Short Communication

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Personalized Medicine

Assessing the implications of positive genomic screening results

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Aim: Before population screening of 'healthy' individuals is widely adopted, it is important to consider the harms and benefits of receiving positive results and how harms and benefits may differ by age. **Subjects & methods:** Participants in a preventive genomic screening study were screened for 17 genes associated with 11 conditions. We interviewed 11 participants who received positive results. **Results:** Interviewees expressed little concern about their positive results in light of their older age, the risk condition for which they tested positive, or other pressing health concerns. **Conclusion:** Researchers and clinicians should recognize that returning positive results may not have the impact they presume given the diversity of the conditions screened and those who choose to undergo screening.

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As genomic technology advances, population screening of healthy individuals for pathogenic variants associated with medically actionable conditions is becoming more feasible [1–6]. Before the screening of 'healthy' individuals is widely adopted, the potential harms and benefits need to be assessed [7]. One important programmatic and scientific question is whether to target screening toward certain age groups, and/or to include an upper age limit on population screening programs since the benefits and harms of screening may not be consistent throughout the lifespan [4,8]. Reducing morbidity and mortality risks and increasing lifespan may not be realized to the same degree among older individuals because of competing causes of death [8,9]. Risks of recommended interventions for those who screen positive may differ, such as increased risk for perforation of the colon during colonoscopy among individuals over 75 [10,11]. However, risks for insurance or employment discrimination may lessen for individuals over 65 who are more likely to be retired and are eligible for Medicare [12]. Likewise, older participants may perceive less personal benefit from learning genomic information, while perceiving greater familial benefit since children or grandchildren could gain from cascade testing [4,13,14].

We examine the issue of older age as it relates to the potential harms and benefits of screening through a preventive genomic study, GeneScreen, in which 262 adults across a broad age range received screening for 17 genes related to 11 diverse, medically actionable conditions [2,15], ranging from cancer syndromes (e.g., hereditary breast and ovarian cancer, Lynch syndrome) to cardiovascular conditions (e.g., long QT, familial hypercholesterolemia). Previously, we examined participants' perceptions of age eligibility criteria prior to receiving screening results [9] and found that participants of all ages perceived the same benefits of screening, including the potential for prevention and treatment, gaining peace of mind, sharing information with family, advancing science/research and helping others. Those who noted risks, including worry and discrimination, did not differ by age. Here, we report on the reactions of participants in GeneScreen who received positive results.

Future Medicine

Subjects & methods

GeneScreen, a preventive genomic study, screened for a panel of 17 genes relating to 11 conditions including Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*), familial adenomatous polyposis (*APC*), MUTYH-associated polyposis (*MUTYH*), hereditary breast and ovarian cancer syndrome (*BRCA1, BRCA2*), multiple endocrine neoplasia type 2 (*RET*), Marfan syndrome (*FBN1*), long QT (*KCNQ1, KCNH2, SCN5A*), familial hypercholesterolemia (*LDLR*), Alpha-1 antitrypsin deficiency (*SERPINA1*), hereditary hemochromatosis (*HFE*) and malignant hyperthermia (*RYR1*). These genes were selected for the panel because they are considered medically actionable. Further information about the recommended care and interventions for the conditions and the clinical utility of these interventions is described elsewhere [2,16].

GeneScreen was conducted with patients at the University of North Carolina, Chapel Hill (UNC) Internal Medicine Clinic and members of Kaiser Permanente's Northwest Biobank (NWBB) in the USA. From the Internal Medicine Clinic, 436 patients who were over 18, not suffering from serious illness, and who had decisional capacity were recruited for the study. From the Biobank, 650 adults with available, stored DNA were recruited. Individuals were contacted through a letter and brochure describing the study. These materials directed individuals to a website which provided information on how genes impact health, the conditions and genes on the panel, and the screening process. The website also included a decision aid and information on study features and goals for the purposes of informed consent. Participants consented to screening through the website. A total of 262 individuals consented to screening and provided samples for analysis. As per the requirements of the study's funding source, participants were also asked on the website if they agreed to have their results submitted to the National Institutes of Health database of Genotypes and Phenotypes (dbGaP) at the conclusion of the study. All but four participants from the Internal Medicine clinic agreed. Participants from the Biobank had previously consented to this. Further details of recruitment, enrollment and informed consent are described elsewhere [17].

Of the 262 individuals enrolled in GeneScreen and whose DNA samples were sequenced, fifteen (5%) screened positive for genetic variants associated with increased risk of a medically actionable condition. These fifteen participants were contacted to provide a second sample for confirmatory testing in a CLIA-certified laboratory. One person declined confirmatory testing. Positive screening results were confirmed for the remaining 14 (Table 1). Results included hereditary hemochromatosis, hereditary breast and ovarian cancer syndrome, malignant hyperthermia, long QT syndrome, familial hypercholesterolemia and multiple endocrine neoplasia 2A. Participants who received a positive result were offered an in-person appointment with a geneticist and/or genetic counselor who recommended clinical follow-up actions and placed the results in the electronic medical record. If they declined an in-person appointment, the counseling could take place by phone. Post-test counseling took place by phone for eight participants and in person for six participants. Recommendations made or suggested referrals for these participants (Table 1) were based on the individual's age, personal history and family history as well as what was individually discussed when the results were disclosed.

Participants who received positive results were subsequently contacted by email to be interviewed. In total, 11 of the 14 people agreed to semistructured phone interviews, which took place approximately 8 weeks after receiving their results. Self-reported demographic characteristics are presented in Table 2. Consent to take part in the interviews was obtained verbally before the interviews began. An interview guide was developed by study team members, including MW, KMM, GEH, and RJC, to address our research questions of how well participants understood the positive result and how learning the result initially impacted their lives. Then, 8 of the 11 agreed to a second semistructured phone interview approximately 9 months after the first. A second interview guide was developed by the same team members to explore longer term impacts of returning positive results and considerations of medical care plans. All interviews were audio recorded and transcribed verbatim. Each interview lasted approximately 30 min. Interview questions are listed in Appendix A.

Transcripts were read in their entirety by MW, KMM, and RJC. Using a constructivist grounded theory approach [18,19], they coded the interviews based on an open coding strategy [20]. The open codes were based on the interview guide and included ways that people responded to receiving a positive result, how they perceived it would affect them or their family, and decisions related to receiving the result, such as pursuing follow-up care. They then moved to the axial coding phase, which involves the interpretation of the data collected from the open codes [20], and met to discuss the open codes and emerging themes. Themes included how people discussed age in relation to their positive result as well as change over time in people's attitudes and actions.

GeneScreen was approved by the Institutional Review Boards of UNC and Kaiser Permanente Northwest.

Table 1. Positive screening results of participants.

ID	Gene (transcript)	Variant cDNA (protein)	Interpretation	Zygosity	Condition	Individual recommendations
1†	*BRCA2* (NM_000059.3)	c.8167G>C (p.Asp2723His)	Pathogenic	Heterozygous	Hereditary breast and ovarian cancer predisposition	Already knew about result. Reviewed cancer screening guidelines. Encouraged follow-up with clinical genetic counselor in future for specific guidelines relevant to her
2†,‡	*HFE* (NM_000410.3)	c.845G>A (p.Cys282Tyr)	Pathogenic	Homozygous	Hereditary hemochromatosis	Already knew about result and followed regularly by hematology. Husband had previously been tested and children are not at risk
3†	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr)	Pathogenic	Homozygous	Hereditary hemochromatosis	Already diagnosed with hereditary hemochromatosis and receiving phlebotomy treatment. Noted the importance of protecting his liver
4†	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr); c.187C>G (p.His63Asp)	Pathogenic; pathogenic§	Suspected compound heterozygous	Hereditary hemochromatosis (reduced penetrance)	Already knew about result; was encouraged to share information with family members and talk to her provider about questions or concerns
5	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr); c.187C>G (p.His63Asp)	Pathogenic; pathogenic§	Suspected compound heterozygous	Hereditary hemochromatosis (reduced penetrance)	Recommended screening, but low likelihood of symptoms or need for treatment
6	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr); c.187C>G (p.His63Asp)	Pathogenic; pathogenic§	Suspected compound heterozygous	Hereditary hemochromatosis (reduced penetrance)	Recommended discussing testing for iron overload periodically, especially after menopause
7	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr); c.187C>G (p.His63Asp)	Pathogenic; pathogenic§	Suspected compound heterozygous	Hereditary hemochromatosis (reduced penetrance)	Reviewed family history and inheritance pattern of symptoms that this result did not fully explain. Was told a clinical counselor could review her additional family history concerns in more detail and get records
8	HFE (NM_000410.3)	c.845G>A (p.Cys282Tyr); c.187C>G (p.His63Asp)	Pathogenic; pathogenic§	Suspected compound heterozygous	Hereditary hemochromatosis (reduced penetrance)	Encouraged to share information with family members and follow through with his PCP as this is a treatable condition
9	*KCNQ1* (NM_000218.2)	c.575G>A (p.Arg192His)	Likely pathogenic	Heterozygous	Long QT syndrome	Cardiology referral. Given information to provide family members
10	KCNQ1 (NM_000218.2)	c.808C>T (p.Arg270Trp)	Likely pathogenic	Heterozygous	Long QT syndrome	No family history of any sudden death. Recently had EKG for fatigue. GC routed info to PCP in order to interpret those results
11‡	*LDLR1* (NM_000527.4)	c.798T>A (p.Asp266Glu)	Pathogenic	Heterozygous	Familial hypercholesterolemia	Data not available
12†,‡	LDLR1 (NM_000527.4)	c.1216C>T (p.Arg406Trp)	Pathogenic	Heterozygous	Familial hypercholesterolemia	Already knew about result and had already been taking steps to address disease symptoms. Recommended follow-up with PCP at next appointment about any additional treatment
13	*RET* (NM_020975.6)	c.1852T>G (p.Cys618Gly)	Pathogenic	Heterozygous	Multiple endocrine neoplasia 2A/familial medullary thyroid cancer	Thyroid removal based on positive family history
14	*RYR1* (NM_000540.2)	c.4711A>G (p.Ile1571Val); c.10097G>A (p.Arg3366His); c.11798A>G (p.Tyr3933Cys)	Likely pathogenic¶	Phase unknown	Malignant hyperthermia	Family testing needed to resolve phase. Encouraged to discuss testing with his relatives. No reported history of adverse reactions to anesthesia

n = 14.

† Participant had prior knowledge of result.

‡ Participant not interviewed.

§ The *HFE* His63Asp variant (also known as H63D) is well known to have reduced penetrance and was therefore interpreted as pathogenic for a reduced penetrance form of hereditary hemochromatosis when present in *trans* with *HFE* Cys282Tyr (also known as C282Y).

¶ Each of the *RYR1* missense variants is considered a VUS individually, but have been reported in association with disease when present together in a complex haplotype (*in cis*).

EKG: Electrocardiogram; GC: Genetic counsellor; PCP: Primary care provider.

Table 2. Sociodemographic characteristics of interviewees.

Characteristic	Percent (n)
Sex:	
– Female	63.6% (7)
– Male	36.4% (4)
Age:	
– Range/mean	43–77/63.73 years
– Race/ethnicity	
– Non-Hispanic White	90.9% (10)
– Asian	9.1% (1)
Education:	
– High school degree or GED	18.2% (2)
– Some college/associate's degree	27.3% (3)
– College degree	27.3% (3)
– Graduate/professional degree	27.3% (3)

n = 11.
GED: General Educational Development High School Equivalency Certificate.

Results

Reaction to results

Most interviewees expressed little concern about their positive genomic screening results. One reason for this was age. As depicted in Table 2, this was an older group of individuals whose mean age was 64, reflecting the average age of the GeneScreen participants, which was 60. Those in their 60s and 70s noted that they would have worried more about the results if they were younger. For instance, when a participant with a positive result indicating a possible increased risk of long QT syndrome was asked if the result had changed anything in her routine, she replied, "Well, I'm 74 so, you know, it's not like I was 20 and found out about this and worried about would I be able to live long enough to have children or not" (Participant 10). Older participants also reasoned that symptoms would have already appeared if they were going to develop. For example, someone with a positive result indicating increased risk of hemochromatosis said he was not worried about his result since he is "already 63 and [has] never experienced a problem with it" (Participant 8). For these reasons, older participants noted that the results were more helpful to their families than to themselves.

Another reason interviewees expressed little concern about their positive genomic screening results was the type of condition. As shown in Table 1, half the participants tested positive for genetic variants in the *HFE* gene associated with increased risk of hemochromatosis, arguably the most benign condition on the panel and the one with the lowest penetrance. The 63 year old mentioned above stated that "if you have to have [a genetic anomaly], this seems to be a pretty good one to have. It's not a high-risk problem" (Participant 8). The type of result, along with his age, made him less concerned. Others with hemochromatosis genomic screening results were dealing with more pressing health concerns, including one woman recently diagnosed with breast cancer (Participant 5).

For some, the result was not a surprise. Three people who were interviewed already knew their results from previous genetic testing, tempering concern about their result. One 60 year old with a *BRCA2* result said she threw out the result report since she already knew the information (Participant 1). Two participants received *HFE* hemochromatosis results for a second time. One, a 76 year old, said she was relieved she did not screen positive for genes related to cancer (Participant 4). The other, a 77 year old, said he tends to forget about his risk of hemochromatosis, so the result made him 'more aware of it again' (Participant 3). He planned to talk to his primary care physician about follow-up care, but when asked if the result would change any future plans, he commented, "No, I'm going to be 78 and, at this age, there are so many other things that could go wrong." This again highlights the role of older age in interpretation of the significance of results, especially for conditions in which the penetrance or risk of developing clinical disease is very low.

Decisions & changes since receiving the results

During their first interview, most reported following up with their physicians after receiving their results. Importantly, they all had health insurance. By the second interview, most reported that their lives had not changed much.

For example, during her first interview, the 74 year old with a possible increased risk of long QT (Participant 10) reported she had followed her physician's recommendation that she stop taking two medications and have an electrocardiogram, the results of which were normal. In the second interview, she said that knowing about the positive genomic result was not terribly helpful and that her doctor did not even mention long QT at her recent appointment, reinforcing her belief that the positive result was not particularly important. The 63 year old with increased risk of hemochromatosis (Participant 8) said at the first interview that he had an iron panel done and will continue to have one every few years, per physician recommendation. In his second interview, he said he will keep up with the iron tests but that the results did not weigh on his mind because he had other health concerns, including Type II diabetes and a history of cancer. Finally, a 47 year old who had *RYR1* variants indicating possible risk of malignant hyperthermia (Participant 14) said he was going to get a medical ID bracelet at his first interview. At the second interview, he had not yet gotten the bracelet and reported that the result is not something he worries about.

For those who did not previously know their results, they had not yet developed signs or symptoms, nor did the results explain any symptoms that previously had no identified cause. One exception was an individual (Participant 13) who received a positive result for a pathogenic variant in the *RET* gene associated with multiple endocrine neoplasia type 2A. Even though she had no symptoms, the management of her case included prophylactic thyroid surgery due to a positive family history.

During the first interview, most recipients of positive results discussed intentions to tell family members about their result and recommend genetic testing. Several participants had already told family members at the time of the first interview. By the second interview, four participants said they did not think any family members had pursued testing. Three participants reported that at least one first degree relative was tested.

Discussion

In the context of returning medically actionable genomic results to research participants, especially anticipating the translational potential in population screening, these findings support continued attention to how older age frames participant perceptions of its relative harms and benefits. These findings also point to challenges when an array of conditions is screened for together.

These results provide evidence supporting the likelihood that voluntary programs without an upper age limit will include interested older adults [9] who will interpret the implications of their positive genetic findings through the lens of age. Given that the average age for all participants was 60, it is not surprising that those who received positive results were also older. Their assessments generally reflect a relatively low level of concern. This aligns with prior research that learning positive genetic results does not lead to significant psychological harm [21–23]. Additionally, revelations of genetic risk later in life are less worrisome, in part because much time has passed without any development of symptoms. The two participants with increased risk of long QT syndrome acknowledged that learning about this at a younger age could have yielded beneficial early interventions. At the same time, our older participants' absence of any long QT arrhythmia symptoms, despite having a positive result, is exemplary of the concern that population genomic screening could lead to overdiagnosis and unnecessary monitoring or interventions [24,25].

The study also revealed the difficulty of assessing harms and benefits of genetic screening for a diverse panel of 11 medically actionable conditions. For instance, the implications of receiving a long QT positive risk result are different at age 70 than at age 20, and are different than receiving a hemochromatosis risk result at any age. Diverse conditions on a panel (or, moreover, in genome sequencing) can also temper participants' interpretation of and reaction to their results, as evidenced by a participant who noted his positive hemochromatosis risk result was relatively 'good' in comparison to other results he could have received. In addition, participants' current and past health status mattered. Some recipients of positive results were dealing with health conditions they deemed of great urgency or import. Other participants already knew about their positive results, making the other negative results from the panel potentially more meaningful than the positive results. These findings remind us that context matters in how people respond to receiving screening results, and that in population screening programs, the information people already know when they undergo the screening cannot be controlled.

Arguably, the biggest potential benefit of population genomic screening of the sort anticipated by GeneScreen is the prevention or early treatment of disease in those with positive results. Thus, adherence to recommended follow-up care is crucial. Most people we interviewed did pursue some or all of the care recommended to them by the time of their first interview, including iron tests for those with hemochromatosis risk results and EKGs

for those with long QT risk. However, by the second interview, almost no one had done anything further. This may have been consistent with clinical recommendations within 8 weeks of result receipt; that is, initial test results may have indicated that no further testing was needed. However, it is also possible that the importance of the result and interest in follow-up care faded for both participants and providers, given the type of result received or the lack of symptoms. Results from prior research on the relationship between receipt of genetic test results and adherence to prevention behavior has been mixed. Some studies show an increase in adherence [22,26]. Others report that screening results have little impact on prevention behavior [27,28], including a study examining follow-up care-seeking behavior among asymptomatic individuals after receiving positive genetic results through direct to consumer testing [29]. Our study further reveals the complexity of predicting behavioral responses to genetic screening results over time when considering the age of those screened and the type of conditions included on the panel. We found initial interest or intent to act upon the result, but further research is needed on the potential disconnect between these temporal motivations and subsequent healthcare utilization within genomic screening contexts.

Another frequently cited benefit of genetic testing, in terms of both population health and cost–effectiveness, is the identification of at-risk family members through cascade testing [30–32]. In fact, many people who joined GeneScreen, especially older participants, cited this benefit as a reason to join [9]. Our interviews with people who received positive results reveal a mixed picture regarding family testing. Telling family members and encouraging them to be tested was mentioned by many in the first interview, but by the second interview, less than half reported that family members had been tested. Other studies have found that while rates of informing relatives of results may be quite high [33], rates of cascade testing for eligible first-degree relatives are quite low [34,35]. What is unclear, however, is whether low rates of cascade testing can be attributed to educational difficulties (e.g., probands who had the benefit of speaking with a genetic counselor about their results may struggle with communicating genetic information to relatives); lack of resources to make testing for family members easily accessible; the nature of the specific finding (e.g., dominant hereditary cancer risk vs recessive hereditary hemochromatosis); or some other combination of factors. Although efforts to implement precision prevention through genetic testing gain momentum, it is important to identify best practices in reaching family members to make testing efforts effective for both cost and health outcomes.

These findings are limited in their generalizability due to the small sample size and the older age of participants. Furthermore, not all participants with positive results agreed to be interviewed, including the two participants who received familial hypercholesterolemia results. Additionally, because this is a research project, these findings cannot be directly equated with clinical population screening. For all these reasons, it is likely that more themes will be revealed in future research about positive genomic screening results, particularly in terms of how participants react to results for conditions not examined in the current study and how younger people interpret the utility of positive results. Given the limited racial and ethnic diversity of the sample, it is also important to continue to investigate these issues in diverse populations as reactions to results can vary by race and ethnicity [36]. Future research should also focus on how people who receive positive results feel about prior decisions to have their results submitted to genetic databases, like dbGaP, and whether a decision to have post-test counseling in person or by phone impacts patients' decisions or follow-up care.

When considering population screening, researchers and clinicians should recognize that receipt of positive results may not have the impact that they presume. Individuals may already know their positive results and be more interested in the negative results also offered by more extensive tests. In fact, it is quite possible that people who have previously received a positive genetic result may be more interested in pursuing other opportunities, such as panel screening or genome sequencing. And age may impact responses to results, as older individuals may perceive themselves to be less at risk of developing the condition than younger individuals. Coupled with the diversity of conditions for which people will potentially be screened, these issues complicate the assessment of harms and benefits of receiving positive results through population screening.

Author contributions

M Waltz, KM Meagher, GE Henderson, KAB Goddard, K Muessig, JS Berg, KE Weck, and RJ Cadigan made substantial contributions to the conception and design of the work. M Waltz, KM Meagher, RJ Cadigan contributed to the analysis and interpretation of the data for the work and drafted the manuscript. M Waltz, KM Meagher, GE Henderson, KAB Goddard, K Muessig, JS Berg, KE Weck and RJ Cadigan contributed to the writing and revising of the work for important intellectual content, give final approval

of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors have obtained appropriate institutional review board approval. Informed consent was obtained from all participants.

Executive summary

- Population screening of healthy individuals for pathogenic variants associated with medically actionable conditions is becoming more feasible, but the potential harms and benefits across a diverse range of ages need to be assessed before the screening of 'healthy' individuals is widely adopted.
- We examine the issue of older age as it relates to the potential harms and benefits of screening through a preventive genomic study in which 262 adults across a broad age range received screening for 17 genes related to 11 diverse, medically actionable conditions.
- In total, 11 of the 14 participants who screened positive were interviewed approximately 8 weeks after receiving their results and then 9 months after results.
- Results reveal that most interviewees expressed little concern about their positive genomic screening results. For some, this was due to their older age, saying that symptoms probably would have appeared already if they were to develop and that the results may have been more helpful earlier in their life. Additionally, a few participants already knew about their positive result from prior genetic testing. Finally, approximately half of the participants screened positive for hemochromatosis and noted that, in comparison to cancer risk conditions, hemochromatosis was fairly innocuous.
- Results reveal that initial interest or intent to act upon the positive result faded for most participants by the time of the second interview. By the second interview, less than half of the interviewees reported that family members had been tested for relevant genetic variants.
- Older adults are interested in and participate in screening, and they interpret their positive results through the lens of age.
- Diverse conditions on a panel complicate the assessment of harms and benefits of population screening, particularly across a diverse age range.
- Receipt of results may not have the impact that clinicians and researchers anticipate.

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