test the clarity of the revised instructions given for the preamble and the scenarios, and 3) to allow for preliminary data to be collected and analyzed.

Given the concern that there were a limited number of GC available for the main study, GC who were not part of the CAGC were preferentially contacted for pilot testing via email. In order to have enough pilot testing participants, some GC who were CAGC members were included. The first recruitment for the pilot study occurred August of 2013. Twenty-four participants were invited via email. A study guide was attached to the email (Not shown as similar to Appendix 3). Each participant was sent an individualized email with their username, password, survey link and the study guide. Each participant was given a unique username and a password that was generated by the Sawtooth Software. This allowed for a participant to complete the survey in multiple sittings. The entire pilot study was administered online. Participants in the pilot study were not eligible for the main study.

A reminder email was sent out. An additional 17 participants were invited to complete the pilot study due to low response rate and data loss from the server in October of 2013. A $5 coffee gift card was provided to all participants by mail regardless of whether they completed the survey or not. The recruitment period for the second group of participants was two weeks.

2.7.1 Pilot Data Analysis

Statistical analysis of the pilot data was performed using Sawtooth Software. The Sawtooth Software hosting site allows for the raw data to be exported into the Sawtooth Software Market Research Tools (SMRT) analysis program, which then can analyze the choice data via multinomial logit regression analysis. The assumptions for multinomial logit regression analysis are: 1) the utility can be measured from the choice questions equally well across choice tasks and across respondents, such that the scale of the random error term is the same between all respondents or all choices tasks, 2) that respondents will choose alternatives to maximize their utility, and 3) that errors follow an independently and identically distributed type 1 extreme-value distribution [75, 90, 93]. Reference levels were coded with the last level omitted then supplied after, to equal the negative sum of the others so that each attribute summed to zero. All attributes were coded as categorical attributes. The proposed model estimate for the main-effects is:

$$U_{ij} = \beta Condition1_{ij} + \beta Condition2_{ij} + \beta Risk1_{ij} + \beta Risk2_{ij} + \beta Fertility_{ij} + \beta Family1_{ij} + \beta Family2_{ij} + \beta Cycle1_{ij} + \beta Cycle2_{ij} + \varepsilon_{ij} \qquad \textbf{Equation 5}$$

In Equation 5, βCondition denotes the preference for PGD indications, βRisk the preference for the risk of the genetic condition, βFertility the preference for fertility status, βFamily the preference based on family history, βCycle the preference for the number of cycles to be covered and ε_{ij} is the unobservable error term of individual *i* for choice *j*. The coefficients for each level were determined as well as the standard error so that the chi-square could be calculated. The attribute levels were effects coded as shown in Table 7. Interactions between the attributes and the demographic data were not done in the pilot study as the numbers were too small. The demographic data were exported into Excel from Sawtooth and the frequencies of categorical variables and means and standard deviations of the continuous variables were calculated.

2.7.2 Pilot Testing Findings

A total of 41 people were invited to participate but one person could not be contacted, and two were on maternity leave for a total of 38 possible respondents. There were 21 respondents and 20 respondents fully completed the survey online.

The survey respondents were primarily from Ontario (62%; 13/21) but included participants from across Canada. There were 71.4% (15/21) who were full-time genetic counsellors. A total of 28.5% (6/21) GC identified themselves as having prenatal genetics as their only area of focus. The majority were full-time genetic counsellors working in a variety of different primary areas, which is representative of the national sample.

The majority of respondents (70%; 14/20) felt that sexual orientation was very unimportant in determining public funding for PGD when offered a five point scale with the options very unimportant, somewhat unimportant, neither important nor unimportant, somewhat important and very important. As there did not seem to be controversy about sexual orientation as a criterion for PGD, it was felt that asking about another policy relevant topic such as age of the mother would be more useful.

The majority of respondents stated that they were thinking about particular diagnoses when they were going through the choice tasks and only 10% (2/20) stated that they were not thinking about a particular diagnosis. For childhood-onset conditions, examples of conditions included Duchenne Muscular Dystrophy, and Cystic Fibrosis. For adult-onset non-cancer conditions, most thought of Huntington disease. For adult-onset cancer predisposition conditions, most thought of Familial Breast and Ovarian Cancer syndrome. The majority of the GC identified similar conditions when prompted about PGD indications. Although severity of a condition or the experience that a GC has had with the condition may vary between GC, it was felt that including relevant conditions as examples in the preamble for the attribute “PGD indications” would be appropriate for the main study.

The mean time for completion of the full pilot survey including the choice set and the demographics and attitude section was 31.9 minutes.

Based on the multinomial logit regression analysis of pilot data using effects coding as outlined in Section 2.6, the attribute level beta estimates and standard errors are presented in Table 9.

Table 9: Multinomial Logit Regression Analysis of the Pilot Choice Data (n=20)

Attribute	Levels	Beta	SE
PGD indication	Risk of childhood-onset condition	1.532	0.1901
	Risk of adult-onset condition	-0.677	0.1375
	Risk of adult-onset cancer predisposition	-0.855	0.1504
Risk of condition	50%	1.133	0.1639
	25%	0.445	0.1282
	1%	-1.578	0.1957
Fertility status	Infertile	0.232	0.0805
	Fertile	-0.232	0.0805
Family history	Affected children	0.172	0.1311
	Unaffected children	-0.205	0.1289
	No children	0.033	0.1287
Number of cycles covered	1 cycle	-0.040	0.1283
	3 cycles	-0.101	0.1289
	6 cycles	0.140	0.1322

Beta: Beta parameter estimate; SE: Standard error; PGD: Preimplantation Genetic Diagnosis;

Although there was evidence of trading off when looking at the part-worth estimates, there were problems with the beta-estimates. They were not easily comparable because some of the levels appeared more frequently than others. This was found to be due to the design having one attribute with 2 levels compared to 3 levels for all the other attributes. Therefore, it was suggested that an “uncertain” level for fertility status could be used. This level was reviewed by one Metabolic GC, one Prenatal GC and one Obstetrics / Gynecology physician who agreed that the level was a clinically reasonable one.

Given that all participants picked the more desirable alternative for the fixed-choice task and none of the respondents used the opt-out for that choice task, it was felt that a rationality test would not be needed in the main study.

The result of the two-stage opt-out analysis showed that there were respondents who used it to signify that they would not prefer either choice. One participant used the “neither” option in 10 of the 17 choice sets. Table 10 showed the distribution of the use of the “neither” option.

Table 10: Distribution of Use of “Neither” Option

Number of choices out of 17 options where “neither” was selected	**Number of Participants**
0	5
1	2
2	2
3	1
4	1
5	2
6	2
7	1
8	3
10	1

The opt-out responses showed that there was variation in the use of the “neither” option. Based on these data, there would be 76 choice tasks (1*2+2*2+3*1+4*1+5*2+6*2+7*1+8*3+10*1) out of a possible 340 (20 participants * 17 non-fixed choice tasks) or 22% (76/340) of the tasks would have preference data lost if a none option was included. Therefore, it was felt that the two-stage opt-out was useful to keep in the main survey to allow for the “no policy” option while limiting the censoring of data that could occur with a traditional opt-out option.

2.8 Post-Pilot Changes to the Survey Instrument

Based on the pilot study, changes were made to the survey instrument.

Within the preamble, 2-3 examples of genetic conditions were added to each level of the “PGD indication” attribute since the majority of the pilot GC reported thinking about specific conditions. In this way, participants had an idea of the sorts of conditions that were relevant without labeling the scenario and limiting generalizability.

The wording of “adult-onset condition” was changed to “adult-onset non-cancer condition” to distinguish it from an adult-onset cancer predisposition in order to make the levels mutually exclusive. The fertility attribute was changed to include a third level known as "Fertility status unknown" as this was felt to be a clinically relevant level and would allow for uniformity of 3 levels per attribute across the study. Cycles covered were changed from 3 cycles and 6 cycles to 4 and 8 cycles to exceed the estimated threshold for coverage.

The two-stage opt-out was retained in the main study but the fixed choice task was removed. A line in the study guide was added to remind those already completing the pilot that they were excluded from the study and the first page of the electronic survey also allowed for exclusion. As there were changes in the survey between the pilot and main study, the pilot data could not be pooled for analysis with the main study.

Within the attitude section of the demographic and attitude questionnaire, a question asking about the importance of the age of the mother undergoing PGD was added to reflect the policy question related to the importance of maternal age [72] instead of asking about the importance of the sexual orientation of the couple undergoing PGD, which was not as disputed based on pilot data. A question was added to ask if the participant was part of the CAGC mailing list to try to account for individuals referred through snowball sampling in order to calculate an accurate response rate.

2.9 Main Study

The method for the main study was similar to the pilot study except for the changes highlighted below.

2.9.1 Attributes and Levels used in the Main Study

The attributes and levels used in the main study are listed in Table 11.

Table 11: Attributes and Levels used in the Main Study and the Effects Coding Used

Attributes	Levels	Effects coding
PGD indications	Risk of childhood-onset condition Risk of adult-onset non-cancer condition Risk of adult-onset cancer predisposition$^{\psi}$	1 0 0 1 -1-1
Risk of condition	50% 25% 1%$^{\psi}$	1 0 0 1 -1-1
Fertility status	Infertile and requires IVF Fertility status unknown* Fertile and requires only PGD$^{\psi}$	1 0 0 1 -1-1
Family history	Have children, at least 1 of whom is affected Have no children Have children, none of whom are affected$^{\psi}$	1 0 0 1 -1-1
Number of cycles covered	One cycle Four cycles* Eight cycles*$^{\psi}$	#1 0 0 1 -1-1

*Levels changed from pilot study PGD: Preimplantation genetic diagnosis; IVF: In-vitro fertilization; $^{\psi}$reference level; # when Number of cycles covered was coded as a categorical variable

By having all 5 attributes with 3 levels, the design was now balanced in terms of level frequency. Therefore, there were a possible 243 scenarios (3^5) and 122 pairs of options. Details about the comparison of designs for the number of choice sets and blocking can be found in Appendix 5. Using four blocks allowed for a small enough number to ensure equal survey completion of all blocks while increasing relative D-efficiency compared to three. Eighteen choice tasks per block balances survey burden with relative D-efficiency. For 18 choice tasks (t=18) with 2 scenarios (a=2) per choice task and a maximum of 3 levels per attribute (c=3), the smallest possible sample size needed for the equation to be equal to 500 is n = 42. However, since the survey was blocked into 4, the total optimal number was 42 * 4 = 168.

2.9.2 Study Recruitment

In order to recruit the optimal number of GC, respondents were recruited based on the inclusion criteria described in Section 2.1. Three email blasts to the entire CAGC membership were utilized. The first email notifying participants of the survey was sent on June 10, 2014. The second email which included the survey link was sent June 17, 2014. Participants were invited to email pgd.study@sickkids.ca upon completion with their mailing address so that a $5 gift certificate could be mailed as a sign of gratitude for their participation. Due to low enrollment, the recruitment plan was altered to include snowball sampling of all GC in Canada regardless of their CAGC membership status as the CAGC list-serve reached a maximum of 204 individuals for the first email blast. Emails were sent to GC or geneticist contacts to the various Canadian genetic centres to invite them to circulate the survey link to their colleagues. The third email blast was sent in September 2014 which increased the response rate. Finally, recruitment took place during the November 2014 CAGC Annual Education Meeting.

2.9.3 Data Collection

Data were collected from respondents through an electronic online survey that could be completed in multiple sittings. The online survey was hosted by Sawtooth (Oren, Utah) which randomly distributed one of four versions of the survey amongst respondents who were recruited through the email blasts and snowball sampling. As well, data were collected using four paper versions of the survey distributed evenly during the keynote session at the CAGC Annual Education Meeting in November 2014. Version 1 of the main study booklet can be found in Appendix 6. The online survey and the paper survey looked the same except for a free text comment section that appeared at the end of the paper survey.

2.9.4 Data Management

For the main survey, all the data from electronic surveys were exported from Sawtooth Software into SAS (version 4.3; Cary, North Carolina). All main study survey hard copy responses collected at the CAGC Annual Education Meeting were entered into a data template created by Sawtooth Software with an assigned study number. The data were cross-checked at the time of transcription and a 10% random sample of hard copy responses were cross-checked by a second individual (FV). No data required re-entry as a result of error. Data were managed and stored in a password protected computer. If a respondent started the main survey but then decided not to participate, the information collected prior to stopping was analyzed. The individual was counted as part of the response rate but was not counted in the completed survey response rate. Access was limited to EG and FV.

There was an opportunity for open ended comments to be provided at the end of the attitude portion of the questionnaire. The opportunity was provided only to the respondents who filled out the survey in paper form. The comments were grouped into categories of whether the comments were related to the survey itself or about specific content of the material presented. Those comments that seemed to explain the choices made were highlighted.

2.9.5 Statistical Analysis

The software program SAS (version 4.3; Cary, North Carolina) was used for statistical analysis of the main study. Effects coding was used for all attributes, except for Number of cycles, which was coded as a continuous variable (see Table 11). Number of cycles was also effects coded as a categorical variable and a sensitivity analysis was done to see if there was a difference whether this variable was coded as continuous or categorical. Descriptive statistics for the demographic questions within the main study were summarized using means and standard deviations (SD) for continuous variables. For categorical variables, frequency distributions were calculated.

Data analysis of the DCE consisted of multinomial logit regression following Equation 5 (from Section 2.7.1) with the exceptions that Fertility was divided into Fertility1 and Fertility2 since there was an extra level added for unknown fertility and that Number of cycles was treated as a continuous variable to estimate beta coefficients for all main study attribute levels. Beta parameter estimates represented the mean part-worth utilities for each level within the attribute.

The attribute weighting was then calculated according to Equation 6 and used to generate importance scores for each attribute based on Equation 7.

$$\textbf{Attribute weighting} = \underline{(\beta_{\text{highest level of attribute}} - \beta_{\text{lowest level of attribute}})} \quad \textbf{Equation 6}$$

$$\textbf{Importance Score}_{\textbf{attribute}} = \underline{(\text{attribute weighting}}/(\text{sum of attribute weightings for condition+risk+family+fertility+cycle})) \times 100 \quad \textbf{Equation 7}$$

The attribute weighting refers to the weighting of the attribute of interest based on subtracting the lowest level β coefficient of the attribute of interest from the β coefficient of the highest level for that attribute. The importance score states the relative proportion of the overall total weighting to which each attribute contributes. Ratcliffe and Longworth have criticized calculation of importance scores as they have found that attributes with a high number of levels were weighted more heavily and therefore had a higher importance score [118]. In the main study, the 5 attributes each have three levels and therefore there is less concern for this attribute-effect bias.

A sensitivity analysis was done to compare results when including or excluding the "none" option.

The main analysis was done using the SAS software (version 4.3; Cary, North Carolina) PROC PHREG function. One-way sensitivity analysis with the attribute Number of cycles covered coded as categorical versus continuous was carried out. One-way sensitivity analysis was performed with the two-stage opt-out data treated as a third option and compared to the forced-choice data without the second stage opt-out. The variance-covariance matrix was obtained (Appendix 7). The standard error for the attribute level coded as -1 -1 (L3) was calculated based on Equation 8 [93].

$$\textbf{Standard error of the L3} = \sqrt{\text{Variance of L1} + \text{Variance of L2} + (2\text{xCovariance between L1 and L2})} \qquad \textbf{Equation 8}$$

where L1 refers to the (1 0) level, L2 refers to the (0 1) level and L3 refers to the (-1 -1) level when attribute levels were effects-coded.

2.9.5.1 The Interaction Models with Demographic, Practice and Attitude Data

Two interaction models were created to determine the degree to which the variables of personal and practice factors of the GC could account for differences in GC preferences. The first interaction was based on the *a priori* hypotheses outlined in Section 1.6. The first interaction model called the Experienced model examined the effects of i) GC having greater than 10 years of experience on PGD condition and Risk, ii) GC having children on Fertility status and Family history and iii) GC having a high household income on Number of cycles.

While the first interaction model was hypothesized based on *a priori* knowledge of the literature and therefore hypothesis driven, the second interaction model was created through purposeful regression to observe, without prior hypotheses, which variables were significant. The method for purposeful regression followed closely to Bursac et al. [119]. Demographic variables with a frequency of less than 5 were not used due to limitations of chi-square. The remaining variables were tested individually as the only demographic variable to interact with the main effects attributes. The interaction term was composed of the demographic variable interacting with a main effect attribute. Interaction terms displaying a p-value of ≥ 0.2 based on univariate demographic variable regression were rejected which is a slight variation from the method used in Bursac et al. which used a p-value cut-off of 0.25 [119]. This was done in order to eliminate variables that did not significantly influence preferences. The remaining interaction terms were combined into a single model and then through purposeful regression, were removed individually starting with the least significant interaction term. Interaction terms that changed the significance of the main effects to ≤ 0.05 were kept in the model even though the p-value for that interaction term was not significant as it was hypothesized that the term had a significant and purposeful contribution based on the changing of main effect significance. This iterative process of removing the interaction terms individually and running the regression again was done until all remaining interaction terms were either statistically significant at a p-value ≤ 0.05 or were shown to contribute to the significance of the main effects. This process was estimated for both p-value ≤ 0.05 and p-value ≤ 0.01 in case there were too many significant interaction terms. Finally the interaction terms that were initially rejected with a p-value of ≥ 0.2 were combined into a new interaction model to ensure that the terms remained non-significant.

The adjusted beta parameter estimates were calculated by adding the parameter estimates of the interaction term to the parameter estimate of the main effect attributes estimated in the interaction model.

2.9.5.2 Assessing Model Fit

Three statistics were employed to assess the model fit. The first was McFadden’s pseudo R^2 statistic which uses the ratio of log likelihoods from the null model with no predictors (-logL(0)) and the fitted model with p predictors (-logL(p)) to help predict how well the estimated model fits with the conjoint analysis data (Equation 9).

$$R^2 = 1 - [-\log L(p)]/[-\log L(0)] \qquad \textbf{Equation 9}$$

McFadden's pseudo R^2 ranges from zero if the explanatory power of the estimated model is very low to one if the estimated model is able to predict every choice. A well-fitted model is generally greater than 0.2 [120] and between 0.2 to 0.4 is still considered a good fit [121].

The second statistic was the adjusted pseudo R^2 to correct for the number of parameters (k) estimated in a model (Equation 10).

$$\text{Adjusted } R^2 = 1\text{-}[\text{-logL(p)-}k]/[\text{-logL(0)}] \qquad \textbf{Equation 10}$$

The adjustment is made to account for too many predictors in the model. A decreased adjusted pseudo R^2 will occur if the model includes predictors that are not adding sufficiently to the model even though the R^2 could increase [122].

The third statistic was the Akaike Information Criterion (AIC) which measures the model fit adjusting for the number of parameters (p) as well as the number of dependent variables (choice = c) (Equation 11).

$$\text{AIC} = -2 \text{ Log L} + 2((c\text{-}1) + p) \qquad \textbf{Equation 11}$$

The lowest AIC when models with the same data set are compared has the greatest likelihood of predicting the data or having the best fit [122].

In assessing the model fit, the recommendation is to use two or three statistics and compare the results as no single statistic is optimal for every study [123]. In general, the chosen statistic should account for adjustment for degrees of freedom especially if the models being compared have different degrees of freedom [123].

2.9.5.3 Generating 95% Confidence Intervals

The 95% confidence intervals for beta estimates were generated with bootstrapping [124] by sampling from the original data with replacement 1000 times. The 1000 new datasets were analyzed via regression analysis with the previously described method in Section 2.9.5 and the 25th and 975th ranked values for each beta estimate were used as the lower and upper confidence limits for each level [125].

2.10 Ethics

This study was approved by the Hospital for Sick Children Research Ethics Board (Protocol number 1000032845) and the University of Toronto Research Ethics Board. The Qualitative Phase 1 was approved June 2012 (Appendix 8) and the addition of Quantitative Phase 2 was approved June 2013. An amendment made to allow for a $5 gift card to pilot study participants was approved October 2013 and an amendment to alter the recruitment strategy to include CAGC Annual Education Meeting recruitment in person was approved October 2014.

Focus group and pretesting consents were obtained by EG during the first part of the focus group. For the pilot and main studies, both hardcopy and online surveys contained statements that consent was implied with completion of the survey. An information sheet was provided in the survey package for the main study. Therefore, this satisfied the requirements for written informed consent as outlined by the Tri-Council Policy Statement on Informed Consent, Section Two [126]. Each electronic survey was assigned a study identifier through the Sawtooth hosting service. No personal identifiers were included in data collection. If someone started the main survey but then decided not to participate, the information collected prior to stopping was analyzed.

Contact information from participants who emailed pgd.study@sickkids.ca to obtain their $5 gift card was kept on a password protected computer until the gift card was mailed. Contact information was subsequently deleted. Hard copies of the surveys and consents were kept in Dr. Wendy Ungar's research office in a locked file cabinet. Seven years after publication of the study, the paper copies will be shredded and disposed of and electronic files will be destroyed as directed in the Sick Kids policy. The privacy and confidentiality of survey participants was respected and protected as per the Hospital for Sick Children (Sick Kids) Research Ethics Board policy.

3 Results

The results chapter first describes the study sample and summarizes the respondent characteristics. The main effects model is then shown, which provides information about the parameter estimates for the attributes and their levels. The results of the interaction models consisting of the Experienced model and the model due to purposeful regression are presented. Finally, the results from the sensitivity analysis of using “Number of cycles” as a continuous variable versus categorical variable and the sensitivity analysis for the second stage opt-out option is included to observe the effect of having an option of no coverage.

3.1 Study Sample

Recruitment occurred between June 2014 and November 2014. A flowchart summarizing the recruitment and response rates is provided (Figure 3).

A total of approximately 306 genetic counsellors were invited to participate through the various recruitment approaches described in Section 2.9.2. A total of 267 were invited in the third email blast. An additional 20 non-CAGC members from snowball recruitment and 19 non-CAGC members from the annual education meeting were recruited to help increase the response rate. The non-CAGC members were identified based on a question that was added to the survey asking if they were CAGC members. Therefore, it is possible that the number of genetic counsellors who were invited to participate through snowball recruitment and the annual meeting was actually higher and that 306 genetic counsellors was an underestimation. The returned survey response rate was 50% (153/306) and the completed survey rate was 41% (126/306). Of the completed surveys, sixty-eight percent completed the survey online and 32% completed it by paper. Of the incomplete surveys, one respondent withdrew because they did not have time to finish. The 126 completed surveys were used for the main analysis. Since 8 of the 126 surveys had incomplete opt-out data, the opt-out sensitivity analysis was conducted using the 118 surveys that had complete opt-out data. Of these, almost 7% (8/118) were not practicing GC and therefore demographic data related to experience, area of practice and location of practice were missing. Thus the interaction analysis was based on 110 surveys from practicing GC.

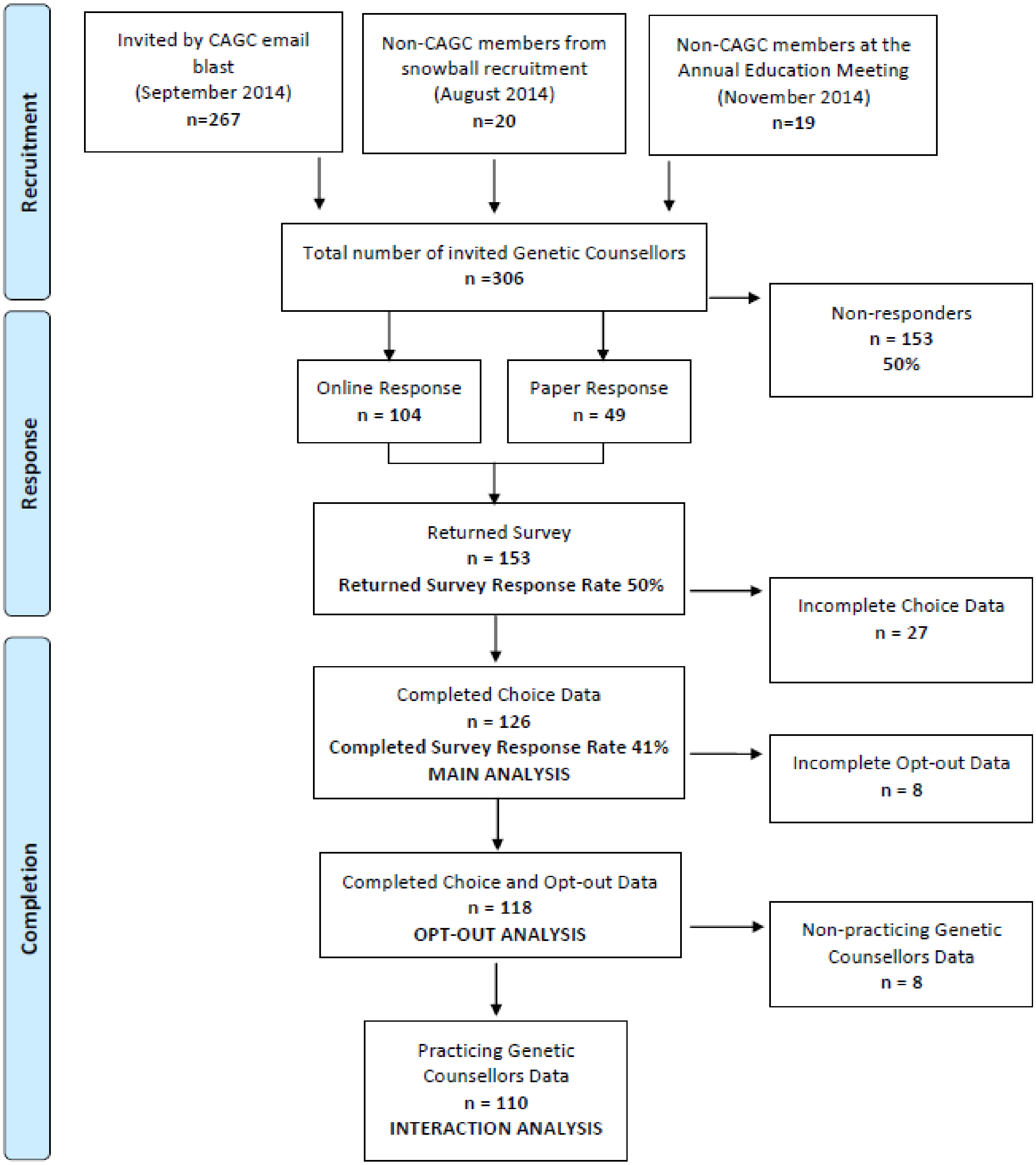


Figure 3: Results of main study recruitment.

CAGC: Canadian Association of Genetic Counsellors; Returned survey response rate=50% (153/306); Completed Survey Response Rate=41% (126/306).

3.2 Characteristics of Respondents

The demographic characteristics of the sample for the main effects analysis (n=126) are presented in Table 12.

Table 12: Demographic Characteristics of Main Effects Respondents (n=126)

Characteristics	**n**	**%**
Mean age in years (SD)		**33.7 (7.5)**
≤ 25	10	7.9
26-49	109	86.5
≥ 50	7	5.6
Female	124	98.4
Male	2	1.6
Ethnic or Cultural Association		
Canadian	81	64.3
Other/Mixed	14	11.1
None	9	7.1
South Asian	6	4.8
Chinese	5	4.0
French	3	2.4
English	3	2.4
Italian	3	2.4
Irish	1	0.8
Prefer not to answer	1	0.8
Religious Association		
None	82	65.1
Roman Catholic	13	10.3
Other Religious denomination	8	6.3
Jewish	7	5.6
Prefer not to answer	4	3.2
United Church of Canada	3	2.4
Evangelical Church	2	1.6
Presbyterian	3	2.4
Anglican	1	0.8
Baptist	1	0.8
Hindu	1	0.8
Jehovah's Witness	1	0.8
Household Income		
No income	3	2.4
Less than $20,000	2	1.6
$20,000 to $39,999	1	0.8
$40,000 to $59,999	8	6.3
$60,000 to $79,999	13	10.3

$80,000 to $99,999	16	12.7
$100,000 to $199,999	55	43.7
Greater than $200,000	11	8.7
Not sure or prefer not to answer	17	13.5
Marital Status		
Married or living common-law	89	70.6
Single (never been married)	35	27.8
Separated or divorced	2	1.6
Children		
None	69	54.8
1 or more biological children	54	42.9
1 or more step-children	1	0.8
1 or more mix of biological, adopted and step-children	2	1.6
Utilized Assistive Reproductive Technology Personally		
No	118	93.7
Yes	8	6.4

SD: standard deviation; %: Percentage

The majority of the respondents were female (98.4%) and the majority identified as being Canadian (64.3%). The mean age of the respondents was 33.7 years with a standard deviation of 7.5 years (ranging from 23-64 years). The majority of respondents did not have a specific religious association (65.1%). Of all respondents, the majority had a household income of $100,000 or over (52.4%). The majority of respondents were married (70.6%) and just over half of the respondents (54.8%) did not have children. Most respondents (93.7%) had never personally used assistive reproductive technology.

The practice characteristics for the main effects analysis (n=126) are presented in Table 13.

Table 13: Practice Characteristics of Main Effects Respondents (n=126)

Characteristics	n	%
Member of Canadian Association of Genetic Counsellors		
Yes	79	62.7
No/Unknown	47	37.3
Education		
Master’s in Genetic Counselling	108	85.7
Bachelors of Science/Arts	9	7.1
Completing or completed a PhD	3	2.4
Other (Masters in Science (2); Masters in	3	2.4

Bioethics (1)		
Bachelors in Nursing	2	1.6
Medical Degree	1	0.8
Employment		
Genetic Counsellor full-time	76	60.3
Genetic Counsellor part-time	20	15.9
Student	11	8.7
Genetic Counsellor and Researcher full-time	5	4.0
Works in another occupation full-time	3	2.4
Genetic Counsellor part-time and Researcher part-time	2	1.6
Works in another occupation part-time	2	1.6
On leave (ex. Maternity or disability)	2	1.6
Genetic Counsellor full-time and in another occupation full-time	1	0.8
Genetic Counsellor part-time and in another occupation part-time	1	0.8
Genetic Nurse Counsellor full-time	1	0.8
Researcher full-time	1	0.8
Unemployed	1	0.8
Experience		
>10 years of practice	33	26.2
Between 1-10 years of practice	71	56.4
Never practiced	22	17.5
Number of Years Practiced		
0	8	6.4
1-2	18	14.3
3-4	21	16.7
5-10	32	25.4
11-14	20	15.9
15-20	8	6.4
>20	5	4.0
Not applicable	4	3.2
Missing	10	7.9
Centre Type of Practice		
Academic only	69	54.8
Community only	18	14.3
Academic and Community	7	5.6
Outreach only	4	3.2
Community and Outreach	3	2.4
Academic and Outreach	1	0.8
Academic and Hospital	1	0.8
Academic, Community and Outreach	1	0.8
Other/Not applicable	12	9.5
Missing	10	7.9

Geographic Location of Practice		
Ontario	48	38.1
British Columbia	21	16.7
Quebec	11	8.7
Alberta	13	10.3
United States	6	4.8
Nova Scotia	4	3.2
Saskatchewan	3	2.4
Newfoundland	2	1.6
Other	3	2.4
Not applicable	15	11.9
Primary Area of Practice as Prenatal Genetics		
Yes	54	42.9
No	56	44.4
Not applicable	6	4.8
Missing	10	7.9
How often in a General consultation is Prenatal Genetics counseled?		
Often or Always	59	46.8
Sometimes	25	19.8
Rarely	20	15.9
Never or Not Applicable	11	8.7
Missing	11	8.7
How often in Prenatal Genetics consultations is PGD discussed?		
Often or Always	29	23.0
Sometimes	47	37.3
Rarely	25	19.8
Never or Not Applicable	14	11.1
Missing	11	8.7
How often in Prenatal Genetics consultations is the cost of IVF with PGD discussed?		
Never	9	7.1
Rarely	20	15.9
Sometimes	31	24.6
Often	17	13.5
Always	24	19.0
Not applicable	14	11.1
Missing	11	8.7
What is the Comfort Level regarding counselling of PGD?		
Comfortable or Very Comfortable	68	54.0
Neither Comfortable or Uncomfortable	21	16.7

Uncomfortable or Very Uncomfortable	13	10.3
Unknown	2	1.6
Missing	22	17.5
Experience of at least one patient undergo PGD		
Yes	54	42.9
No or not applicable	72	57.1

PGD: Preimplantation Genetic Diagnosis; %: Percentage

The majority of the respondents graduated with a Master's degree in Genetic Counselling (85.7%) and most of the genetic counsellors practiced full-time in the field (60.3%). There were 11 students who responded (8.7%). A quarter of the genetic counsellors practiced between 5-10 years (25.4%) and 4.0% practiced over 20 years. Most practicing genetic counsellors were situated in an academic setting only (54.8%). There was representation of genetic counsellors across Canada with the most representation from Ontario (38.1%). GC from Quebec represented 8.7% of the respondents. There was one genetic clinic covering New Brunswick, Nova Scotia and Prince Edward Island, which represented 2.4% of respondents. Less than half of respondents (42.9%) practice primarily in the area of prenatal genetics. Almost half of respondents (46.8%) "always" or "often" counseled about prenatal genetics within a general genetics consultation. Of those consultations, PGD was discussed "always" or "often" in 23.0% of the sessions and cost of IVF was discussed "always" or "often" in 32.5% of the consultations. The majority of the respondents were "comfortable" or "very comfortable" with counselling about PGD (54.0%). The percentage of GC having experience with at least one patient undergoing PGD is 42.9%. The attitudes of survey respondents for the main effects analysis (n=126) are presented in Table 14.

Table 14: Attitudes of Main Effects Respondents (n=126)

Characteristics	n	%
Preferences regarding public coverage		
Coverage for PGD and IVF	104	82.5
Coverage for PGD only and not IVF	20	15.9
No coverage for PGD or IVF	2	1.6
Knowledge of PGD (4 knowledge questions presented)		
All four answers were correct	119	94.4
At least one answer incorrect / did not know/no answer	7	5.6
Know PGD Policy in own area		
Yes	95	75.4
No (or outside Canada)	24	19.0
Not applicable	6	4.8
Missing	1	0.8
Certainty of Choice Task Answers		
Certain or Very Certain	57	45.2
Neither Certain or Uncertain	6	4.8
Uncertain or Very Uncertain	63	50.0
Importance of age of mother to coverage		
Very unimportant	13	10.3
Somewhat unimportant	39	31.0
Neither important nor unimportant	20	15.9
Somewhat important	47	37.3
Very important	5	4.0
Missing	2	1.6

PGD: Preimplantation Genetic Diagnosis; IVF: In-vitro fertilization

The majority of respondents (82.5%) agreed with public coverage by the government for both PGD and IVF but only 1.6% preferred no public coverage for either PGD or IVF. The majority of respondents were knowledgeable, answering all four knowledge questions about PGD correctly (94.4%). The majority of respondents claimed that they were knowledgeable about PGD policy within their own geographic region (75.4%). Approximately one third of respondents (31.0%) felt that the age of mother was “somewhat unimportant” while 37.3% felt that the age of mother was “somewhat important” as a criteria for coverage.

Respondents who filled out the survey in paper form were given the opportunity to provide feedback at the end of the attitude questionnaire section. Of the 49 respondents who filled out the paper version of the survey, 16 respondents offered comments (Data not shown). A total of seven comments related to coverage recommendations. One person supported coverage for PGD and IVF (Respondent 130) while one suggested limited coverage of PGD and IVF (Respondent 125). The third suggested coverage for IVF but not PGD (Respondent 143). One respondent wanted "the guidelines for funding to be generous but very clear" (Respondent 125). One respondent agreed to public funding but not for 8 cycles, not for predisposition conditions and not for 1% risk (Respondent 112). One respondent thought that 1-2 cycles would be more reasonable and the attribute greatly influenced their answers (Respondent 138). Finally, one respondent supported "any severe, untreatable, highly penetrant adult or childhood onset condition where the couple's risk is >25%" (Respondent 141).

Two survey comments showed interest in the study (Respondents 127 and 136). One survey comment questioned the face validity of having affected children have adult-onset conditions (Respondent 145). Another respondent expressed concern that they were not weighing all the factors and usually picked one on which to focus (Respondent 126). One respondent gave more information about the practice background being from the United States (Respondent 113).

Details of the demographic, practice and attitude data for the interaction analysis (n=110) did not greatly differ compared to the main effects analysis sub-group. The only difference was that those who did not practice genetic counselling were removed from the interaction data to avoid missing data and therefore, the mean respondent age was increased to 34.2 years (with a standard deviation of 7.3 years and a range of 23-64 years) in the interaction sub-group (Appendix 9).

3.3 Stated Preferences

3.3.1 Relative Importance of Main Study Attributes

The weighting of the attributes relative to each other as calculated from the main effects multinomial logit regression are presented in Table 15 with importance scores for the main study attributes in decreasing order of magnitude.

Table 15: Relative Importance of Main Study Attributes (n=126)

Attribute	Weighing of Attributes	Importance Score
Risk of condition	2.78	41.4
PGD indication	2.07	30.8
Family history	0.76	11.3
Fertility status	0.56	8.3
Number of cycles	0.55	8.2
Total	**6.72**	

PGD: Preimplantation Genetic Diagnosis

Based on the main-effects model and given the attribute levels that were specified in the experimental design, the most important attribute was found to be Risk of condition, followed by PGD indication, and Family history. Fertility status and Number of cycles were found to be the least important attributes.

3.3.2 Main Effects Model

The results of the main effects logit regression are presented in Table 16. The model goodness-of-fit was examined by calculating the McFadden's pseudo R^2, adjusted pseudo R^2 and Akaike's information criterion (AIC) (see Section 2.9.5.2). A comparison of the models used in the study will be presented in Section 3.3.6.

Table 16: Results from the Main Effects Multinomial Logit Regression Model (n=126)

Attribute	Levels	Beta	95% CI		SE	T-ratio	p-value	Pr>Chi Square
			Lower	Upper				
Risk of condition	50%	1.057	1.002	1.115	0.059	17.915	<0.001	<0.0001
	25%	0.669	0.621	0.724	0.056	11.946	<0.001	<0.0001
	1%$^{\psi}$	-1.725	-1.839	-1.622	0.079	-21.835	<0.001	-
PGD indication	Childhood-onset	1.122	1.060	1.191	0.070	16.029	<0.001	<0.0001
	Adult-onset non-cancer	-0.179	-0.219	-0.140	0.055	-3.255	0.010	0.001
	Adult-onset cancer predisposition$^{\psi}$	-0.944	-1.051	-0.841	0.058	-16.276	<0.001	-
Family history	Affected children	0.396	0.352	0.444	0.057	6.947	<0.001	<.0001
	No children	-0.033	-0.071	0.002	0.050	-0.660	0.526	0.515
	Unaffected children$^{\psi}$	-0.363	-0.446	-0.280	0.052	-6.981	<0.001	-
Fertility Status	Infertile	0.369	0.329	0.409	0.054	6.833	<0.001	<.0001
	Unknown	-0.173	-0.206	-0.143	0.052	-3.327	0.009	0.0008
	Fertile$^{\psi}$	-0.195	-0.266	-0.123	0.051	-3.824	0.004	-
Number of cycles^{T}	1	-0.079	-0.088	-0.069	0.013	17.915	<0.001	<.0001
	4	-0.314	-0.353	-0.278				
	8	-0.629	-0.706	-0.556				

-2Log Likelihood of model without predictors (null)	3144
-2Log Likelihood (predictor)	1672
Pseudo R^2	0.468
Adjusted Pseudo R^2	0.474
Akaike Information Criterion	1690
Degrees of Freedom	9

CI = Confidence interval; SE=Standard error; Pr=Probability; $^{\psi}$ reference level; ^{T} continuous coding; α=0.05

A graphical representation of the mean part-worth utilities categorized by attributes as defined in Section 2.9.5 is presented in Figure 4.

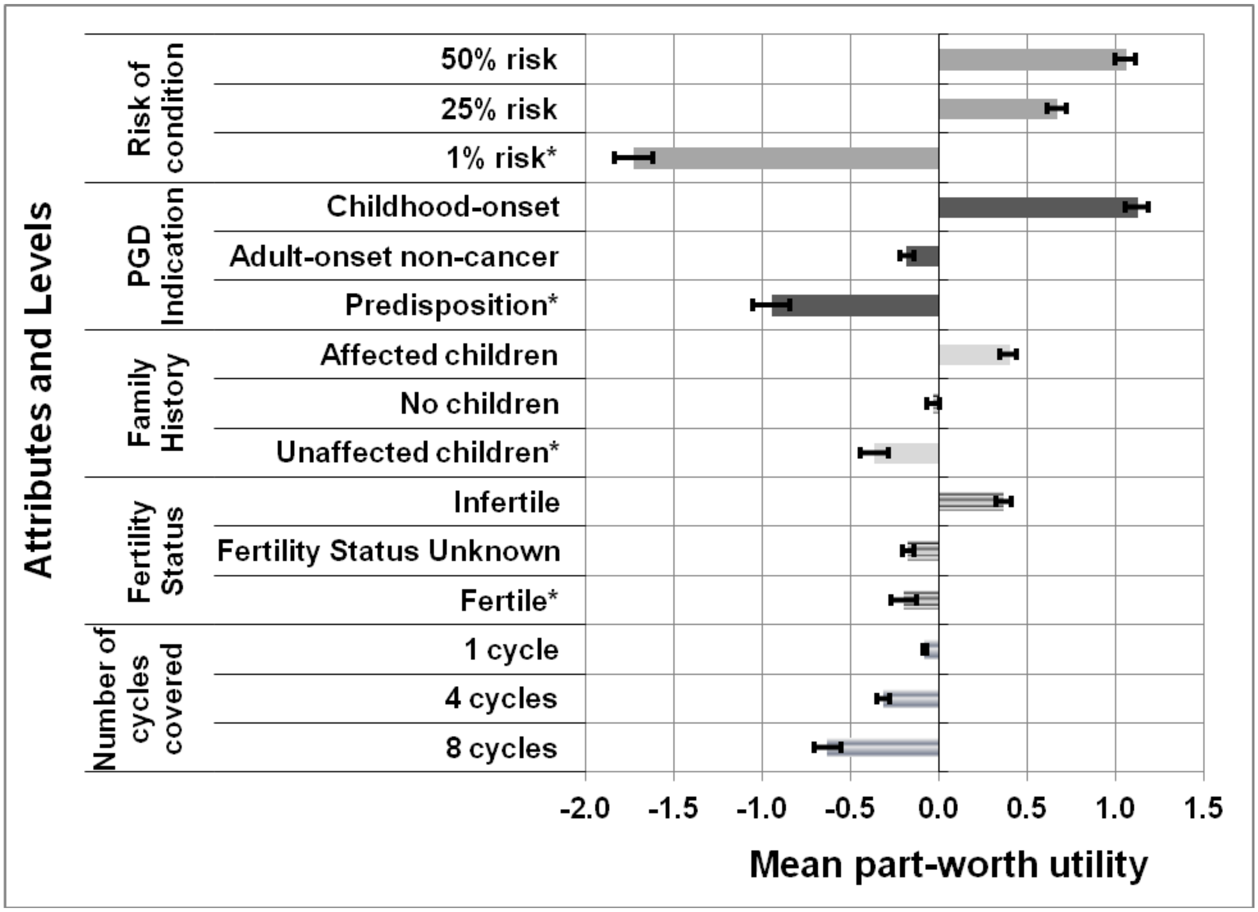


Figure 4: Mean part-worth utilities by attributes
PGD = Preimplantation Genetic Diagnosis; *represents reference level for the attribute; Black bars refer to the error bars for the 95% confidence intervals

Overall, all the part-worth utilities were statistically significant except for No Children. Among the attribute for Risk, 1% risk had the largest negative preference (-1.725). Among the attribute PGD indication, the largest positive preference was for Childhood-onset condition (1.122), while Adult-onset cancer predisposition (-0.944) was the least preferred. The largest positive preference among the Family history attribute was for Affected children (0.396), while Unaffected children had the largest negative preference. In regards to Fertility status, the Infertile couple (0.369) had the largest positive preference. The Fertile couple and the couple with Unknown Fertility status had similar small negative preferences.

In general, attributes related to characteristics of the condition showed a larger strength of preference compared to the various attributes related to inclusion criteria of the patient for PGD.

Number of cycles was an attribute that was coded as a continuous variable and was found to have negative part-worth utility, with the magnitude of the disutility increasing with the increased number of cycles.

The certainty of the choices made by the respondents was assessed in the attitude section of the questionnaire as shown in Table 14. Overall, the respondents were split with respect to the level of certainty of their answers with 45.2% stating they were “certain” or “very certain” with their choice responses and 50.0% stating they were “uncertain” or “very uncertain” with their choice responses.

3.3.3 Interaction Model with Demographics, Practice and Attitude Data

A total of 110 respondents provided sufficient demographic, practice and attitude data for interaction analyses. The results from a main effects multinomial regression for this sample are shown in Table 17.

The direction, magnitude and the significance of the parameter estimates in Table 17 were similar to the main effects analysis for n=126 (Table 16).

Table 17: Main effects analysis for n=110

Attribute	Levels	Beta	95% CI Lower	95% CI Upper	SE	T-ratio	p-value	Pr>Chi Square
Risk of condition	50%	1.107	1.046	1.171	0.065	17.039	<0.0001	<0.0001
	25%	0.727	0.674	0.781	0.062	11.698	<0.0001	<0.0001
	1%$^{\psi}$	-1.833	-1.952	-1.720	0.089	-20.497	<0.0001	-
PGD indication	Childhood-onset	1.166	1.095	1.237	0.078	14.871	<0.0001	<0.0001
	Adult-onset non-cancer	-0.209	-0.252	-0.168	0.061	-3.443	0.007	0.0011
	Adult-onset cancer predisposition $^{\psi}$	-0.956	-1.070	-0.843	0.064	-14.992	<0.0001	-
Family history	Affected children	0.395	0.348	0.443	0.063	6.293	0.0001	<0.0001
	No children	-0.038	-0.078	0.000	0.055	-0.701	0.501	0.4835
	Unaffected children$^{\psi}$	-0.357	-0.444	-0.270	0.057	-6.295	0.0001	-
Fertility status	Infertile	0.347	0.305	0.389	0.059	5.890	0.0002	<0.0001
	Unknown	-0.189	-0.224	-0.158	0.057	-3.325	0.009	0.0009
	Fertile$^{\psi}$	-0.158	-0.232	-0.081	0.055	-2.864	0.02	-
Number of cycles^{T}	1	-0.077	-0.088	-0.068	0.013	-6.005	0.0002	<0.0001
	4	-0.308	-0.351	-0.274				
	8	-0.617	-0.702	-0.547				

-2Log Likelihood of model without predictors (null)	2745
-2Log Likelihood (predictor)	1420
Pseudo R^2	0.483
Adjusted Pseudo R^2	0.489
Akaike Information Criterion	1438
Degrees of Freedom	9

CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\psi}$denotes reference level; ^{T}denotes continuous coding

Two models estimated interactions between attribute levels and the demographic, practice and attitude variables as previously described (Section 2.9.5.1). The first model was based on hypothesized interactions while the second model was based on data to investigate additional factors that may help to explain preferences. The hypotheses for the *a priori* model are described in Section 1.6. Briefly, the first model hypothesized that GC having greater than 10 years of experience would have a stronger preference for higher risk conditions compared to those with less experience as they were trained in a more traditional environment. The model also hypothesized that GC who have their own children would be more supportive for the couple to have children regardless of fertility status or family history of the couple. Finally, having a higher household income for the GC was thought to make them less likely to recommend funding of increased cycles (Table 18). The second model used purposeful regression to identify terms significant at p-value ≤ 0.05 (Appendix 10) and p-value ≤ 0.01 (Table 20) without *a priori* hypotheses.

Table 18: Experienced Interaction Model

Attribute/ Interaction	Levels	Beta	95% CI Lower	95% CI Upper	SE	T-ratio	p-value	Pr>Chi Square
Risk of condition	50%	1.058	1.000	1.127	0.067	15.817	<0.0001	<0.0001
	25%	0.713	0.656	0.776	0.065	11.005	<0.0001	<0.0001
	1%$^{\psi}$	-1.771	-1.903	-1.656	0.139	-12.718	<0.0001	-
PGD indication	Childhood-onset	1.123	1.061	1.199	0.080	14.126	<0.0001	<0.0001
	Adult-onset non-cancer	-0.174	-0.216	-0.133	0.063	-2.761	0.012	0.0058
	Adult-onset cancer predisposition$^{\psi}$	-0.949	-1.066	-0.845	0.099	-9.607	<0.0001	-
Family history	Affected children	0.405	0.357	0.454	0.063	6.404	<0.0001	<0.0001
	No children	-0.045	-0.086	-0.007	0.055	-0.816	0.425	0.4144
	Unaffected children$^{\psi}$	-0.360	-0.447	-0.271	0.057	-6.316	<0.0001	-
Fertility status	Infertile	0.358	0.317	0.402	0.060	6.010	<0.0001	<0.0001
	Unknown	-0.194	-0.229	-0.163	0.057	-3.390	0.003	0.0007
	Fertile$^{\psi}$	-0.163	-0.238	-0.088	0.055	-2.949	0.008	-
Number of cycles^{T}	1	-0.079	-0.091	-0.070	0.015	-5.265	<0.0001	<0.0001
	4	-0.317	-0.363	-0.279				

8	-0.635	-0.727	-0.558				
Worked >10 years*50% risk	-0.205	-0.260	-0.144	0.066	-3.127	0.005	0.0018
Worked >10 years*25% risk	-0.080	-0.131	-0.025	0.060	-1.334	0.199	0.1822
Worked >10 years*1% risk$^{\psi}$	0.285	0.169	0.392	0.184	1.551	0.138	-
Worked >10 years*Childhood-onset condition	-0.227	-0.296	-0.159	0.077	-2.961	0.008	0.0031
Worked >10 years*Adult-onset non-cancer condition	0.156	0.121	0.193	0.061	2.576	0.019	0.01
Worked >10 years*Adult-onset cancer predisposition$^{\psi}$	0.071	-0.035	0.175	0.142	0.498	0.624	-
Has a child*Affected children	-0.041	-0.861	0.005	0.060	-0.683	0.504	0.4949
Has a child*No children	-0.074	-0.112	-0.036	0.053	-1.398	0.179	0.1621
Has a child*Unaffected children$^{\psi}$	0.115	0.030	0.974	0.056	2.052	0.055	-
Has a child*Infertile	-0.049	-0.092	-0.009	0.057	-0.865	0.398	0.3868
Has a child*Fertility unknown	0.037	0.001	0.069	0.055	0.676	0.507	0.4988
Has a child*Fertile$^{\psi}$	0.012	-0.060	0.091	0.055	0.226	0.824	-
>\$100,000 income*1 cycle^{T}	0.004	-0.006	0.014	0.014	0.281	0.782	0.7787
>\$100,000 income*4 cycle^{T}	0.016	-0.024	0.057				
>\$100,000 income*8 cycle^{T}	0.031	-0.047	0.114				

-2Log Likelihood of model without predictors (null)	2745
-2Log Likelihood (predictor)	1400
Pseudo R^2	0.490
Adjusted Pseudo R^2	0.503
Akaike Information Criterion	1436
Degrees of Freedom	18

All interaction terms are shown in decreasing order of significance. CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\psi}$denotes reference level; ^{T}denotes continuous coding

In the Experienced interaction model, the parameter estimates (Table 18) were similar to the main effects analysis (Table 17).

The interaction terms act as parameter estimate modifiers to the part-worth utility. These estimates were calculated by adding the parameter estimates of the interaction term to the parameter estimate of the main effect attributes estimated in the interaction model. For instance, for the Experienced model, the parameter estimate for 50% risk was 1.058, while the interaction term between 50% risk and GC with greater than 10 years experience was -0.205 (Table 18). Thus, the parameter estimate for 50% risk for GC who have greater than 10 years experience was reduced by 0.205 resulting in a part-worth utility of 0.853 (1.058+ (-0.205)=0.853). The adjusted parameter estimates for all significant interactions within the Experienced model are summarized in Table 19.

Table 19: Adjusted Parameter Estimates for Significant Experienced Model Terms

Interaction	**Main parameter estimate**	**Adjusted parameter estimate**
Worked >10 years*50% risk	1.058	0.853
Worked >10 years*Childhood-onset condition	1.123	0.896
Worked >10 years*Adult-onset non-cancer condition	-0.174	-0.018

There were three statistically significant interaction terms (Table 19). The first was 50% risk among GC who worked greater than 10 years. When there was more experience, there was a reduced preference for the high risk condition which was contrary to the hypothesis that the experienced GC would prefer higher risk conditions. The second statistically significant interaction term was for childhood-onset conditions among GC with greater than ten years experience. The third significant interaction term showed an increased preference for coverage of PGD for adult-onset non-cancer conditions among those who worked as a GC for greater than ten years. GC who had children and those of higher income were not found to have statistically significant interactions with the main parameter estimates.

The second interaction model was formulated through purposeful regression as described in Section 2.9.5.1 as opposed to stepwise regression where the terms are removed one at a time based on significance alone. The multinomial regression analysis for the purposeful regression interaction model with p-value ≤ 0.05 is presented in Appendix 10 and contained 27 interaction terms that were significant. The number of significant terms decreased to nine when the model contained only terms significant at p-value ≤ 0.01 (Table 20).

Table 20: Purposeful Regression Interaction Model (p-value ≤ 0.01)

Attribute/ Interaction	**Levels**	**Beta**	**95% CI Lower**	**95% CI Upper**	**SE**	**T-ratio**	**p-value**	**Pr>Chi Square**
Risk of	50%	0.887	0.763	1.011	0.134	6.643	<0.0001	<0.0001

condition	25%	0.456	0.323	0.598	0.135	3.375	0.0023	0.0007
	1%ψ	-1.343	-1.608	-1.086	0.182	-7.363	<0.0001	-
PGD indication	Childhood-onset	1.185	1.115	1.274	0.097	12.255	<0.0001	<0.0001
	Adult-onset non-cancer	-0.128	-0.178	-0.081	0.076	-1.692	0.1030	0.0906
	Adult-onset cancer predispositionψ	-1.057	-1.193	-0.937	0.097	-10.917	<0.0001	-
Family history	Affected children	0.166	0.046	0.294	0.159	1.045	0.306	0.296
	No children	-0.035	-0.079	0.007	0.057	-0.617	0.543	0.5372
	Unaffected childrenψ	-0.131	-0.301	0.033	0.157	-0.835	0.412	-
Fertility status	Infertile	0.187	0.112	0.267	0.114	1.642	0.113	0.1005
	Unknown	0.005	-0.064	0.077	0.114	0.047	0.963	0.9628
	Fertileψ	-0.192	-0.344	-0.048	0.110	-1.747	0.093	-
Number of cyclesT	1	-0.171	-0.190	-0.153	0.030	-5.760	<0.0001	<0.0001
	4	-0.682	-0.758	-0.613				
	8	-1.364	-1.516	-1.227				
Identifies as a Canadian*50% risk		0.206	0.149	0.263	0.056	3.711	0.001	0.0002
Has a Masters in Genetic Counselling*25% risk		0.347	0.211	0.476	0.094	3.703	0.001	0.0002
Income >$100,000 (+ prefer not to answer)*Childhood-onset condition		-0.191	-0.243	-0.148	0.057	-3.341	0.002	0.0008
Practices Prenatal and other areas*Childhood-onset condition		0.414	0.310	0.521	0.123	3.359	0.002	0.0008
Practices in Canada*1 cycle		0.094	0.077	0.112	0.028	3.288	0.002	0.0010
Practices in Canada*4 cycles		0.375	0.307	0.448				
Practices in Canada*8 cycles		0.749	0.614	0.895				
Has a child*Adult-onset non-cancer condition		0.163	0.130	0.197	0.050	3.245	0.003	0.0012
Has had patient undergo PGD*Adult-onset non-cancer condition		-0.143	-0.178	-0.113	0.050	-2.883	0.007	0.0039
Practices in a PGD permissive province*Childhood-onset condition		0.145	0.101	0.192	0.051	2.852	0.008	0.0043
Agrees with covering IVF with PGD*Adult-onset non-cancer condition		-0.171	-0.218	-0.127	0.065	-2.648	0.013	0.0081

-2Log Likelihood of model without predictors (null)	2745
-2Log Likelihood (predictor)	1320
Pseudo R^2	0.519
Adjusted Pseudo R^2	0.538
Akaike Information Criterion	1372
Degrees of Freedom	26

Only interaction terms significant at p=<0.01 are shown. CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\Psi}$denotes reference level; ^{T}denotes continuous coding

There were a total of nine statistically significant interactions within the purposeful regression model at $p \leq 0.01$ (Table 20). The adjusted beta parameter estimates for the significant terms from purposeful regression are listed in Table 21.

Several adjusted beta parameter estimates were associated with an increased preference in the Purposeful Regression model based on specific demographic subgroups. Among GC who identified as being Canadian compared to the total group of study respondents, there was increased preference for public coverage of conditions with 50% risk. Among those who had a Masters in Genetic counselling, the parameter estimate was increased to 0.803 for conditions with 25% risk of a condition, which means that these GC would more likely recommend coverage for conditions related to a 25% risk for recurrence. Childhood-onset condition was associated with an increased parameter estimate among GC who practiced in both Prenatal and other areas, which means that Childhood-onset conditions were more preferred when GC practiced in a mixed area with some prenatal care. When GC practiced in Canada, Number of cycles as a continuous variable was associated with an increased parameter estimate, which means that practicing GC in Canada preferred an increased number of cycles covered. When the GC specifically practiced in a PGD permissive area (Ontario, Quebec, Manitoba, New Brunswick or Europe), conditions with childhood onset were associated with a more positive parameter estimate, meaning that regions who are already providing some support for IVF have a positive preference for conditions which manifest before 18 years of age. Finally, when GC have children of their own, Adult-onset non-cancer condition was associated with an increased parameter estimate, which means that these GC prefer to support recommendations to cover Adult-onset non-cancer conditions.

Table 21: Adjusted Parameter Estimates for all Significant Purposeful Regression Terms

Interaction	**Main parameter estimate**	**Adjusted parameter estimate**
Identifies as a Canadian*50% risk	0.887	1.093
Has a Masters in Genetic Counselling*25% risk	0.456	0.803
Income >$100,000 (+ prefer not to answer)*Childhood-onset condition	1.185	0.994
Practices Prenatal and other areas*Childhood-onset condition	1.185	1.599
Practices in Canada*1 cycle	-0.171	-0.077
Practices in Canada*4 cycles	-0.682	-0.307
Practices in Canada*8 cycles	-1.364	-0.615
Has a child*Adult-onset non-cancer condition	-0.128	0.035
Has had patient undergo PGD*Adult-onset non-cancer condition	-0.128	-0.271
Practices in a PGD permissive province*Childhood-onset condition	1.185	1.330
Agrees with covering IVF with PGD*Adult-onset non-cancer condition	-0.128	-0.299

IVF=In vitro fertilization; PGD=Pre-implantation Genetic Diagnosis

In contrast, several significant interaction terms were associated with reduced parameter estimates in purposeful regression. Among GC who agreed with covering IVF with PGD, there was a reduced preference for recommending coverage for Adult-onset non-cancer condition. For GC who have had a patient undergo PGD, the preference of Adult-onset non-cancer condition was also reduced. Finally, in those GC who either had a household income of over $100,000 or who preferred not to answer the income question, Childhood-onset condition was associated with a reduced adjusted beta parameter estimate, which means that those with higher incomes over $100,000 had a decreased preference for recommending coverage of conditions that present before the age of 18.

As described in Section 2.9.5.1, purposeful regression involves retaining interaction terms that are significant at the desired p-value level and also those that make significant differences to the main effects attributes. In comparison to the main effects analysis (Table 16), several parameter estimates lost significance within the purposeful regression interaction analysis due to the influence of interaction terms. The main attribute level for Adult-onset non-cancer condition was no longer statistically different with a p-value of 0.09. Having Affected children was no longer statistically different compared to zero with a p-value of 0.296. Both Infertile and Unknown fertility status lost their statistical significance with p-values of 0.100 and 0.963 respectively. These changes in significance may be related to the interaction terms that were kept in the purposeful regression model as shown in Table 22. The terms shown changed the significance of the main attribute levels from non-significant in the main effects analysis (n=110) to significant. Although these individual interaction terms may not have been significant at either the p-value ≤0.05 or the p-value ≤0.01 levels, their existence in the model modifies the main attributes.

Table 22: Interaction Terms which Changed the Significance of Main Attributes

Interaction Term	Main effects Beta	Beta of the interaction term	Adjusted Beta estimate	SE	p-value	Changed significance of:
Always or often counsels about cost*50% risk	0.887	0.384	1.271	0.151	0.011	Affected children
Neither comfortable or uncomfortable about counselling for PGD*Affected children	0.166	0.351	0.517	0.173	0.042	Affected children
Personally used ART*Fertility Unknown	0.005	0.214	0.219	0.112	0.055	Fertility unknown
Rarely counsels about cost*50% risk	0.887	0.276	1.163	0.144	0.055	Affected children
Personally used ART*Infertile	0.187	-0.180	0.007	0.112	0.108	Infertile
Comfortable or very comfortable about counselling about PGD*Affected Children	0.166	0.164	0.330	0.164	0.317	Affected children
Personally used ART*25% risk	0.456	0.019	0.475	0.099	0.849	Fertility unknown

SE=standard error; IVF=in vitro fertilization; PGD=Preimplantation Genetic Diagnosis; ART=assisted reproductive technologies

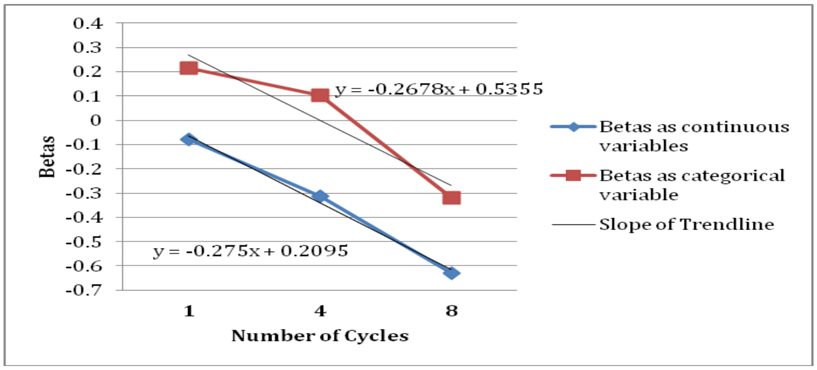
Among the GC who personally used assisted reproductive technologies (ART), having Unknown fertility in a couple or having a 25% risk of a condition were associated with small magnitudes of increased preference and affected the significance of the Fertility unknown attribute level. When these same GC who had used ART were asked about coverage for couples who are infertile, there was a small magnitude of reduced preference almost to zero, and this significantly affected the Infertile Fertility status attribute level. GC who counseled about costs either “often” or “always” had increased preference related to 50% Risk of Condition and it significantly changed the Family history of Affected children attribute level. Counselling “rarely” about cost also had an associated positive preference for 50% risk and affected the significance of the Family history of Affected children attribute level. Among GC who were counselling about PGD, those who were “comfortable” or “very comfortable”, as well as those that were “neither comfortable” nor “uncomfortable”, regarded the Family history of Affected children with increased preference. These interaction terms had implications on the significance of Affected children as a main attribute level.

In comparing the two interaction models, the first was based on *a priori* hypotheses related to the effects of working greater than 10 years experience, having one’s own children and household incomes greater than $100,000. Household income and having one’s own children did not seem to affect preferences. However, experience over 10 years seemed to affect the directionality and magnitude of the Risk and PGD indications levels with reduced preference for 50% risk and Childhood-onset conditions and increased preference for 1% and Adult-onset cancer predisposition. By providing a regression model that was not restricted to *a priori* hypotheses, increased Number of cycles covered was more preferred among GC who practiced in Canada. GC with income over $100,000 did not interact significantly with Number of cycles but did show significant reduced preference for Childhood-onset conditions. When GC have their own children, there was increased preference for Adult-onset non-cancer conditions.

3.3.4 Sensitivity Analysis of “Number of cycles” Attribute as Continuous Variable versus Categorical Variable

The Number of cycles attribute was coded as continuous and therefore assumed to be linear with a slope of -0.275. For every additional cycle added, there would be the same marginal effect on choice. Thus, for 4 cycles, the assumption is that the parameter estimate would be the product of the slope and the number of cycles (i.e. 4*(-0.275) = -1.1). A sensitivity analysis shows the results of removing the assumption of linearity and treating Number of cycles as a categorical variable by effects coding (Appendix 11). A graphical representation of the relationship is shown as Figure 5.

Figure 5: Slope of the "Number of cycles" when Treated as a Categorical Variable



The slope of the line through the three categorically coded variables shown in Figure 5 as the red line with squares was similar to the marginal utility of cycles estimated when number of cycles was treated as a continuous variable. However, between 1 cycle and 4 cycles, there was a less negative slope observed compared to the slope between 4 cycles and 8 cycles. When Number of cycles was treated as a categorical variable, each additional cycle did not represent the same marginal effect on choice. Respondents had a lesser preference to move from 4 cycles to 8 cycles. There were also positive preferences for 1 cycle and 4 cycles and a negative preference for 8 cycles. Despite this, the main effects analysis utilized cycle as a continuous variable as there was not a significant difference between the two analyses based on model fit.

3.3.5 Sensitivity Analysis of the Second-Stage Opt-Out Option

The opt-out option was used at least once for each choice task with the exception of three tasks (task 8 and 16 from version 1 and task 11 from version 2) (Appendix 12). The percentage use of the opt-out option within each choice task ranged from 3%-65%. The choice task which demonstrated the highest percentage opt-out is shown in Table 23.

Table 23: Choice Task with the Highest Percentage of Respondents who Opted-out

Risk of condition	25%	1% risk
PGD indication	Adult-onset cancer predisposition	Childhood-onset condition
Family history	No children	Unaffected children
Fertility status	Fertility unknown	Fertile
Number of cycles	8 cycles	1 cycle

Sixty-five percent of respondents for this choice task (20/31) preferred the option of covering neither scenario.

As shown in Figure 3, the sensitivity analysis for the second stage opt-out option was based on a lower number of respondents (n=118 compared to n=126 for the main study) since there was missing opt-out data for 8 respondents. The main effects regression analysis for n=118 is shown in Appendix 13. The directionality and significance of the parameter estimates for all levels from the regression analysis using the second-stage opt-out were similar to the n=118 main effects analysis (Appendix 13). The exception was one sign change in parameter estimates for having No children from -0.022 analyzed as a two option regression (Appendix 13) compared to 0.047 analyzed as a three option regression (Table 24). However, this term was not significant. The difference between the parameter estimates is 0.267 (0.047-(-0.022) = 0.267). In terms of significance, there was no difference in which levels were statistically significant ($p \leq 0.05$) when analyzed as a three-choice option.
In the opt-out option regression which provides no coverage as a third option, there was a greater spread between the parameter estimate magnitudes for the Risk of condition and PGD indication attributes, while the spread between magnitudes of the Number of cycles decreased. The spread between the magnitudes for Family history and Fertility status were similar between the two analyses.

Table 24: Results of Regression Analysis for Second-Stage Opt-out Option

Attribute	Levels	Beta	95% CI Lower	95% CI Upper	SE	T-ratio	p-value	Pr>Chi Square
Risk of condition	50%	1.192	1.142	1.247	0.059	20.161	<0.0001	<0.0001
	25%	0.803	0.749	0.855	0.059	13.704	<0.0001	<0.0001
	1%$^{\psi}$	-1.995	-2.102	-1.891	0.050	-40.222	<0.0001	-
PGD indication	Childhood-onset	1.327	1.262	1.388	0.065	20.468	<0.0001	<0.0001
	Adult-onset non-cancer	-0.205	-0.251	-0.159	0.055	-3.719	0.0048	0.0002
	Adult-onset cancer predisposition$^{\psi}$	-1.122	-1.229	-1.011	0.062	-18.028	<0.0001	-
Family history	Affected children	0.383	0.338	0.426	0.059	6.502	0.0001	<0.0001
	No children	0.047	0.010	0.084	0.053	0.884	0.3997	0.3767
	Unaffected children$^{\psi}$	-0.430	-0.510	-0.348	0.057	-7.485	<0.0001	-
Fertility status	Infertile	0.397	0.361	0.435	0.056	7.076	<0.0001	<0.0001
	Unknown	-0.181	-0.215	-0.150	0.055	-3.270	0.0097	0.0011
	Fertile$^{\psi}$	-0.215	-0.285	-0.146	0.056	-3.826	0.0041	-
Number of Cycles^{T}	1	-0.036	-0.048	-0.023	0.010	-3.648	0.0053	0.0003
	4	-0.144	-0.192	-0.020				
	8	-0.287	-0.384	-0.184				

-2Log Likelihood of model without predictors (null)	4667
-2Log Likelihood (predictor)	3055
Pseudo R^2	0.345
Adjusted Pseudo R^2	0.349
Akaike Information Criterion	3073
Degrees of Freedom	9

CI=Confidence Interval, SE=Standard error; Pr=Probability; $^{\psi}$denotes reference level; ^{T}denotes continuous coding

3.3.6 Comparison of Models

The model goodness-of-fit was examined for the main effects analysis, interaction models and the sensitivity analyses by calculating the McFadden's pseudo R^2, adjusted pseudo R^2 and Akaike's information criterion (AIC) (see Section 2.9.5.2). Table 25 shows the comparison of model fit for the main effects analyses and the interaction analyses. All models had pseudo R^2 greater than 0.2 which suggested that they were well fit [120].

For the main effects analysis, the final results of the study are based on the main effects analysis with Number of cycles as a continuous variable (Table 16). Although the pseudo R^2 and the adjusted pseudo R^2 for the main effects model with Number of cycles as categorical was slightly higher (Appendix 11), there was no significant difference between treating cycles as a continuous variable versus a categorical variable. Since there was one less degree of freedom with Number of cycles as a continuous variable, the main findings of this study are based on the main effects analysis with number of cycles as a continuous variable.

For the interaction analysis, the model that had the highest pseudo R^2 as well as the lowest AIC was "Significant interactions (<0.05)" due to purposeful regression (Appendix 10). However, there were 27 significant interaction terms which were deemed to be too many to interpret. Instead the "All significant interactions (<0.01)" model was chosen as the purposeful regression model on which the main exploratory results of interactions was based. The "Experienced" model was chosen as a final results model given that the interactions were hypothesized *a priori*. The adjusted R^2 was highest for the interaction model that included all the non-significant terms but it contained the most degrees of freedom. This model was created to ensure that there were no terms from the purposeful regression analysis that were wrongly rejected with a p-value of ≥ 0.2.

Table 25: Comparison of model fit

Table	Description of Model	minus 2LogL Null (0)	minus 2LogL Predict (p)	Pseudo R^2	Adj. pseudo R^2	AIC	DF
	MAIN EFFECTS ANALYSIS						
Table 16	Main effects n=126 cycle as continuous	3144	1672	0.468	0.474	1690	9
Appendix 11	Main effects n=126 cycle as categorical	3144	1670	0.469	0.475	1690	10
	INTERACTION ANALYSES						
Table 17	Main effects cycle as continuous	2745	1420	0.483	0.489	1438	9
Table 18	Hypothesized Experienced Model	2745	1400	0.490	0.503	1436	18
Appendix 10	Significant interactions (<0.05)	2745	1231	0.552	0.587	1327	48
Table 20	All significant interactions (<0.01)	2745	1320	0.519	0.538	1372	26
Not shown	Most significant interactions (<.0001)	2745	1382	0.496	0.510	1418	18
Not shown	All non-significant factors	2745	1281	0.533	0.656	1617	168

AIC=Akaike's information criterion; Adj-pseudo R^2 = Adjusted pseudo R^2; DF = Degrees of freedom; Yellow shaded cells refer to the best fit of the compared models for each analysis; Gray shaded rows represent the models used for the main findings and conclusions.

Thus, the main findings of this study as explored in Chapter 4 are based on the main effects continuous Number of cycles model, and the *a priori* hypothesized Experience model.

4 Discussion

Through a DCE with Canadian genetic counsellors, insight is offered into their preferences related to public coverage for preimplantation genetic diagnosis. In particular, the study addresses some conditions under which public coverage of PGD could be recommended. The indications for PGD testing as well as the criteria for patient inclusion were explored from the genetic counsellor perspective.

This chapter is divided into four sections. The first section discusses the main findings based on the main regression analysis and the Experience interaction model regarding genetic counsellor preferences for the main study attributes. These findings will be compared to the literature and the policy implications will be discussed in the context of the current policy milieu. The second section considers the limitations related to the study. The third section proposes avenues for extension of this research and the fourth section provides important conclusions and closing remarks.

4.1 Key Findings Based on Preferences for Preimplantation Genetic Diagnosis

This is the first discrete choice experiment to quantify genetic counsellors' preferences for PGD coverage accounting for both clinical testing factors and patient inclusion factors. These key findings contribute to certain policy implications that could be considered. The discussion begins with two key findings that can be drawn from genetic counsellor preference results relative to the attributes and levels included in the study.

1. Genetic counsellors prioritize clinical considerations above patient inclusion factors. The study provides evidence that clinical need, based on the risk of the condition and indications for testing, is the major decision criterion in determining public coverage preferences.

2. Notwithstanding this orientation to the clinical status of the potential child, there is still some valuation of patient criteria in regards to family history and fertility status.

The key findings will now be described in greater detail to highlight the supporting evidence from the study, to compare the findings with the literature and to apply the findings to suggest policy implications.

4.1.1 Clinical Consideration as the Major Decision Criterion

The present study provides evidence that clinical consideration is the major decision criterion for genetic counsellors when asked about PGD coverage preferences. The greatest magnitudes of preference were for the risk of the condition and the types of indications for testing as compared to patient inclusion factors such as family history or fertility status. Furthermore, when considering the different levels of risk or the indications for the testing, there is a novel suggestion that there is greater tolerance towards lower risk conditions and adult-onset conditions among genetic counsellors with increased experience.

The key finding of clinical considerations as important is consistent with two studies. Severin et al. reported that risk of a condition was highly valued in a DCE study of various stakeholders assessing preferences for genetic test prioritization [7]. Severin et al. studied five attributes: risk of having the condition, severity of the condition, aim of test, benefit from test and cost of test [7]. Risk of a condition was most valued after the attribute of medical benefit of a test. In a DCE study that looked at a sample of Australian genetic counsellors asking about preferences for disclosure of incidental findings from genetic testing, age of onset (childhood versus adulthood) was found to be the second most preferred characteristic after availability of treatment, which was not an attribute considered in the current DCE study [127]. However, the present study included attributes related to patient inclusion factors which were not directly examined in the previous studies. Thus, this study highlights that clinical considerations of the test are prioritized even above patient characteristics for eligibility of coverage.

A possible explanation as to why genetic counsellors prioritize clinical considerations over other criteria is related to their role as health care professionals. Assessment and understanding of risk is an important part of the role of a genetic counsellor [128]. Genetic counsellors may prefer to base decisions on clinical knowledge of risk and the types of conditions rather than on patient characteristics for eligibility, which may have more social and ethical connotations.

While the importance of clinical consideration is supported by literature and the role of genetic counsellors, the suggestion of more tolerance toward lower risk conditions and adult-onset conditions was incongruous with existing policy and literature. For instance, in regards to risk, testing for conditions of autosomal recessive (25% risk) and autosomal dominant (50% risk) inheritance patterns are standard and acceptable. Testing for germline mosaicism (1%) is more contentious as reflected in the National Health Services – England guidelines to limit PGD testing for genetic conditions to a risk of 10% or more [33]. In regards to PGD indications, Kalfoglou and colleagues concluded that there is consensus for "severe, life-threatening genetic illness" to be covered but there is debate about adult-onset genetic disease [50].

A possible explanation for the potential increased tolerance toward lower risk conditions and adult-onset conditions could be due to increased experience of the genetic counsellor over time. Increased experience usually means that there is increased interaction with patients. The practice of genetic counselling for extended periods of time makes one consider the patient's perspective. Although a GC could consider 1% as a low risk, Wertz and colleagues showed that some patients would indicate that their child would "probably" or "definitely" be affected independent of the numeric risk [129]. This is the perspective that once a family has a child who is affected, they perceive their risks to be higher than the actual numeric risk [129]. If patients view 1% as a higher risk, they may be more likely to undergo an invasive test or intervention to resolve the risk. As GC are typically asked to provide non-directive counselling [101], GC may be more likely to prefer PGD coverage even for a lower risk of the condition. A similar argument could be made for patients who have adult-onset conditions and have negative experiences with the condition. It is possible based on their negative experience that the patient would prefer not to transmit the condition to their child.

From a policy perspective, the finding of clinical consideration as the major determinant criterion and that genetic counsellors with more experience, have more tolerance towards lower risk conditions and those of later onset, would align with Quebec's PGD policy from 2010-2015. The policy was for "all PGD tests" to be covered "when they are necessary" for "serious diseases" [18] and there was no restriction based on risk level. While the United Kingdom valued the need for specifications of clinical indications through their list of funded conditions, funding lower risk conditions challenges the United Kingdom policy as funding is restricted to >10% risk [33].

Clear guidelines about which conditions or risk levels could be covered could help to limit the volume of patients eligible for coverage. However, as more experienced GC may have increased preference towards lower risk conditions and adult-onset conditions, the scope of testing could increase and therefore increase the potential volume of patients eligible for coverage. Increased volumes eligible for coverage would therefore increase total costs of a funded program similar to the situation in Quebec which went over-budget and consequently requiring reevaluation of the program [23]. Alternatively, if an upper limit is placed on the budget of the program similar to the plan in Ontario [27], milder indications for testing could be covered based on a first-come first-served basis and as a result, utilize the resources which might have otherwise been spent for couples testing for earlier onset or higher risk conditions. As clinical consideration is a major decision criterion for genetic counsellors, contemplation of these issues is important for policy implications.

4.1.2 Valuation of Patient Criteria for PGD Coverage

Notwithstanding the importance of clinical need for testing, the second key finding is that there is still some valuation of the status or characteristics of the woman and her family for PGD coverage considerations given the attributes and levels that were included in the main survey. Genetic counsellors were found to prefer PGD coverage for the infertile couple, which is supported in the literature. However, it was surprising that consideration of couples having no children was not a significant determinant on preference. When asked about the importance of maternal age, the results were split between those who felt it was important compared to those who did not, which is not consistent with the current policy perspective. The findings related to infertile couples, couples having no children and maternal age will now be discussed in further detail.

Genetic counsellors prefer coverage of PGD for infertile couples. This result is in keeping with suggestions from De Wert and colleagues about the proportionality principle for infertile couples. Specifically, the authors argue that infertile couples could be more accepting of risks of IVF for a broad range of PGD criteria since they have already accepted the risks of IVF for treatment of infertility [130]. In contrast, those who are fertile and require IVF for PGD may be held to a more restrictive medical threshold for PGD coverage given that they could have otherwise become pregnant naturally [130].

From a policy perspective, Quebec previously placed no restrictions on PGD coverage based on fertility status [18]. Couples who were either fertile or had unknown fertility status could avoid pregnancy termination of an affected child by using PGD if there were religious or personal objections to termination. The current situation regarding fertility status in Quebec is unclear with the 2015 changes in policy [4]. Based on the preferences of GC from this study, two policy options could be considered if PGD were to be covered. One option could be to restrict PGD coverage to infertile couples regardless of the other testing and patient factors. This would restrict coverage of PGD for couples who also need IVF for treatment of infertility. A second option could be to provide coverage for fertile couples who need PGD for medical indications, thus taking the patient's autonomy and culture into consideration. If so, the question could then become whether the threshold for other factors such as risk of the condition, PGD indication, and family history could be set differently between infertile and fertile couples.

While the preference of GC for infertile couples was consistent with the literature, it was surprising that couples having no children did not seem to affect preference for public coverage significantly. Even among a group of GC who have their own children, the *a priori* hypothesis that GC respondents with children would have more tolerance for levels of family history and fertility status was not proven. This finding was surprising because Jain and colleagues had reported that having no children and having children all of one sex increased the demand for sex selection, which in the context of the current study was analogous to having affected children [107]. Similarly, the majority of women seeking PGD in a study by Karatas et al. had no children [69]. Yet the results for both studies were based on patient responses. Therefore, a possible explanation for the finding of couples with no children not significantly affecting preference is that genetic counsellors value the family history differently than patients.

In contrast, policy makers take into account family history as evidenced by the restriction of coverage based on family history for PGD coverage in the United Kingdom [68]. More recently, the policy in Quebec related to family history has been challenged as recommended by the Health and Welfare commissioner in Quebec. Based on the experience in Quebec, the Health and

Welfare commissioner felt that the assisted reproduction program should be maintained but not based on the model started in 2010 [23]. His recommendations included limits to access depending on odds of success, maternal age and family history of number of existing children.

Just as there is a trend towards limiting coverage regarding family history, there has also been further restriction based on maternal age. Since the recommendation of limits to access based on maternal age by the Quebec Health and Welfare commissioner, maternal age has become a restriction in Quebec and in Ontario for IVF [5, 25]. It is interesting that genetic counsellors were divided about the importance of maternal age within the current study. Based on evidence provided by a systematic review of reviews and primary studies, maternal age was thought to be an appropriate consideration for public funding policies if the purpose was to maximize IVF clinical effectiveness [131].

Taken together, the preferences of genetic counsellors consider clinical needs in the form of risk and PGD indications as the first decision criterion and factors related to the couple's eligibility in the form of family history and fertility status secondarily. The following section describes the current study's limitations and the efforts to minimize the limitations.

4.2 Limitations

The above key findings were based on genetic counsellors' preferences from the attributes and levels included in the DCE survey with several acknowledged limitations. The limitations can be categorized into 1) instrument design, 2) preamble content 3) sampling 4) response rate and 5) interpretation issues.

First, the hypothetical nature of the scenarios and the restriction of the choice tasks to defined attributes in the instrument design have been described in the literature as limitations in DCE studies [8-9, 127, 132]. By limiting the study to five important PGD attributes, there may be other unobserved factors that genetic counsellors may be considering in selecting their preferences regarding public coverage attributes such as sexual orientation and financial status of the couple. Focus groups were held to verify and add to the factors found in literature. While attempts were made to control for these factors by asking respondents to hold all other characteristics equal, unrecognized social and behavioural factors could be contributing to the decision. In a DCE study looking at uptake factors for Human Immunodeficiency Virus (HIV) prevention technologies, Terris-Prestholt et al. argued that the policy DCE findings should be interpreted as “potential” uptake factors [133]. Thus, the findings presented about PGD characteristics from this study can be used as information rather than a prescribed set of restrictions based on genetic conditions or types of patients.

Second, no information could be obtained about the importance of severity and treatability of the condition on preferences for PGD coverage which was originally proposed from the literature review. The study restricted the types of conditions based on the onset of the condition and whether the condition was a predisposition or not. Therefore the generalizability of the types of conditions for coverage was restricted. However, GC were asked within the pilot study about the examples of conditions they had thought about for each criterion. Since the answers from the pilot study were consistent, the preamble content was altered to include a few examples of conditions to ensure that respondents were considering similar clinically relevant conditions in their decision-making process.

Third, there may have been survey sampling bias since participants were not randomly selected to participate but rather invited from email blasts and through an educational meeting. Individuals who chose to complete the survey may have done so because of their experience in the field or interest in the study topic which results in volunteer bias. Therefore, the results of the testing may over-represent individuals with stronger views on coverage for PGD. However, the demographic and practice characteristics seemed to be comparable between the current study participants and the 2011 CAGC survey [104]. Furthermore, there is an inherent limitation in sampling genetic counsellors as compared to patients and policy makers since GC are not the only PGD stakeholders. For reasons highlighted in Section 1.4 and for the fact that GC are valued for their clinical perspective, the study was purposefully limited to GC with the acknowledgement that other perspectives may be equally valued and can be surveyed as part of future directions for this type of research.

Fourth, the response rate affected the sample size, which was slightly lower than the targeted number of 168 based on Equation 4 in Section 2.4.1 or the 213 respondents based on the methods recommended by de Bekker-Grob et al. [117]. The response rate for returned surveys was 50% and the rate for the completed DCE choice data surveys was 41.2%. The response rate range for choice-based conjoint analysis studies in health care is 18-88% [81] and the current study is on the lower side of this range. The reviewed studies typically employed postal questionnaires and were more successful if the survey was sent out as part of a randomized trial, included financial incentives, accompanied physician covering letters, or were distributed through clinics [81]. Factors that could have affected the low response rate in this study included the timing of the current study and the recruitment method. The initial launch in June 2014 was problematic due to the subsequent summer months when individuals may have been on vacation and not checking work email. In addition, a personally addressed mailed survey could not be sent to GC because of the lack of a mailing list available and telephone follow-up could not be done due to concerns over confidentiality and a change in policy by the CAGC. Response rate improved with the ability to advertise at the Annual Education Meeting and by providing paper copies that respondents could fill out throughout the conference instead of relying on access to a computer.

As a result of the lower response rate, there was a lower than expected sample size. A smaller sample size decreased the power of the study to fail to reject the null hypothesis when the alternative hypothesis is true, which is a type 2 error. The null hypothesis is that the parameter estimate associated with each attribute level is the same and not statistically significantly different from the mean parameter estimate which is zero. While it does not appear there was evidence of type 2 errors for the main effects attributes, there may be significant factors affecting preference for attribute levels related to the interaction of demographics, practice and attitudes which may have been under powered due to further sub grouping of the sample size. Therefore, the interaction models within this study should be considered exploratory analyses with limited confidence in the estimates given the small sample size. While the recruitment and resultant sample size were not ideal, this study represents the largest study of Canadian GC related to obtaining preferences for PGD coverage.

Finally, there was a limitation in considering number of cycles covered as a surrogate for cost as an attribute. Cost itself was excluded as an attribute as GC are not the payers and would not be expected to weigh the opportunity costs. However, there was value in using number of cycles to determine the preferred extent of public coverage. While a marginal rate of substitution using number of cycles could be estimated, the interpretation is complex. Typically, the marginal rate of substitution refers to the amount of a certain item that one would accept as part of a trade to lose one unit of the other item [75]. Although the number of cycles was used as a surrogate, the cycle number is not the same as cost. There is increasing disutility with too many cycles covered as there is a decreased IVF success rate. The exact measurement for the ideal number of cycles is unknown [43]. Furthermore, there are increased maternal risks related to the medications used with increasing number of cycles. Therefore a marginal rate of substitution using number of cycles was not used. While some of the respondents' comments from the paper survey suggest their concern about 8 cycles being too much, there was no opportunity for those who answered the online survey to provide comments. Therefore, there is a limitation in the ability to interpret these comments as being representative for all respondents when respondents who completed online did not get an opportunity to comment. However, there was still inherent value in using number of cycles as an attribute even without the ability to calculate marginal rate of substitution as it allows for quantification of the amount of coverage preferred.

While there were several limitations in the study, techniques were employed to promote validity. First, the response to the dominant scenario in the pilot study gave confidence that the respondents were completing the choice task in the intended manner, contributing to internal validity. Since 100% of pilot study respondents chose the dominant choice scenario, a dominant choice question was not included in the main study to permit an increased number of informative choice tasks. Evidence of external validity was supported by comparison of the respondents to the target population for the study, who were Canadian genetic counsellors. The demographic and practice characteristics of the respondents within this study were found to be comparable to the characteristics from the 2011 Professional Status Survey by the Canadian Association of Genetic Counsellors [104]. A total of 158 people were surveyed in the CAGC 2011 Survey, with 97.1% being female, which is consistent with the current study [104]. The current study had comparable representation of genetic counsellors from all provinces except for Manitoba. There was an overrepresentation of respondents from academic sites in the current study (53.8% versus 39.8% in the 2011 study). In 2011, 52.8% worked in prenatal genetics [104], which was similar to the current study. Thus, the respondents within the survey were representative of the GC population in Canada and therefore the preference findings can be generalized to the target population.

4.3 Future Directions for Research

The goal of this thesis work was to obtain genetic counsellors' preferences for PGD coverage through a discrete choice experiment. While the objectives of the study were met, there were limitations to the study and further extension of the present work could inform a more comprehensive framework for PGD policy development. An immediate extension of this work would be to obtain preferences from other stakeholders such as patients and policy makers using a discrete choice experiment. Future directions for this work could focus on two areas: 1) evaluation of policy changes, and 2) health technology assessment which includes economic evaluation and ethical, legal and social implications.

4.3.1 Evaluation of Policy Changes

As significant policy changes have been recently implemented in the coverage of PGD and IVF in Quebec and IVF in Ontario, there is a prime opportunity to study the impact of these policy changes. A future direction of study is to capture whether there is an increased use of privately paid for PGD in couples who are infertile and are able to have one cycle of IVF funded in Ontario. The data would come from comparing the 2014 and 2015 ART cycle reports [134] to the future report generated from the 2016 ART cycles. These annual ART cycle reports are generated by the Better Outcome Registry and Network (BORN), which is a provincial initiative funded by the Ministry of Health and Long Term Care to track pregnancy, birth and childhood outcomes [135]. The registry is linked to the Canadian Assisted Reproductive Technologies Register known as CARTR Plus, which is a national registry that obtains information about assistive reproductive cycles for all clinics offering IVF [136]. The number of PGD cycles in Ontario can be compared from the yearly data within the 2014-2016 periods, which may reflect any differences seen as a result of the December 2015 policy change granting coverage for 1 cycle of IVF for any infertile patient. An increase in PGD-included cycles could be associated in part to having 1 cycle of IVF publicly funded. This information would then add knowledge to the policy discussion of the potential uptake of PGD if a fully funded program including IVF and PGD were to be available.

4.3.2 Health Technology Assessment

4.3.2.1 Economic Evaluation

In addition to evaluating policy changes, a full economic evaluation can be performed. Economic evaluations are a standard and integral part of a health technology assessment (HTA) [137-138], and policy makers use these assessments to inform important policy decisions. For instance, a health technology assessment for PGD was done in Denmark and found that while introduction of PGD via public health care sector would moderately increase costs, there were advantages such as avoiding abortions [139]. Alberta has recently looked at the clinical effectiveness and safety of IVF in the context of patient characteristics including smoking, body mass index and age of the mother to help develop eligibility criteria for coverage [131].

Future direction for this study could be an economic evaluation of PGD using a cost-utility analysis comparing publicly funded infertile couples who use PGD for adult-onset conditions and publicly funded fertile couples who use PGD for childhood-onset conditions with a control group of individuals with no coverage for PGD. The modeling would be done based on numbers from the Quebec experience [23]. The unit of benefit would require an additional component within the study looking at time-tradeoff utilities ranging from 0 to 1 from a group of IVF couples in Quebec who have used the publicly funded system similar to a recent prenatal testing study [140]. The resultant utilities could be multiplied by the average lifespan of woman in years. The time horizon would be lifetime for the resultant child. This research could explore cost from the Ministry of Health perspective and from a societal perspective. The advantage of the Ministry perspective would be to determine whether it would be cost-effective to cover couples based on their fertility status and onset of the condition. The advantage of the societal perspective would be to account for contributions made to society for additional healthy individuals born due to funded PGD.

4.3.2.2 Ethical, Legal and Social Implications

Ethical, legal and social implications can augment HTA to help policy-makers make decisions that take into account the consequences of the technology [141]. There are many ethical, legal and social implications related to PGD. For instance, consideration of financial contribution based on family income was recommended and later implemented in Quebec with the use of tax credits based on income [23]. In a health care system where pregnancy management is covered regardless of patient's income, there may be ethical concerns related to distributive justice to offer tax credits based on family income for IVF and PGD. Another example of social implications is that utilization of PGD in Europe has increased for "social characteristics" including same-sex sexual orientation and couple's relationship status regardless of marriage [38]. In a recent newspaper article by Blackwell about the increased demand for IVF since one cycle was being covered in Ontario, comments from readers ranged from supporting the treatment for infertility and decreasing multiple birth rates to concerns regarding funding IVF as a means to buy political votes from same sex couples, when there is a wait list for more urgent health care concerns [27]. Dr. Francoise Baylis who is a bio-medical ethicist was quoted in a newspaper article saying that IVF funding is not on the priority list when almost 20% of Quebecers do not have family doctors [142].

A future research direction for this study would be to perform formal qualitative focus groups and semi-structured interviews with stakeholders such as patients, policy makers and the public about whether they would recommend PGD coverage and whether they would feel comfortable based on the findings of this study to restrict coverage based on the scope of testing and the patient inclusion criteria. Interviews could be conducted with legal and ethical experts to explore whether a publicly funded PGD program could and should discriminate based on social factors such as family history or fertility status. Future work within the ethical, legal and social implications context could further provide direction about PGD coverage especially in the context of limited health care resources.

4.4 Conclusions

In summary, this is the first study to quantify genetic counsellors' preferences for publicly funded PGD. Using a discrete choice survey, important characteristics of PGD were presented for consideration as criteria under which PGD could be publicly funded keeping in mind the caveat that the preferences are based on the attributes and levels explored in the current study.

One of the greatest policy issues was about whether to cover later onset or predisposition conditions and those of lower risk. This study concludes that while higher risk conditions are the most preferred, exploratory analysis suggests GC who had more experience showed more tolerance and consideration for coverage of lower risk conditions. Similarly, while earlier onset conditions were most preferred, genetic counsellors with over ten years of experience may have increased preference for later onset conditions. A study using a larger sample size could be useful to see whether there is robust statistical evidence to support these suggestions. In addition, the study concludes that infertile couples are the most preferred for coverage. It is unclear whether fertile couples could be held to a higher threshold and only be covered for childhood-onset or highest risk conditions given that they could become pregnant naturally and would not necessarily require IVF for the treatment of fertility.

Overall, the main conclusion of the study is that the most important characteristics for PGD coverage according to the genetic counsellors were the scope of testing for the clinical indications based on risk and onset of the condition. This is where the strengths of genetic counsellors' clinical expertise lay. There was still valuation for patient related eligibility criteria such as being infertile or having affected children with the caveat that these findings are in the context of the attributes and the levels within the current study according to the perspective of genetic counsellors. The clinical context and the objective of the policy both need to be considered when applying evidence to policy [143-144]. There is recognition that criteria for decision making should not dictate rules to follow but rather guidelines that should be taking into account [145].

In the current climate of unlimited health care demands and limited economic resources, prioritization and allocation based on evidence and on the clinical utility of new technologies provided to the most appropriate patients would help to address the imbalance. The findings from this study add a novel national perspective from genetic counsellors through preference elicitation regarding PGD. While technology is constantly advancing, the issues raised about criteria for public coverage of reproductive technologies will always centre along similar themes of limited resources, maximizing health and fairly distributing health gains. While the study was limited to genetic counsellors, the results of the study increase the knowledge around provider preferences and can help inform discussion about relevant policy issues. Discussion of these issues is timely, especially in the midst of ambiguity surrounding the scope of PGD testing and patient inclusion criteria. Combined with further research, there is hope of improving consistency in coverage practice for PGD patients and decreasing the ambiguity surrounding PGD policy issues.

References

1. IVF Canada. *General Fee Schedule and Preimplantation Genetic Diagnosis Fee Schedule.* 2011 October 6, 2011]; Available from: http://www.ivfcanada.com/services/fees/general_fee_schedule.cfm.

2. Gouvernement du Quebec, *Regulation respecting clinical activities related to assisted procreation.* Gazette Officielle Du Quebec, 2010. **142**(29): p. 2253-2257.

3. Blackwell, T., *Ontario to fund in-vitro fertilization with a caveat - one embryo at a time to cut risky multiple births*, in *National Post*. 2014, Postmedia Network Inc.: Toronto.

4. Gouvernement du Quebec, *Assisted Human Procreation Services*. 2016: Quebec City.

5. Ministry of Health and Long-Term Care, *Improving Access to Fertility Treatments for Ontario Families; Removing Barriers for Ontarians Who Want to Grow Their Families*. 2015, Queen's Printer for Ontario: Toronto.

6. Golan, O., et al., *Health technology prioritization: Which criteria for prioritizing new technologies and what are their relative weights?* Health Policy, 2010.

7. Severin, F., et al., *Value judgments for priority setting criteria in genetic testing: a discrete choice experiment.* Health Policy, 2015. **119**(2): p. 164-73.

8. Beulen, L., et al., *Women's and healthcare professionals' preferences for prenatal testing: a discrete choice experiment.* Prenat Diagn, 2015. **35**(6): p. 549-57.

9. Hill, M., et al., *Women's and health professionals' preferences for prenatal tests for Down syndrome: a discrete choice experiment to contrast noninvasive prenatal diagnosis with current invasive tests.* Genet Med, 2012. **14**(11): p. 905-13.

10. Marshall, D., et al., *Conjoint analysis applications in health - how are studies being designed and reported? An update on current practice in the published literature between 2005 and 2008.* The Patient – Patient Centered Outcomes Research, 2010. **2**: p. 249-256.

11. de Bekker-Grob, E.W., M. Ryan, and K. Gerard, *Discrete choice experiments in health economics: a review of the literature.* Health Econ, 2012. **21**(2): p. 145-72.

12. Clark, M.D., et al., *Discrete choice experiments in health economics: a review of the literature.* Pharmacoeconomics, 2014. **32**(9): p. 883-902.

13. Reed Johnson, F., et al., *Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force.* Value Health, 2013. **16**(1): p. 3-13.

14. Bridges, J.F.P., et al., *Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force.* Value in Health, 2011. **14**(4): p. 403-413.

15. CBC News (2014) *Infertility treatment financial assistance fund launched; Provincial government offering one-time grant of up to $5,000 to help ease financial burden*. CBC News.

16. Schwass-Bueckert, K., *Funding IVF will save provinces money: Advocates*, in *Winnipeg Sun*. 2011: Winnipeg.

17. Government of Manitoba, *Frequently Asked Questions About the Fertility Treatment Tax Credit*, M. Finance, Editor. 2011: Winnipeg.

18. Gouvernement du Quebec, *Preimplantation Genetic Diagnosis*, Q.A.R. Program, Editor. 2014: Quebec City.

19. Canadian Agency for Drugs and Technologies in Health, *Status of Public Funding for In Vitro Fertilization in Canada and Internationally*, in *Environmental Scan*. 2010.

20. CBC News, *In vitro fertilization services being considered by Eastern Health*, in *CBC News*. 2014.

21. Kennedy, C.J.J., *IVF not a medically necessary treatment*, N.S.S. Court, Editor. 1999: Nova Scotia Supreme Court.

22. Gouvernement du Quebec, *Tax credit for the treatment of infertility*, S. Quebec, Editor. 2011.

23. Salois, R., *Summary Advisory on Assisted Reproduction in Quebec*, C.a.l.s.e.a. bien-etre, Editor. 2014, Government of Quebec.

24. CBC News, *Quebec's controversial health care bill passes at National Assembly*, in *CBC News*. 2015, CBC News: Montreal.

25. CBC News, *Quebec in-vitro fertilization: A breakdown of new restrictions on treatment.* CBC News, 2015.

26. Mississauga News, *Peel clinics now offering government funded fertility treatment*, in *Mississauga News*. 2015: Mississauga.

27. Blackwell, T., *"Huge" demand for IVF treatment in Ontario - where it's fully funded - has wait lists stretching to 2018*, in *National Post*. 2016, National Post.

28. McKinnon, M., *Sask. group makes Family Day push for IVF funding*, in *Global News*. 2014: Regina.

29. Health Technology & Policy Unit, *Assisted Reproductive Technologies (ARTs)*. 2014, Alberta Health.

30. CBC News, *Alberta pressed to pay for fertility treatment. Could save millions, advocates say*, in *CBC News*. 2010: Calgary.

31. Infertility Awareness Association of Canada. *Legislation - BC Funding*. 2015 September 8 2015]; Available from: http://www.iaac.ca/en/780-438-bc-funding.

32. Healthwise Staff, *Fertility Problems - Treatment Overview*, HealthLinkBC, Editor. 2014, Healthwise: Vancouver.

33. NHS England Clinical Reference Group for Medical Genetics, *Clinical Commissioning Policy: Pre-implantation Genetic Diagnosis (PGD)*, N. England, Editor. 2013, NHS Commissioning Board, 2013: England.

34. Isasi, R.M. and B.M. Knoppers, *National Regulatory Frameworks Regarding Human Reproductive Genetic Testing (Preimplantation genetic Diagnosis/Prenatal Diagnosis)*. 2006, Genetics and Public Policy Center: Montreal.

35. Department of Human Services, *IVF Program*, D.o.H. Services, Editor. 2015, Australian Government.

36. Hughes, E.G. and M. Giacomini, *Funding in vitro fertilization treatment for persistent subfertility: the pain and the politics.* Fertility and Sterility, 2001. **76**(3): p. 431-442.

37. Petrjanosova, M., C. Moulin-Doos, and J. Plichtova, *The debate over reproductive rights in Germany and Slovakia: Religious and secular voices, a blurred political spectrum and many inconsistencies.* Politics in Central Europe 4, 2008. **2**: p. 61-78.

38. Berg Brigham, K., B. Cadier, and K. Chevreul, *The diversity of regulation and public financing of IVF in Europe and its impact on utilization.* Hum Reprod, 2013. **28**(3): p. 666-75.

39. Redmayne, S. and R. Klein, *Rationing in practice: the case of in vitro fertilisation.* BMJ, 1993. **306**(6891): p. 1521-4.

40. Knoppers, B.M., M. Hirtle, and K.C. Glass, *Policy forum: genetic technologies. Commercialization of genetic research and public policy.* Science, 1999. **286**(5448): p. 2277-8.

41. Expert Panel on Infertility and Adoption, *Raising Expectations: Recommendations of the Expert Panel on Infertility and Adoption*. 2009.

42. Giacomini, M., J. Hurley, and G. Stoddart, *The many meanings of deinsuring a health service: the case of in vitro fertilization in Ontario.* Soc Sci Med, 2000. **50**(10): p. 1485-500.

43. Crosignani, P.G. and B.L. Rubin, *Optimal use of infertility diagnostic tests and treatments. The ESHRE Capri Workshop Group.* Hum Reprod, 2000. **15**(3): p. 723-32.

44. Zegers-Hochschild, F., et al., *The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009.* Human Reproduction, 2009. **24**(11): p. 2683-2687.

45. Dulberg, C. and T. Stephens, *The prevalence of infertility in Canada, 1991-1992: analysis of three national surveys*. The Prevalence of Infertility in Canada: Research Studies of the Royal Commission on New Reproductive Technologies. 1993, Ottawa: Minister of Supply and Services Canada.

46. Bushnik, T., et al., *Estimating the prevalence of infertility in Canada.* Hum Reprod, 2012. **27**(3): p. 738-46.

47. Verlinsky, Y. and A. Kuliev, *Human preimplantation diagnosis: needs, efficiency and efficacy of genetic and chromosomal analysis.* Baillieres Clin Obstet Gynaecol, 1994. **8**(1): p. 177-96.

48. Canadian Institute of Health Information, *Giving Birth in Canada: The Costs*. 2006, Canadian Institute for Health Information: Ottawa.

49. Cram, D. and A. Pope, *Preimplantation genetic diagnosis: current and future perspectives.* J Law Med, 2007. **15**(1): p. 36-44.

50. Kalfoglou, A.L., J. Scott, and K. Hudson, *PGD patients' and providers' attitudes to the use and regulation of preimplantation genetic diagnosis.* Reprod Biomed Online, 2005. **11**(4): p. 486-96.

51. Speechley, K.N. and J. Nisker, *Preimplantation Genetic Diagnosis in Canada: A Survery of Canadian IVF Units.* Journal of Obstetrics and Gynaecology of Canada, 2010. **32**(4): p. 341-347.

52. Simpson, J.L., *Preimplantation genetic diagnosis at 20 years.* Prenat Diagn, 2010. **30**(7): p. 682-95.

53. Geraedts, J.P., et al., *Preimplantation genetic diagnosis (PGD), a collaborative activity of clinical genetic departments and IVF centres.* Prenat Diagn, 2001. **21**(12): p. 1086-92.

54. Goossens, V., et al., *ESHRE PGD Consortium data collection VIII: cycles from January to December 2005 with pregnancy follow-up to October 2006.* Hum Reprod, 2008. **23**(12): p. 2629-45.

55. Baruch, S., D. Kaufman, and K.L. Hudson, *Genetic testing of embryos: practices and perspectives of US in vitro fertilization clinics.* Fertility and Sterility, 2008. **89**(5): p. 1053-1058.

56. Gouvernement du Quebec, *Quebec Assisted Reproduction Program*. 2013: Quebec City.

57. Japan Society of Human Genetics, *Guidelines for Genetic Testing.* J Hum Genet., 2001. **163**(46): p. 3.

58. Ministry of Health, L.A.B., *Directives for Private Healthcare Institutions Providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations (CAP 248, Reg 1)*. 2006.

59. The Health Council of the Netherlands, *Pre-implantation genetic diagnosis*. 2006, Health Council of the Netherlands: The Hague.

60. Human Fertilisation and Embryology Authority and Advisory Committee, G. and Testing, *Consultation Document on PGD.* 2000.

61. Human Fertilisation and Embryology Authority, *PGD conditions licensed by the HFEA*, in *For Patients & Their Supporters*. 2011.

62. Robertson, J.A., *Extending preimplantation genetic diagnosis: the ethical debate. Ethical issues in new uses of preimplantation genetic diagnosis.* Hum Reprod, 2003. **18**(3): p. 465-71.

63. Ethics Committee of the American Society for Reproductive Medicine, *Preconception Gender Selection for Nonmedical Reasons.* Fertil Steril, 2004. **82**(Suppl 1): p. S232-235.

64. The Ethics Committee of the American Society of Reproductive Medicine, *Sex selection and preimplantation genetic diagnosis.* Fertility and Sterility, 1999. **72**(4): p. 595-508.

65. Government of Canada, *Assisted Human Reproduction Act*, D.o. Justice, Editor. 2004.

66. Rodeck, C.H. and M.J. Whittle, *Fetal medicine - Basic Science and Clinical Practice 2nd edition*. 2009: Churchill Livingstone Elsevier.

67. Thornhill, A.R., et al., *ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'.* Hum Reprod, 2005. **20**(1): p. 35-48.

68. Mercer, L., *PGD update in UK*, E. Goh, Editor. 2014: Toronto.

69. Karatas, J.C., et al., *Psychological adjustment, knowledge and unmet information needs in women undergoing PGD.* Hum Reprod, 2010. **25**(6): p. 1481-9.

70. Liu, K. and A. Case, *Advanced reproductive age and fertility.* J Obstet Gynaecol Can, 2011. **33**(11): p. 1165-75.

71. Hook, E.B., *Rates of chromosome abnormalities at different maternal ages.* Obstet Gynecol, 1981. **58**(3): p. 282-5.

72. Vendeville, G., *Bill 20 endangers McGill Reproductive Centre, MUHC says*, in *Montreal Gazette*. 2015: Montreal.

73. Commissaire a la sante et au bien-etre, *Summary Advisory on Assisted Reproduction in Quebec*. 2014, Government of Quebec.

74. Hendry, L., *Quebecers hope government is open to compromise over IVF program*, in *CBC News*. 2015: Montreal.

75. Hensher, D., J. Rose, and W. Greene, *Applied Choice Analysis - A Primer*. 2005, Cambridge: Cambridge University Press.

76. Bates, J., *Econometric issues in stated preference analysis.* Journal of Transport Economics and Policy, 1988. **XXII**(1): p. 59-69.

77. Bekker-Grob, E.W.d., et al., *Patients' preferences for osteoporosis drug treatment: a discrete choice experiment.* Osteoporosis International, 2008. **19**: p. 1029-1037.

78. Gray, E., et al., *Valuing Preferences for the Process and Outcomes of Clinical Genetics Services: A Pilot Study.* Patient, 2015.

79. Allison, P.D. and W. Kuhfeld, *PHREG.Allison.choice_chocolate.DISCRETE_vs_BRESLOW.MDC_and_LOGISTIC.sas*. 2011, SAS Institute Technical Support.

80. Bridges, J.F., et al., *Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force.* Value Health, 2011. **14**(4): p. 403-13.

81. Ryan, M., et al., *Eliciting public preferences for healthare: a systematic review of techniques.* Health Technology Assessment, 2001. **5**(5): p. 1-186.

82. Green, C. and K. Gerard, *Exploring the Social Value of Health-Care Interventions: A Stated Preference Discrete Choice Experiment.* Health Economics, 2009. **18**: p. 951-976.

83. Skjoldborg, U.S. and D. Gyrd-Hansen, *Conjoint analysis. The cost variable: an Achilles' heel?* Health Economics, 2003. **12**: p. 479-491.

84. Bech, M. and D. Gyrd-Hansen, *Effects coding in discrete choice experiments.* Health Economics, 2005. **14**: p. 1079-1083.

85. Ryan, M. and S. Farrar, *Using conjoint analysis to elicit preferences for health care.* BMJ, 2000. **320**(7248): p. 1530-3.

86. Yoo, H.I. and D. Doiron, *The use of alternative preference elicitation methods in complex discrete choice experiments.* J Health Econ, 2013. **32**(6): p. 1166-79.

87. Lancsar, E., et al., *Best worst discrete choice experiments in health: methods and an application.* Soc Sci Med, 2013. **76**(1): p. 74-82.

88. Lancsar, E., J. Louviere, and T. Flynn, *Several methods to investigate relative attribute impact in stated preference experiments.* Soc Sci Med, 2007. **64**(8): p. 1738-53.

89. Severin, F., et al., *Eliciting preferences for priority setting in genetic testing: a pilot study comparing best-worst scaling and discrete-choice experiments.* Eur J Hum Genet, 2013. **21**(11): p. 1202-8.

90. Whitty, J.A., et al., *Australian Public Preferences for the Funding of New Health Technologies: A Comparison of Discrete Choice and Profile Case Best-Worst Scaling Methods.* Med Decis Making, 2014. **34**(5): p. 638-654.

91. Grindrod, K.A., et al., *Pharmacists' Preferences for Providing Patient-Centered Services: A Discrete Choice Experiment to Guide Health Policy.* The Annals of Pharmacotherapy, 2010. **44**: p. 1554-1564.

92. Koopmanschap, M.A., E.A. Stolk, and X. Koolman, *Dear policy maker: Have you made up your mind? A discrete choice experiment among policy makers and other health professionals.* International Journal of Technology Assessment in Health Care, 2010. **26**(2): p. 198-204.

93. Hauber, A.B., et al., *Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force.* Value Health, 2016. **19**(4): p. 300-15.

94. Lagarde, M. and D. Blaauw, *A review of the application and contribution of discrete choice experiments to inform human resources policy interventions.* Human Resources for Health, 2009. **7**(62).

95. McFadden, D., *Conditional logit analysis of qualitative choice behavior*, in *Frontiers in Econometrics*, P. Zarembka, Editor. 1974, Academic Press: New York. p. 105-142.

96. Huber, J. and K. Zwerina, *The importance of utility balance in efficient choice designs.* Journal of Marketing Research, 1996. **33**(3): p. 307-317.

97. Carlsson, F. and P. Martinsson, *Design techniques for stated preference methods in health economics.* Health Econ, 2003. **12**(4): p. 281-94.

98. Kuhfeld, W., *Discrete Choice*, in *MR2010F*. 2010, SAS support - technote.

99. Peters, J.A. and J.E. Stopfer, *Role of the genetic counselor in familial cancer.* Oncology (Williston Park), 1996. **10**(2): p. 159-66, 175; discussion 176-6, 178.

100. Silversides, A., *The wide gap between genetic research and clinical needs.* CMAJ, 2007. **176**(3): p. 315-6.

101. Wertz, D.C. and J.C. Fletcher, *Attitudes of genetic counselors: a multinational survey.* Am J Hum Genet, 1988. **42**(4): p. 592-600.

102. Moore, J. and L.K. Low, *Factors that influence the practice of elective induction of labor: what does the evidence tell us?* J Perinat Neonatal Nurs, 2012. **26**(3): p. 242-50.

103. Sakala, C. and M. Corry, *Evidence-Based maternity Care: What It Is and What It Can Achieve.* 2008, New York: Childbirth Connection, Reforming States Group and Milbank Memorial Fund.

104. Canadian Association of Genetic Counsellors, *2011 Professional Status Survey*, J. Ruberg, A. Secord, and D. Verbaan, Editors. 2012. p. 21.

105. Coast, J., et al., *Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations.* Health Econ, 2012. **21**(6): p. 730-41.

106. Hurley, K., et al., *Incorporating information regarding preimplantation genetic diagnosis into discussions concerning testing and risk management for BRCA1/2 mutations: a qualitative study of patient preferences.* Cancer, 2012. **118**(24): p. 6270-7.

107. Jain, T., et al., *Preimplantation sex selection demand and preferences in an infertility population.* Fertil Steril, 2005. **83**(3): p. 649-58.

108. Simpson, J.L., *Clinical challenges in application of prenatal technologies.* Reproductive BioMedicine Online, 2013. **26**(Suppl. 1): p. S1-S11.

109. Amaya-Amaya, M., K. Gerard, and M. Ryan, *Discrete choice experiments in a nutshell*, in *Using discrete choise experiments to value health and healthcare.*, G.K. Ryan M, Amaya-Amaya M, Editor. 2008, Springer: Dordrecht. p. 13.

110. Onwuegbuzie, A.J., et al., *A Qualitative Framework for Collecting and Analyzing Data in Focus Group Research.* International Journal of Qualitative Methods, 2009. **8**(3): p. 1-21.

111. Fraser, F.C., *Genetic counseling.* Am J Hum Genet, 1974. **26**(5): p. 636-59.

112. Gnoth, C., et al., *Final ART success rates: a 10 years survey.* Human Reproduction, 2011. **26**(8): p. 2239-2246.

113. Maheshwari, A., L. Stofberg, and S. Bhattacharya, *Effect of overweight and obesity on assisted reproductive technology--a systematic review.* Hum Reprod Update, 2007. **13**(5): p. 433-44.

114. Sawtooth Software, *Sawtooth SSI Web Help*, in *Choice-Based Conjoint Help*, Sawtooth Software, Editor. 1998-2011: Sequim, WA.

115. Louviere, J., D. Hensher, and J. Swait, *Stated Choice Methods: Analysis and Applications*. 2000, Cambridge, UK: Cambridge University Press.

116. Orme, B. *Sample size issues for conjoint analysis studies*. 1998 January 22, 2012]; Available from: http://business.nmsu.edu/~mhyman/M310_Articles/CA_and_Sample_Size.pdf.

117. de Bekker-Grob, E.W., et al., *Sample Size Requirements for Discrete-Choice Experiments in Healthcare: a Practical Guide.* Patient, 2015. **8**(5): p. 373-84.

118. Ratcliffe, J. and L. Longworth, *Investigating the structural reliability of a discrete choice experiment within health technology assessment.* Int J Technol Assess Health Care, 2002. **18**(1): p. 139-44.

119. Bursac, Z., et al., *Purposeful selection of variables in logistic regression.* Source Code Biol Med, 2008. **3**: p. 17.

120. Hoyos, D., *The state of the art of environmental valuation with discrete choice experiments.* Ecological Economics, 2010. **69**(8): p. 1595-1603.

121. McFadden, D., *Quantitative methods for analysing travel behavour of individuals: some recent developments.*, in *Behavioural travel modelling.*, D.A.a.S. Hensher, P.R., Editor. 1979, Croom Helm: London. p. 279-318.

122. UCLA: Statistical Consulting Group, *Introduction to SAS [Internet]*.

123. Amemiya, T., *Qualitative response models: A survey.* Journal of Economic Literature, 1981. **XIX**(December 1981): p. 1483-1536.

124. Miller, D.P. (2004) *Bootstrap 101: Obtain Robust Confidence Intervals for Any Statistic*. Statistics and Data Analysis **SUGI 29**.

125. Hole, A.R., *A comparison of approaches to estimating confidence intervals for willingness to pay measures.* Health Econ, 2007. **16**(8): p. 827-40.

126. Canadian Institute of Health Research, N.S.a.E.R.C.o.C., *Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans.*, P.W.a.G.S. Canada, Editor. 1998: Ottawa.

127. Turbitt, E., et al., *Availability of treatment drives decisions of genetic health professionals about disclosure of incidental findings.* Eur J Hum Genet, 2014. **22**(10): p. 1225-8.

128. Canadian Association of Genetic Counsellors. *Career Brochure*. 2006 October 5, 2011]; Available from: https://cagc-accg.ca/images/docs/GC_Career_Brochures/j3521n%20welcome%20to%20cagc%202.pdf.

129. Wertz, D.C., J.R. Sorenson, and T.C. Heeren, *Clients' interpretation of risks provided in genetic counseling.* Am J Hum Genet, 1986. **39**(2): p. 253-64.

130. De Wert, G., et al., *ESHRE task force on ethics and Law22: preimplantation genetic diagnosis.* Hum Reprod, 2014. **29**(8): p. 1610-7.

131. Menon, D., et al., *Defining Eligibility Criteria for Funding Policies around in Vitro Fertilization.* Int J Technol Assess Health Care, 2015. **31**(6): p. 426-33.

132. Regier, D.A., et al., *Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete-choice experiment.* CMAJ, 2015. **187**(6): p. E190-7.

133. Terris-Prestholt, F., et al., *How much demand for New HIV prevention technologies can we really expect? Results from a discrete choice experiment in South Africa.* PLoS One, 2013. **8**(12): p. e83193.

134. Canadian Fertility and Andrology Society and Better Outcomes Registry Network. *Canadian Assisted Reproductive Register Plus (CARTR Plus)*. in *Canadian Fertility and Andrology Society 61st Annual Meeting*. 2015. Halifax, Nova Scotia.

135. BORN Ontario. *About BORN*. 2016 [cited 2016 June 4, 2016]; Available from: https://www.bornontario.ca.

136. BORN Ontario. *CARTR Plus*. 2016 [cited 2016 June 4, 2016]; Available from: https://www.bornontario.ca/en/partnership-projects/cartr-plus/.

137. Luce, B.R., et al., *EBM, HTA, and CER: clearing the confusion.* Milbank Q, 2010. **88**(2): p. 256-76.

138. Mathes, T., et al., *Methods of international health technology assessment agencies for economic evaluations--a comparative analysis.* BMC Health Serv Res, 2013. **13**: p. 371.

139. Danish Centre for Evaluation and Health Technology Assessment, *Preimplantation genetic diagnosis - an HTA*. 2002: Copenhagen.

140. Kaimal, A.J., M.E. Norton, and M. Kuppermann, *Prenatal Testing in the Genomic Age: Clinical Outcomes, Quality of Life, and Costs.* Obstet Gynecol, 2015. **126**(4): p. 737-46.

141. Ali-Khan, S.E., et al., *Socio-Ethical Issues in Personalized Medicine: A Systematic Review of English Language Health Technology Assessments of Gene Expression Profiling Tests for Breast Cancer Prognosis.* Int J Technol Assess Health Care, 2015. **31**(1-2): p. 36-50.

142. Brown, J., *Should the healthcare system pay for In Vitro Fertilization treatments?*, in *The 180*. 2014, CBC Radio.

143. Dobrow, M.J., et al., *The impact of context on evidence utilization: a framework for expert groups developing health policy recommendations.* Soc Sci Med, 2006. **63**(7): p. 1811-24.

144. Andermann, A., et al., *Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years* Bulletin of the World Heatlh Organization, Editor. 2008, World Health Organization.

145. Stafinski, T., et al., *Health technology funding decision-making processes around the world: the same, yet different.* Pharmacoeconomics, 2011. **29**(6): p. 475-95.

146. Unicef (2006) *The Convention on the Rights of the Child; Guiding principles: general requirements for all rights*.

147. National Institute of Health (2011) *Definitions and Acronyms, Further Resources for NIH Grantees*. U.S. Department of Health & Human Services.

148. Government of Canada, *Life expectancy, at birth and age 65, by sex and by province and territory*, S. Canada, Editor. 2011: Ottawa.

149. American College of Obstetrics and Gynecology, C.o.E.a.C.o.G., *Ethical Issues in Genetic Testing.* ACOG Committee Opinion, 2008. **410**: p. 1-8.

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Appendix 2: Focus group guides for moderators

Focus Group Type 1 (To collect information about attributes suggested for inclusion)

3) Discussion (Moderated by Jessica Bytautas)

Question 1: Imagine that you have been invited to work to be part of an advisory committee reporting to the government about policy-related issues involving PGD.

a) What considerations do you think would be needed to take into account if the government were to provide public coverage for PGD?

b) Do you think issues like marital status, age of woman, sexual orientation of woman should be included as they have been used for policy recommendations in other countries?"

Question 2: "What are the extreme situations / categories within each consideration?" (Note – this question is used to find out potential levels within each attribute)

Question 3: "What other important information / details do you feel would be needed to help advise policy"

Question 4: "Could you please rank these characteristics individually in order of importance from 1 being the most important and "n" being the least important?"

4) Study details

Question 5: Do you think that the setting in which a genetic counsellor practices (i.e. subspecialty like prenatal, cancer, cardiac) versus general counselling practice would make a difference in the importance of the considerations to a GC?"

Question 6: "What is the best way to engage genetic counsellors in completing the main survey instrument? Online? By mail?"

"What would be the top 5 most important considerations that should be presented to the MOH? Please discuss the ranking as a group"

Focus Group Type 2 (To clarify some of the attributes and levels discovered from the literature and focus group 1)

Discussion

*Question 1: "*Please discuss what you think about the considerations listed. How would you rank them?"

Question 2: "What other important information / details do you feel would be needed to help advise policy"

Reading of Background and Preamble

Discussion

Question 3: "Please comment about the background information given."

a) Should there be more information or less information given in the background?

b) Would you want an idea of percentages of success for pregnancy or any further information?

c) What do you think about the attributes and levels that are selected in the preamble? Are the descriptions clear?

d) Do you think that we should label the genetic conditions with examples of actual conditions? Do you think that would help or limit how you think about the situation?

Reading of Choice Set (including Scenario)

Discussion

Question 4:

a) "Do you think that the instructions for the survey are clear? How can it be better worded?"

*b) "*Would this be a type of scenario you would face in practice? Do you think we should highlight a non-smoking, non-obese individual?

Study details

Question 5: Do you think that the setting in which a genetic counsellor practices (i.e. subspecialty like prenatal, cancer, cardiac) versus general counselling practice would make a difference in the importance of the considerations to a GC?"

Question 6: "What do you think the best way to advertise this study to your colleagues? Via listserv? Via mail? Via a champion in each centre to increase recruitment?"

Appendix 3: Material for focus group type 2

1) List of Considerations for PGD (Obtained from the Literature and the First Focus Group)

Considerations	**Individual Ranking (1 = most important, N = least important)**
Age of Mother	
Amount of Coverage based on Number of Cycles	
Characteristics of the Genetic Condition (Age of onset, Severity, Life-limiting, Treatability, Predisposition)	
Cost (Medical) Lifelong of the Condition versus Cost of Procedure Itself	
Family History of the Couple (Number of Affected / Unaffected Children)	
Family Income	
Fertility Status of the Couple (Fertile/Infertile)	
Mandatory Genetic Consultation	
People's Motivation for PGD	
Social Work Assessment	

2) Background and Preamble

Genetic Counsellors' Preferences for Preimplantation Genetic Diagnosis: A Discrete Choice Experiment **Question Booklet**

Introduction to the Survey

This is a survey designed to help us understand the values and priorities you have if you were asked by Canadian policy makers regarding preimplantation genetic diagnosis.

The survey will ask you to make choices between two scenarios that describe characteristics of a woman and her family interested in undergoing preimplantation genetic diagnosis (PGD). It will also ask about what the level of public coverage should be for the technique. Please read both scenarios carefully as they may differ slightly in the description. Please check Scenario A or Scenario B to show which option you would lend greater support to if asked by a policy maker. *There are no right or wrong choices.*

There will be a number of choice questions and following the scenarios, there will be questions related to your current practice situation, your own demographics and how clear the survey was. These questions will help us understand your answers to the choice questions.

The questionnaire will take approximately __________ minutes to complete.

Please note, by answering the questions within this survey, it implies that you consent to take part in this research.

If you have started the survey but wish to withdraw from the study at any time, please indicate this on the last page of the survey and if possible, please provide a reason for your withdrawal. The data from the completed questions will not be read or analyzed. The only information collected will be the fact that there was a withdrawal and the reason if it was provided.

Thank you very much for your time!

Description of the Patient Characteristics

Please read carefully. The following definitions will assist you in answering the choice questions.

The scenarios below will differ according to five characteristics. A list of these characteristics as well as their descriptions appears below. **If characteristics are not listed, please consider that they are the same in all scenarios.**

1. Characteristics of the genetic condition

Genetic conditions can vary based on:

- **Age of onset:** relates to onset of symptoms where "childhood" onset is defined as up to the age of 18 years [146] and "adult" onset is over the age of 18 years.
- **Severity:** A genetic condition is defined as "severe" if "left untreated, will progress from a less serious condition to a more serious one" to a situation where "the likelihood of death is high unless the course of the disease is interrupted" [147].
- **Life-limiting:** defined as death earlier than the average expected life expectancy at birth in Canada of 80.9 years [148].
- **There may be overlap between severity and life-limiting**
- **Treatability:** the ability to treat the symptoms of the condition based on current clinically established and validated treatments.
- **Predisposition:** A significantly elevated risk of developing the condition if a gene mutation is present but does not guarantee that the condition will occur.

The characteristics of the genetic condition examined will be:

i) Severe childhood-onset life-limiting non-treatable condition

ii) Moderately severe childhood-onset non-life-limiting condition

iii) Severe adult-onset non-treatable condition *iv) HLA matching for a sibling with a severe haematological condition that requires stem cell or bone marrow transplantation*

v) Adult-onset cancer predisposition

2. Fertility status of the couple

"Infertility" according to the World Health Organization is defined as a "disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular sexual intercourse" [44].

The two options will be:

i) Infertile and requires IVF – The couple is infertile and would require IVF treatment to become pregnant regardless of whether they undergo PGD.

ii) Fertile and only for PGD – The couple is able to become pregnant without IVF treatments but would undergo IVF only because they are undergoing PGD.

3. Family history of couple

i) Have children, some of who are affected – The children who are affected with the genetic condition may be living, have passed away or had been terminated during the pregnancy for the condition being tested.

ii) Have children, none of whom are affected – These children are not affected with the genetic condition. An assumption is made that carrier status of the child is unknown according to the guidelines for testing minors [149].

iii) Have no children – The couple has never had children, living or who have passed away.

4. Medical Lifelong Cost of the Condition versus Cost of Procedure Itself

Medical lifelong cost of the condition is the average amount of medical costs incurred per 1000 children with the condition in Canadian dollars. The cost of the procedure itself is the total cost of PGD which includes the cost of 3 cycles of IVF treatment and the genetic testing in Canadian dollars. The following is a series of ratios if the medical lifelong cost was divided by the cost of 3 cycles of the IVF+PGD.   This is very unclear; better to use 1000-fold increase cost above average healthy child?

i) 1000:1

ii) 1:1

iii) 1:1000

5. Amount of coverage

This characteristic relates to how much you would feel would be fair for the amount of public coverage depending on the above characteristics. This is based on the number of fresh IVF cycles to achieve a pregnancy. The costs of the laboratory fees, physician fees, procedure fees and complications would be included but the costs of drugs would not.

i) None

ii) One cycle

iii) Three cycles

iv) All cycles – This option implies that financial support would be given until a pregnancy is achieved.

<u>All other characteristics of the couple undergoing PGD are the same in all scenarios if not defined above.</u>

7) Reading of Choice Set and Scenario

Example of a choice question

Below is an example of what a choice will look like.

The patient in each scenario is a 35 year old non-obese, non-smoking female undergoing PGD with a single embryo transfer and the following characteristics:

Characteristics	Scenario A	Scenario B
Genetic Condition to be Tested	Severe childhood-onset life-limiting non-treatable condition	Adult onset-cancer predisposition
Fertility Status of Couple	Infertile and requires IVF	Fertile and only for PGD
Couple's Family	No children	Have children, none of whom are affected
Ratio of Cost of Condition vs Procedure	1:1000	1000:1
Number of Cycles Covered	3 cycles	All cycles

After reading each scenario, you will be asked:

Given your role as a genetic counsellor advising policy makers, which scenario would you recommend for coverage by the government?

☒ Scenario A ☐ Scenario B

The genetic counsellor that answered this question preferred the characteristics described in Scenario A BETTER than in Scenario B. They made this decision by first reading the descriptions of each scenario and then comparing the two scenarios.

START HERE

CHOICE QUESTION #1

Imagine that as a genetic counsellor, you are asked to sit on an advisory committee to inform public policy regarding PGD. Which scenario would you recommend to Canadian policy makers for consideration of coverage? The patient is a 35 year old non-obese, non-smoking woman undergoing single embryo transfer with the following characteristics:

Characteristics	Scenario A	Scenario B
Genetic Condition to be Tested	Adult onset-cancer predisposition	Severe childhood-onset life-limiting non-treatable condition
Fertility Status of Couple	Infertile and requires IVF	Fertile and only for PGD
Couple's Family	No children	Have children, some of who are affected
Cost of Condition vs Procedure	1000:1	1:1
Number of Cycles Covered	1 cycle	3 cycles

Given your role as a genetic counsellor advising policy makers, which would you recommend for coverage by the government?

☐ Scenario A ☐ Scenario B

Appendix 4: Pretest Guide

PRETESTING COGNITIVE INTERVIEW PROTOCOL

General Information

Start Time: End Time:

Pre - interview Goals:

Location of Interview:

Instructions to be read to Participant:

Thanks for coming in/ helping with our study. Let me tell you a little more about what we'll be doing today.

1. We're testing survey instrument for our main study with the help from people such as yourself. The survey instrument includes: instructions, preamble, the choice sets and the demographic questionnaire.
2. We'll do this in 3 steps: First we'll go through the instructions and preamble, next, the choice sets, and the final step will be the demographic questionnaire.
3. You'll read through the instructions, preamble, as well as the choice sets and questionnaire, which you'll answer, just like a regular survey.
4. However, our goal here is to get a better idea of how clear the instructions and preamble are and how the questions in the questionnaire are working. So I'd like you to write notes, circle things to remind yourself about things you or others would not understand/are not clear.
5. After you're finished reading the instructions and preamble, I will come back to get your reaction to it. Please keep in mind that I really want to hear all of your opinions and reactions. Don't hesitate to let me know about anything that seems unclear or is hard to understand. I'll also take notes.
6. After this I will ask you more questions about the terms and phrases in the instruction and preamble.
7. Do you have any questions before we start?

8. Let's begin with the instructions and preamble. I'm going to step out of the room; please let me know when you have finished reading the instructions and preamble.

Instructions/preamble Reading Start Time:_______End Time: _________

Participant's General Comments:

Verbal Probes:

Instruction Info (pg 1): *"scenarios"*

1. What does the term "*scenarios*" mean to you?
2. How easy or difficult was it to understand this term?

Interviewer's Notes:

Instruction Info (pg 1): *"Coverage"*

3. Tell me what you were thinking when you read about policy making?
4. What does the term "*coverage*" mean to you?
5. How do you think 'public' is different from 'private' coverage?
6. How easy or difficult was it to understand these terms?

Interviewer's Notes:

Preamble Info (pg 2): *"Genetic conditions"*

7. Tell me what you were thinking when you read about *characteristics of the genetic condition?*
8. Do you agree with the wording of the definitions for *age of onset, severity, life-limiting, treatability and predisposition*?
9. How easy or difficult was it to understand these terms?
10. Would examples / labels of genetic conditions help with the understanding of the 5 combined categories?

Interviewer's Notes:

____

____

____

Preamble Info (pg 3): *"Fertility status of couple."*

11. Tell me what you were thinking when you read about *the two options regarding the fertility status of the couple.*
12. What does the term "*infertility*" mean to you?

Interviewer's Notes:

____

____

____

Preamble Info (pg 3): *"Family history of couple"*

13. Tell me what you were thinking when you read about *family history of the couple*.
14. Are the three categories reasonable?
15. Would it be easy to make a choice between them?

Interviewer's Notes:

____

____

____

Preamble Info (pg 4): *"Amount of coverage."*

16. Tell me what you were thinking when you read about *amount of coverage.*
17. What does the term "cycle" mean to you?
18. Is this an easy to understand concept to use: number of cycles to determine coverage?
19. Was it difficult for you? What about for other people?

Interviewer's Notes:

____

____

____

Instructions to be read to Participant:

1. Ok, now I'll ask you to read questionnaire, and answer it, just like a regular questionnaire.
2. Again, our goal here is to get a better idea of how the questions are working. So I'd like you to write notes, circle things to remind yourself about things you or others would not understand or are not clear.
3. After you're finished the questionnaire, I will come back to get your reaction to it. Please keep in mind that I really want to hear all of your opinions and reactions. Don't hesitate to let me know about anything that seems unclear, is hard to answer, or doesn't seem to apply to you. I'll also take notes.
4. After this I will ask you more questions about the terms and phrases in the questionnaire.
5. Do you have any questions before we start?
6. Just like before, I'm going to step out of the room; please let me know when you have finished the questionnaire.

Questionnaire Start Time:__________ **End Time: ___________**

Participant's General Comments:

____

____

Verbal Probes:

Choice Sets: Introduction, (pg 1): *"Imagine that as a genetic counsellor, you are asked to sit on an advisory committee to inform public policy regarding PGD"*

1. Tell me what you were thinking when you read "*inform public policy"*
2. What is one's role on an advisory committee?

3. Would you be able to see yourself in this role?
4. Was it difficult for you? What about for other people?
5. In general, how do you feel about being placed in this position?

Interviewer's Notes:

Choice Sets: Patient scenario (pg 1): *"The patient is a 35 year old non-obese, non-smoking woman undergoing single embryo transfer with the following characteristics:"*

6. Tell me what you were thinking when you read the age of the patient?
7. Can you tell me why non-obese, non-smoking woman would be included?
8. Does single embryo transfer make a difference in your decision?
9. Would you prefer to have an explanation in the preamble about why this patient was chosen?

Interviewer's Notes:

Choice Sets: Question (pg 1): *Question leading to choice*

"Given your role as a genetic counsellor advising policy makers, which would you recommend for coverage?"

10. Tell me what you were thinking when you read *recommend for coverage*?
11. How easy or hard was it to choose your answer on that list?
12. Did you have to remind yourself that you were advising policy makers?
13. Tell me why you chose [answer] instead of the other?
14. Would your choice have been different if you were asked to answer from a different perspective (e.g. As an advocate for your patient, Based on financial realities?) Was it difficult for you to decide on a response? What about for other people?

Interviewer's Notes:

Demographics Questionnaire: Questions about Your Practice (pg 3)

1. In general, how do you feel about these questions?
2. Can you tell me in your own words what these questions are asking?
3. Did you think there were too many / too few questions in this Section?

Interviewer's Notes:

Demographics Questionnaire: Questions about You (pg 5)

4. In general, how do you feel about these questions?

5. Can you tell me in your own words what these questions are asking?

6. Did you think there were too many / too few questions in this Section?

7. Did any question make you feel uncomfortable?

Follow Up Probes

1. How is the format of the instruction and preamble? And questionnaires? (Suggestions for format: bound workbook, separate booklets)

2. How is the length of the instructions / preamble? And questionnaire?
3. Are there things that you wanted to write but didn't have space or the option?
4. Are there things that you would change?
    a. Is there any information or questions that should be removed?
    b. Is there any information or questions that should be added?
5. What would make it easier to fill out?

Interviewer's Notes:

____

____

____

Post – Interview Information

- **Nonverbal Behaviour** (e.g. tone of voice, posture, facial expressions, eye movements/contact, forcefulness of speech, body movements, and hand gestures):

- **Content of Interview** (e.g. use key words, topics, focus, exact words, or phrases that stand out):

- **Researcher's impressions** (e.g. discomfort of participant with certain terms or questions, emotional responses to issues)

- **Analysis** (e.g. researcher's questions, tentative hunches, trends in data, and emerging patterns):

Appendix 5: Comparison of designs for main study

A comparison of the standard errors and the strength of the model based on the Sawtooth software generated CBC test design report appears as shown.

Comparison of Designs for Main Study

Design	**Maximum difference in frequency**	**Approx standard errors**	**Strength of design for model**	**Relative D-efficiency**
1) 21 choice tasks and 3 versions	0	0.0249	1876.6274	0.9958
2) 21 choice tasks and 4 versions	0	0.0248	1880.6042	0.9979
3) 21 choice tasks and 6 versions	1	0.0248	1884.4810	Reference design
4) 18 choice tasks 3 versions	0	0.0269	1605.8586	0.8521
5) 18 choice tasks 4 versions*	1	0.0268	1611.1807	0.8550
6) 18 choice tasks 7 versions	0	0.0268	1614.1082	0.8565

*Chosen design

However, since a paper version of the survey needed to be used in addition to the online version, 6 versions was thought to be too many to ensure that enough completed surveys from each version was represented. Therefore blocking into 4 versions was selected.

Appendix 6: Version 1 of the main study booklet (Preamble and background omitted for brevity – see Appendix 3)

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

PREIMPLANTATION GENETIC DIAGNOSIS:

What is YOUR opinion?

SickKids

Institute of Health Policy, Management & Evaluation
UNIVERSITY OF TORONTO

Genetic counsellors' preferences for public coverage of preimplantation genetic diagnosis

About this study

As a front-line healthcare professional with the knowledge and skills to counsel patients about preimplantation genetic diagnosis (PGD), you have a unique perspective on what's important in choosing this service. This study is designed to seek your input regarding the conditions under which PGD should be paid for publicly.

Your opinion is important to us.

The questionnaire includes a choice experiment that asks you to make choices between two options that describe the characteristics of a woman and her family interested in undergoing PGD. In choosing which of the two options you prefer, we ask you to imagine that you have been asked to advise the government on the conditions under which public funding would be provided for PGD.

In addition to the section where you make choices between PGD options, the questionnaire includes questions related to your current practice situation, your own demographics, your views on PGD issues and how clear the questionnaire was. These questions will help us understand your answers to the choice experiment.

The questionnaire will take approximately 20 minutes to complete.

Please note that answering any of the questions within this survey confirms that you consent to take part in this research study. If you wish to withdraw from the study, or if you participated in the pilot study or main online study, we would appreciate it if you would complete the following page and indicate 'yes' to question about wishing to withdraw (question 4).

If you wish to withdraw from the study after you have started the survey, we would greatly appreciate it if you would please skip back to the beginning and provide a reason for your withdrawal. Data from partially completed questions will be analyzed.

PLEASE DROP OFF THE COMPLETED/WITHDRAWN QUESTIONNAIRES in the COLLECTION BOX labeled "PGD Study" by the end of the conference.

Thank you very much for your time!

BEFORE WE BEGIN, please tell us about yourself:

Are you a member of the CAGC?

☐ a. Yes ☐ b. No

1. Which best describes your current employment status? (Please check all that apply)

☐ a. Full-time genetic counsellor ☐ b. Part-time genetic counsellor

☐ c. Full-time researcher ☐ d. Part-time researcher

☐ e. Full-time in another occupation ☐ f. Part-time in another occupation

☐ g. Full-time (genetic counsellor + researcher) ☐ h. Student

☐ i. Retired ☐ j. On leave (ex. Maternity, disability)

☐ k. Homemaker ☐ l. Unemployed

☐ m. Other (Please specify____)

2. What is your sex?

☐ a. Female ☐ b. Male ☐ c. Prefer not to answer

3. What is your current age in years?

____

4. Please indicate here if you wish to withdraw from the research study. The information collected up to the point of withdrawal will be used in the analysis.

☐ a. I DO NOT wish to withdraw

☐ b. I wish to withdraw from the research study but would prefer not to provide a reason.

☐ c. I wish to withdraw because I am not comfortable answering the questions.

☐ d. I wish to withdraw because I no longer have time to do the survey.

☐ e. I wish to withdraw because I participated in the pilot study.

☐ f. I wish to withdraw for the following reason: (please specify)

____

PLEASE START HERE: There will be 18 choice questions.

1. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset non-cancer related condition	Risk of childhood-onset condition
Risk	25%	50%
Fertility Status	Fertile and only for PGD	Infertile and requires IVF
Couple's Family	Have children, at least 1 of whom is affected	Have no children
Number of Cycles Covered	Eight cycles	One cycle
	◯	◯

If you had a third choice not to pick either option, would you still make the same choice as above?

- ◯ Yes
- ◯ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random13

2. **Given your role as a genetic counsellor, which PGD option would you prefer?**

PGD Indication	Risk of adult-onset cancer predisposition	Risk of adult-onset non-cancer related condition
Risk	1%	25%
Fertility Status	Fertility unknown	Infertile and requires IVF
Couple's Family	Have children, none of whom are affected	Have no children
Number of Cycles Covered	Four cycles	One cycle
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random14

3. **Given your role as a genetic counsellor, which PGD option would you prefer?**

PGD Indication	Risk of adult-onset cancer predisposition	Risk of childhood-onset condition
Risk	1%	50%
Fertility Status	Fertile and only for PGD	Fertility unknown
Couple's Family	Have children, at least 1 of whom is affected	Have children, none of whom are affected
Number of Cycles Covered	Four cycles	Eight cycles
	◯	◯

If you had a third choice not to pick either option, would you still make the same choice as above?

◯ Yes

◯ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random15

4. **Given your role as a genetic counsellor, which PGD option would you prefer?**

PGD Indication	Risk of adult-onset non-cancer related condition	Risk of adult-onset cancer predisposition
Risk	1%	50%
Fertility Status	Fertile and only for PGD	Infertile and requires IVF
Couple's Family	Have children, none of whom are affected	Have children, at least 1 of whom is affected
Number of Cycles Covered	One cycle	Four cycles

If you had a third choice not to pick either option, would you still make the same choice as above?

- Yes
- No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random16

5. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset non-cancer related condition
Risk	50%	1%
Fertility Status	Infertile and requires IVF	Fertile and only for PGD
Couple's Family	Have children, none of whom are affected	Have children, at least 1 of whom is affected
Number of Cycles Covered	Four cycles	Eight cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

- ○ Yes
- ○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random1

6. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset non-cancer related condition	Risk of adult-onset cancer predisposition
Risk	50%	25%
Fertility Status	Infertile and requires IVF	Fertility unknown
Couple's Family	Have children, at least 1 of whom is affected	Have no children
Number of Cycles Covered	Four cycles	One cycle
	◯	◯

If you had a third choice not to pick either option, would you still make the same choice as above?

◯ Yes

◯ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random2

7. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset cancer predisposition	Risk of childhood-onset condition
Risk	25%	1%
Fertility Status	Fertility unknown	Fertile and only for PGD
Couple's Family	Have no children	Have children, none of whom are affected
Number of Cycles Covered	Eight cycles	One cycle
	◯	◯

If you had a third choice not to pick either option, would you still make the same choice as above?

◯ Yes

◯ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random3

8. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset non-cancer related condition
Risk	25%	1%
Fertility Status	Infertile and requires IVF	Fertility unknown
Couple's Family	Have children, at least 1 of whom is affected	Have children, none of whom are affected
Number of Cycles Covered	One cycle	Four cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random4

9. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset cancer predisposition
Risk	1%	50%
Fertility Status	Fertility unknown	Fertile and only for PGD
Couple's Family	Have children, at least 1 of whom is affected	Have no children
Number of Cycles Covered	Four cycles	Eight cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random5

10. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset cancer predisposition	Risk of adult-onset non-cancer related condition
Risk	50%	25%
Fertility Status	Fertile and only for PGD	Infertile and requires IVF
Couple's Family	Have no children	Have children, none of whom are affected
Number of Cycles Covered	One cycle	Eight cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

- ○ Yes
- ○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random6

11. **Given your role as a genetic counsellor, which PGD option would you prefer?**

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset cancer predisposition
Risk	1%	25%
Fertility Status	Infertile and requires IVF	Fertile and only for PGD
Couple's Family	Have no children	Have children, none of whom are affected
Number of Cycles Covered	Eight cycles	Four cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random7

12. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset non-cancer related condition
Risk	25%	50%
Fertility Status	Fertile and only for PGD	Fertility unknown
Couple's Family	Have no children	Have children, at least 1 of whom is affected
Number of Cycles Covered	Four cycles	One cycle

If you had a third choice not to pick either option, would you still make the same choice as above?

- Yes
- No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random8

13. **Given your role as a genetic counsellor, which PGD option would you prefer?**

	Option 1	Option 2
PGD Indication	Risk of adult-onset non-cancer related condition	Risk of adult-onset cancer predisposition
Risk	50%	1%
Fertility Status	Fertility unknown	Infertile and requires IVF
Couple's Family	Have children, none of whom are affected	Have children, at least 1 of whom is affected
Number of Cycles Covered	Eight cycles	One cycle

If you had a third choice not to pick either option, would you still make the same choice as above?

- Yes
- No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random9

14. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset non-cancer related condition
Risk	50%	1%
Fertility Status	Fertile and only for PGD	Infertile and requires IVF
Couple's Family	Have children, at least 1 of whom is affected	Have no children
Number of Cycles Covered	Eight cycles	Four cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random10

15. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset cancer predisposition	Risk of adult-onset non-cancer related condition
Risk	25%	50%
Fertility Status	Fertility unknown	Fertile and only for PGD
Couple's Family	Have children, none of whom are affected	Have no children
Number of Cycles Covered	One cycle	Four cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random11

16. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of adult-onset cancer predisposition	Risk of childhood-onset condition
Risk	1%	25%
Fertility Status	Infertile and requires IVF	Fertility unknown
Couple's Family	Have children, none of whom are affected	Have children, at least 1 of whom is affected
Number of Cycles Covered	Eight cycles	One cycle

If you had a third choice not to pick either option, would you still make the same choice as above?

- Yes
- No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random12

17. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset cancer predisposition
Risk	25%	50%
Fertility Status	Fertility unknown	Infertile and requires IVF
Couple's Family	Have no children	Have children, none of whom are affected
Number of Cycles Covered	Eight cycles	One cycle

If you had a third choice not to pick either option, would you still make the same choice as above?

- Yes
- No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random17

18. Given your role as a genetic counsellor, which PGD option would you prefer?

PGD Indication	Risk of childhood-onset condition	Risk of adult-onset non-cancer related condition
Risk	25%	1%
Fertility Status	Fertile and only for PGD	Fertility unknown
Couple's Family	Have children, at least 1 of whom is affected	Have no children
Number of Cycles Covered	Eight cycles	Four cycles
	○	○

If you had a third choice not to pick either option, would you still make the same choice as above?

○ Yes

○ No, I would not recommend either option.

D - 1, T - CBCthesispractice_Random18

You are now finished with the choice questions!

QUESTIONS ABOUT YOUR PRACTICE

5. What is the highest level of education that you have attained?

☐ a. Some post-secondary (university or college) ☐ b. Bachelor in Nursing

☐ c. Bachelor in Social Work ☐ d. Bachelors of Science / Arts

☐ e. Master's in Genetic Counselling ☐ f. Medical Degree

☐ g. Completing or completed a PhD (please specify area________________________)

☐ h. Other (please specify_______________________________________)

6. If you work as a genetic counsellor, where do you currently practice?

☐ a. Newfoundland ☐ b. Prince Edward Island ☐ c. Nova Scotia

☐ d. New Brunswick ☐ e. Quebec ☐ f. Ontario

☐ g. Manitoba ☐ h. Saskatchewan ☐ i. Alberta

☐ j. British Columbia ☐ k. Northwest Territories ☐ l. Yukon

☐ m. Nunavut ☐ n. United States ☐ o. Europe

☐ p. Other (Please specify____)

☐ q. Not applicable ➔ Please skip to Question 10

7. If you work as a genetic counsellor, what is/are your primary area(s) of practice? (Please check all that apply)

☐ a. General Genetics ☐ b. Adult Genetics ☐ c. Paediatric Genetics

☐ d. Cancer ☐ e. Prenatal ☐ f. Neurogenetics

☐ g. Cardiac Genetics ☐ h. Research

☐ i. Other (Please specify____)

☐ j. Not applicable ➔ Please skip to Question 13

8. If you work as a genetic counsellor, what type of centre do you practice in? (Please check all that apply)

☐ a. Academic ☐ b. Community ☐ c. Outreach

☐ d. Other (Please specify____)

☐ e. Not applicable ➔ Please skip to Question 13

9. How many years have you practiced as a genetic counsellor?

☐ a.0 ☐ b.1-3 ☐ c.3-5 ☐ d.5-10 ☐ e.10-15

☐ f.15-20 ☐ g. >20

☐ h. Not applicable ➔ Please skip to Question 13

10. How often in your consultations do you counsel about prenatal genetics?

☐ a. Never

☐ b. Rarely

☐ c. Sometimes

☐ d. Often

☐ e. Always

☐ f. Not applicable ➔ Please skip to Question 13

11. How often in your consultations involving prenatal genetics do you discuss PGD?

☐ a. Never

☐ b. Rarely

☐ c. Sometimes

☐ d. Often

☐ e. Always

☐ f. Not applicable ➔ Please skip to Question 13

12. How often in your consultations involving prenatal genetics is the cost of IVF with PGD discussed?

☐ a. Never

☐ b. Rarely

☐ c. Sometimes

□ d. Often

□ e. Always

□ f. Not applicable

13. Are you familiar with the policy related to public payment for IVF/PGD in your province or territory of residence? (N.B. The policy may be to not provide public payment, or may be to provide public payment under any or specific conditions)?

□ a. Yes □b. No □ c. Not applicable (if live outside Canada)

14. Have you ever had a patient undergo PGD?

□ a. Yes □b. No ➔ Please skip to Question 20

□ c. Not applicable ➔ Please skip to Question 20

15. What was/were the genetic indication(s) for PGD? *Please check all that apply.*

□ a. Childhood-onset condition □ b. Adult-onset non-cancer condition

□ c. HLA matching for affected sibling □ d. Adult-onset cancer predisposition

□ e. Other (Please specify)

____

16. Did your patient(s) have a successful pregnancy of an unaffected child?

□ a. Yes □b. No □c. Unknown

17. What was the most common fertility status of your patients?

□ a. Infertile and required IVF □b. Fertile and only IVF for PGD

18. What was the couple's most common existing family history?

☐ a.1 or more affected children ☐b.1 or more unaffected children

☐ c. No children

19. How did the majority of couple(s) pay for PGD?

☐ a. Public funding paid directly/reimbursed ☐b. Out of pocket

☐ c. Private Insurance

☐ d. Mix (out of pocket + private insurance) ☐e. Mix (private + public funding)

20. How comfortable are you counselling about PGD?

☐ a. Very uncomfortable

☐ b. Uncomfortable

☐ c. Neither comfortable or uncomfortable

☐ d. Comfortable

☐ e. Very comfortable

21. Please circle whether you think the statement is true, false, or you don't know:

Statements			
a) PGD requires the use of IVF	i.True	ii.False	iii.Don't Know
b) The genetic testing is only performed on the cells that have been biopsied, not on the entire embryo	i.True	ii.False	iii.Don't Know
c) PGD will guarantee that a woman will not have a child affected by a genetic condition	i.True	ii.False	iii.Don't Know
d) When a woman is fertile, she is guaranteed to get pregnant if an embryo is transferred	i.True	ii.False	iii.Don't Know

QUESTIONS ABOUT YOU

While the information is private (and will be kept confidential), answering these questions will help us understand reasons for differences in preferences.

22. Is there an ethnic or cultural group that you most strongly identify with? *Please check one.*

☐ a. No ☐ b. Prefer not to answer

☐ c. Canadian	☐ d. Ukrainian	☐ e. Jamaican	☐ f. Irish
☐ g. French	☐ h. Dutch	☐ i. South Asian	☐ j. Cree
☐ k. English	☐ l. Polish	☐ m. Lebanese	☐ n. Chilean
☐ o. Chinese	☐ p. Greek	☐ q. Portuguese	☐ r. Inuit
☐ s. Italian	☐ t. Micmac	☐ u. Vietnamese	☐ v. Scottish
☐ w. German	☐ x. Métis	☐ y. Filipino	

☐ z. Other/Mixed (*please specify: ____)*

23. Is there a specific religious denomination that you most strongly identify with? *Please check one.*

☐ a. No ☐ b. Prefer not to answer

☐ c. Anglican	☐ d. Baptist	☐ e. Congregationalist
☐ f. Evangelical Church	☐ g. Greek Orthodox	☐ h. Hindu
☐ i. Jehovah's Witness	☐ j. Islam	☐ k. Jewish
☐ i. Lutheran	☐ m. Mennonite	☐ n. Methodist
☐ o. Pentecostal	☐ p. Presbyterian	☐ q. Roman Catholic
☐ r. Salvation Army	☐ s. Ukrainian/Greek Catholic	☐ t. United Church of Canada

☐ u. Other religious denominations ☐ v. Religious denominations unknown

24. What is your marital status?

□ a. Married or living common-law □b. Widowed or widower

□ c. Single (never been married) □ d. Separated or divorced

25. How many children do you have?

□ a. none □ b.1 or more biological children

□ c. 1 or more adopted children □ d.1 or more step-children

□ e. 1 or more mix of biological, adopted and step children

26. Have you ever required the use of assisted reproductive technology for yourself personally?

□ a. No ➔Please skip to Question 29. □ b. Yes

27. Which assisted reproductive technologies (ART) have you used? *Please check all that apply.*

□ a. Clomiphene (Clomid) □ b. Intrauterine insemination

□ c. Preimplantation genetic diagnosis □ d. *In-vitro* fertilization

□ e. Other (Please specify)____

28. What was the reason for using ART?

□ a. Infertility □ b.PGD

□ c. Other (Please specify____)

29. This question asks about your household income. While the information is private (and will be kept confidential), answering this question will help us understand reasons for differences in preferences between income groups. Please indicate the best estimate of your total annual household income, before taxes, including all household members.

☐ a. Not sure ☐ b. Prefer not to answer ☐ c. No income

☐ d. Less than $20,000 ☐ e.$20,000 to $29,999 ☐ f.$30,000 to $39,999

☐ g.$40,000 to $49,999 ☐ h.$50,000 to $59,999 ☐ i.$60,000 to $69,999

☐ j.$70,000 to $79,999 ☐ k.$80,000 to $89,999 ☐ l.$90,000 to $99,999

☐ m.$100,000 to $119,999 ☐ n.$120,000 to $149,999 ☐ o.$150,000 to $200,000

☐ p. Greater than $200,000

QUESTIONS ABOUT THE SURVEY

30. In general, how certain were you about your decisions of the scenarios?

☐ a. Very uncertain

☐ b. Uncertain

☐ c. Somewhat uncertain

☐ d. Neither certain nor uncertain

☐ e. Somewhat certain

☐ f. Certain

☐ g. Very certain

31. Do you think that there should be public coverage by the government as part of a provincial / territorial health insurance program for the following?

☐ a. No coverage for PGD or IVF

☐ b. Coverage for PGD only and not IVF

☐ c. Coverage for PGD and IVF

32. What condition(s) if any were you thinking about when presented with the various PGD indications in the scenarios:

□ a. I was not thinking about a particular condition

b) Childhood-onset condition

____

c) Adult-onset non-cancer condition

____

d) Adult-onset cancer predisposition condition

____

33. How important do you think the *age of the mother* is in determining public funding for PGD?

□ a. Very Unimportant

□ b. Somewhat Unimportant

□ c. Neither Important nor Unimportant

□ d. Somewhat Important

□ e. Very Important

THE END

Thank you very much for taking the time to complete our survey! Your insight and responses are very valuable to us.

If you would like to provide us with feedback or comments about the survey, please do so or email PGD.study@sickkids.ca

Appendix 7: Variance – Covariance Matrix

Variance – Covariance Matrix for Main Effects (n = 126) Cycle as Continuous Regression

	indic1	indic2	risk1	risk2	fert1	fert2	fam1	fam2	cycle
indic1	0.00488	-0.00228	0.00198	0.00159	0.00072	-0.00069	0.00108	-0.000844	-0.000044
indic2	-0.00228	0.00302	-0.00091	-0.00034	-0.00047	0.00034	-0.00064	0.000736	-0.000093
risk1	0.00198	-0.00091	0.00343	-0.00019	0.00040	-0.00017	0.00088	-0.000323	-0.000052
risk2	0.00159	-0.00034	-0.00019	0.00317	0.00066	-0.00094	0.00062	-0.000317	-0.000218
fert1	0.00072	-0.00047	0.00040	0.00066	0.00292	-0.00152	0.00044	-0.000225	-0.000136
fert2	-0.00069	0.00034	-0.00017	-0.00094	-0.00152	0.00270	-0.00048	0.000251	0.000097
fam1	0.00108	-0.00064	0.00088	0.00062	0.00044	-0.00048	0.00326	-0.001528	-0.000138
fam2	-0.00084	0.00074	-0.00032	-0.00032	-0.00022	0.00025	-0.00153	0.002499	0.000015
cycle	-0.00004	-0.00009	-0.00005	-0.00022	-0.00014	0.00010	-0.00014	0.000015	0.000165

Appendix 8: REB approval

SickKids **Research Ethics Board (REB)**

The Research Ethics Board for The Hospital for Sick Children is organized and operates according to the principles and practices outlined in the Tri-Council Policy Statement, the ICH Harmonized Tripartite Guidelines: Good Clinical Practice, and Division 5 and the Medical Devices Regulations of the Food and Drug Act as well as the Natural Health Products Regulations of Health Canada. This signed document is in lieu of the Health Canada Research Ethics Board Attestation Form.

RECEIVED

JUN 20 2012

Approval & Terms of Agreement

Investigators: Dr. Wendy Ungar, E.Goh, F.Miller, D.Marshall

Study Title: Genetic Counsellor's Preferences for Preimplantation Genetic Diagnosis: A Discrete Choice Experiment - Qualitative Study Phase I

REB File number: 1000032845 **Level of Continuing Review:** II C
Protocol Version Date: May 6, 2012
Consent & Assent Form Version Date(s): Research Consent Form May 6, 2012; Audio Taping Consent Form May 6, 2012
Investigator's Brochure Version Date: Not Applicable
Other Approved Recruitment Document Dates: Recruitment Email May 16, 2012; Recruitment Poster May 16, 2012

I agree to carry out the proposed research involving human subjects in accordance with the above-noted guidelines and regulations (as applicable) and using only the REB-approved study protocol and consent/assent form(s). I shall notify the division/department head and the REB prior to implementing any amendments in the protocol and consent/assent forms and of any deviations or any changes in study activity. I shall also notify the REB of any unexpected adverse events as per REB guidelines. As applicable, I certify that the research contract and corresponding protocol are consistent and will inform the contract manager of any protocol amendments as required.

I agree that, in accordance with the Personal Health Information Protection Act of Ontario, I am responsible for adhering to all conditions and restrictions imposed by the REB governing the use, security, disclosure, return and disposal of the research subjects' personal health information. I am also responsible for reporting immediately any privacy breaches to the REB Chair and to Janice Campbell, the Sick Kids privacy officer. I will ensure that the personal health information is used, only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB.

Signature of Principal Investigator W Ungar **DATE** 19 June 2012

I approve of this research protocol, agree to share responsibility for its proper conduct, and will ensure that the REB is notified of concerns, as appropriate.

Signature of Division/Department Head ________ **DATE** 20 June

The REB of the Hospital for Sick Children has reviewed and approved the above-named research study.

Mr. Richard Sugarman, REB Chair
555 University Avenue, Toronto, Ontario, M5G 1X8
Tel: 416-813-6152 Fax: 416-813-5085 Email: richard.sugarman@sickkids.ca

DATE OF APPROVAL June 21, 2012 **EXPIRY DATE** June, 2013

REB Form Version Date: 2008-02-01

Appendix 9: Characteristics of Interaction Analysis Respondents (n=110)

Demographic Characteristics of Interaction Analysis Respondents (n=110)

Characteristics	**N**	**% / Mean (SD)**
Age (years)		**34.2 (7.3)**
≤29	33	30.0
30-34	36	32.7
≥ 35	41	37.3
Gender		
Female	108	98.2
Male	2	1.8
Ethnic or Cultural Association		
Canadian	70	63.6
Other/Mixed	11	10.0
None	9	8.2
South Asian	6	5.5
Chinese	4	3.6
Italian	3	2.7
English	3	2.7
French	2	1.8
Irish	1	0.9
Prefer not to answer	1	0.9
Canadian		
Identifies as Canadian	70	63.6
Identifies as another ethnicity/prefer not to answer	40	36.4
Identifies with a Religion		
No	71	64.5
Yes / Prefers not to answer	39	35.5
Has High Income >$100,000		
Yes / Prefer not to answer / Not sure	74	67.3
No	36	32.7
Breakdown of Household Income		
>$100,000 in Household income	61	55.5
Prefer not to answer / Not sure	13	11.8
<$100,000 in Household income	36	32.7
Married		
Yes	81	73.6
No	29	26.4
Have Children (regardless of biological or not)		
No	57	51.8
Yes	53	48.2
Personally used Assistive Reproductive Technology		

No	102	92.7
Yes	8	7.3

Practice Characteristics of Interaction Analysis Respondents (n=110)

Characteristics	**N**	**%**
Member of Canadian Association of Genetic Counsellors		
Yes	69	69.7
No/Unknown	30	30.3
Has a Master's in Genetic Counselling		
Yes	103	93.6
No	7	6.4
Experience as a Genetic Counsellor		
>10 years of practice	32	29.1
Between 5-10 years of practice	32	29.1
Practiced less than 5 years	46	41.8
Greater than 10 years experience practice		
No	78	70.9
Yes	32	29.1
Practices at an Academic Site		
Yes	78	70.9
No	32	29.1
Practices only in Academic Site		
Yes	68	61.8
Mixed practice	10	9.1
No	32	29.1
Practices at a Community Site		
Not Community site only	89	80.9
Only Community and not academic	21	19.1
Practices in any Outreach Site		
No	101	91.8
Yes	9	8.2
Practices in Canada		
Yes	104	94.5
No	6	5.5
Practices in Quebec		
No	100	90.9
Yes	10	9.1
Practices in province that aids IVF (ON, QC, MB, NB, Europe)		
Yes	58	52.7
No	52	47.3
Practices in Regions across Canada		
Central (ON, QC)	58	52.7
Western (MB, SK, AB, BC)	37	33.6

Eastern (NFD, PEI, NS, NB)	6	5.5
Missing (United States and Other)	9	8.2
Practices in Prenatal Genetics		
No	89	80.9
Yes	21	19.1
Degree of Prenatal Practice		
Does not practice in Prenatal	57	51.8
Works in Mixed practice with Prenatal	32	29.1
Works in Prenatal only	21	19.1
How often in Genetics consultations is Prenatal discussed?		
Often or Always	59	53.6
Sometimes or rarely	45	40.9
Never or not applicable	6	5.5
How often in Prenatal Genetics consultations is PGD discussed?		
Often or Always	29	26.4
Sometimes or rarely	72	65.5
Never or not applicable	9	8.2
How often in Prenatal Genetics consultations is the cost of IVF with PGD discussed?		
Often or Always	41	37.3
Sometimes or rarely	51	46.4
Never or not applicable	18	16.4
What is the Comfort Level regarding counselling of PGD?		
Comfortable or Very Comfortable	61	55.5
Neither Comfortable or Uncomfortable	37	33.6
Uncomfortable or Very Uncomfortable	12	10.9
Had at least one patient undergo PGD		
No	61	55.5
Yes	49	44.6

Attitudes of Interaction Analysis Respondents (n=110)

Characteristics	**N**	**%**
Opinion Regarding IVF coverage in addition to PGD		
Cover IVF	91	82.7
Would not cover	19	17.3
Knowledge of PGD (4 knowledge questions presented)		
All four answers were correct	105	95.5
At least one answer incorrect / did not know/not answer	5	4.6

Know PGD Policy in own area		
Yes	85	77.3
No	25	22.7
Importance of age of mother		
Very unimportant	11	10.2
Somewhat unimportant	36	29.6
Neither important nor unimportant	19	17.6
Somewhat important	41	38.0
Very important	5	4.6

Appendix 10: Interaction Model with p-values ≤ 0.05 n=110

Attribute/ Interaction	Levels	Beta	95% CI		SE	T-ratio	p-value	Pr>Chi Square
			Lower	Upper				
Risk of condition	50%	2.020	1.870	2.228	0.446	4.532	<0.001	<0.001
	25%	1.057	0.908	1.241	0.229	4.625	<0.001	<0.001
	1%$^{\psi}$	-3.077	-3.469	-2.778	0.535	-5.753	<0.001	-
PGD indication	Childhood-onset	1.987	1.783	2.256	0.430	4.618	<0.001	<0.001
	Adult-onset non-cancer	-0.126	-0.176	-0.078	0.078	-1.626	0.110	0.1039
	Adult-onset cancer predisposition$^{\psi}$	-1.861	-2.178	-1.606	0.431	-4.322	<0.001	-
Family history	Affected children	0.300	0.143	0.456	0.228	1.316	0.194	0.1882
	No children	-0.179	-0.318	-0.043	0.131	-1.362	0.180	0.1732
	Unaffected children$^{\psi}$	-0.121	-0.412	0.174	0.224	-0.541	0.591	-
Fertility status	Infertile	-0.189	-0.363	-0.019	0.191	-0.992	0.326	0.3212
	Unknown	0.341	0.223	0.471	0.199	1.712	0.093	0.0869
	Fertile$^{\psi}$	-0.152	-0.453	0.140	0.204	-0.745	0.460	-
Number of cycles^{T}	1	-0.174	-0.197	-0.154	0.031	-5.547	<0.001	<0.001
	4	-0.697	-0.787	-0.616				
	8	-1.395	-1.575	-1.231				
Practices Prenatal and other areas*Childhood-onset condition		0.722	0.584	0.878	0.190	3.797	0.0004	0.0001
Income >$100,000 (+ prefer not to answer)*Childhood-onset condition		-0.224	-0.280	-0.179	0.060	-3.720	0.0005	0.0002
Has a child*Adult-onset non-cancer condition		0.194	0.156	0.234	0.054	3.618	0.0007	0.0003
Has had patient undergo PGD*Adult-onset non-cancer condition		-0.166	-0.203	-0.135	0.053	-3.148	0.0028	0.0016
Practices in Canada*1 cycle		0.094	0.075	0.114	0.030	3.096	0.0033	0.002
Practices in Canada*4 cycles		0.374	0.299	0.457				
Practices in Canada*8 cycles		0.748	0.599	0.915				
Agrees with covering IVF with PGD*Adult-onset non-cancer condition		-0.206	-0.258	-0.161	0.067	-3.064	0.0036	0.0022
Age >35 years*Infertile		0.703	0.519	0.902	0.233	3.023	0.0040	0.0025
Practices in Academic setting*50% risk		0.227	0.157	0.300	0.076	2.995	0.0043	0.0027
Identifies as a Canadian*50% risk		0.177	0.116	0.238	0.061	2.918	0.0053	0.0035
Personally used ART*Infertile		-0.488	-0.643	-0.346	0.169	-2.883	0.0059	0.0039

Has a Masters in Genetic Counselling*25% risk	0.304	0.187	0.421	0.108	2.826	0.0069	0.0047
Practices in a PGD permissive province*Childhood-onset condition	0.145	0.100	0.195	0.053	2.711	0.0093	0.0067
Practices in any Outreach setting*50% risk	0.448	0.354	0.556	0.166	2.707	0.0094	0.0068
Worked >10 years*Infertile	-0.607	-0.809	-0.440	0.231	-2.629	0.0115	0.0086
Personally used ART*Childhood-onset condition	0.916	0.756	1.142	0.354	2.589	0.0127	0.0096
Practices in Academic setting*Childhood-onset condition	0.181	0.116	0.241	0.071	2.537	0.0145	0.0112
Practices Only Prenatal*50% risk	-0.413	-0.572	-0.232	0.164	-2.522	0.0151	0.0117
Practices in Community setting only*Affected children	-0.171	-0.220	-0.127	0.069	-2.480	0.0167	0.0132
Personally used ART*Fertility unknown	0.400	0.292	0.514	0.171	2.332	0.0239	0.0197
Personally used ART*50%	0.937	0.824	1.103	0.403	2.324	0.0244	0.0201
Practices in any Outreach setting*25% risk	0.315	0.229	0.410	0.139	2.266	0.0280	0.0235
Has a Masters in Genetic Counselling*50% risk	0.250	0.166	0.338	0.114	2.185	0.0338	0.0289
Sometimes or rarely counsels about PGD cost*Affected children	-0.384	-0.525	-0.225	0.177	-2.172	0.0348	0.0299
Sometimes or rarely counsels about Prenatal*Childhood-onset condition	0.492	0.315	0.670	0.231	2.131	0.0383	0.0331
Always or often counsels about PGD cost*50% risk	0.354	0.205	0.479	0.172	2.064	0.0445	0.0391
Practices in Canada*Fertility unknown	-0.218	-0.285	-0.156	0.107	-2.030	0.0479	0.0423
Practices in any Outreach setting*Childhood-onset condition	0.314	0.230	0.405	0.158	1.987	0.0527	0.0469

-2Log Likelihood of model without predictors (null)	2745
-2Log Likelihood (predictor)	1231
Pseudo R^2	0.552
Adjusted Pseudo R^2	0.587
Akaike Information Criterion	1327
Degrees of Freedom	48

Only interaction terms significant at p=<0.05 are shown. CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\Psi}$denotes reference level; ^{T}denotes continuous coding

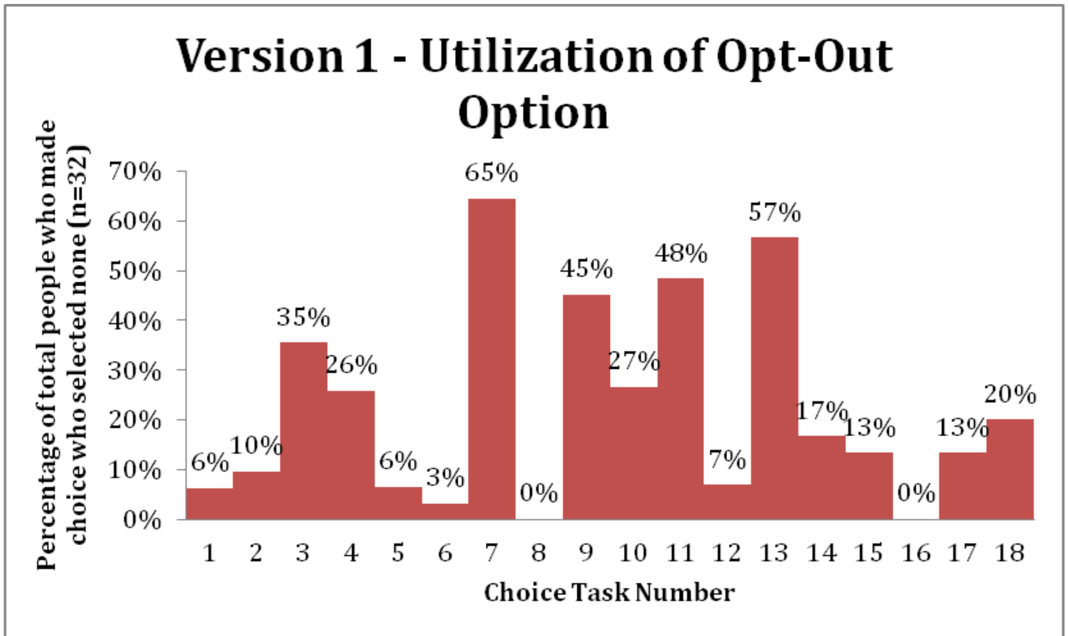
Appendix 11: Sensitivity Analysis of "Number of cycles" as categorical variable (n=126)

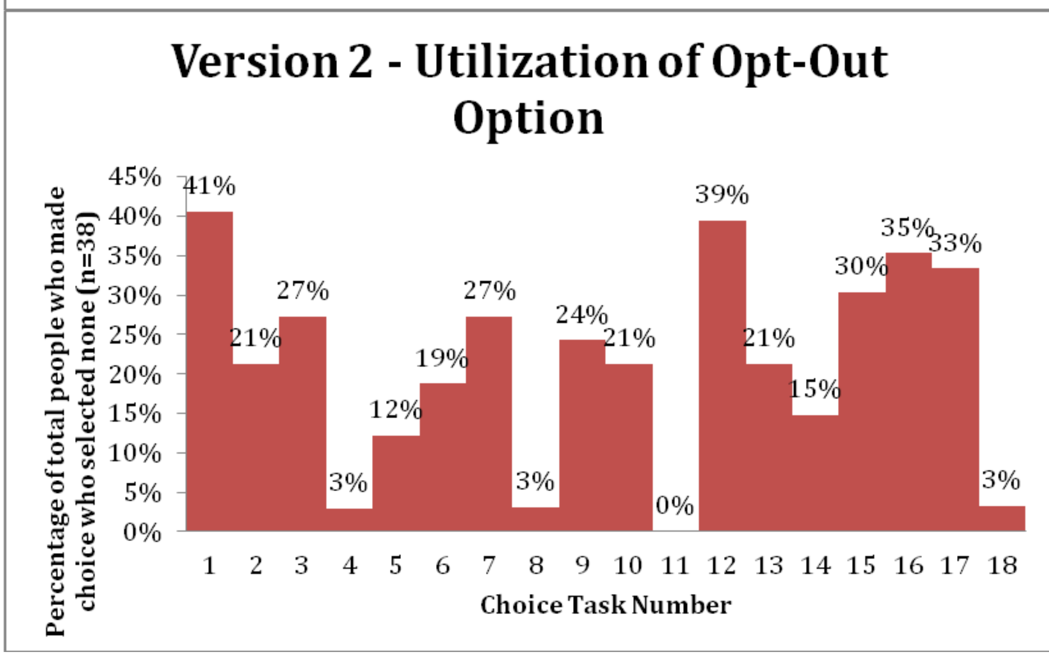
Attribute	Levels	Beta	95% CI		SE	T-ratio	p-value	Pr>Chi Square
			Lower	Upper				
Risk of condition	50%	1.053	0.999	1.111	0.058	18.019	<0.0001	<0.0001
	25%	0.654	0.607	0.708	0.057	11.478	<0.0001	<0.0001
	1%$^{\psi}$	-1.708	-1.819	-1.605	0.079	-21.638	<0.0001	-
PGD indication	Childhood-onset	1.115	1.054	1.181	0.069	16.058	<0.0001	<0.0001
	Adult-onset non-cancer	-0.173	-0.212	-0.135	0.055	-3.152	0.0103	0.0016
	Adult-onset cancer predisposition$^{\psi}$	-0.941	-1.046	-0.842	0.058	-16.241	<0.0001	-
Family history	Affected children	0.395	0.351	0.442	0.057	6.927	<0.0001	<0.0001
	No children	-0.020	-0.057	0.015	0.051	-0.391	0.7038	0.6956
	Unaffected children$^{\psi}$	-0.375	-0.457	-0.294	0.053	-7.080	<0.0001	-
Fertility status	Infertile	0.361	0.321	0.401	0.054	6.654	<0.0001	<0.0001
	Unknown	-0.169	-0.201	-0.139	0.052	-3.263	0.0085	0.0011
	Fertile$^{\psi}$	-0.192	-0.262	-0.120	0.051	-3.767	0.0037	-
Number of cycles	1	0.216	0.176	0.256	0.054	4.014	0.0025	<0.0001
	4	0.103	0.076	0.130	0.056	1.855	0.0933	0.0637
	8$^{\psi}$	-0.319	-0.386	-0.253	0.052	-6.088	0.0001	-

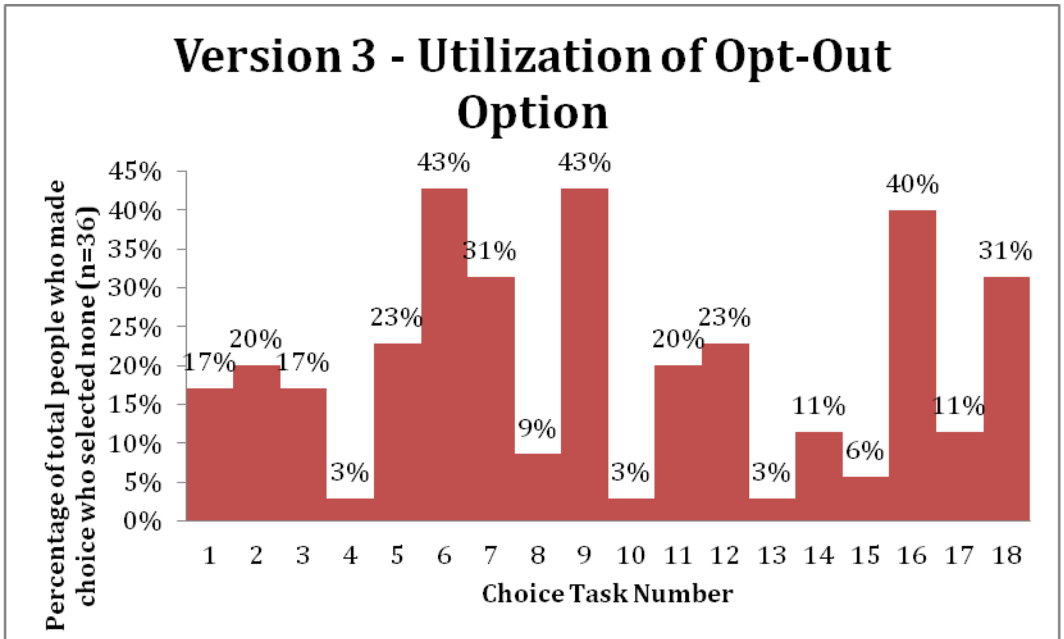
-2Log Likelihood of model without predictors (null)	3144
-2Log Likelihood (predictor)	1670
Pseudo R^2	0.469
Adjusted Pseudo R^2	0.475
Akaike Information Criterion	1690
Degrees of Freedom	10

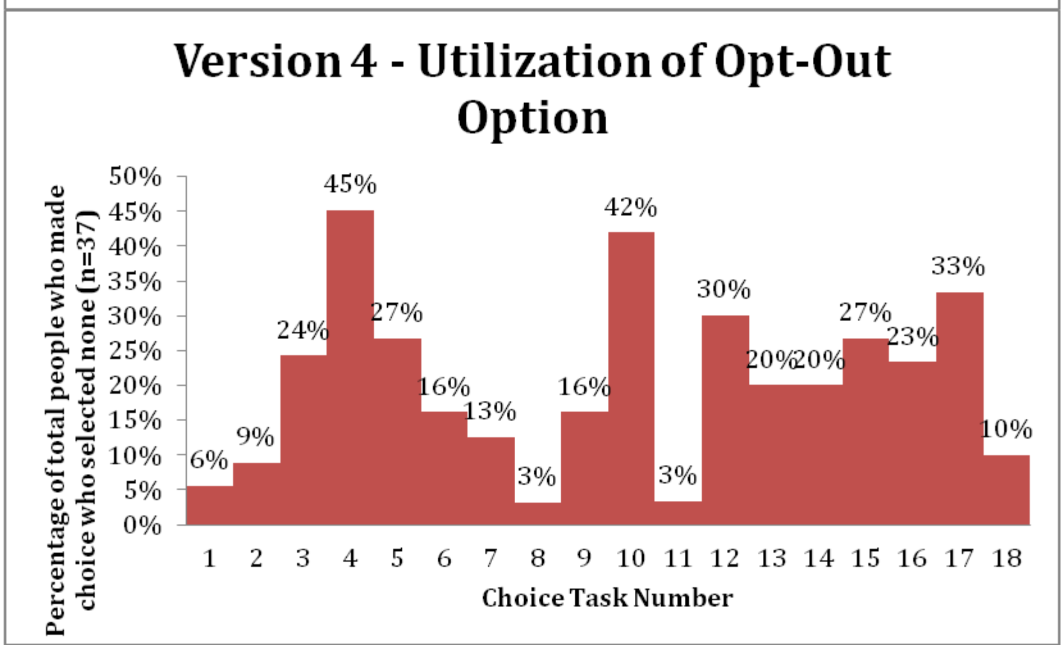
CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\psi}$denotes reference level;

Appendix 12: Utilization of Opt-Out Option for each survey version






Version 3 - Utilization of Opt-Out Option
Percentage of total people who made choice who selected none (n=36)
Choice Task Number
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
17% 20% 17% 3% 23% 43% 31% 9% 43% 3% 20% 23% 3% 11% 6% 40% 11% 31%


Version 4 - Utilization of Opt-Out Option
Percentage of total people who made choice who selected none (n=37)
Choice Task Number
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
6% 9% 24% 45% 27% 16% 13% 3% 16% 42% 3% 30% 20% 20% 27% 23% 33% 10%

Appendix 13: Sensitivity analysis of second-stage opt-out main effects analysis (n=118)

Attribute	Levels	Beta	95% CI Lower	95% CI Upper	SE	T-ratio	p-value	Pr>Chi Square
Risk of condition	50%	1.046	0.994	1.098	0.060	17.438	<0.0001	<0.0001
	25%	0.650	0.602	0.704	0.057	11.338	<0.0001	<0.0001
	1%$^{\Psi}$	-1.696	-1.802	-1.596	0.080	-21.218	<0.0001	-
PGD indication	Childhood-onset	1.114	1.052	1.178	0.071	15.627	<0.0001	<0.0001
	Adult-onset non-cancer	-0.186	-0.228	-0.147	0.056	-3.307	0.0091	0.0009
	Adult-onset cancer predisposition$^{\Psi}$	-0.927	-1.031	-0.824	0.059	-15.720	<0.0001	-
Family history	Affected children	0.378	0.334	0.424	0.058	6.477	0.0001	<0.0001
	No children	-0.022	-0.056	0.014	0.051	-0.423	0.6825	0.6726
	Unaffected children$^{\Psi}$	-0.356	-0.438	-0.278	0.053	-6.699	<0.0001	-
Fertility status	Infertile	0.367	0.329	0.402	0.055	6.616	<0.0001	<0.0001
	Unknown	-0.169	-0.203	-0.138	0.053	-3.172	0.0113	0.0015
	Fertile$^{\Psi}$	-0.198	-0.264	-0.126	0.052	-3.795	0.0042	-
Number of cycles^{T}	1	-0.078	-0.088	-0.069	0.013	-5.967	0.0002	<0.0001
	4	-0.314	-0.352	-0.276				
	8	-0.627	-0.704	-0.552				

-2Log Likelihood of model without predictors (null)	2944
-2Log Likelihood (predictor)	1581
Pseudo R^2	0.463
Adjusted Pseudo R^2	0.469
Akaike Information Criterion	1599
Degrees of Freedom	9

CI=Confidence interval; SE=Standard error; Pr=Probability; $^{\Psi}$denotes reference level; ^{T}denotes continuous coding;

Relative part-worth utilities for regression analysis (n=118)

Attribute	PW-Utility	Importance Score
Risk of condition	2.74	41.4
PGD indication	2.04	30.8
Family history	0.73	11.0
Fertility status	0.56	8.5
Number of cycles	0.55	8.3
Total	**6.62**	

PW-Utility: Part-worth utility; PGD: Preimplantation Genetic Diagnosis