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RESEARCH ARTICLE

Patient Perspectives on Personalized Risk Communication Using Polygenic Risk Scores to Inform Colorectal Cancer Screening Decisions

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Introduction: Colorectal cancer is increasingly diagnosed in people aged <50 years. New U.S. guidelines recommend screening initiation at age 45 years. Providing personalized risk for colorectal cancer using polygenic risk scores may be an opportunity to engage this younger population in colorectal cancer screening. There is limited research on patient understanding of polygenic risk scores results and use of polygenic risk scores to inform colorectal cancer screening decisions.

Methods: From May 2022 to June 2023, 20 Kaiser Permanente Colorado members aged 46−51 years who had been offered colorectal cancer screening but had never completed it signed consent to provide a saliva sample for colorectal cancer polygenic risk score analysis. After receiving personalized polygenic risk scores for colorectal cancer, participants completed a semistructured interview regarding the understanding of their polygenic risk scores, perceived colorectal cancer risk, and intention to screen. Thematic analysis was conducted using Atlas.ti, Version 8.

Results: Of the 19 participants who successfully completed polygenic risk score−related testing and a semistructured interview, 13 were female, 14 never smoked cigarettes, 6 were Hispanic, and 13 were non-Hispanic White. One participant had high risk for colorectal cancer on the basis of polygenic risk score results. Qualitative interviews showed participants' understanding of their results, trust in polygenic risk scores, perception of risk for colorectal cancer, plans to complete colorectal cancer screening, intent to share polygenic risk scores with healthcare providers, and concerns about genetic results impacting health care.

Conclusions: Qualitative analyses suggest that participants were interested in and understood their polygenic risk score results. Further study is needed to develop guidelines, effective calls to action, provider engagement, and health education materials on use of polygenic risk scores for health decision making.

INTRODUCTION

Colorectal cancer (CRC) screening detects CRC precursors and cancer at early stages,[1,2] and treatment is more effective when the disease is treated at an earlier stage.[3] Over the last 30 years, there have been increases in CRC screening in the U.S.,[4] leading to decreases in incidence and mortality from CRC among those aged >50 years.[5]

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However, there has been a worrisome increase in the incidence of CRC in people aged <50 years,[6,7] highlighting the importance of expanding the CRC screening guidelines to include people in their 40s. Updated CRC screening guidance from the U.S. Preventive Services Task Force recommends screening for CRC starting at age 45 years.[8,9] Thus, it is imperative to understand how to best reach this newly eligible population, given that CRC screening uptake in younger individuals has historically been lower than in older individuals.[10,11]

Precision medicine uses specific diseases and patient characteristics, including genetics and environmental risk factors, to develop tailored care plans and provide targeted treatment to patients.[12] Precision medicine has improved cancer treatment[13] and may be useful in cancer prevention. One area of promise in precision prevention is polygenic risk scores (PRSs) that sum common genetic risk alleles carried by an individual, weighing each by their estimated effect on risk. CRC is highly polygenic, with each risk variant contributing small but cumulative effects.[14–19] Polygenic inheritance follows a normal distribution, and PRSs can stratify the entire population into those at high risk for CRC and those at average or low risk for CRC.[20] Previous studies suggested that PRS-informed cancer screening is likely to be more cost-effective than alternatives.[21,22]

There is increased interest from the public in genetic testing. On the basis of prior research, 90%–95% of study participants in the U.S. expect to receive genetic test results if they participate in genetic research,[23] and evidence supports that providing genetic test results to study participants increases participation rates.[24,25] Therefore, sharing risk information based on PRS may interest younger populations and promote participation in health-related activities, including cancer screening. Researchers have found that providing PRSs for atherosclerotic cardiovascular disease encouraged health behavior change and the likelihood of seeking medical care,[26] indicating that PRSs may be a helpful tool to motivate health behavior changes.

The objective of this study is to conduct a qualitative assessment of participant understanding of their CRC PRS results and determine the influence of PRS results on perceived CRC risk and intention to initiate CRC screening among a sample of younger patients who are newly eligible for CRC screening. This work is guided by the Health Belief Model.[27] This model describes that individuals' decisions to perform a health behavior are based on their evaluation of the perceived threat for a health outcome (perceived susceptibility and perceived severity) and the perceived benefits of engaging in the behavior to avoid that outcome.[27] On the basis of the Health Belief Model framework, receiving personalized CRC risk information based on PRSs may modify individuals' perceived susceptibility to CRC and perceived benefits of CRC screening (Figure 1).

Prior research suggests that screening rates are higher among individuals who are at increased risk for CRC, including those with a family history of CRC,[28–30] inflammatory bowel disease,[31] or hereditary cancer syndrome,[32] and among those who perceive that screening is effective.[33] Thus, through this study, the authors aim to identify ways to improve the presentation of CRC PRS to inform perceived susceptibility to CRC and perceived benefits of CRC screening as well as determine whether there are major concerns related to providing personalized CRC PRS information to patients.

METHODS

Study Sample

This study was conducted from May 2022 through June 2023 among Kaiser Permanente Colorado (KPCO) members aged 46–51 years who identified as Hispanic

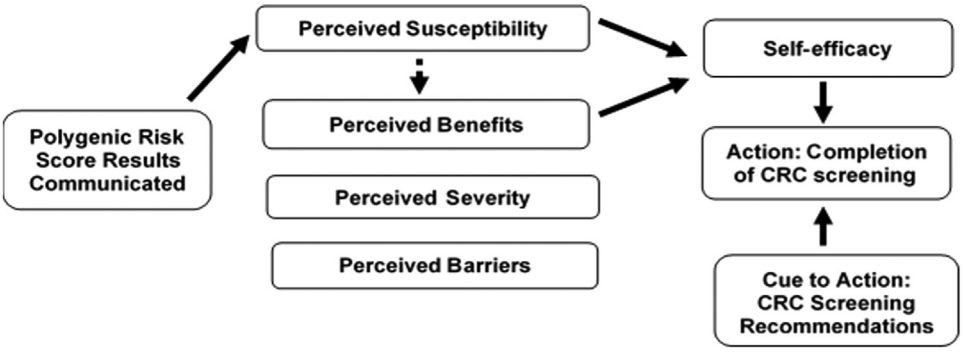

Figure 1. Framework for colorectal cancer risk interviews.
CRC, colorectal cancer.

or non-Hispanic White according to electronic health record (EHR) data (other racial and ethnic groups were not included due to small numbers). Eligible participants had previously been offered CRC screening as part of usual care but never completed a colonoscopy or fecal-based CRC screening test prior to study outreach.

One hundred and twenty KPCO members were invited to participate through email, text message, and calls, and 20 enrolled. The authors invited equal numbers of Hispanic and non-Hispanic White members and equal numbers of females and males. Prior to joining the study, potential participants responded to 2 study eligibility screening questions about personal history of (1) CRC and (2) CRC hereditary cancer syndromes (e.g., Lynch syndrome or familial adenomatous polyposis). Negative responses to these items indicated eligibility, and participants were directed to electronic consent and Health Insurance Portability and Accountability Act of 1996 authorization. The authors also collected information regarding family history of CRC in first-degree relatives owing to the guidelines from the American Gastroenterology Association[34] highlighting the importance of family history of CRC in first-degree relatives to inform CRC risk and screening recommendations.

Consented participants received a saliva sample kit in the mail, completed self-collection, and mailed the kit. All 20 consented participants completed sample collection. One participant's sample failed genotyping and was excluded from analyses. Nineteen participants received PRS results through secure log-in to the vendor's website and completed an interview. All participants were offered optional genetic counseling to review their results. Data collected from the EHR included age, race, ethnicity, BMI, smoking history, and CRC screening initiation and screening modality (colonoscopy versus fecal-based testing) after receipt of PRS results. The KPCO IRB reviewed and approved all study protocols and materials.

Measures

Phenogen Sciences completed genetic testing in an accredited laboratory in compliance with International Standards Organization 15189 and certification by the Clinical Laboratory Improvement Amendments (99D2023356). These certifications ensure high-quality results that can be returned to consented participants. Phenogen Sciences developed a PRS for CRC by analyzing the UK Biobank resource of 500,000 volunteers' specimens to calculate a PRS using 45 single-nucleotide polymorphisms that were found to be associated with CRC.[35] Age, sex, and family history were incorporated with the PRS model to calculate 10-year and lifetime risk of CRC according to methods previously described by Hsu et al.[36] Participant specimens underwent an automated DNA extraction (Qiagen) process using liquid handlers. After extraction, DNA was quantified and prepped for genotyping using a custom Infinium global screening array beadchip (Illumina). Genotypes were called for all specimens that have >98% call rates. The analysis of the sample included information about the participants' ethnicity, family history of CRC, age, and sex to be used in the risk calculation. Participant race, ethnicity, age, and sex were based on EHR data, and family history was from self-report, as described earlier.

Results were returned to participants in 4−12 weeks. The PRS result report included 10-year risk for CRC, lifetime risk for CRC, PRS result in the context of a distribution from low to high risk, PRS interpretation (average CRC risk or high CRC risk), lifestyle behaviors to reduce CRC risk, and contact information for optional genetic counseling telehealth consultation. Study staff contacted participants for interview 1 week after receiving results.

The research team developed a semistructured interview guide informed by the Health Belief Model (Figure 1).[27] Interview questions included feedback on the PRS report, understanding participants' thoughts and worries about CRC before and after receiving PRS results, and plans to screen for CRC (Appendix I, available online). Interviews lasted approximately 30 minutes and were conducted through phone and audio recorded.

Analysis

Interviews were professionally transcribed, verbatim. Transcripts were managed and analyzed in Atlas.ti, Version 8. Two members of the research team experienced in qualitative analysis led the coding of the transcripts. The codebook was developed using deductive and inductive coding. First, 2 analysts reviewed the first transcript and developed a tentative list of codes.[37,38] Using an iterative process, the tentative codes were used by the analysts to code 4 additional transcripts, adding, removing, and revising codes as needed to address inter-rater agreement and resolve discrepancies, meeting twice per week to compare new data with existing data. Once it was deemed that the analysts were applying the codebook similarly, the remaining 14 transcripts were divided between the 2 analysts and independently coded. To continue to assess consistent application of codes, the analysts randomly selected 4 transcripts to assess agreement of code application.

The authors built consensus around themes that were identified throughout the coding and analysis process between the analysts and the larger research team. The authors compared the themes arising from the data and determined possible linkages across participants and thematic categories. CRC screening information was

collected from the EHR from date of consent for 12 months after consent.

RESULTS

Of the 19 participants who completed interviews, 12 were aged 46–48 years, 13 were female, 14 had never smoked cigarettes, 6 were Hispanic, and 13 were non-Hispanic White. Nine participants had a normal BMI (18.5–24.9 kg/m^2), 5 were overweight (25.0–29.9 kg/m^2), and 5 were obese (≥30.0 kg/m^2) (Table 1). One participant received a CRC PRS consistent with a high risk for CRC (i.e., >2-fold increase in CRC risk); the rest received CRC PRSs that were interpreted as average risk (a combined category of low and average risk). The low- and average-risk categories were combined to discourage low-risk participants from delaying screening.

The authors identified 6 themes in the interviews: (1) understanding of results, (2) trust in PRS, (3) perception of risk for CRC, (4) plans to complete CRC screening, (5) intent to share PRS with healthcare providers, and (6) concerns about genetic test results impacting health care.

The majority of participants reported understanding their PRS results when presented as bar graphs comparing personalized risk with average and high risk over 10 years and lifetime (Figure 2). After seeing the report, one participant mentioned, "I wouldn't know if 0.15 was good or bad. But then when I look at the bar graph and I see, oh, my risk is a lot lower than the average, then that's good."

Another participant shared similar thoughts: "I thought [the report] was very clear, so I liked that. And I liked how they gave me the ten-year risk, lifetime risk, and the graphs. I like the graphs because it helps me look at other people versus myself. . . made it easy to read."

The PRS distribution graph was not as universally understood by participants, and several expressed preferences for the bar graphs (Figure 3).

Most participants reported having trust in the report because it came through their trusted healthcare system. Others noted that the inclusion of clinical laboratory credentials on the report as well as the ordering physician's name provided a high level of trust in the report.

Two participants were unsure about whether the report could be trusted, directly stating that the results were "only a study." Another participant mistakenly thought that this research study was to study the validity of the PRS.

Many participants' thoughts about personal risk for developing CRC did not change after receiving PRS, whereas other participants felt relief after receiving an average-risk result and reduced anxiety. One participant with background in statistics mentioned, "My read on this was. . .from my genetic contributions to my risk, it's one standard deviation below the mean. . .So if I had a more extreme result, that may change my thinking about it." Another participant felt similarly: "I'm not too concerned. . .if [the PRS] would [have] come back a little higher, I'd be more concerned. I'm relieved more than anything."

There were mixed responses in interpretation and use of results to make health decisions. After receiving personalized CRC risk, participants felt that average risk PRS meant that CRC screening could wait. Two participants shared, "This would probably make me put [screening] off longer just because my risk is so low." "Honestly, it makes me feel like I can wait a little bit longer to get screened. . . because of where I sat on the results. Since it was so low compared to the average person and all that."

However, other participants felt that they should proceed with recommended screening even though they had average risk for developing CRC: "I've lost two friends to CRC. I know it's a big deal, so it's something I'm willing to do." "I'm sure I still need to do it. I'm sure my doctor still wants me to do it."

Most participants reported knowledge of steps to screen for CRC. Study staff provided instructions to participants who wanted additional information to schedule screening. Participants provided suggestions to increase

Table 1. Study Population Characteristics

Characteristic	*n*	%
Age, year		
46–48	12	63.0
49–51	7	37.0
Sex		
Female	13	68.4
Male	6	31.6
Ethnicity		
Hispanic	6	31.6
Non-Hispanic White	13	68.4
Smoking history		
Never smoker	14	73.7
History of smoking	5	26.3
PRS risk score		
Low/average	18	94.7
High	1	5.3
BMI		
Normal (18.5–24.9 kg/m^2)	9	47.4
Overweight (25.0–29.9 kg/m2)	5	26.3
Obese (≥30.0 kg/m^2)	5	26.3

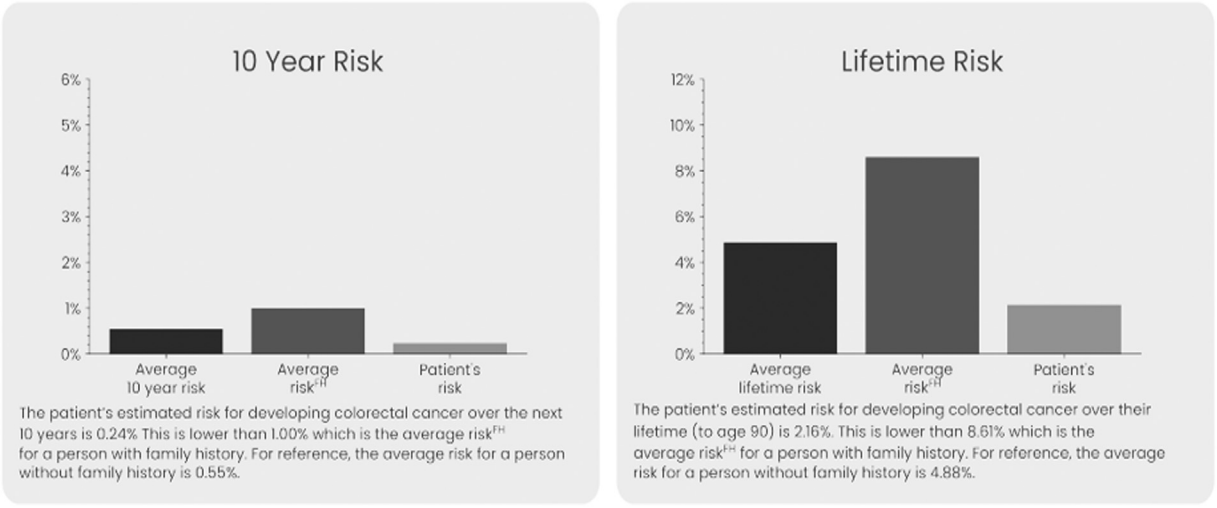

Figure 2. Sample PRS report section, including bar graphs illustrating 10-year and lifetime risk of CRC on the basis of personalized PRS results.
CRC, colorectal cancer; PRS, polygenic risk score.

the impact of providing PRS results to patients. One suggestion was to provide a sample PRS report at the time of saliva collection to prepare participants to understand the results when they are received. Participants suggested that the PRS reports first address the call to action (i.e., complete CRC screening through fecal immunochemical test or colonoscopy) and then PRS results. Participants also recommended that the report clearly specify that CRC screening is needed, regardless of PRS result.

Participant opinions were divided on whether to discuss PRS with their doctor. Some participants felt that they should share results with their doctor: "For me, it's just so they have a better picture of those results combined with the colonoscopy results."

Others believed that because the risk was not higher than average, sharing the result was not necessary: "I would say no, because the numbers are so low, and my doctor and I already have a colonoscopy scheduled."

During interviews, many participants expressed interest in a telehealth appointment with the genetic counselor to discuss the PRS. However, at time of study completion, no study participants had chosen to schedule this appointment with the genetic counselor.

Some participants had concerns about how the CRC PRS would impact their health insurance and their health care. One participant asked whether less screening would be conducted on a patient with low PRS: "Would this risk drive any of the policies that Kaiser has and how they would provide recommendations to patients? Would they do less testing and stuff like that if somebody had lower risk?"

Another participant had concern about whether it could be detrimental to insurability if an insurer were to

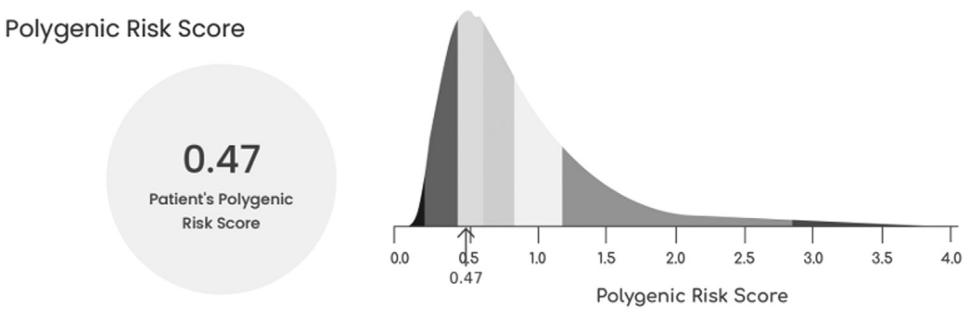

Figure 3. Sample PRS report section displaying PRS value and patient PRS value in the context of the population-level distribution of PRS values from low to high risk for CRC.
CRC, colorectal cancer; PRS, polygenic risk score.

receive genetic information indicating that the individual is at higher risk of cancer: "Is this something the insurance company's getting information so if something is bad, are they going to drop you?"

Following participants for 12 months after consent, 12 of 19 (63%) completed CRC screening within the 12 months after receiving the PRS result.

DISCUSSION

Despite most participants reporting high levels of understanding of PRS results, trust in the PRS report, and intent to share PRS results with their doctor, some participants expressed concern over the possibility of their PRS being used by their health insurance provider to discriminate against them. There were also participants who mistakenly thought that they should delay CRC screening on the basis of the interpretation of their PRS result as low/average risk for CRC. These findings underscore the importance of ensuring that risk communication materials include a clear call to action and that patients completing genetic-based risk assessments be provided with information about protective laws, including the Genetic Information Nondiscrimination Act,[39] that protect against health insurance discrimination on the basis of genetic information.

In reviewing comments on trustworthiness of PRS results, most participants viewed the PRS for CRC report as trustworthy because of the study's affiliation with their trusted healthcare provider. Furthermore, most participants expressed interest in sharing PRS results with their doctor. Prior studies have also demonstrated that patients are more willing to trust information and initiate behavior change when they receive information from their healthcare provider.[40] In a nationwide study of 4,200 participants who were aged ≥50 years and completed the Health Information National Trends Survey, having a CRC screening discussion with their healthcare provider was associated with almost a 9-fold increase in the odds of completing CRC screening.[40] Another study among 740 African American men from a medically underserved area of Los Angeles, California, reported about a 49-fold increase in the odds of the CRC screening completion associated with receiving a provider recommendation for CRC screening.[41] Our findings and the results from other studies suggest that incorporating trusted providers in personalized risk communication based on PRS will be important to any potential future use of PRS in clinical settings. Additional research is needed to determine provider readiness to interpret, use, and communicate PRS results.

Although provider engagement in potential future use of PRS for clinical decision making will be needed, clear patient-friendly results reports will also be instrumental to the use of PRS. Most participants reported understanding their PRS for CRC, citing specific understanding of the 10-year and lifetime risks of CRC graphs from the PRS results report (Figure 2). Participants also found that the comparison of their results with the population average of CRC risk helped them to interpret their results, as has been found in other work.[42] Other studies have also used visual graphics to enhance patient understanding of PRS. In a European study of about 7,300 participants who received PRS results with graphics displaying 10-year risk for atherosclerotic cardiovascular disease, those at high risk based on risk score incorporating PRS and other risk factors were more likely to initiate behavior changes to reduce their risk than those at low/average risk for disease.[26] Thus, PRS results reports should include clear graphics to allow for better patient and provider understanding of results and should report absolute risk estimates with a comparison with the risk in the general population.

Several participants believed that because PRS report indicated average risk, this meant that they were low risk and could delay CRC screening initiation. This misinterpretation of results has been found in other research of patient understanding of PRS.[43,44] This is an important finding, because it highlights the importance of communicating specific, straightforward steps that patients need to take to be screened regardless of PRS result.

Limitations

This study included robust qualitative methods employing a semistructured interview guide and thematic analysis to evaluate the potential to use PRS to inform CRC screening decisions. The authors were also able to capture information on intent to initiate CRC screening and completed CRC screening initiation. Despite these strengths, the authors acknowledge several study limitations. This study population was small and included only individuals with health insurance coverage, thereby lacking representation from uninsured individuals who may have beliefs and experiences with genetic risk assessment and cancer screening different from those of an insured population, impacting generalizability to the larger U.S. population. The authors were also limited in their ability to explore whether PRS risk level differentially impacts CRC screening decisions, because only 1 participant was categorized as high risk on the basis of their PRS. This is likely in part explained by the PRS used in this study, which only included 45 risk variants. Over 200 CRC risk loci have been identified so far, and newer models have improved predictive power[45] and improved performance in population with diverse ancestry,[46] which could be further enhanced using a genome-wide

approach.[46,47] Additional research is needed to improve the performance of PRS and to develop transancestral PRS that perform well across populations with diverse ancestry. Finally, those who chose to participate in this study may have been individuals who were more interested in genetics or CRC screening than those who chose not to participate, so responses may be more favorable toward genetic research than in the general population.

CONCLUSIONS

These qualitative analyses suggest that participants were interested in personalized CRC risk results and, overall, understood their personalized risk estimates. However, for some participants, their results led to the perception that CRC screening could be delayed and concerns over potential discrimination from their health insurance provider due to their genetic results. Further study is needed to develop effective call to action and health education materials for patients and providers to understand how PRS results influence healthcare decision making. It is also important that genetic counselors and healthcare providers communicate the importance of CRC screening for all adults starting at age 45 years and present information on how Genetic Information Nondiscrimination Act study patients against genetic discrimination from health insurance providers. In addition, the results inform strategies for communicating CRC PRS in future large, quantitative studies. These large, quantitative studies are needed to evaluate potential impacts of the use of CRC PRS on CRC screening uptake and decision making about CRC screening modality and to compare differences by age group, sex, race, and ethnicity.

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CREDIT AUTHOR STATEMENT

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.focus.2024.100308.

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