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Patient perspectives after receiving simulated preconception polygenic risk scores (PRS) for family planning

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Abstract

Purpose The study investigates patient perspectives on the use of Preimplantation Genetic Testing for Polygenic disease (PGT-P) to select embryos with lower risks for common polygenic diseases. Participant responses and attitudes were evaluated after receiving simulated embryo PRS generated from their personal genetic profile.

Methods Couples seeking OB/GYN or Reproductive Endocrinology and Infertility (REI) care with an interest in genetic risks for common diseases in their prospective children participated. A tool provided PRS scores for 11 conditions, using parental DNA to simulate genetic risks for hypothetical embryos produced during IVF. Participants received counseling, reviewed results online, and completed a post-test survey. Feedback from 90 participants assessed understanding and attitudes toward PRS use in IVF.

Results Participants were overall more supportive of screening embryos for childhood-onset diseases (80%) compared to adult-onset conditions (63%); however, among specific diseases, participants expressed the greatest interest in screening for adult-onset cognitive disorders (Schizophrenia, 86%, Alzheimer's disease, 82%). Participant-free responses noted the importance of personalized counseling and participants not of European ancestry expressed frustration with limited PRS applicability. Negative reactions to testing (nervousness or anxiety 5%, regret 2%) were explored.

Conclusions The findings examine the receipt of simulated embryo PRS in a patient population in which support for using PRS during embryo prioritization is high. Positive patient interest was consistent with other US studies; as prior studies identify significant clinician discomfort, these results highlight the need for comprehensive genetic counseling and inclusive stakeholder input in shaping guidelines for PRS during IVF.

Keywords In vitro fertilization · Polygenic risk scores · Genetic counseling · Survey

Introduction

Chronic diseases are typically multifactorial and influenced by a complex interplay of genetic and environmental factors [1]. Many common chronic diseases display high heritability (52%, type 2 diabetes [2]; 40–60% Coronary artery disease [3]); however, in most of these cases, the inheritance cannot be attributed to a single gene or variant.

The genetic basis of this heritability is increasingly captured by Genome-Wide Association Studies (GWAS) on large biobanks. In the absence of an identified single-gene (monogenic) etiology, Polygenic Risk Scores (PRS) can be used to quantify cumulative genetic risk combining many genetic variants, suggesting higher or lower predisposition to specific diseases [4]. PRS are created by analyzing large data sets to identify specific genetic variations, known as single nucleotide polymorphisms (SNPs) that are associated with common diseases [5]. While the impact of individual SNPs on disease risk may be small, the combined effect of these SNPs provides a more comprehensive assessment than considering family history alone [6]. The establishment of large biobanks, such as the UK Biobank and the All of Us

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Research Program, has enabled the development of many PRS models; additionally, the inclusion of diverse datasets, such as those found in BioBank Japan, is expected to enhance the accuracy and clinical utility of PRS for individuals of non-European ancestry [7, 8]. The recent inclusion of whole genome sequencing (WGS) data in national biobanks, such as WGS data in the UK Biobank, also enables PRS which incorporate high-impact rare variants [9, 10]. In parallel, improved statistical methods have been developed for distinguishing within-family environmental effects from genetic effects [11]. In recent years, the primary focus of PRS research has been translating analytical results into clinical utility [12–14], for example, by stratifying patient populations and recommending high-risk groups for more frequent preventative screening [15].

Preimplantation Genetic Testing for Monogenic conditions (PGT-M) is indicated for parents known to be affected by, or who jointly carry variants causative of, an identified monogenic disease [16]. However, parents with elevated genetic risk or a family history of a heritable disease not attributable to monogenic causes have limited clinical options to mitigate risk in their children. While the inheritance of polygenic traits is more complex than monogenic traits, on average, offspring will have the same genetic risk as the average of their parents, and siblings of the same parents will express approximately 70% ($1/\sqrt{2}$) of the variation in genetic risk as measured between unrelated individuals [17]. An emerging practice to address this gap is the integration of PRS into IVF procedures by evaluating the genetic risk of each embryo during preimplantation genetic testing and prioritizing the transfer of embryos with a low predisposition to disease, known as Preimplantation Genetic Testing for Polygenic disease (PGT-P) [18]; for example, type 1 diabetes has been suggested as a candidate for clinical recommendations of polygenic screening when one or both parents are affected, where selecting between 5 embryos has been estimated to result in a 72% relative reduction in disease risk [19].

Due to limitations and uncertainty regarding the clinical utility of PGT-P, no clinical guidelines yet indicate PGT-P for high-risk patients or a family history of specific diseases; therefore, the decision to polygenically screen embryos is almost always patient-initiated. Current clinical PGT-P services offer screening for multiple diseases simultaneously, sometimes generating a combined score balancing the risk across these diseases [20]. Current clinical PGT-P services do not distinguish between families seeking to minimize the risk of a family history of a certain disease(s) and those seeking general screening [18, 21].

Several studies have begun to explore the perspectives of health professionals and the general public towards PGT-P [22]. Surveys of the general public in the United States have found strong support for PGT-P for diseases, with minority support for selection for traits [23]. On the other hand, physicians in the United States and Europe express broad hesitation around polygenic screening, citing concerns such as IVF patients discarding viable embryos and requiring additional IVF cycles, the small absolute risk reduction for many diseases, patients undergoing IVF without an infertility diagnosis, and patient choice overload when deciding which embryo(s) to transfer [18, 23, 24]. Other studies in the United States and Europe have begun to explore how patients actively receiving reproductive care would consider utilizing PGT-P in the perspective of their own healthcare journey [25–27]. As PRS during IVF becomes increasingly clinically implemented, it is essential to develop counseling and educational methodologies regarding potential reproductive applications of polygenic risk that do not lag behind the clinical practice.

This survey study aimed to further explore patient opinions surrounding PGT-P by assessing the perceived utility of results as applied to a simulated average IVF cycle (the "Couples Report") in the IVF decision-making process. Directly analyzing an individual's genome enables the reporting of genetic risk scores specific to an individual; by combining the genomes of two individuals, including a simulation of recombination events, PRS measures can be generated to predict the average range of predispositions found across theoretical embryos produced by any two individuals. This predictive assessment, the "Couple's Report," aimed to provide insights into the genetic risk profile of the couple's future prospective children. As researchers have identified the need for decision aids to help patients understand the impact and limitations of preimplantation genetic screening, an online visualization tool was designed to present these findings [28]. Through a post-test survey, this research evaluated patients' comprehension of PRS and their perspectives on the potential use of PGT-P to evaluate a simulated embryo's future genetic risk of developing certain polygenic diseases.

Subjects and methods

Subject recruitment

Couples were enlisted under IRB #59,928 (Stanford) from Stanford Gynecology and Reproductive Endocrinology and Infertility (REI) clinics. All couples lived in the United States at the time of testing and were receiving REI or OB/GYN care at the Stanford clinic (Sunnyvale, CA, USA). Potential participants were initially screened through telehealth clinic visits, in-person standard-of-care appointments, and a prescreening survey link. Clinic staff without outside commercial affiliations recruited patients. Initial patient recruitment was limited to patients of European descent, part

of a heterosexual couple, and eager to conceive. Because maternal age is a key factor influencing the number of viable embryos produced in an IVF cycle, only women aged 21 to 38 were recruited, ensuring enough euploid embryos could be generated for polygenic prioritization of multiple embryos [29]. During patient recruitment, clinic staff evaluated patient interest in exploratory genetic risk testing, and interested patients proceeded to informed consent. Exclusion criteria encompassed a desire to avoid preconception genetic screening (carrier screening and/or PGT-A), documented cognitive impairment, inability to provide written informed consent in English, and female participants falling outside the age bracket of 21 to 38.

During the ethical review process for this study, potential risks of participant harm were identified and mitigated. The primary risk identified by the IRB was that participants would lack access to qualified Genetic Counseling resources to understand their results. Genetic Counseling resources were made available both in a live counseling session when receiving results, and as needed for follow-up questions. To ensure participants received appropriate counseling, recruitment was limited to patients proficient in English. An additional concern was that patients would receive PRS underpowered for their genetic ancestry; as described in the methods, PRS were only released for a participant which had sufficient predictive power for their ancestry.

A complication arose because this study involved both male and female partners, but typically, only the female partner was available during initial recruitment in a gynecology or REI setting, and it was later discovered during consenting that the male partner identified as non-European (most frequently when the partner had multiple ancestries). To minimize patient frustration caused by revoking eligibility, eligibility was expanded to East and South Asian patients and partners, ancestries for which genetic risk scores for at least three conditions would be sufficiently powered to report.

Following consent, participants provided a saliva sample using the collection kit (on-site or by mail) and completed an optional pre-consultation survey that collected health and demographic information (online or via the portal). Once PRS results were available, participants joined a Genetic Counseling session during which they received their simulated test results. A link to complete an online post-counseling survey assessing the impact of receiving these results was sent during the counseling session; all surveys were completed within two days of the Genetic Counseling session. The study workflow is outlined in Fig. 1. Each couple received two individual genetic risk score reports and one simulated couples report. No financial incentives were offered (participants were not paid and did not pay for testing).

Saliva collection and PRS computation

Parental saliva samples were self-collected using AccuGene AccuSaliva Collection Kits and sent to the Psomagen (certified CAP #8,742,212, CLIA #21D2062464) laboratory for DNA extraction and sequencing at 5 × depth. Saliva samples were run through low-pass whole genome sequencing. Statistical imputation was performed by vendor Gencove to generate high-confidence calls at millions of sites associated with the PRS models, filling in genotypes for any missing loci using population-based imputation. Custom software was written to compute raw, unadjusted PRS for each disease for both individuals and simulated progeny. PRS models for 11 common diseases were developed using GWAS summary statistics using various methods depending on the disease. The methods for developing each of these PRS measures are available as whitepapers [30]. For some diseases, the average score differed by ancestry, as captured by principal components; however, this did not usually reflect an actual difference in disease susceptibility, and adjusted scores were created via principal component normalization [31].

A total of 11 genetic risk scores were computed, including for Atrial Fibrillation, Late-onset Alzheimer's disease, Bipolar disorder, Breast cancer (sex-dependent), Class III obesity, Coronary artery disease, Celiac disease,

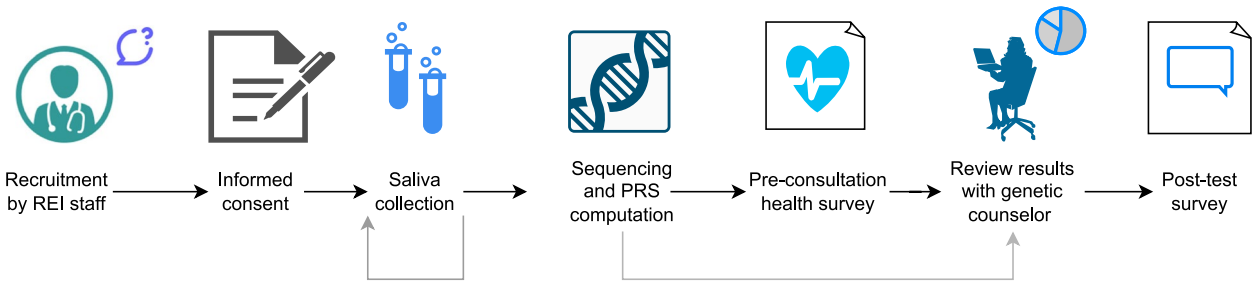


Fig. 1 Study design. Participants were screened for participation by clinic staff. Saliva was collected from participants who consented to participate (recollecting if sequencing failed) and used to generate PRS scores. Before receiving results, participants completed a health survey. Participants reviewed results with a genetic counselor, and then completed a post-test survey

Inflammatory bowel disease, Prostate cancer (sex-dependent) Schizophrenia, Type 1 diabetes, and Type 2 diabetes. Results were reported as either "normal" or "elevated" risk for each common disease provided, with risk reported as "elevated" if the ancestry-adjusted percentile was at or above the ~ 97th percentile, while any score below this threshold was considered a "normal" genetic risk score. Only models with strong predictive power for an individual or simulated embryo's ancestry were reported; diseases were masked if an individual or embryo at the 97th percentile of PRS had a smaller than 2 × elevated risk of disease versus the population baseline (odds ratio < 2), after adjusting for ancestry. As a result, the number of PRS reported differed depending on the couple's ancestry; supplementary Table 1 shows the PRS generally reported for each broad ancestry group.

Individual and couples report generation

PRS reports were generated for each partner in the couple, including their relative risk for disease, lifetime risk compared to the population average, and population risk percentile (Fig. 2). The Couples Report simulated the range of risks for embryos produced within a standard IVF cycle by generating 100 batches of 5 embryos using parental DNA and expected recombination rates [32]. This assumption of five embryos per cycle is based on the typical yield among couples of the relevant maternal age range who undergo IVF for fertility preservation, embryo banking, or PGT (rather than for infertility) [29]. The PRS from the embryo with the lowest genetic risk in each of the 100 cycles were averaged and used as the lower bound of expected risk; the maximum risk was similarly calculated. Elevated risk was noted if the simulation indicated the highest-risk simulated embryo was above the > 97th population risk percentile. A range of absolute and relative risks were reported similar to the individual report (Fig. 3).

Genetic counseling

After completion of the testing phase, all patients were required to attend post-test counseling before gaining access to the online portal to review results and visual interpretations of the report and findings. Counseling consisted of a live demonstration and discussion of the results, followed by a post-test survey. During this visit, the results were thoroughly reviewed, including an in-depth discussion of polygenic risk scores, their creation, and interpretation. The online portal served as a tool to facilitate this discussion. Patients were offered the opportunity to ask any questions.

Counseling included a discussion about monogenic versus polygenic disease and explained that both environmental and genetic factors contribute to the risk of polygenic disease. It was emphasized that polygenic risk scores do not replace carrier screening or any other traditional medical genetics recommendations. Participants were counseled that

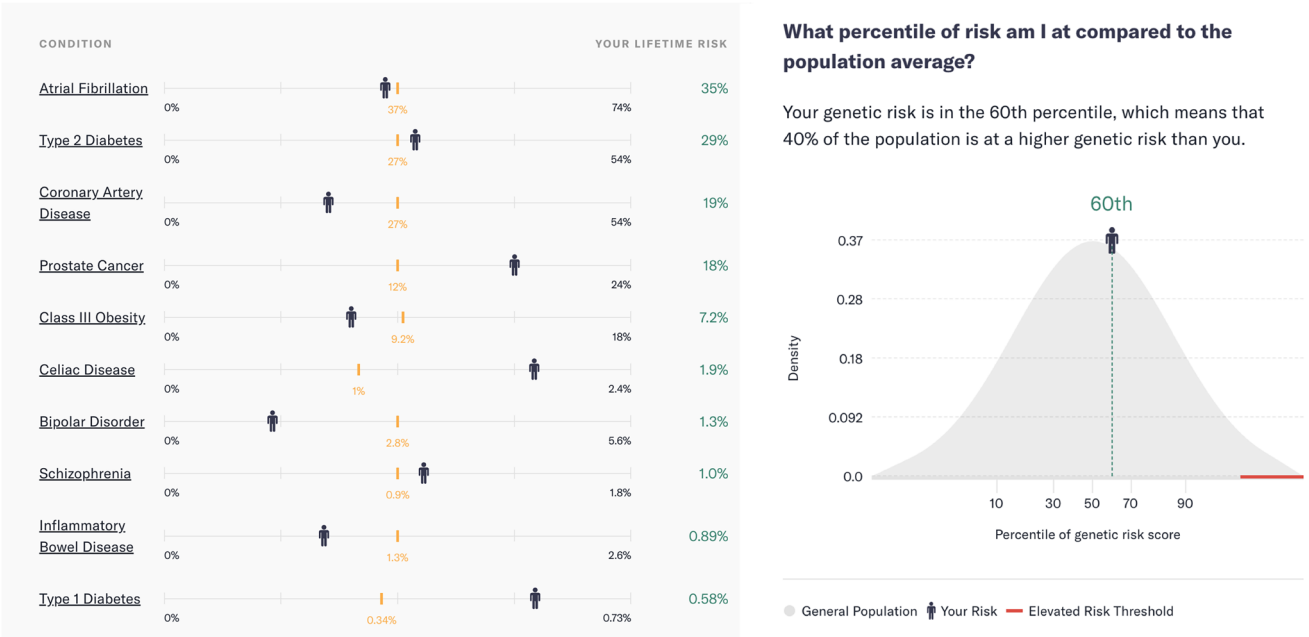


Fig. 2 Individual PRS report visualizations. Left: an individual PRS report summary table for a male partner. A PRS for breast cancer is not displayed due to the participant's sex. Right: a visualization of risk for Type 2 Diabetes against the population. Here, a 60th percentile population risk for Type 2 Diabetes translates to a lifetime risk of 29% vs a population average of risk 27%

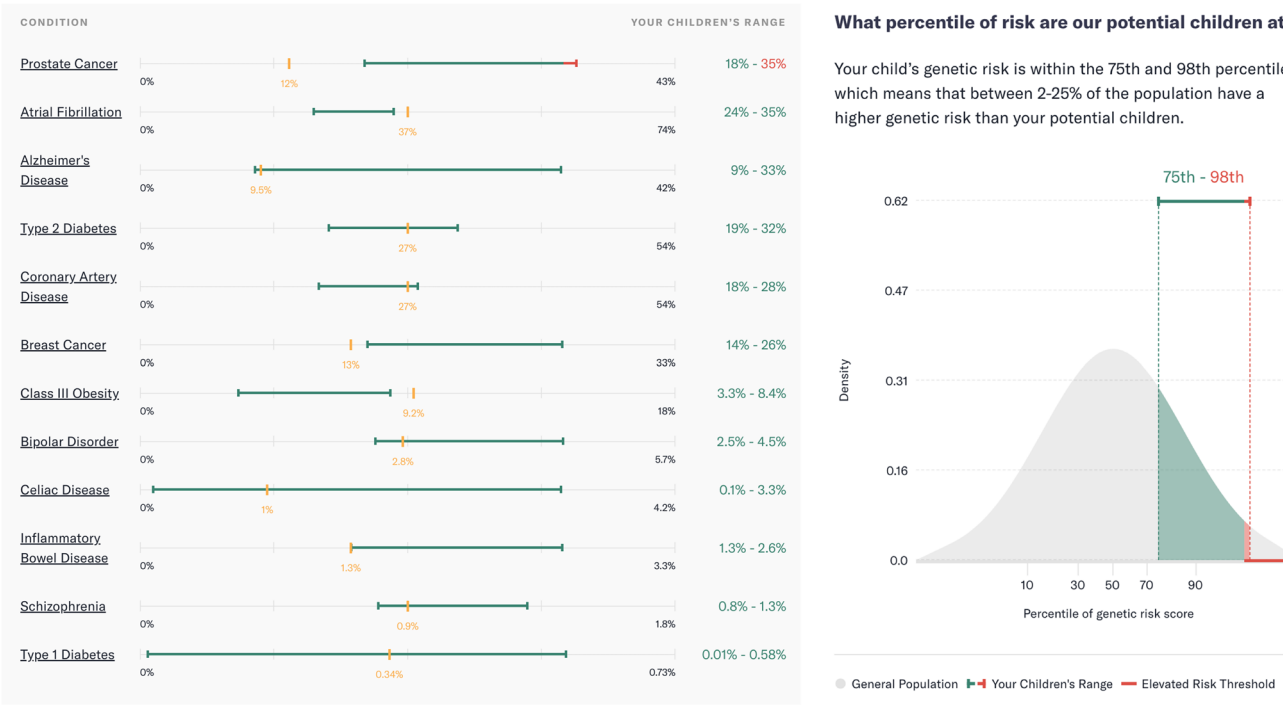


Fig. 3 Couple report PRS visualizations. Left: an example Couples Report summary table. Right: a detailed visualization of absolute risk for Prostate Cancer, where the highest-risk embryo falls within the elevated range. In the simulation, the lowest-risk embryo had a 75th percentile population risk, and the highest-risk embryo fell within the elevated range at 98th percentile

a PRS measures common variants across the genome, each linked to a small risk of disease, unlike rare monogenic variants, which have a large impact on disease.

Survey development

To determine themes for exploration in the survey, a literature review was conducted to assess overarching concerns in the field associated with implementing Polygenic Risk Scores (PRS) in adult preventative care, where clinical guidelines are being actively developed, and their impact on patient perception and experience. Recurrent themes that arose were concerns regarding patients' limited understanding of PRS, particularly regarding results being too complex and patients' challenges in interpreting relative risk compared to more unequivocal genetic results, such as carrier screening, potential negative psychological effects upon receiving this information, and perceived constraints on clinical utility [33, 34]. The professional genetics community has expressed apprehension regarding the potential negative impact on patients receiving PRS, especially in the context of IVF [35–37]. Several studies have investigated this concern in the context of adult genetic testing, revealing that individuals may exhibit an initial negative response to the information; however, there may be long-term benefits including engaging in health promoting behaviors such as surveillance for symptoms [38, 39].

The survey questions in this study were designed to assess patient attitudes toward PRS during IVF and perception of a preconception PRS report. These questions included knowledge-based inquiries, which test similar key concerns as those highlighted by the American College of Medical Genetics and Genomics (ACMG), such as the fact that patients may not understand that PRS is not diagnostic and that a low PRS does not preclude the possibility of developing a disease [35].

This study investigated this issue by incorporating open-ended questions focused on satisfaction and feedback as well as having patients respond to both positive and negative statements related to the psychological response. The survey questions centered around patients' perceived opinion on the clinical utility of utilizing PRS for informed family planning [12]. The survey sought to understand the circumstances under which patients would consider using embryo PRS to guide the implantation of embryos in an IVF cycle. Knowledge-based questions gauged whether the participants understood that the risk reduction possible via PRS prioritization of embryos was a statistical estimate and not a guarantee. Additionally, a pre-consultation health and demographic survey evaluated the personal and family history of disease; this optional

survey was administered prior to viewing PRS results to preclude an elevated PRS influencing a described family history of the disease. This survey additionally collected self-reported participant ancestry ("*What is your ancestry? (check all that apply)*: *European, Ashkenazi Jewish, East, Asian, South Asian, African, South American, Other (specify), Unknown"*), ancestry groups that are relevant to the computation of genetic risk scores. This health survey was used to evaluate whether a personal or family history of disease influenced opinions towards using PRS during IVF.

During survey analysis, thematic analysis was employed to evaluate the open-ended questions [40]. Two researchers independently reviewed the open-ended responses and generated initial codes from the responses, capturing key features of the data relevant to themes for positive and constructive feedback. These codes were collated into preliminary themes, which were discussed and refined through collaborative review. Through this process, the researchers agreed upon three final themes for each type of feedback. The questions were then re-examined and categorized into these themes, with a single comment potentially fitting multiple themes. Quantitative survey results were coded 1–5 (ex, "Strongly disagree", "Disagree", "Neutral", "Agree", "Strongly agree"); blank responses were omitted. Mean responses were computed and are presented alongside the breakdown of responses.

Results

Participant demographics and health

One thousand one hundred-four potential participants completed the prescreening survey, and those who met the inclusion criteria met with a member of the study team via telephone or Zoom to explain the study in detail. A total of 176 individuals completed electronic consent forms, 150 individuals (75 couples) chose to enroll in the study, 16 individuals withdrew their participation, and 44 were lost to follow-up (causes of participant drop-out are discussed in "study limitations"). The post-test survey was completed by 90 individuals, of which 24 responses were from individuals and 66 responses were from both members of the couples in the study; questions were optional, and not all individuals answered all questions. Additionally, 80 patients completed the optional pre-consultation survey detailing their demographics and family disease history. Demographic information collected was limited to data relevant to the computation of PRS (sex, ancestry) or genetic counseling (age, family history of disease). The participant completion breakdown is outlined in Fig. 4.

Patient ancestries were predominantly European, as originally recruited (Table 1); notably, despite study inclusion criteria limiting to patients of European, East and South Asian ancestries, several patients self-identified conflicting

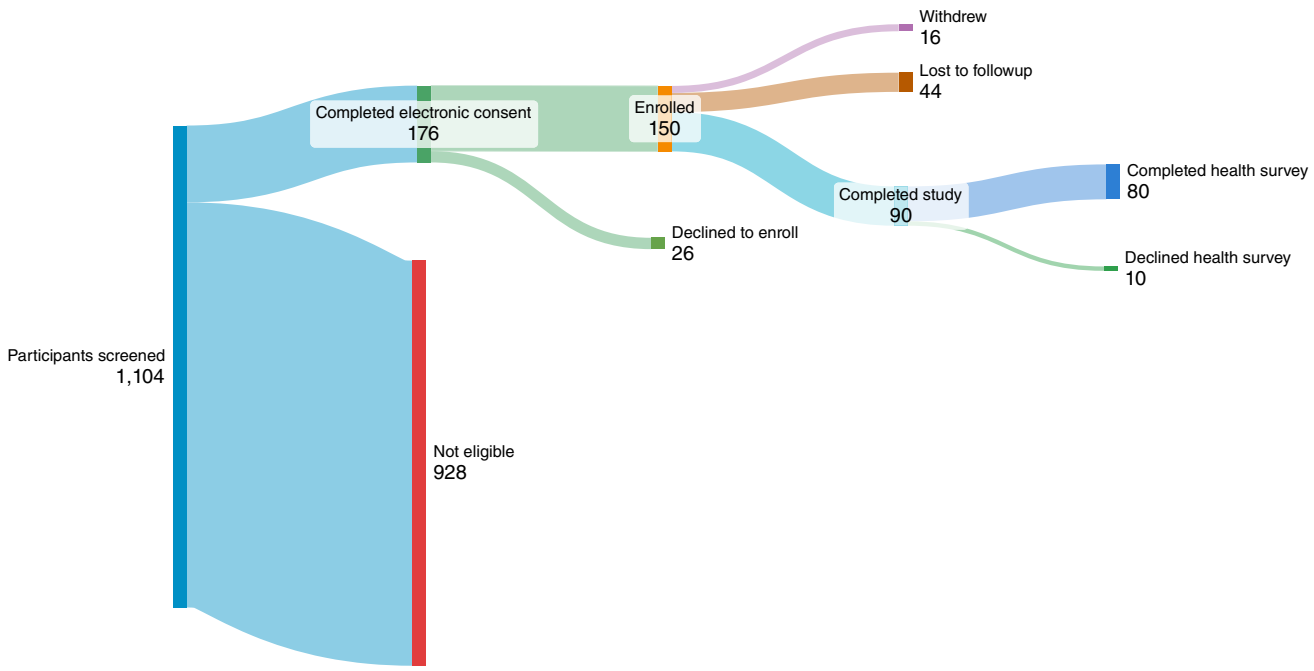


Fig. 4 1104 participants were approached for study enrollment. Of the 176 eligible screened participants who expressed interest, 150 enrolled, and 90 completed testing. 10 completed the post-test survey but did not complete the pre-consultation health survey

Table 1 Demographics. Self-reported ancestry and sex. 77 participants optionally self-reported one or more ancestries; values for ancestry do not sum to 100% due to mixed ancestries

Demographics		# Responses	% Responding participants
Ancestry	European	61	79.2
	East Asian	13	16.9
	South Asian	5	6.5
	Ashkenazi	5	6.5
	African	2	2.6
	Middle Eastern	2	2.6
	South American	1	1.3
	Other	7	9.1
	Unknown	2	2.6
Sex	Female	57	63.3
	Male	33	36.6

ancestries during the post-test survey. The minority of participants who reported having one or more previous children (6/80, 7.5%) had on average 2.0 children.

In the pre-consultation survey, participants were asked to note either a personal or family history of Prostate cancer, Breast cancer, Heart disease, Atrial fibrillation, Stroke, Type 2 diabetes, Type 1 diabetes, Inflammatory bowel disease, Schizophrenia, or Alzheimer's. Only 8/80 (10%) of participants had themselves been diagnosed with one of the included conditions, but 27/80 (33.8%) had a close relative (mother, father, or sibling) diagnosed with a matching condition, and in total 31/80 (38.8%) had either a personal diagnosis or an affected relative (Fig. 5).

Individual and couple report risk

On average individuals received a PRS report with scores for 9.97 diseases. 25% of individuals received an elevated risk for at least one disease. No individual was noted as high-risk for 3 or more diseases. Couple reports averaged slightly less than one elevated disease (0.96). No couples report was elevated for greater than 3 diseases. A disease was considered to be "Elevated" if the top range of simulated embryo outcomes for the disease was within the "elevated" risk range; in total, in 72.6% (61/84) of Couples Reports, one or more diseases were reported as elevated. A summary of results is shown in Table 2.

Patient motivations, perceptions, and impact

To gauge participant motivations for participating in the study, participants were asked to agree or disagree with several reasons for participating (Fig. 6). Participants consistently expressed higher interest in understanding the health of their potential child than their own individual health outcomes; "Curiosity about my genetic makeup" (important, somewhat important) ranked highly (83%), but lower than "Interest in finding out how my partner and I's [sic] genetics can impact our future child's health" (94%); similarly,

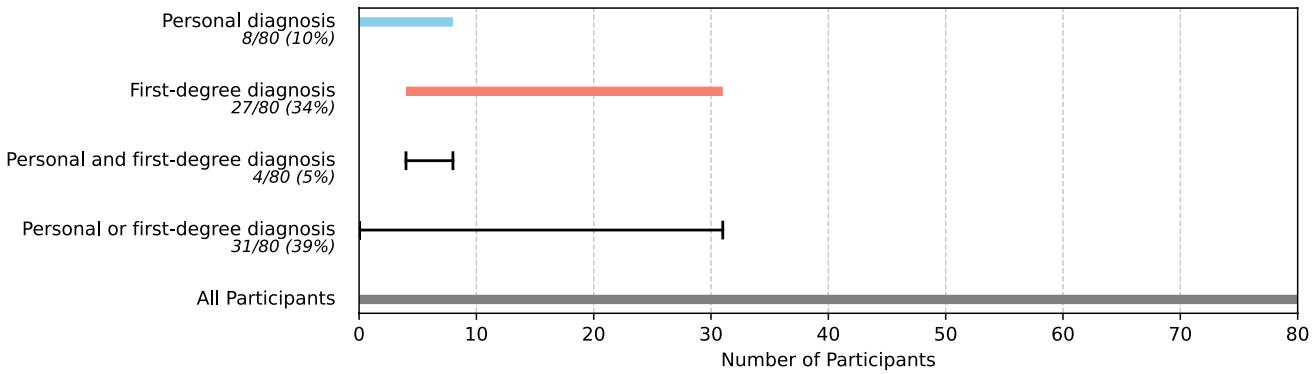


Fig. 5 Fractions and overlap between participants reporting a personal diagnosis and close relative with a diagnosis for one of the conditions with a PRS reported in this study

Table 2 Number of elevated disease risk scores. Individuals who received an individual or couples report with the N conditions at elevated risk. Analysis scoped to individuals who also completed the post-test sentiment survey

Number of elevated PRS	0	1	2	3	4+	Average
Individual report	63	15	6	0	0	0.32
Couples report	23	46	11	4	0	0.96

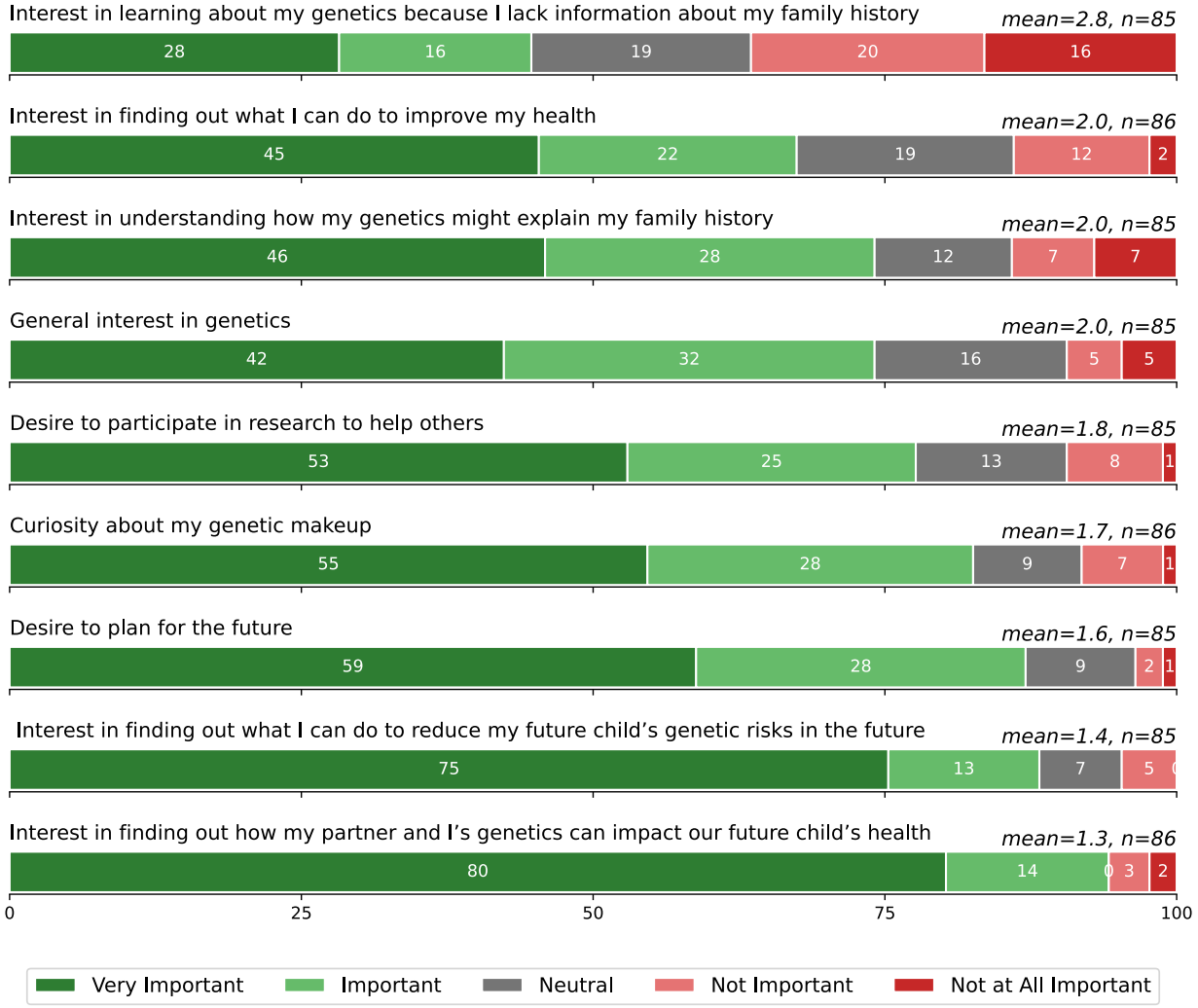


Fig. 6 Motivations for study participation. Patient responses to the prompt: "Ranking on a scale of 1 to 5, which of the following motivations for pursuing preconception screening is important to you?"

"Interest in finding out what I can do to improve my health" (67%) ranked lower than "Interest in finding out what I can do to reduce my future child's genetic risks in the future" (88%). Only a minority of participants (44%) participated in order to compensate for a lack of information about their family's health history.

Participants were surveyed on both their broad views on the utility of adult genetic screening and the applicability of genetic screening to embryos (Fig. 7). Patients expressed broad belief in the utility of genetic testing as preventative care in adults (4.2/5). Patients also evaluated the ethics of using embryo screening in various scenarios. Stronger support was expressed for assessing embryos for childhood-onset conditions (4.2/5) than for adult-onset diseases (3.8/5); however, participants did not perceive embryo genetic screening for adult-onset diseases as unethical (1.67/5). Patients moderately disagreed (2.37/5) with the notion that embryo genetic screening should be limited to couples at risk for a disease.

Participants were polled on the extent to which the survey results motivated behavior changes with regards to their own health, the health of their future child, and their perception of the utility of the provided testing (Fig. 8). More participants expressed that the results motivated them to "take better care of my future child's health" (85% agree or strongly agree) than were motivated to "take better care of my health" (70%).

After undergoing testing, patients were presented with a series of questions to gauge their positive and negative sentiments towards the screening experience they underwent (Fig. 9). Positive sentiments encompassed statements such as *"It was the right decision to pursue testing"* and "*I feel happy about my results."* Using a scale ranging from 1 (strongly disagree) to 5 (strongly agree), the average rating

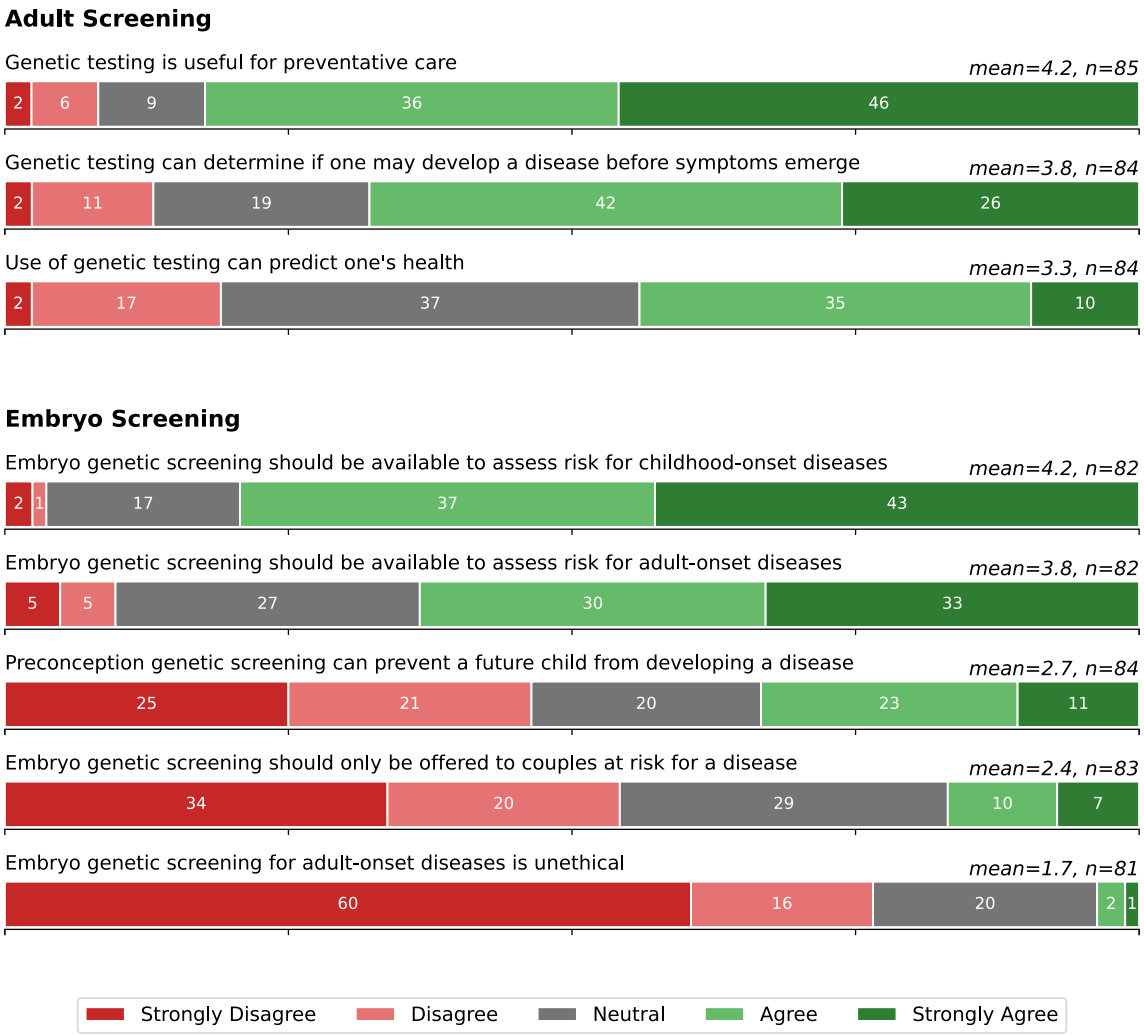


Fig. 7 Views regarding the ethics of adult and embryo genetic screening. Responses rated on a scale of 1 (strongly disagree) to 5 (strongly agree)

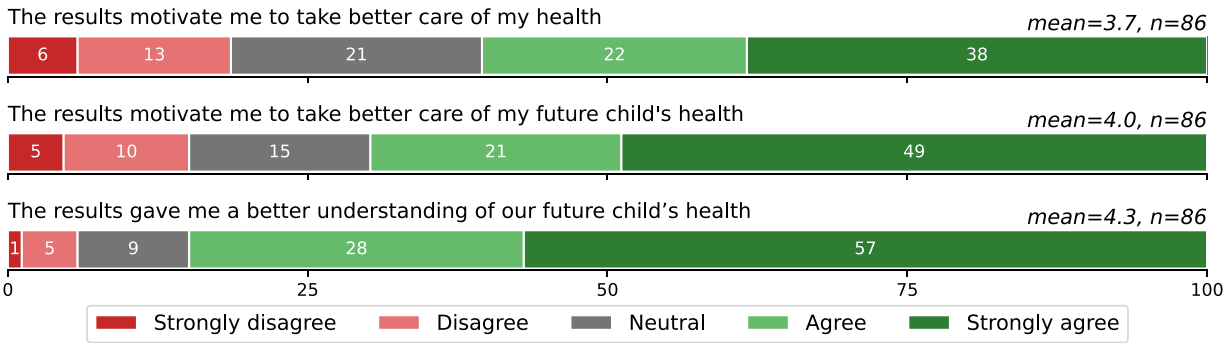


Fig. 8 Questions gauging personal impact of receiving PRS results. Responses rated on a scale of 1 (strongly disagree) to 5 (strongly agree)

for positive sentiments was 4.15, indicating a generally favorable response. In total, 83% of participants agreed or strongly agreed that they would pursue adult preconception screening, as offered in this study, again.

In contrast, negative sentiments received an average rating of 1.3, suggesting participants generally did not have negative sentiments towards the preconception report they received. For the negative sentiment, "I feel nervous or

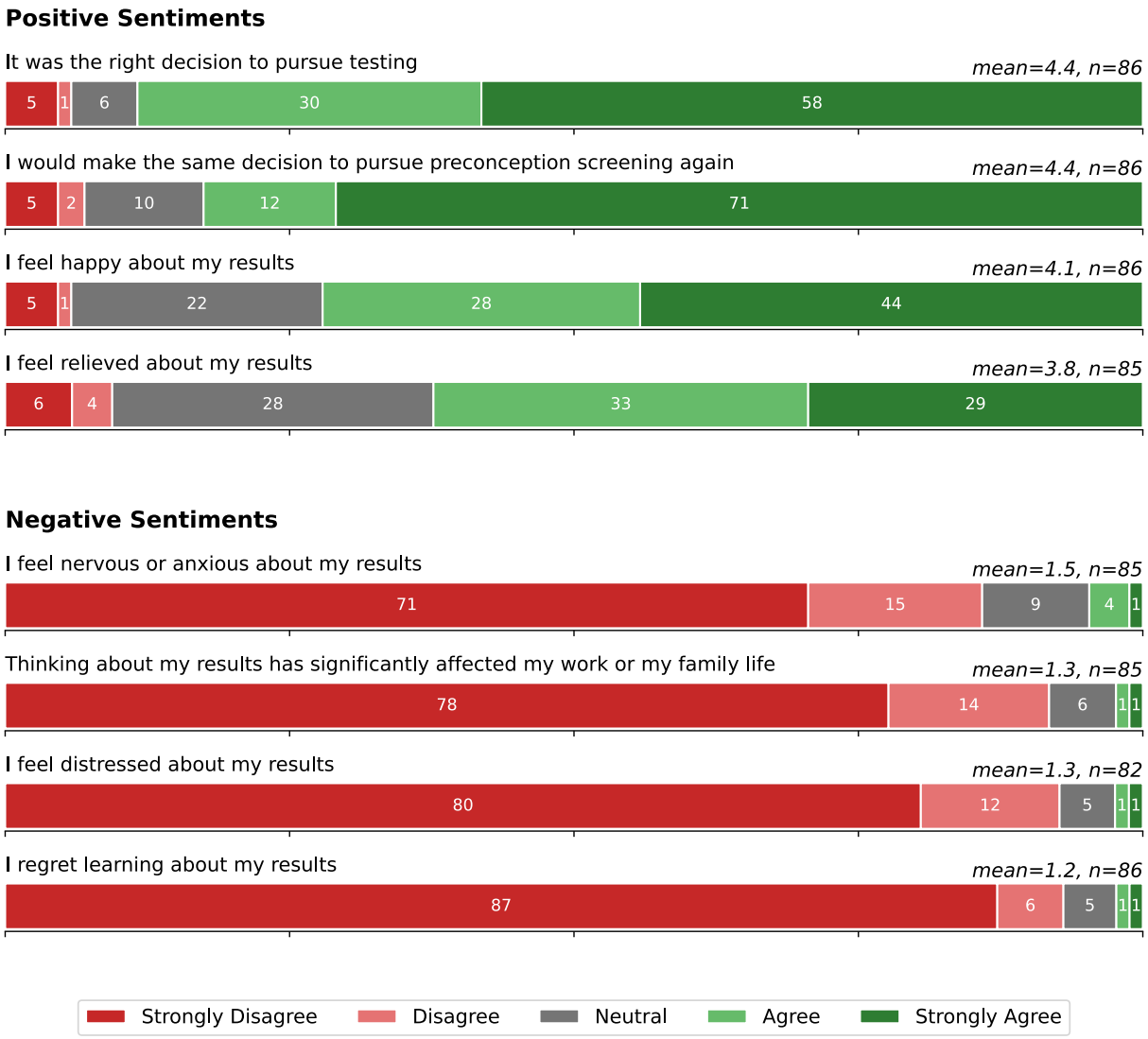


Fig. 9 Positive and negative sentiments regarding PRS testing. Responses rated on a scale of 1 (strongly disagree) to 5 (strongly agree)

anxious about my results" 4 of 87 participants agreed or strongly agreed with the statement. Of the remaining 3 negative sentiments, 2 of 82–86 participants agreed or strongly agreed.

When asked about which conditions they were most concerned about, 60 respondents (67%) provided answers. Among them, 18 individuals expressed concerns about multiple or all conditions. The most common concern mentioned was Alzheimer's disease, mentioned by 21 respondents. Other specific conditions included schizophrenia (8), prostate cancer (8), breast cancer (7), coronary artery disease (4), bipolar disorder (4), diabetes (either type 1 or type 2, not specified) (4), and atrial fibrillation (2). Six (10%) said no conditions were concerning, one respondent was unsure, and another expressed concerns about conditions that could significantly deteriorate quality of life or lack of treatment options.

Free responses

Participants were asked to rate their overall satisfaction with the preconception results and provide a reason for their rating in an open-ended question. Participants specifically mentioned an online portal as a valuable tool for visualizing the data clearly and accessing it at their convenience after the counseling session. Participants also reported gaining new knowledge through the screening process, expressing satisfaction with the explanations provided during the post-test counseling session. Participants did express constructive feedback notably sharing a desire for additional adult PRS

scores related to different ancestral backgrounds, implementing both monogenic and polygenic results, and expressed interest in having the option to opt out of receiving certain scores (Table 3).

PRS comprehension

Participants were asked a limited panel of true/false questions to confirm that participants came out of testing with a basic comprehension of genetic risk and the limitations inherent in applying PRS to the health of their future children; the results are shown in Table 4. Nearly all questions were answered correctly (98.4% average across 6 questions), indicating that counseling and the data presentation gave participants a baseline comprehension of their reported PRS.

Perceived utility and planning

Participants were polled on the extent to which they would use PRS to guide their own health decisions and their reproductive decisions (Fig. 10). While roughly half of patients (15% yes, 31% maybe) expressed they would use their own PRS results to guide their personal health decisions ("Will you change anything in the way you address your own healthcare?"), more (26% yes, 44% maybe) considered using these results to address the genetic risk of a future child ("Will you consider discussing this result with an IVF doctor to address the genetic risk of your future child?").

Overall, 20% of study participants expressed a desire to undergo IVF, absent any infertility diagnosis, to select embryos with the lowest genetic risk for a specific disease of interest and 38% expressed possible openness (Fig. 11). Responses were indicative of greater openness ("yes" or "maybe/I am not sure") among individuals who had received at least one elevated Couples Report PRS (64.5%) than those who did not (42.8%) but did not reach significance (χ^2 (1, N = 83) = , $p = 0.137$) with the available responses.

Participants were asked a scenario question: *"Suppose you received elevated preconception results for [X disease]. If embryo screening was available to assess risk for [X disease], I would elect to know each embryo's risk"* and were asked to respond on a scale of "Strongly disagree" through

Table 3 Participant free-response feedback. Positive and constructive feedback from free-text responses regarding their overall satisfaction with the preconception results. "N" indicates the number of responses matching each theme, and a representative statement is provided for each

Type of feedback	Themes	Sample quote	N
Positive	Gained knowledge or appreciated the knowledge	"It's more than we knew before and is a great starting place for discussions about building a family."	19
	Positive counseling session	The counselor "did a great job explaining the results clearly and answered all our questions."	19
	Online Portal was valuable	"I really liked how clear the results were for showing risk, especially the combined results. Would be interested in seeing what other information could be gained from the sequencing results!"	10
	Easy to understand	"Everything was very clear and easy to read and understand"	10
Constructive	The desire for more scores per ancestry	"I'm satisfied with the results received, but I do wish more data were available for my ethnicity."	6
	Have the report include monogenic with polygenic	"The preconception screening was very limited with only 10 common diagnoses described. I would prefer information about other disorders such as mutations, etc."	2
	Option to opt out of scores	"I did not want to know about my Alzheimer's risk status. There was no way to indicate this specifically on the consent form"	1

Table 4 Participant evaluation on knowledge questions

Questions. Response options: True/False	Answered correctly (N,%)
My future child's genetic risk is reported as a range instead of a single number (*True*)	82 (97.6%)
The results are based on many genetic markers found in large scale studies that either increase or decrease genetic susceptibility to the conditions tested (*True*)	83 (98.8%)
The results provide a genetic risk assessment rather than a diagnosis (*True*)	84 (100%)
An elevated genetic risk result means that my future child will definitely develop a condition (*False*)	84 (100%)
A normal genetic risk result guarantees my future child will NOT develop a condition (*False*)	80 (95.2%)
Genetics completely determines whether or not an individual will develop a condition (*False*)	83 (98.8%)

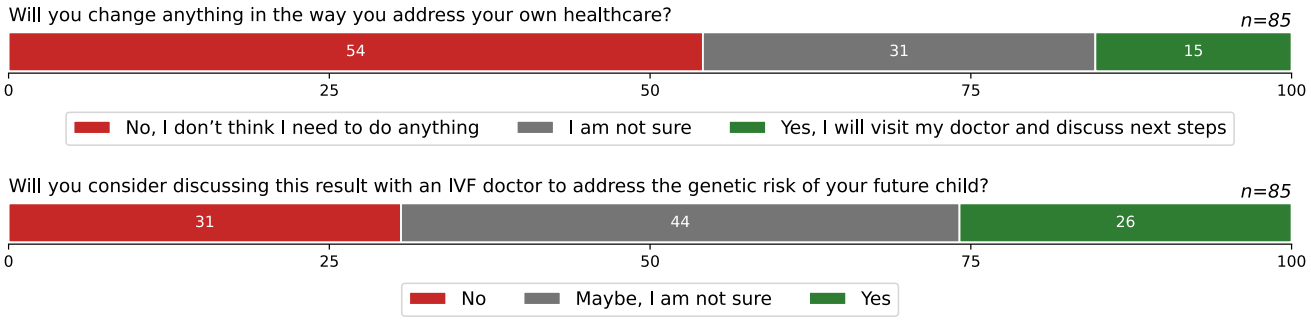


Fig. 10 Participant plans to utilize PRS to make health decisions

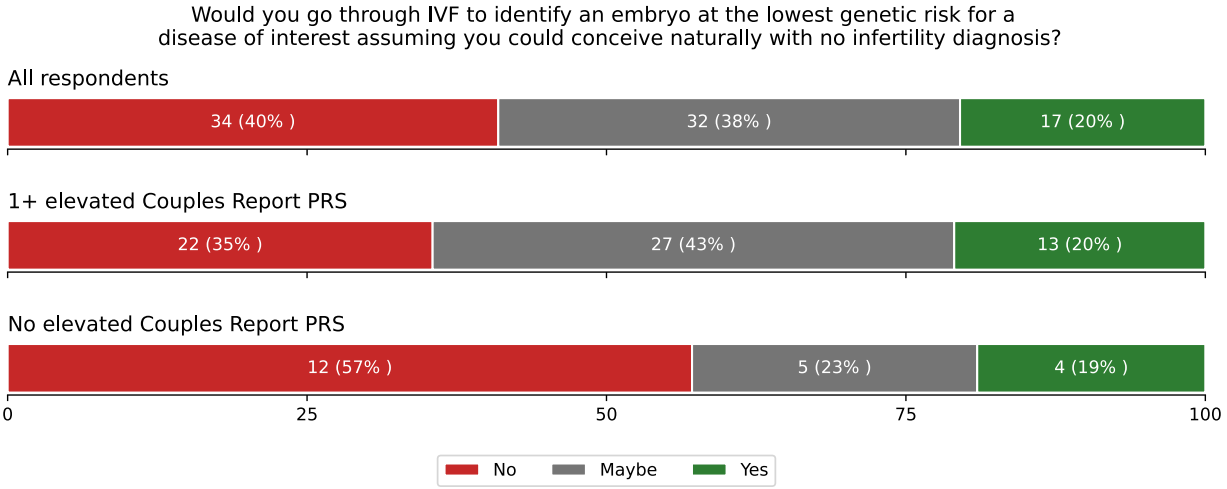


Fig. 11 Personal willingness to pursue utilization of PRS during IVF

"Strongly agree" (Fig. 12) for 9 diseases. Celiac Disease and Bipolar Disorder were omitted for brevity. Participants expressed strongest support for the cognitive disorders Schizophrenia and Alzheimer's, and lowest support for Type 2 diabetes and Inflammatory Bowel Disease.

Discussion

Ethics of PGT-P

The integration of polygenic screening into IVF embryo prioritization is a controversial subject of active debate [41]. While PGT-P is commercially available, no physician guidelines currently indicate it for use on patients. Several professional societies have spoken against the practice in clinical care [37, 42]; others have suggested making PGT-P available only for patients with an unexplained family history of severe disease without a diagnosable monogenic cause, or only in a research setting [18]. Particular concerns have been raised as to whether patients adequately understand the disease-reduction limitations of polygenic screening as compared to aneuploidy screening (PGT-A) or monogenic screening (PGT-M), whether commercial PGT-P providers will accurately represent the limitations of this technology, and whether PGT-P providers will provide adequate genetic counseling to patients before and after receiving test results, and whether more information is always better when managing patient anxiety and choices [27]. It is critical that PRS only be presented alongside monogenic findings and that patients understand that PRS does not usually confer disease risk comparable to an identified monogenic variant; accordingly, patients must be made aware that adult PRS does not replace standard carrier-screening recommendations [42, 43]. Others have raised concerns that if a patient undergoes IVF for the purposes of polygenic screening, IVF may incur a higher risk of adverse outcomes than natural conception, implying different tradeoffs regarding the impact of polygenic screening between couples already undergoing IVF for fertility preservation or infertility, and those pursuing IVF for polygenic screening [42, 44]. Additionally, while polygenic screening during IVF requires the same embryo biopsy as routine aneuploidy screening, some researchers have questioned whether some adverse pregnancy outcomes

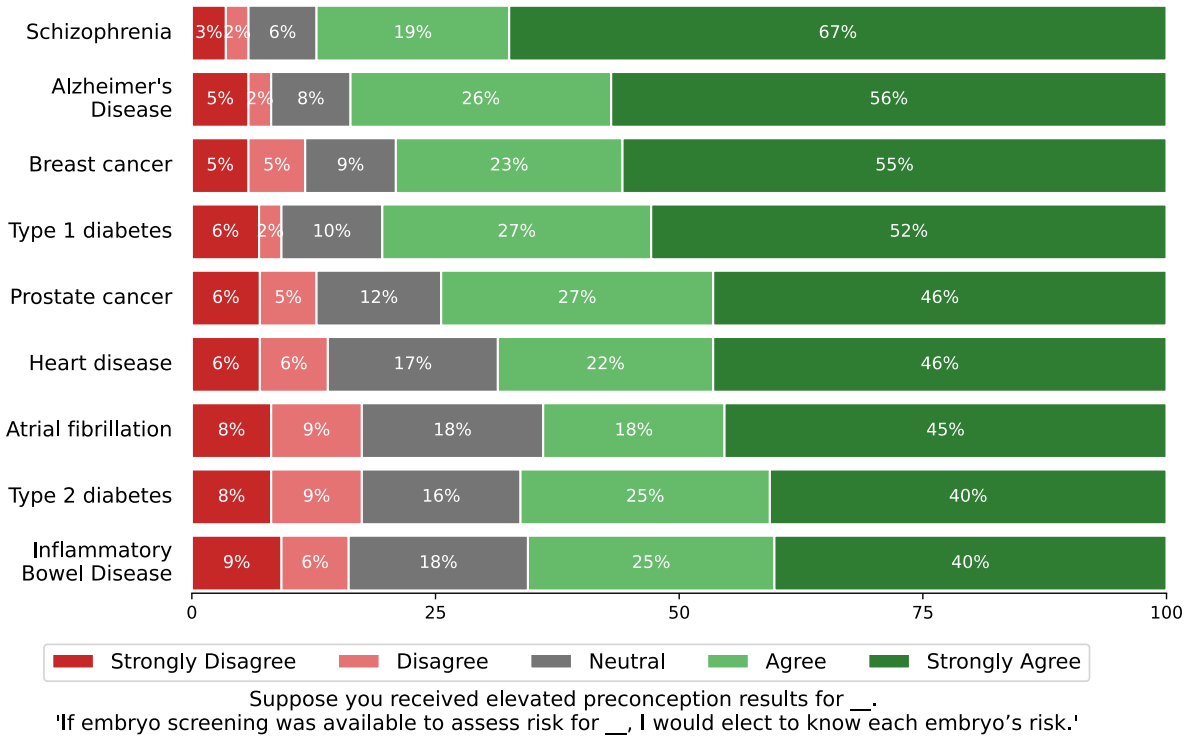


Fig. 12 Participant openness to receiving embryo risk scores per disease. Participant interest in knowing embryo PRS, conditional on elevated adult risk result, for 9 diseases

can be attributed even to a routine PGT-A biopsy [45]. Last, the long-term psychological effects of embryo PRS screening on the parents themselves have not been extensively studied; however, studies have found conflict and dissatisfaction among parents deciding whether to disclose monogenic risk-conferring variants such as BRCA1/2 to their children, especially when the parents choose not to inform their children of an inherited genetic risk [46].

Many other questions have been raised concerning the societal impact of PGT-P, such as the applicability of existing PRS to the lifetime environment of a child born today and the negative effects of pleiotropy when prioritizing embryos by genetic risk [42]. A major concern is the accuracy of disease risk prediction when using PRS in diverse populations due to the limited representation of non-European ancestry individuals in publicly available genomic datasets; however, recently, multi-ancestry BioBanks into PRS training data are beginning to enable accurate PRS across more non-European ancestries [7, 12]. Additionally, concerns have been raised that the reduction of individual genetic risk comes at the cost of a population-level reduction of genetic diversity [47].

However, it is increasingly clear that a gap exists between patient interest and clinician hesitation regarding the polygenic screening of embryos. Recent studies have shown a majority of the US public is open to using PRS during IVF for physical and psychiatric conditions, and a large minority is even open to prioritizing complex behavioral and physical traits [23]. In one study of patients receiving IVF care in the United States, over half (53%) elected to receive polygenic risk scores in addition to PGT-A results [26]; in a retrospective study in Belgium, PGT-M/SR patients expressed concerns about generally available polygenic screening but were more supportive of screening for patients with a family history of severe polygenic disease [27]; a 2021 survey of US IVF patients found 82% of participants supported polygenic screening for adult-onset disease [48]; a 2023 survey of US adults showed a majority found PGT-P either "Morally acceptable" or "Not a moral issue", though only 43% were willing to personally make use of the testing [49]. This enthusiasm contrasts with the opinions of many US healthcare providers [24]. Broader community engagement may help address this divide, ensuring that patients are well-informed about the balance of harms and benefits from PGT-P, balancing the adult-outcome interests of prospective patients against clinician concerns about pregnancy harms and unnecessary testing.

Findings

This study evaluated patient responses after using a tool built to simulate the outcome of IVF cycles utilizing polygenic

screening in the context of the participant and partner's personal genetic risk. These responses were collected after post-test genetic counseling. The survey questions were designed to evaluate participant opinions on the ethics in using PGT-P including for specific diseases, knowledge regarding the limitations of PGT-P, negative and positive reactions, and to gather free responses.

In abstract questions, patients demonstrated stronger support for embryo screening for PRS associated with childhood-onset conditions compared to PRS associated with adult-onset conditions. However, late-onset Alzheimer's Disease was the most frequently mentioned condition of concern; similarly, patients expressed the highest support for embryo screening to reduce the risk of psychiatric disorders (Schizophrenia, Alzheimer's disease) versus other conditions. This may be due to a perception that psychiatric conditions are perceived as more severe and less treatable than well-characterized diseases such as Type 2 diabetes. While a majority of participants supported the availability of PGT-P, fewer participants expressed a strong desire to use it themselves, suggesting that participants may view embryo screening as a targeted tool to minimize disease risk in a family concerned about a history of a specific disease rather than a broadly applied intervention.

Numerous scholarly articles and authoritative institutions have raised concerns regarding patients' comprehension of PRS and their ability to interpret them accurately [42, 50]. While the survey knowledge questions in this study did not deeply test participant knowledge of PRS and absolute vs relative risk, participants broadly demonstrated a baseline comprehension of the limitations of genetic risk and recognized the role of PRS as a screening and prioritization tool rather than a diagnostic tool.

Participants in several contexts in this study expressed greater motivation to act on the PRS of their potential offspring than to use their personal PRS results to address their own healthcare. This difference may reflect the limited clinical utility of adult PRS scores [51]. On the other hand, this may mirror other contexts in which parents more heavily weigh the health of their children than their own, for example, vaccinating children in situations where they do not vaccinate themselves or prioritizing healthy diets for their children [52, 53].

Concerns have been raised in the professional genetics community regarding potential adverse effects on patients receiving elevated adult PRS [38]. In this study, 23% of individuals received at least one elevated risk score for themselves, and 72.6% of Couples Reports received an elevated risk for at least one disease; the psychological response among participants, who opted into testing and were supported by genetic counseling, was more positive than negative toward their personal and simulated embryo PRS results. While open questions remain, these results are in line with previous studies which have suggested that initial negative reactions may not persist as long-term negative psychological outcomes [39].

Among free responses, the most notable participant frustration was the limited PRS available to people of non-European ancestry, mirroring concern among PRS researchers. While participants were not surveyed about their interest in monogenic vs polygenic screening, several participants in free responses (Table 3) expressed a preference for monogenic screening for specific mutations rather than ranges of polygenic risk, underscoring the need for clinical pre-test counseling to ensure patients receive the form of genetic testing they intended to undergo. However, these comments do underscore an appropriate understanding of the limited risk reduction attainable via polygenic screening and demonstrate that participants recognized PRS as a complement to preconception genetic information rather than a replacement for existing offerings like carrier screening. Last, the option to opt out of PRS for certain diseases, particularly diseases with few therapeutic options (e.g., Alzheimer's) was raised; the ability to opt out of receiving certain scores should be available to all patients during clinical reporting of both embryo and adult PRS.

Study limitations

The primary focus of this survey was to investigate patients' perspectives on preconception PRS. Consequently, the findings from this study may offer limited insights into other applications of PRS, such as disease stratification or prevention in adults. Study participation was inherently biased towards prospective parents who expressed an interest in preconception genetic screening — for example, 90% of participants expressed a concern about one or more of the studied diseases. This enthusiasm for preconception screening may not be representative of the broader patient population. Income and educational attainment were not surveyed in the participant population, which could be a major limitation of the study as sentiments may not reflect that of the general public; accordingly, the analysis in this study is limited to relative support within this cohort for screening for different classes of disease and on the impact of testing and counseling within the study population. As the cohort was recruited among patients already receiving REI or OB/GYN care, the cohort was likely already more positively predisposed towards IVF than the general population. Additionally, the survey did not investigate the extent to which motivation to participate in this research was driven by a desire to receive adult PRS versus preconception embryo PRS.

Additionally, a significant fraction of patients dropped out of the study before completion (44/150); ex-participant

demographics and reasons for withdrawal were not collected to respect the revoked consent. Because the study involved many steps including physical saliva sample collection, many couples were lost to follow-up at various points in the process: several patients consented to testing, but failed to complete saliva collection during follow-up; due to collection contamination, recollection was required for ~ 20% of samples, and in several cases, participants did not attempt recollection; several patients completed testing, but failed to schedule post-test counseling or complete the exit survey. This likely significantly further biases results towards patients who came into the study positively inclined towards preconception screening. Importantly, the mid-study change to admit non-European ancestry participants into the study population means that conclusions regarding intent and perceptions among those of non-European ancestry should be treated cautiously.

Furthermore, this study did not formally assess psychological distress; instead, it evaluated general positive and negative feelings toward the results. Additionally, due to the absence of long-term follow-ups, the study did not assess the enduring psychological responses of patients. As a result, the study could not evaluate the prolonged or shifting psychological effects associated with the use of PRS.

While participants performed well on the knowledge-based questions regarding genetic risk, participants were surveyed regarding their knowledge of genetic risk scores within two days of their genetic counseling appointment. A topic for future work may be to evaluate the retention of this knowledge in the weeks or months following a genetic consultation.

A challenging question exists regarding how patient perspectives on embryo screening translate into the approval of specific screening technologies. For example, participants strongly supported the general statement "Embryo genetic screening should be available to assess risk for childhood-onset diseases". However, it is possible that some participants supported embryo screening for monogenic childhood-onset disorders (for example, Cystic fibrosis) but not polygenic screening for disorders such as Type 1 diabetes, where the risk reduction achieved via screening is smaller.

Last but importantly, the results of simulated embryo screening may not accurately model patient behavior when making transfer decisions on real, rather than theoretical, embryos. Similarly, IVF performed to address infertility rather than elective PGT-P is expected to produce fewer embryos; genetic counseling for patients considering PGT-P as an adjunct to IVF for infertility must discuss the likely lower risk reduction achievable than using the 5 embryos in this study. Therefore, while this study gauges patient interest and motivations when using PRS during IVF, the results likely do not fully model real patient adoption of the technology in a clinical setting.

Future research

Many questions regarding the clinical application of PGT-P merit further research. The stronger patient support for screening for psychiatric conditions suggested in these results and the relation to perceived severity should be explored in future work; additionally, studies should survey a broader demographic slice of the population with an emphasis on non-European populations. This study focuses on patient perspectives to the simulated use of PGT-P, and does not attempt to address critical questions regarding whether PGT-P can meaningfully reduce the lifetime risk of polygenic disease.

Research on the clinical utility of PRS has predominantly focused on assessing the opinions of medical and professional organizations, and only recently has concerted attention been given to understanding the perspectives of patients regarding the use of PRS for family planning and how to ensure results are appropriately communicated and counseled; this study aims to add to this conversation by exploring patient perspectives when presented with potential outcomes of embryo prioritization informed by their own genetic predispositions.

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Author contribution Study conceptualization by NS and BB. Methodology by BB, YX, NS. Software by BP and DC. Formal analysis by MK and BP. Patient counseling by MK. Manuscript written by MK and BP. Review and editing by FS. Project administration by NS and BB.

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Data availability As the health survey and genetic testing data contains highly sensitive participant PHI, the data is not publicly available. Anonymized subsets of the data are available on request to the corresponding author after consultation with IRB.

Declarations

Consent and ethics approval Couples were recruited and consented under IRB #59928 (Stanford) from Stanford Gynecology and Reproductive Endocrinology and Infertility (REI) clinics.

Competing interests MK, NS, DC, QZ, BP, FS, and YX are employees, and BB is a scientific advisor for Orchid Health which performed the testing and developed a commercial offering based on the software and methodology studied here.

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