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Examining the Impact of Polygenic Risk Information in Primary Care

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Abstract

Background: Polygenic risk testing examines variation across multiple genes to estimate a risk score for a particular disease, including risk scores for many common, chronic health conditions. Although polygenic risk information (PRI) may be a promising tool for enhancing preventive counseling and facilitating early identification of disease, its potential impact on primary-care encounters and disease prevention efforts has not been well characterized. **Methods:** We conducted in-depth, semi-structured interviews of patients to assess their understandings of PRI and their beliefs about its relevance to disease prevention. **Results:** We completed interviews with 19 participants. Participants described enthusiasm for the generation of PRI and recognized its utility for disease prevention. Participants also described the value of PRI as limited if not corroborated by non-genetic risk factors. Finally, participants noted that PRI, by itself, would be insufficient as a trigger for initiating many preventive interventions. **Conclusion:** PRI has the potential to become an important tool in primary care. However, patient views about PRI as well as the complexities of disease prevention in the primary care context may limit the impact of PRI on disease prevention.

Keywords

polygenic risk, genomic screening, disease prevention

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Introduction

Polygenic testing is a form of individualized genomic evaluation that aggregates variation in multiple genes into a single lifetime risk score for a particular disease, including for several common, chronic health conditions.[1] With a better understanding of the contribution of polygenic variation to common health conditions affecting a significant proportion of adults, there are multiple opportunities for early initiation of preventive interventions and medical screening in primary-care settings.[2,3] As polygenic risk information (PRI) is more widely adopted, the vision of improving population health through individualized medicine[4] may become a reality. This vision supports efforts like the National Institutes of Health's eMERGE IV consortium,[5] which is studying the impact of integrating PRI into primary care.

Despite the appeal of this vision for disease prevention, there is need to examine the potential impact of PRI in the primary care context—the clinical setting where most PRI would be addressed. Primary care involves complex and compacted workflows which make the introduction of new tools into existing patient encounters a non-trivial matter. Primary care physicians may serve large caseloads of patients, requiring efficient clinical workflows (e.g., briefer patient encounters, asynchronous communication) even as many patients have complicated care management needs. Whether or not PRI, in the primary care context, can make a meaningful impact on disease prevention efforts may depend not so much on the quality of the risk information it provides, but rather on the ways patients respond to disease prevention discussions prompted by PRI, including how

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likely patients are to accept new preventive interventions indicated by elevated polygenic risk.

The eMERGE IV consortium sites plan to insert PRI into the primary care context, with the goal of achieving (and measuring) early identification of disease risk and initiating preventive interventions in patients with elevated polygenic risk scores. In a prior study, conducted in preventive cardiology, the incorporation of PRI into patient care was productive—provider and patient, together, were able to process the patient's PRI and agree upon next steps (initiation of a statin medication).[6] In that study, the integration of PRI acted as a trigger for early initiation of a preventive medication with the goal of significantly reducing the patient's risk of a future severe health outcome. Whether a similar outcome will be achieved when PRI is addressed in primary care settings is unclear.

Recognizing the complexities of the primary care context and the importance of patient receptivity to PRI for achieving improved disease prevention outcomes, we conducted an interview study to examine patients' understandings of PRI and its potential relevance to disease prevention. Our results speak to the potential benefits and limitations of integrating PRI into primary care.

Methods

Participants and Setting

We drew a random recruitment frame of patients from among individuals who received primary care in the last year at one of the Mayo Clinic campuses in Rochester, MN, USA. We limited our sample to patients between 41 and 75 years of age, which was the same age criteria for patients who would later be invited to the eMERGE IV study in Rochester. eMERGE IV is a multi-site genomic screening study funded by the National Human Genome Research Institute which aims to generate and return PRI on 10 conditions to approximately 25,000 participants and measure the impact of those results in guiding disease prevention. Of the 25,000 participants, 20,000 are expected to be adults who will receive PRI for eight conditions. It is anticipated that over 20% of study participants will receive a "high risk" polygenic result in the course of their participation in eMERGE IV.[5]

Recruitment and Data Collection

Our study was approved by the Mayo Clinic Institutional Review Board (IRB# 20-012806). A research assistant made recruitment calls, and interested participants were scheduled for an interview. Interviews were conducted by phone and followed a semi-structured interview guide. After obtaining oral consent from participants, interviews began with the interviewer giving a description of PRI, including how a biological sample would be collected and examples of the kinds of results and information that would be returned from the genetic testing. Participants were then asked to imagine being invited to the eMERGE IV study and were probed about whether they would have questions or concerns before deciding to participate. Participants were also asked to describe the ways they felt polygenic risk results might be valuable or limited in value. Finally, we queried participants about the kinds of actions they might be willing to take on the basis of PRI (e.g., lifestyle changes, new preventive medications).

Data Analysis

Interviews were audio recorded, and recordings were transcribed by a professional transcription service. Transcripts were verified by research staff. To facilitate analysis of the transcripts, a codebook was developed based on the interview guide and expanded based upon themes identified during an initial review of the transcripts. Transcripts were then coded independently by two coders who subsequently reconciled their coding activities through consensus deliberation.

Results

We reached out to 110 eligible individuals from our sample frame. We were unable to make contact with 65 of these individuals; 18 individuals declined to participate, and 7 individuals who were interested in participating were unable to be scheduled for an interview. Additionally, one individual who was scheduled for an interview did not complete the HIPAA form required by the IRB. We were able to complete interviews with the 19 remaining individuals, which averaged 20.5 minutes in length (min = 13 minutes 46 seconds, max = 35 minutes 09 seconds).

Three themes emerged from our data related to participants' enthusiasm for PRI-informed disease prevention in the primary care context: (1) most participants described PRI as valuable for disease prevention, (2) many participants felt that PRI should be corroborated by other methods of determining disease risk, and (3) participants expressed hesitation about accepting preventive interventions prompted only by elevated polygenic risk.

PRI is Valuable for Disease Prevention

After describing the study to interview participants, we asked participants if they would consider PRI to be valuable. Most affirmed the value of PRI and noted its potential relevance to disease prevention:

> *I think it would all be good. I mean, it might kinda wake ya up too to a fact that maybe somethin' you're doin' is, you know, somethin' you need to quit too— or-or change-change habits or*

whatever too. You know, it could be dietary or-or smoking or whatever. I mean, you know, underlying conditions that, you know, if-if it points it out, yeah— I-is everybody gonna proceed to do somethin' about it? I don't think so— but, uh, I think most people if-if they know there's a-a risk, you know, they're gonna wanna see what they can do to— you know, eliminate it or make it less severe. [P5, 67 y.o. male]

Participants regularly described indications for "lifestyle change" as a desirable outcome of the genetic testing, including modified diet, increased exercise, environmental adjustments, and modifications of other health-related activities. Although some participants described PRI as "good to know" information, most stated that they would consider taking some sort of action if they received a high-risk result.

Most participants also affirmed that they would want their primary care physician to have access to their results. While some participants assumed that their primary care physician would have access to their polygenic results and would review those results in a future clinical encounter, if necessary, other participants described plans to proactively share their results with a physician to ensure that appropriate actions were taken:

I use the [Mayo Clinic Patient] portal. I probably would send a message to my provider to say—you know, "I just found this out. What do ya think?" As far as, like, seeking, you know, additional testing or anything like that, that would be something that I would, um, you know—would leave up to my provider whether they would just say, "Yeah, let's talk about it at your next appointment," or, "Yeah, let's get you in right away," I guess. But, yeah, would I take initiative even if I didn't have an upcoming appointment, you know, not wait? I wouldn't wait 'til my next upcoming appointment to throw it out there to my-my primary care. [P16, 51 y.o. female]

Although less common, some participants reasoned that elevated polygenic risk scores might indicate a need for more frequent preventive-health screenings (e.g., more frequent colonoscopies) and were generally favorable about preventive screening and disease monitoring as a valuable outcome of a polygenic risk evaluation:

Maybe you do need to, you know, go in for those-those exams, like those colonoscopies— that they say now at 45 you should do— rather than wait, I mean, if I—if I get something back that they say genetically you may be at risk. I guess that would encourage me to-to do my well checks, I guess. [P11, 45 y.o. female]

PRI Needs to be Corroborated by Other Methods of Determining Disease Risk

Participants qualified the value or actionability of PRI in a number of ways. For example, one participant questioned the value of PRS information unless it could provide unique information that could not be ascertained through other means:

So, if I know, for example, I've got colon cancer in the family or I have heart disease in the family, uh, and I have hypertension, well, you know, I pretty much have an idea already that I'm at some risk for heart attack or stroke. Um, and, um, uh, so I'd - I'd like an increment to what I know—to what I already know, uh, for this to be, uh, to—for this to be interesting. [P1, 68 y.o. male]

Many participants also expressed a desire for conventional testing to corroborate PRS results. In one case, a participant felt that results he had received in another genetic testing study "weren't true" and called into question whether PRS information could be trusted:

From the results I saw, from the [other genetic screening] study, there was a—I know that—well, maybe it's getting better, but there were some things in the results that definitely weren't true—based on what they found. So I-I know that it probably wouldn't be universally true, so I'd go to the provider for as to get, if possible, get-get additional testing to determine the likelihood of having a certain disease. [P6, 47 y.o. male]

Participants who qualified the value or actionability of PRI also included those who recognized the relative newness of the polygenic risk evaluation, those who questioned whether there were clear guidelines for responding to polygenic risk, and those who questioned the preparedness of their primary care physician to take appropriate action. Some participants indicated that they would need to be convinced of the actionability of their results in the context of a conversation with a provider:

Unless there was something that they told me that would convince me that— you know, I mean, you know, like, okay, well, yeah, but once you get the high cholesterol, we—you know, it takes us six months to get it down, and you know, during that six months it could be—you know, you could have a heart attack. Then, I might go, oh, okay, yeah, maybe preventative is better. [P11, 45 y.o. female]

Finally, some participants described PRI as just one factor to consider in the context of adopting preventive interventions and described a need for additional clarity about disease progression and the potential efficacy of non-pharmacological interventions:

I would not start on anything [any medication] until I-I had sort of the diagnostic confirmation—that, yes, this is now becoming an issue [and] confirmation of a trajectory or a pattern that says it's getting, it's kinda progressing, and you know, despite, um, other efforts. At that point, I would—I would entertain, okay, what-what are the—what are the other—what are the other possibilities here? [P12, 42 y.o. male]

Polygenic Risk, by Itself, is not a Sufficient Reason to Initiate Preventive Interventions

Our interviews examined participants' views of the actionability of PRS results and explored the extent to which participants would be willing to initiate a preventive management plan or take new prescription medications based on PRS results. In a few interviews, we also asked about participants' willingness to consider preventive surgery.

Participants offered several reasons why they would be hesitant to start new medications based exclusively on polygenic indications of risk. Sometimes this was described as an aversion to medications in general: "This is just my own predisposition, I'm pretty adverse to any kind of med in general" [P12, 42 y.o. male]. Participants also expressed a desire for their genetic risk to be more clearly actionable or else corroborated by other, non-genetic tests. For example, one participant seemed not to appreciate the actionability of genetic risk factors without corroborating evidence of need:

> *I don't think that I would wanna be taking a medication until my bloodwork or whatever test you're doing is saying that I'm in need of it. [. . .] To me, the pill is treating something that you don't have. [P20, 72 y.o. female]*

Another participant described hesitancy about interventions without manifest symptoms of illness or inputs from other corroborating diagnostic tests:

> *Taking some sort of intervention without additional, like, scanning or imaging. Or, you know, I guess—you know, when you say alone, just going in and doing something without doing, you know, any-anything additional like that, yeah, that would make me a little hesitant, um, just because I feel like, any time I ever had procedures it's all kind of a protocol. "Well, let's look at this. We see the symptoms. Well, let's look at this. Let's look at this. Let's look at this." And so, you know, just going on the—that particular testing seems just out of the ordinary where—you know, there wouldn't be other exploratory things to really get a full diagnosis of, you know, what the issue might be. [P16, 51 y.o. female]*

Similarly, another participant described misgivings about the certainty of genetic risk and described concern about overtreatment in the absence of manifest symptoms of disease:

> *Given the information that I have and the limited knowledge that I have— you know, if they were just to say, well, yeah, let's just start you on this [medication] 'cause we think you're gonna get, um, issues with cholesterol later— oh, okay. Um, probably I wouldn't. [P11, 45 y.o. female]*

Some participants also expressed concerns about the side-effects of preventive medications, acknowledging that preventive interventions often involve quality-of-life tradeoffs. For these participants, the perceived actionability of a high-risk polygenic result was reduced if the recommended preventive intervention introduced other risks:

> *You know, statins, that's kind of a slippery slope. They have some significant side effects. I mean, you know, you can end up with liver enzyme issues and all of that. So, um, I don't know. I think I would probably have to see something-something else— you know, either a lab value or, yeah, somethin' else [in addition to genetic risk information] to make me wanna start on a statin. [P13, 60 y.o. female]*

When we asked about preventive surgeries that might be suggested by a high polygenic risk score, participants expressed considerably more hesitancy. Sometimes this was due to their recognition of advanced age and the risks of undergoing surgery. Other participants simply described surgery as a significant intervention for which they would require additional information before making a decision. For example:

> *I guess it would depend on how invasive [the interventions] were. For instance, if I'm being told to actually remove a breast because I might get breast cancer, that's fairly invasive. I'd be a little more hesitant to do something that serious too quickly. But, yeah, taking a medication, I'd be willing to take something, I think, if it prevents some disease down the road. [P9, 67 y.o. female]*

In only a few cases, participants expressed willingness to do whatever intervention was indicated by PRI.

> *I would be open to [a new prescription medication]. I think that would be—if they're recommending that, and they know my body, and if that's—this is something that I may get in the future for diagnosis, I would be positive to— move ahead and pre— try to prevent that from— from me getting that disease. [P10, 54 y.o. female]*

Discussion

Our findings illuminate how patient expectations for PRI in the primary care context could moderate the impact of PRI on patient adoption of disease prevention strategies. Our findings suggest three points regarding the effective integration of polygenic risk evaluation into primary care.

First, PRI may be useful for initiating conversations about disease prevention. Among individuals who agreed to participate in one-on-one qualitative interviews, we found consistent interest in polygenic risk evaluation for common conditions. In almost every case, we also found that individuals wanted to learn personal risk information and recognized the value of PRI for disease prevention. This is an encouraging finding, as it suggests that patients may be willing to accept this kind of genetic evaluation in the context of primary care and may be amenable to taking

preventive actions based on their genetic results. Given the interest in PRI that we observed, it is possible that elevated polygenic risk may serve as a trigger for earlier initiation of conversations about disease prevention in the primary care context. In situations where polygenic testing flags elevated genetic disease risk—especially before other risk factors have been detected—the frequency of preventive screenings may be increased, and preventive measures may be discussed.

Second, while participants were generally interested in PRI, their interest in initiating preventive interventions as indicated by PRI was mediated by the perceived burden of the intervention. This is consistent with an extensive literature on health behaviors (most notably, the Health Belief Model) which acknowledges the impact of barriers to action in patient decisions about health and disease prevention.[7] For many individuals, initiating preventive medications may be a burdensome threshold to cross because for them it symbolizes a loss of personal agency in disease prevention (they are now dependent on a medication to maintain health),[8,9] or it represents a resignation to a "sick identity"[10] or the choosing of an unhealthy lifestyle (i.e., one that requires medications).[11] For other individuals, initiation of a preventive medication contradicts their understandings of prescription medications and their impact.[12,13] For others, the risks of preventive medications are deemed to be greater than the risks of attempting to mitigate disease risk through lifestyle modifications alone.[13,14] Many patients will elect to pursue lifestyle modifications to address disease risk before accepting preventive medications.[15,16]

This second finding is consistent with an extensive literature on disease prevention and medication adherence. PRI is intended to inform one of the more challenging aspects of primary care—engaging patients in disease prevention. Not only does the urgency of managing existing disease compete with conversations about disease risk and prevention, but more than that, patients and providers are not always aligned in how they propose to manage disease risk.[17] Patients' personal goals for their health as well as the health concerns that are most important to them may contradict the epidemiological reductionisms that inform clinical guidelines and evidence-based approaches to disease prevention. Often characterized as a problem of patient "hesitancy" or "nonadherence," patients' reluctance about evidence-based preventive interventions can sometimes be understood by physicians as a "barrier" they are obligated to overcome.[18] The pervasiveness of this misalignment is perhaps most profoundly evident in high rates of primary non-adherence to prescribed medications, where patients are given prescriptions but choose not to fill them.[19-21] Even among individuals known to be risk of heart disease, type-II diabetes, and hypertension, initiation of preventive medications is difficult and rates of adherence are problematic.[22-25] Our findings add to this literature by suggesting that PRI is unlikely to have a major impact on the long-standing challenge of promoting disease prevention in primary care.

Third, our findings suggest that PRI will most likely be one more tool in the physician's communication toolbox to persuade patients to accept (and adhere to) preventive interventions they would prefer to avoid. Although patients may be disinclined to initiate certain preventive interventions, many nonetheless will be agreeable to the generation of PRI. As such, PRI may be a helpful tool for nudging patients toward preventive interventions (particularly medications).[26] This value may be increased when PRS is combined with a review of non-genetic risk factors, as well as a review of pharmacological and non-pharmacological approaches to addressing those risks.[27,28]

Importantly, because PRI is likely to be one of several factors in a patients' decision, its direct contribution to disease prevention will be difficult to measure.[29] Primary care providers and other clinicians charged with encouraging disease prevention activities in their patients should continue to leverage emerging strategies and interventions advanced by behavioral psychology and other similar supportive sciences in parallel with PRI.[30] Furthermore, physicians may find that more traditional risk determinants in conjunction with the discovery of early manifestations of disease will continue to be an effective motivator for patients to initiate interventions to prevent more severe disease. Our findings suggest that PRI may provide clinicians with an additional opportunity to socialize notions of risk in ways that begin to move patients toward evidence-based risk-reduction behaviors.

Limitations

Our findings are limited by the following factors: First, our study employed qualitative interviews intended to characterize a diversity of perspectives; as such, our data do not speak to the generalizable prevalence of specific opinions. Second, our study was conducted at a large academic medical center in the upper Midwest, which serves a predominantly white, well-insured, and well-educated population, and may not correspond with perspectives found in more diverse populations and healthcare settings. Third, our study employed a hypothetical scenario to assess participants' perspectives. As such, our findings might not be representative of patient perspectives when they experience real-life scenarios.

Conclusion

Generating PRI is a worthy enterprise, and efforts like those of the eMERGE IV consortium to move PRI into the clinical context are essential to the continued evaluation of the potential roles of genomics in medicine. However, achieving the vision of improving the health of populations

through genomic medicine will be a long journey with many hurdles, setbacks, and difficult-to-measure gains. Those pursuing this vision for genomics-informed disease prevention will inevitably have to engage the complexities of primary care itself, where patients and physicians work together to achieve a shared vision for health.

Declaration of Conflicting Interests

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