

ARTICLE



Why do people seek out polygenic risk scores for complex disorders, and how do they understand and react to results?

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We sought to explore individuals' motivations for using their direct-to-consumer genetic testing data to generate polygenic risk scores (PRSs) using a not-for-profit third-party tool, and to assess understanding of, and reaction to their results. Using a cross-sectional design, users of Impute.me who had already accessed PRS results were invited to complete an online questionnaire asking about demographics, motivations for seeking PRSs, understanding and interpretation of PRSs, and two validated scales regarding reactions to results—the Impact of Event Scale Revised (IES-R) and the Feelings About genomic Testing Results (FACToR). Independent samples *T*-tests and ANOVA were used to explore associations between the variables. 227 individuals participated in the study. The most frequently reported motivation was general curiosity (98.2%). Only 25.6% of participants correctly answered all questions assessing understanding/interpretation of PRSs. Over half of participants (60.8%) experienced a negative reaction (upset, anxious, and/or sad on FACToR scale) after receiving their PRSs and 5.3% scored over the threshold for potential post-traumatic stress disorder on the IES-R. Lower understanding about PRS was associated with experiencing a negative psychological reaction (*P* values <0.001). Higher quality pre-test information, particularly to improve understanding, and manage expectations for PRS may be useful in limiting negative psychological reactions.

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INTRODUCTION

Most common conditions that affect humans are etiologically complex, with the genetic risk being conferred by an accumulation of many genetic variants of small effect [1]. These variants can be summarized into a single variable, a polygenic risk score (PRS), that measures the genetic contribution for a given trait or condition. While for most disorders PRSs are not yet being used in clinical practice [2], they are likely to become a more routine part of clinical care in the future [1]. However in the meantime, public interest in genetic information has led companies that already provide direct-to-consumer (DTC) genetic testing online [3–5] to include PRSs in their offerings. Third-party services have also emerged which allow users to upload their raw personal genetic information obtained from DTC sites (like 23andMe or Ancestry) and generate PRSs for a wide variety of conditions [6]. Emerging data demonstrate very rapid increase in the usage of these third-party sites [6].

Despite the rapid growth in rate with which people are accessing their own PRSs without the involvement of a healthcare provider [6], little is known about what motivates people to seek this information, or how they understand and react to the results that they receive. Historically, patient outcomes of genetic testing have been found to be generally benign, however, most studies have focused on individuals who were known to be at high-risk for a monogenic disease based on personal or family history [7, 8]. Importantly, the majority of studies assessing the emotional impacts of genetic testing have been conducted in a clinical

context that was accompanied by genetic counseling [7, 8]. There have been studies which have focused on outcomes of DTC genetic testing, although the majority have not explored the experiences of actual consumers and instead used hypothetical scenarios or provided free 'DTC' genetic testing for recruited participants [9–11]. A number of these studies have suggested the potential for slight negative reactions, however, current research that has examined actual reactions to DTC tests is limited and remains less clear [11].

There is a small but growing body of literature about individuals' reactions to receiving PRSs, however these studies have predominantly focused on recruiting people to receive PRSs for specific conditions (e.g., cancer) for which the participants already had increased risk due to personal or family history and the PRS results were delivered in the context of carefully designed interventions [12–15]. To our knowledge, only one study has explored the impact of a variety of PRSs on individuals who were not specifically at risk for a particular condition. In this study, participants were recruited from the staff of health and technology companies, and education, informed consent, and genetic counseling about PRSs accompanied the testing [16]. There is very little known about the experiences of our population of interest, where individuals are self-initiating the process of seeking out PRSs and uploading their DTC genetic testing data into third-party websites to access this information for themselves. We sought to elicit motivations for seeking PRSs, understanding of the results, and psychological reactions to

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receiving this information among individuals who had sought out PRSs for themselves by uploading their own raw genetic testing data into a third-party PRS website.

MATERIALS AND METHODS

Recruitment

Participants were recruited from users of Impute.me; a third-party non-profit tool that provides PRSs for 166 different conditions from personalized raw genetic data (e.g., generated by 23andMe) to users at no cost. The website (<https://www.impute.me>) was established in 2015 and is run by independent academics. Impute.me has strict privacy standards; all personally traceable and non-traceable genetic information is deleted two weeks and two years after imputation, respectively [6]. Users upload their raw genetic data to Impute.me and access the complex disorders module on the website to receive polygenic risk scores for a variety of traits and conditions. The user chooses which conditions to query and after performing five or more queries on the website's complex disorders module with their personal results, users were invited to complete a questionnaire on the REDCap [17] platform via a pop-up banner containing a link. Individuals were eligible to participate if they: (1) had received PRS results from the Impute.me website for at least five complex disorders and were (2) at least 18 years of age, and (3) fluent in English. The study was launched in June 2019 and data collection ended in April 2020. The study was approved by the University of British Columbia's Research Ethics Board (H19-00427). For more information on how PRS are provided by Impute.me, we have included sample reports in the Supplementary Information (Supplementary Figs. 1 and 2).

Questionnaire

The questionnaire contained three main sections: users' motivations for seeking PRSs, their understanding and interpretation of the results, and the psychological impacts of receiving this information (see Supplementary materials). The survey also included demographic items (age, sex, gender, ethnicity, education level, household income, history of psychiatric illness, and the time elapsed since participants received their results from Impute.me, see Table 1) and a three-item numeracy scale previously found to have acceptable reliability [18]. The survey did not collect or link responses to the participants' PRS data.

Motivations: To explore motivations for seeking PRS information, participants were asked to rate ten items (see Fig. 1) on a four-point Likert scale ranging from "this was NOT part of the reason for me to upload my data to Impute.me" to "this was the MAIN reason for me to upload my data to Impute.me". During data analysis the middle categories were combined to form a new category: "PART of the reason". Participants were provided a list of the 58 most inquired-about conditions (those reviewed by $\geq 25\%$ of all users) and asked to select those for which they were initially interested in learning about their risk. Because individual PRS results were not linked to the survey responses, we used this question to explore if there were specific conditions that motivated interest in PRSs. There were also two free text items regarding initial motivations.

Understanding and interpretation of results: Participants' understanding of the meaning of the PRS results was explored with three true/false statements (see Table 2), and to assess interpretation of PRS result information, participants were provided an example Impute.me PRS result, and asked to answer five true/false statements.

Reactions: We used two established scales to explore psychological reactions to PRSs, the Feelings About genomic Testing Results (FACToR) questionnaire, and the Impact of Event Scale—Revised (IES-R). Wording for both instructed participants to use the receipt of the PRS results as the reference point for answering the items.

The FACToR scale is a 12 item, preliminarily validated [19] tool adapted from the MICRA scale [20] that contains four subscales: Negative Emotions, Positive Feelings, Uncertainty and Privacy Concerns. Summary scores for each subscale are calculated by adding scores from individual items in that subscale, with possible scores ranging from 0-12 for the Negative Emotions and Uncertainty Subscales, 0-16 on the Positive Feelings Subscale, and 0-8 on the Privacy Concerns Subscale. For items that measure positive feelings, scores were first reversed before being summed, such that for all scales, a higher score indicates greater functional impairment [19]. We focused on the negative emotions subscale because understanding factors that

contribute to patient harm has the greatest likelihood to impact clinical practice around the delivery of PRS information.

The IES-R is a 22 item validated instrument [21] that assesses subjective distress associated with events. IES-R scale scores range from 0 to 88, with a score >23 indicating likely clinically significant distress, scores between 33 and 38 suggesting a probable diagnosis of post-traumatic stress disorder (PTSD), and scores >38 indicating significant PTSD [21].

Data analysis

Analysis was primarily descriptive, but given the clinical importance of negative reactions to PRS, we used exploratory statistical tests to examine relationships between these reactions and other variables. Specifically, we explored relationships between the IES-R and FACToR Negative Emotions Subscale scores and demographic variables using independent samples *t* tests and ANOVA, with post-hoc Tukey to further explore significant relationships. We also compared IES-R and FACToR Negative Emotions Subscale scores between those who did/did not: (a) chose "curiosity" as a main reason for seeking their PRS, (b) answer all of the numeracy questions correctly, (c) answer all three of the understanding questions correctly, and (d) answer all five of the interpretation questions correctly (independent sample *t* tests). As well, we explored relationships between the number of motivators participants selected and, first, IES-R (those who scored above and below cutoff for PTSD), and second, FACToR Negative Emotions Subscale score (independent samples *t* tests, and Pearson correlation/linear regression respectively).

All statistical analyses were performed using IBM SPSS Statistics Version 23 (IBM Corp., Armonk, New York). Although this was an exploratory study, we used a conservative approach, and set our threshold for statistical significance at $p < 0.002$ (Bonferroni correction accounting for the 26 tests we conducted). Text that participants provided in the free-form text fields was used to provide illustrative quotes around key findings.

RESULTS

Of the 10,650 people who were eligible to participate, 438 (4.1%) clicked on the link for more information and 277 participated in the study (2.6% of eligible). Respondents tended to be female ($n = 144$, 63.7%), White ($n = 200$, 88.5%), with high levels of education ($n = 121$, 53.3% had a bachelor's or graduate degree), and most ($n = 162$, 71.7%) had received their results for the first time within the week prior to completing the questionnaire (see Table 1). Incomplete surveys were included in analysis and therefore response rate varied by question.

Motivations

Almost all participants indicated that general curiosity ($n = 270$, 98.2%) and accessing additional health information ($n = 265$, 96.0%) were at least part of their reason for seeking PRSs (see Fig. 1). The conditions that were most frequently identified by participants as being of interest included Alzheimer's disease ($n = 127$, 50.0%), anxiety disorder ($n = 105$, 41.3%), major depressive disorder ($n = 98$, 38.6%), type 2 diabetes ($n = 97$, 38.2%), and breast cancer ($n = 81$, 31.9%). Free-text responses for motivations to pursue PRS information were generally consistent with results shown in Fig. 1. Although the free-text responses were not formally analyzed, three main concepts were mentioned by multiple respondents including (i) their personal curiosity about genetic information (e.g., "Curious about heritability of traits linked to psychology and personality"), (ii) personal diagnoses or undiagnosed health conditions which they wanted to learn more about (e.g., "Currently dealing with medical problems that my doctors cannot figure out... hoping my DNA would explain"), and (iii) adoptions in the family that drove their investigations (e.g., "I'm adopted, I have no idea what my family history is... this is a chance to have some idea").

Understanding and interpretation of results

Regarding general understanding of the meaning of PRSs, 35.5% ($n = 93$) of participants incorrectly classified one or more

Table 1. Demographic information and reactions to polygenic risk scores (PRSs).

Demographic characteristic	Total		Mean FACToR Negative Emotions Subscale Score ^c	p value	Mean IES-R Score ^d	p value	IES-R Score > Threshold for PTSD (N) ^e
	N ^a	% ^b					
Age	223			n/a		n/a	11
Mean = 37.1 (Range 18–67)	223	100	1.7		5.1		11
Sex Assigned at Birth	226			0.075		0.003*	12
Male	81	35.8	1.4		3.0		2
Female	145	64.2	1.9		6.5		10
Gender	226			0.075		0.003*	12
Male	82	36.3	1.4		3.0		2
Female	144	63.7	1.9		6.6		10
Trans male/Trans man	0	0.0	N/A		N/A		0
Trans female/Trans woman	0	0.0	N/A		N/A		0
Genderqueer/Gender non-conforming	0	0.0	N/A		N/A		0
Other	0	0.0	N/A		N/A		0
Ethnicity	226			0.840		0.083	12
White ^f	200	88.5	1.7		5.2		11
African	2	0.9	0.5		1.5		0
South Asian	3	1.3	1.7		12.0		0
East Asian	4	1.8	2.3		4.3		0
Middle Eastern	2	0.9	5.5		17.5		1
Hispanic/Latino	2	0.9	1.0		0.0		0
Indigenous	2	0.9	0.5		0.0		0
Prefer not to answer	0	0.0	N/A		N/A		0
Other	11	4.9	1.6		5.1		0
Education	227			0.774		0.083	12
Less than high school	2	0.9	4.5		25.0		1
High school or equivalent	25	11.0	1.9		4.7		1
Some college/university	61	26.9	2.0		8.0		7
Associate degree/diploma	18	7.9	1.9		5.0		0
Bachelor's degree	57	25.1	1.5		3.1		1
Graduate degree	64	28.2	1.5		4.2		2
Income	222			0.097		0.080	11
<40,000	83	37.4	1.7		4.9		2
40,000–69,000	49	22.1	2.2		7.6		4
70,000–99,000	48	21.6	1.1		2.5		1
100,000+	42	18.9	2.0		5.9		4
Time since receiving results	226			0.340		0.097	11
<1 week	162	71.4	1.5		4.6		7
1–2 weeks	23	10.1	1.8		5.2		1
2–8 weeks	21	9.3	2.4		10.5		3
>8 weeks	20	8.8	2.3		3.7		0
Numeracy	217			0.004*		0.002*	11
0 of 3	6	2.8	3.2		10.8		1
1 of 3	24	11.1	3.0		10.3		4
2 of 3	51	23.5	2.2		6.7		4
3 of 3	136	62.7	1.3		3.3		2
Psychiatric History	92			0.330		0.276	1
Self-reported symptoms/treatment	17	18.5	1.9		2.9		0
Previous and/or current diagnosis	51	55.4	1.2		2.4		0
No reported psychiatric history	24	26.1	1.5		4.5		1

*Statistical significance set at $p < 0.002$.

^aNumber of respondents varied by question (ranging from 92 to 227).

^bPercentage out of the total number of participants who answered that demographics question.

^cMean Feelings About genomic Testing Results (FACToR) Negative Emotions Subscale Score, which considers participants' degree of sadness, anxiety and how upset they felt after receiving results. Higher scores indicate greater functional impairment.

^dMean Impact of Event Scale—Revised (IES-R) scores of individuals in the row.

^eNumber of participants who scored above the threshold for possible PTSD on the IES-R.

^fThe survey option used was "Caucasian" however we are reporting it as "White" in this table to be aligned with current practices for asking about race and ethnicity.

statements (see Table 2). When asked to *interpret* an example Impute.me result, 61.6% ($n = 149$) of participants incorrectly identified one or more statements. Overall, only 25.6% ($n = 67$)

of participants answered all understanding and interpretation questions correctly.

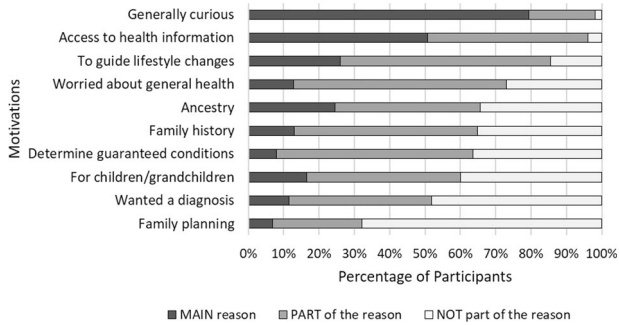


Fig. 1 Motivations that contributed to participants' decisions to seek PRSs ($n = 277$). Motivations were not mutually exclusive; participants could choose as many as they liked.

Reactions

Given that negative reactions to genetic information are of clinical interest, we explored the Negative Emotions Subscale further. Average scores for each of the four FACToR subscales are shown in Supplementary Table 1, and overall spread of scores is shown in Supplementary Fig. 3. We assessed the proportion of respondents who reported that they experienced a negative reaction (upset, anxious and/or sad) either a little, somewhat, a good deal or a great deal after receiving their personal PRSs. Overall, 60.8% of participants ($n = 146$) reported that they experienced a negative reaction. Of those participants, 14.4% ($n = 21$); 8.8% of total participants) reported that they experienced one or more of those negative reactions either a good or great deal.

The mean IES-R score was 5.38 ± 10.0 , and most participants (94.7%, $n = 213$) had a total score of 23 or below. Of the remaining 5.3% ($n = 12$), 33% ($n = 4$) scored less than 33 (indicating clinically significant distress), 17% ($n = 2$) scored between 33 and 38

Table 2. Results of two categories of statements investigating users' understanding: (1) Understanding of the test; and (2) Interpretation of an example PRS result.

		Correct Answer ^a	Selected Answer ^b	N ^c	% ^d	% All Correct ^e
Understanding of the Test	The results I received from Impute.me...					
	Definitively tell me whether or not I will develop a health condition	False	True	10	3.8	64.5
			False	200	76.6	
			Unsure	51	19.5	
	Include only some of the genetic factors that can contribute to risk for health conditions	True	True	225	85.9	
			False	5	1.9	
			Unsure	32	12.2	
	Show that my lifestyle and environment play no role in whether I develop a health condition	False	True	23	8.8	
			False	205	78.2	
		Unsure	34	13.0		
Interpretation of an Example PRS Result	The example PRS result above shows that... ^f					
	There is a chance of about 0.25% for the person to develop this condition	False	True	21	9.1	38.4
			False	144	62.3	
			Unsure	66	28.6	
	The person has a slightly higher chance than the average person to develop the condition	True	True	209	87.4	
			False	15	6.3	
			Unsure	15	6.3	
	The person will definitely develop the indicated condition	False	True	2	0.9	
			False	211	92.5	
			Unsure	15	6.6	
	The person has a chance of just over 50% to develop the condition	False	True	52	22.3	
			False	152	65.2	
		Unsure	29	12.4		
The person has a chance of over 90% to develop the condition	False	True	5	2.2		
		False	211	91.3		
		Unsure	15	6.5		

^aThe correct answer to each statement (true or false).

^bThe answers which participants could select (true, false, or unsure). The correct answer, indicated in the column to the left, is bolded.

^cNumber of participants who selected the answer in that row.

^dPercentage of participants, of those who answered that statement, who selected the answer in that row.

^ePercentage of participants who correctly answered all statements in that category.

^fParticipants were given an example PRS result showing a person's risk for an unknown complex condition at the ~55th percentile on which to base their answers for this category.

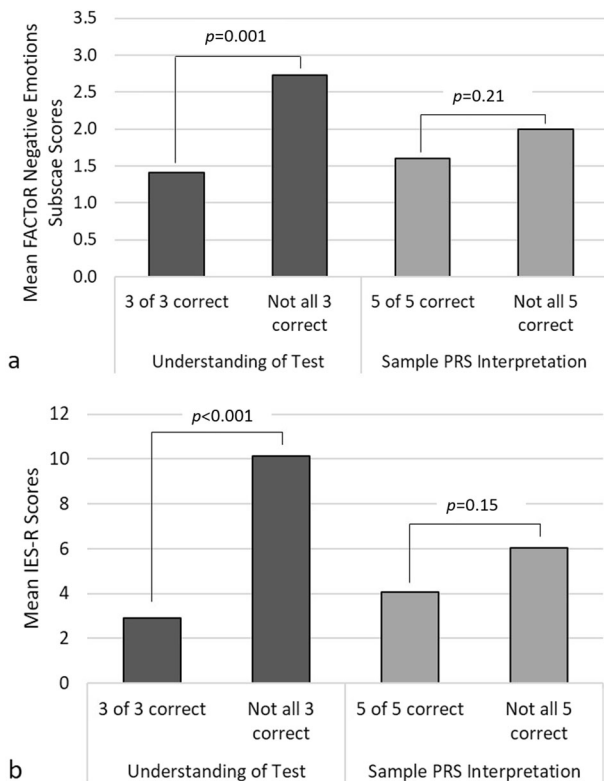


Fig. 2 Relationships between understanding/interpretation of PRS and FACToR Negative subscale, and IES-R scores. a Grouped bar chart showing relationship between mean FACToR Negative Emotions Subscale and both understanding of the test and example PRS interpretation ($n = 236$). **b** Grouped bar chart showing relationship between mean IES-R and both understanding of the test and example PRS interpretation ($n = 224$).

(indicating a probable diagnosis of PTSD), and 50% ($n = 6$) scored above 38 (indicating significant PTSD). Every participant who scored above the IES-R cut-off of 23 also reported some degree of negative reaction on the FACToR. Overall spread of scores is shown in Supplementary Fig. 3.

Variables associated with negative reactions

Demographic variables: There was 99% concordance between sex and gender of participants, and the statistical analyses of these variables resulted in the same findings. No association (all p values > 0.002) was found between any demographic characteristic and the psychological impact of receiving PRSs (Table 1). Regarding numeracy, the mean FACToR Negative Emotions Subscale scores of participants who did not get all three numeracy questions correct (mean = 2.5, SD = 3.3) was significantly higher ($t(43.8) = -3.2, p = 0.002$) than those who did (mean = 1.3, SD = 1.6). Reaction scores for each of the most commonly inquired-about conditions offered on Impute.me are shown in Supplementary Table 2.

Understanding and interpretation of PRSs: We identified significant relationships between understanding of and reactions to the PRS test as measured by FACToR and IES-R (Fig. 2). Specifically, the mean FACToR Negative Emotions Subscale score for participants who did not get all three understanding questions correct (2.7 ± 3.2) was significantly higher ($(t(29.9) = 3.3, p = 0.001)$) than those who did get all three correct (1.4 ± 1.9). Similarly, the mean IES-R score for participants who did not get all three understanding questions correct (10.2 ± 14.8) was significantly higher ($(t(59.6) = 4.1, p < 0.001)$) than those who did get all three correct (2.9 ± 5.3).

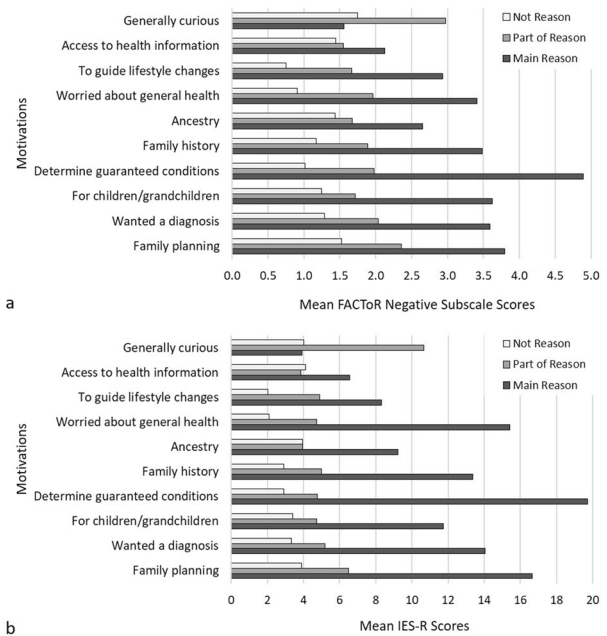


Fig. 3 Motivations for seeking PRS and relationships with FACToR negative, and IES-R scores. a Clustered bar chart showing mean FACToR Negative Emotions Subscale scores for users who selected each motivation as not a reason, part of the reason or the main reason for pursuing polygenic risk information online ($n = 240$). **b** Clustered bar chart showing mean IES-R scores for users who selected each motivation as not a reason, part of the reason or the main reason for pursuing polygenic risk information online ($n = 225$).

However, there was no relationship between the number of questions about interpretation of an example PRS result that was correctly answered and either FACToR Negative Emotions Subscale scores or IES-R scores ($p = 0.21$, and $p = 0.15$, respectively).

Motivations for seeking PRSs: The average FACToR Negative Emotions Subscale and IES-R scores for the 10 different motivations for seeking PRS information are shown in Fig. 3. The motivations were not mutually exclusive (people could select as many as they liked). We found that individuals who *did not* choose curiosity as a main reason for seeking out their PRS scores had statistically significantly higher IES-R scores (mean = 10.3, SD = 16.6) and FACToR Negative Emotions Subscale scores (mean = 2.7, SD = 3.1) compared to those who chose curiosity as a main reason for seeking out their PRS scores (IES-R; mean = 4.1, SD = 7.2, FACToR; mean = 1.6, SD = 2.2). IES-R; ($t(33.4) = -3.8, p \leq 0.001$). FACToR; ($t(3.8) = -2.7, p = 0.009$). We found a small correlation between the number of motivations chosen and higher FACToR Negative Emotions Subscale scores ($R^2 = 0.122$), and the number of motivations chosen predicted 35.5% of the FACToR Negative Emotions Subscale score ($B = 0.355, p < 0.001$). Similarly, we found that participants who scored above threshold for PTSD on the IES-R scale chose more motivations (mean = 8.4, SD = 1.0) than those who scored below the threshold (mean = 6.7, SD = 1.8) ($t(4.2) = -5.3, p \leq 0.001$).

DISCUSSION

Our study involved individuals who self-initiated the process of seeking out PRSs by uploading their DTC genetic testing data into a third-party website to access this information for themselves. To our knowledge, this is the first study to investigate the motivations for seeking PRSs, understanding and interpretation of the results, and reactions to receiving this information among this type of user. We found that over 60% of participants experienced some

degree of negative reaction after receiving their personal PRSs, and ~5% scored over the threshold for potential PTSD. We found that having poorer understanding of PRS, being motivated by reasons other than general curiosity to seek out this information, having lower levels of numeracy, and reporting more motivations for seeking out PRS were related to having a negative psychological impact of PRS information. It is important to note that the cohort of participants in this study is early adopters of PRS who overcame financial and logistical barriers to seek out this information for themselves. This is relevant to bring attention to because the participants in our study likely do not represent how the average member of the public would respond to this type of information, and our findings may underestimate the potential harms of PRSs in a broader population.

It is well known that numerical risks are both easily misinterpreted (due to common scientific and mathematical limitations) as well as subjectively perceived (personal experiences that can impact one's risk perception) [22]. In our study population, lower numeracy was associated with having a negative reaction to PRS information. There are unique challenges in communicating PRSs, not only are they probabilistic rather than deterministic, but also they are usually presented as risk stratifications or relative risks compared to the general population [22]. Theoretically, if people misunderstand PRS results, and assume that lifestyle plays no role in disease risk, this could have important impacts on engagement with risk reduction behaviors. More information is needed regarding how to effectively communicate relative and absolute risks to patients and consumers, and to determine if improved communication about risk improves experience with complex genetic information.

Our findings suggest that many participants had some understanding about the general concepts of multifactorial/complex conditions and PRSs, and this has been similarly reflected in other recent studies [23–25]. However, many participants in this study had incomplete understanding and interpretation of PRS, as demonstrated by 74.4% of participants incorrectly answering at least one of the questions in this area. Poorer understanding of PRSs was associated with experiencing a negative reaction from receiving the information. There are a number of solutions that could be employed to increase understanding and interpretation of PRS results including more pretest education, changes in data visualization or presentation to make the results easier to understand and more meaningful for users, and involvement of a genetic counselor or other healthcare providers in pretest and/or results disclosure of PRSs. One example of improved data visualization for PRS communication that could be implemented in the future is the use of dynamic visuals and additional information about normal distribution curves that is present on this website (<http://polygeniccores.org/explained/>). Prior to considering the implementation of PRSs as a screening tool, health systems must consider the infrastructure and personnel required for service delivery without causing patient harm.

A major motivation for participants seeking their PRS in this study was curiosity, and while there are no studies with which to compare directly, this is observation is broadly consistent with studies of why people upload their DTC genetic testing data to other types of third-party genetic interpretation platforms [23, 26]. We found that when participants chose curiosity as a main motivation for seeking out PRS information, they were less likely to experience a negative reaction from this information. Similar findings exist in the literature, specifically, in a study of people's reactions to receiving *non-PRS* third-party interpretation of their genetic information, recipients whose motivation was curiosity were more satisfied than recipients who pursued interpretation of genetic information for health-related reasons [27]. We also found that individuals who experienced negative reactions chose more motivations for seeking out their PRSs compared to those who did not have negative reactions. A possible explanation for this

finding is that individuals who had more unmet needs or higher expectations for the types and certainty of results they could get from PRS were more likely to experience a negative reaction. Due to the nature of our study, we were unable to explore this relationship further and it could be of interest for future research studies.

This study has several limitations. The demographic make-up of our participants was self-selected and homogenous and the findings from our study may not capture the breadth of experiences of all individuals, particularly since there are limitations for PRS data in non-white populations further research should be done to specifically investigate these study questions in a more diverse population. We asked about participants' motivations for seeking PRSs after they had already reviewed their results, which may have led to imperfect recall in this section of the questionnaire. Our sample also includes mainly participants who received their results within one week of answering the questionnaire and therefore cannot be used to draw conclusions about long-term effects of receiving PRSs. Additionally, without the demographic information from non-responders; it is difficult to say whether there may have been sample bias. It is possible that users who felt more strongly about their results may have been more likely to participate in our study, or conversely, that those who were feeling more distraught about their results may have been less inclined to participate. Although the IES and FACToR scales specifically ask about and were anchored on participants' experience with genetic information, it is possible that there were other confounding factors that contributed to individuals' having a negative reaction to PRS information that are beyond the relationships explored through the demographic variables. Lastly, as this was a retrospective study and Impute.me is committed to providing confidential results, we were unable to correlate these responses with the level of risk for individuals.

Future research is needed in this area on more a diverse demographic sample, as our study included those who were self-selected and may have under-represented harms. It is also possible that there is a more complex relationship between the variables that were explored in this study and future research could undertake a more complex multivariable model to better understand how these variables may or may not predict a negative reaction to PRS information. In addition, future studies should explore how outcomes are related to actual and perceived genetic risk levels, which will be important to understand as PRSs become more utilized in both clinical and population-level screening. There is also the opportunity to perform qualitative research in this area to better understand the individual experiences of receiving PRSs. Lastly, because we have shown that people with lesser understanding about PRSs are more likely to experience negative reactions, future research should compare outcomes after providing more comprehensive pre-analysis information to consumers.

CONCLUSION

The need to understand motivations for seeking, understanding and interpretation of, and reactions to PRSs becomes increasingly urgent as we look to a future where these types of risk estimates are used regularly in clinical care, population screening, and consumer settings. Higher quality pretest education, particularly to address the limitations of PRSs and more effectively communicate the differences between relative and absolute risks, may mitigate the risk of negative psychological reactions in response to receiving personal PRSs. Although our study sample originates from a consumer genetics population, our results could inform the use of PRSs in clinical practice, as the data we have gathered here can help inform the development of effective communication strategies of PRSs, with the ultimate goal of improving care as PRSs become more prevalent in both consumer and clinical settings.

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AUTHOR CONTRIBUTIONS

LP, KB, and JA contributed to the design of the study, the interpretation of the data, and the drafting, revision and final approval of the manuscript. LF was consulted on the design of the study and contributed to the revision and final approval of the manuscript.

ETHICAL APPROVAL

All procedures followed were in accordance with the ethical standards of the University of British Columbia. Informed consent was obtained from all individual participants included in the study. The study was approved by the University of British Columbia's Research Ethics Board (H19-00427).

COMPETING INTERESTS

LP, KB, and JA declare no conflict of interest. Dr. Lasse Folkersen is the founder of Impute.me but does not make a profit from this service. The voluntary donations received by Impute.me go to a registered company, from where it is used to pay for server costs. The company is a Danish-law IVS company with ID 37918806, financially audited under Danish tax law.

ADDITIONAL INFORMATION

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