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Age and Perceived Risks and Benefits of Preventive Genomic Screening

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Abstract

Purpose—As genome sequencing moves from research to clinical practice, sequencing technologies focused on “medically actionable” targets are being promoted for preventive screening despite the dearth of systematic evidence of risks and benefits and criteria for who should be screened. This study investigates researchers’ and research participants’ perceptions of these issues within the context of a preventive genomic screening study, GeneScreen.

Methods—We recorded researcher deliberations regarding age eligibility criteria and the risks and benefits of screening, and conducted interviews with 50 GeneScreen participants about their motivations for joining and perceptions of risks and benefits.

Results—Researchers made assumptions about who would want and benefit from screening based on age. After discussion, researchers opted not to have an upper age limit for enrollment. Participants of all ages perceived similar benefits, including prevention, treatment, and cascade testing, and similar risks such as insurance discrimination and worry.

Conclusion—While clinical benefits of preventive genomic screening for older adults are debatable, our respondents perceived a range of benefits of screening in both clinical and research settings. Researchers and clinicians should carefully consider decisions about excluding older adults and providing information about benefits and risks across age groups.

Keywords

Genomic research; preventive genomic screening; age; risks and benefits

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INTRODUCTION

Questions regarding which patients are most likely to receive benefits from medical screening in relation to their age raise complex issues in clinical care and research alike. In the clinical realm, age questions commonly arise in preventive screening (for diseases such as cancer or cardiac conditions) regarding when it is medically justifiable and beneficial both to initiate and end screening. In research, age comes into play when deciding whether to exclude children who cannot provide full legal consent or older adults who may have an increased potential for comorbidities. Thus, screening programs in both clinical practice and research often establish age criteria for patients or participants that exclude children and/or older adults. Whereas inclusion or exclusion of children in such studies is hotly debated,[1–5] there is little literature regarding older age groups.

What literature there is focuses more generally on the exclusion of older adults from clinical research and indicates that upper age limits often exist without justification.[6] Clinical trials commonly have upper age limits for participation, even when the trials involve illnesses that are associated with old age, like Alzheimer's Disease,[7] Parkinson's Disease,[8] heart failure,[7,9] diabetes,[10] and colorectal cancer.[7] Upper age limits also exist for clinical trials involving medications.[11] One review of over 300 clinical intervention research protocols sent to a research ethics committee found that one-third had an upper age limit that was arbitrary and applied even when the condition under study was prevalent among older adults.[12] Justifications for excluding older people in research studies include suspected comorbidities,[13] communication difficulties,[8,14] cognitive impairment,[8] and inability to attend follow-up appointments.[8] Without further investigation, it is difficult to know if exclusion criteria are based on chronological age or involve social assumptions related to aging.

Research initiatives that promote preventive genomic screening programs in the general population provide an opportunity for examining tenets underlying inclusion and exclusion age criteria. These programs seek to screen individuals for a targeted set of conditions which can be prevented or ameliorated if found early.[15–20] One review of existing studies of preventive genomic screening found five studies that returned results to participants.[21] All had a lower age limit for study eligibility, but only one had an upper limit (which was 80 years old).[21] Another study, the Geisinger MyCode Community Health Initiative, through its partnership with Regeneron Pharmaceuticals, sequences DNA samples of all biobank contributors in their research biobank, regardless of their age, for preventive genomic screening of 76 genes associated with 27 medically actionable conditions.[22]

Age is an important criteria for screening, but calls for population based preventive genomic screening programs[15–17, 19] do not mention whether upper age should be a consideration in developing such programs. Questions remain whether such programs will employ upper age limits, as for other clinical screenings, on the assumption that older individuals would not benefit. In this paper, we analyze data from GeneScreen, a research study of preventive genomic screening aimed at adults to examine how both researchers who designed the study and the individuals who joined understood and valued age in relation to screening. For the researchers, we focus on the assumptions and assertions involved in deciding what ages to

include. For participants, we examine how age affected their desire to undergo genomic screening and calculation of its risks and benefits. Social understanding of age is an underappreciated factor at play in how genomic screening progams are designed and offered and in decisions to participate. We propose that this factor be recognized in conjunction with evidence of clinical utlity based on chronological age as genomic screening programs are developed.

METHODS

GeneScreen, which was based at the University of North Carolina at Chapel Hill (UNC), used a screening panel consisting of 17 genes associated with 11 rare conditions for which treatment and/or prevention options were available.[23–25] There are currently no guidelines for age-related clinical utility for screening the genes related to the GeneScreen conditions. Participants were recruited at two sites: a general internal medicine clinic at UNC Hospitals where clinicians nominated 436 patients as potential participants; and the Kaiser Permanente Northwest (KPNW) research biobank which selected 650 individuals to be contacted. As far as possible, we attempted to recruit equal numbers at both sites by gender, race/ethnicity, and age groups. Both groups received a brochure with general information about the study and a letter directing them to the GeneScreen website where extensive information about the study and the conditions being screened was provided. Informed consent was obtained through the website. This process resulted in 262 adults enrolling, all of whom were asked whether they would be willing to be contacted to participate in a telephone interview. Seventy-seven percent indicated they would be willing to be interviewed, and these participants did not differ demographically from those who declined.

We report on data collected from two sources. The first was observations and audio-recordings of 11 GeneScreen research team meetings that occurred from July 2013 through April 2014. In these meetings, researchers (including bioethicists, social scientists, genomic researchers, and clinicians) debated which conditions and genes would be included on the targeted screening panel and what the eligibility criteria should be, especially regarding age and insurance status. All authors were GeneScreen researchers, with one (RJC) serving as an ethnographic observer during these meetings.[24]

The second source of data were semi-structured telephone interviews conducted with individuals who joined GeneScreen. Fifty interviewees were purposively selected, from those who indicated willingness to be interviewed, to represent three different age categories, two gender categories, and three race/ethnicity categories (see Table 1).[25] Interviews took place from March through June of 2016 and were conducted approximately two to four weeks after participants joined GeneScreen. All participants were still awaiting their genetic screening results at the time of the interview. The interview was designed to elicit in-depth information about participants' motivations for joining, how they made the decision to join, and their understanding of the risks and benefits of targeted genomic screening and various facets of the GeneScreen protocol. All interviews were audio-recorded and transcribed verbatim.

To conduct the analysis of researcher meetings and participant interviews, the transcripts were read in their entirety, and using conventional content analysis,[26] coded through an iterative, collaborative process. Codes captured segments of text pertaining to perceived benefits and risks of participating in GeneScreen, participants' decision-making processes, and references to age in relation to these topics. We reviewed the coded segments to derive the themes reported below.

The Institutional Review Board (IRB) of UNC approved all procedures. The IRB of KPNW approved the procedures related to the participants recruited from the KPNW biobank.

RESULTS

Researchers' Discussions of Age

GeneScreen researchers deliberated about eligibility criteria, specifically participants' age as it related to potential risks and benefits of being screened for the 11 conditions. Initial suggestions were that older individuals might not benefit from the information they could receive from screening. Clinicians in the group were more inclined to think that screening should not be offered to anyone who, based on population statistics, had fewer than 10 years of life ahead of them, which is a general rule of thumb for clinical screenings. Discussions positioned younger and older individuals differently in relation to the potential benefits of genomic screening, as shown in this example:

> Researcher A: And I think we'd all agree that 80-year-olds would be stupid to test.
>
> Researcher B: For anything.
>
> Researcher A: No offense to 80-year olds, but-
>
> Researcher B: No. You shouldn't do colonoscopies in an 80-year-old.
>
> Researcher A: Right.
>
> Researcher B: You shouldn't do mammograms in an 80-year-old. You shouldn't do this either […]
>
> Researcher C: Speaking as a person in my 20s, I think that all of this is more useful to folks in my period of life […]
>
> Researcher B: I agree. I mean if nothing else because of competing morbidities.
>
> Researcher A: Right.
>
> Researcher B: Right. By the time you're 60 there's all kinds of things that can kill you.

Because older individuals would not receive the same benefits from screening as younger people, an upper age cutoff for participation was proposed. Multiple possible cutoff points were discussed, including age 60, 65, and 80, but with no agreement. One clinician worried that without a cutoff, GeneScreen would run the risk of reinforcing the desire for screening among older adults as well as the misconception among lay individuals that screening "does a lot of good when you're 80."

This initial assertion that older individuals should be ineligible to participate was reconsidered when notions of familial benefit entered the discussion. Researchers stated that one benefit of including older adults would be the information screening could provide to their children, grandchildren, and other relatives who could be tested if a pathogenic variant was found. As one researcher said, participation "might not actually save the 80-year-old that we test, but [it] could save his grandchildren."

In addition to the identification of familial benefit, researchers had to remind themselves that they were conducting research and not implementing clinical practice. Their comments reflected awareness of blurred boundaries between the two. On the one hand, researchers wanted screening to mirror as much as possible what they envisioned genetic screening for healthy adults to look like in a clinical setting. On the other hand, the reminders that GeneScreen was a research study, addressing as yet unanswered questions about an upper age cut-off, prompted researchers to see the benefits of including and studying older adults. One researcher's comments brought the research and clinical realms together in a rationale to include older adults:

> I think for a research study, [including older adults] makes a lot of sense because we would like to have some people who are positive and identify what their feelings are and those sorts of things. [And] for a clinic, there's good arguments that a broader range would still benefit people especially as we learn more about the penetrance of this.

The recognition that the inclusion of older adults in a genomic screening research study could lead to familial benefit and to understanding their perspectives on screening, as well as provide data to inform clinical practice, ultimately motivated the decision against excluding adults based on age.

Participants' Perceptions of Benefits

The 50 interviewees included equal numbers of men and women, ranging in age from 23–84, with the majority being white, non-Hispanic, highly educated, and with relatively high incomes (See Table 1). Participants of all ages had similar responses when asked about the possible benefits of participating in GeneScreen, noting five primary categories of benefits (See Table 2). Each benefit was endorsed by members of all age groups.

Participants across all age groups noted the societal benefits of advancing science and helping other people. They also mentioned familial benefit as a reason to participate. Grandparents discussed wanting the information for their children and grandchildren. Those who did not yet have grandchildren talked about wanting the information for future generations. Younger people's responses echoed those of older people. For instance, a young mother talked about being motivated to join because of her young children who depended on her. She wanted to learn if she had any of the GeneScreen mutations to know if she had transmitted a genetic risk to her children for any of the conditions. Participants who did not have children talked about the genetic information being potentially helpful to siblings and other relatives.

Participants saw the identification of conditions that could be prevented or treated as a personal benefit of GeneScreen. Interestingly, while participants both young and old cited prevention and treatment as reasons to join, some older individuals did not think they would personally benefit from GeneScreen because of their age. For example, when asked "Do you see any possible benefits to you personally or for your family of joining the study?", one participant answered, "Not for me personally. You know, I'm 60 years old." Yet other older participants saw as a major benefit information they might learn that could prolong their life. For example, one older participant commented, "On a more selfish side, I'm curious about my own structure, and although I'm 85 now, maybe there are some things I can do to prolong my life." Participants of all ages also stated that just having the GeneScreen test results would be a benefit, particularly because they could gain peace of mind if the results were negative.

Participants' Perceptions of Risks

Similar to perceived benefits, participants of all ages endorsed the same risks when asked about any hesitations they had in joining GeneScreen. Of the 50 participants interviewed, 14 (28%) saw no risks. For example, when asked whether he saw any possible risks or harms, one 66-year-old said, "No, I don't. Absolutely not." A 35-year-old participant echoed this sentiment, saying, "No, I don't really see any risks or harm. It's just having more information about your health."

Others participants did cite possible risks (see Table 3). The most commonly mentioned potential risk was discrimination. It is possible that this perception was intensified by GeneScreen's policy that a positive screening result, once it was CLIA-confirmed, would be placed in the participant's medical record. Despite the protections of the Genetic Information Nondiscrimination Act (GINA), individuals across all age groups voiced fears that the revelation of a positive result could cause them to be denied health insurance in the future or to have their current health insurance cancelled. Individuals also worried that health insurance companies could consider a positive result as constituting a preexisting condition, possibly raising their insurance rates. Others brought up the fact that they could be denied life insurance or experience employment discrimination if they received a positive result.

Participants from all age groups also mentioned that joining the study carried a potential risk for worry. Individuals were worried about waiting for sequencing results as well as being at risk for a condition associated with a positive result. This risk of worry was alleviated somewhat by the perceived benefits of participating, particularly knowing that the conditions being screened were treatable and manageable.

While individuals across all age groups mentioned these risks, older participants (age 60 and up) thought their risks were minimal compared to younger individuals because of their age. For example, people over 65 viewed insurance discrimination as less of a threat because of Medicare coverage. As one stated:

> I did have a bit of concern that if I have a condition, that it could adversely affect health insurance or something like that. Now given that I'm 66 and on Medicare it's less of a concern to me, but it does – it did cause me some second thoughts.

Similarly, older individuals saw life insurance discrimination as less of an issue as most already had it. It is important to note, though, that most of those interviewed were financially secure, with an average household income over $100,000.

Older adults also cited their age as lowering their risk of employment discrimination. As a 60-year-old participant explained, “I’m already approaching retirement age, and so I don’t think I could be discriminated against for job placement because of it. So no, I don’t think there’s any real serious issues.” Not everyone in their 60s may have the desire or means to retire, but for individuals like this participant, social status combined with age may be viewed as reducing the potential for employment discrimination based on genetic information.

Finally, older individuals stated that their risk of worrying about their future health was less than that of younger adults. An older participant explained:

> I know some people don’t want to find out something because then they think they’ll worry about it, or it’ll influence how they live their life, or something like that. But maybe cause of my age—I am 75—I’m like, ‘Hey. Whatever. I’ll shoot for the moon. Whatever.’ You know, it doesn’t matter.

DISCUSSION

We have investigated the ways in which the meanings individuals attach to age matter (or do not matter) when considering participation in a preventive genomic screening research project. GeneScreen researchers originally debated having an upper age limit as an inclusion criterion for participation, but struggled with how to consider age and eligibility in the context of GeneScreen. Although a research study, GeneScreen had strong clinical implications for those who ultimately tested positive for a pathogenic variant. This blurring of lines between research and clinical practice, especially when it comes to deliberations about what results are returned and to whom, produces various challenges.[27, 28] It is therefore not surprising that the researchers had difficulties at times trying to sort out appropriate frameworks with which to discuss the implications of returning medically actionable results to older adults who may not clinically benefit from the information. However, once they thought beyond individual benefit to familial benefit and learning about how older individuals perceived risks and benefits of participation, researchers ultimately decided not to implement such a limit. As it turned out, over half of GeneScreen participants were 60 and older, and 7 percent were 80 and older. This supports the findings of Mahlmann and colleagues that older adults are interested in participating in genomic research, and similar to GeneScreen, both young and old saw familial benefit as a reason to participate.[29]

GeneScreen researchers were initially concerned that not having an upper age limit might reinforce the misconception that screening has clinical benefit for older people. Interview data demonstrate that many older adults understood that participating in GeneScreen might not yield personal benefit, given their age, in terms of prevention and treatment. Other older adults did see the benefit of participation as gaining peace of mind from negative results and having the possibility of prolonging their life if they received positive results. Yet they may have overestimated the potential for clinical benefit for themselves. That is, the older the

person who screens positive, the less likely he or she is to experience symptoms of the conditions being screened. This likelihood translates into potentially fewer health concerns to worry about when undergoing genomic screening. Thus, if older adults are included in future genomic screening programs, the diminishing personal clinical benefit should be clearly communicated to them.

Not only do the types of potential personal benefits vary by age, but so do the risks. GeneScreen participants saw their older age as a protective factor against some of the potential risks for insurance and employment discrimination, especially if retired and on Medicare. GINA prohibits employers and health insurers from discriminating on the basis of genetic information, so most individuals regardless of age should be protected. However, recent Congressional activities threaten some of the protections in health insurance for manifested symptoms and in employment for wellness programs. If passed, these types of legislation may create greater risks for younger individuals who are not yet retired and eligible for Medicare.

In contrast, life, long-term care, and disability insurers are allowed to take genetic information into consideration. If older adults have not yet secured these types of insurances, they may effectively be barred given the prohibitive costs associated with their age alone, but the results of a preventive genomic screening program could potentially affect the insurability of individuals of all ages for these types of insurance.

Limitations

Despite our attempt to interview a diverse group of GeneScreen participants, the majority were female, White, and non-Hispanic. Over half had annual incomes of $100,000 or more, and over 90 percent had at least a college degree. High socioeconomic status may have influenced their minimization of risk. Additionally, everyone interviewed had joined GeneScreen and therefore presumably had an interest in screening. Taken together, these interviewees may well be typical of “early adopters” of genomic technologies.[30] A study of ClinSeq participants suggests that early adopters of genomic technologies also have high levels of optimism.[30] While our study did not assess optimism, it is possible that the reason the vast majority of interviewees, regardless of their age, saw great benefit and few risks for themselves in joining GeneScreen was due to this selection bias. Additional research is needed to investigate how a diverse public may understand age in relation to the risks and benefits of genomic screening.

Implications

Inclusion of older adults in research programs has implications for cost, communication during informed consent and return of results discussions, and risks for overdiagnosis and overtreatment. In research projects with limited resources, sequencing participants primarily for familial benefit may not be feasible or central to study aims. GeneScreen paid for testing for family members of UNC participants who could come to UNC facilities. This fit into the overall research aims of assessing the ethical, legal, and social implications of an adult genomic screening program, and researchers’ valuing of cascade testing for familial benefit. For other research studies, however, these costs could be exorbitive or deviating from

research goals. Cost issues are mirrored in the clinical realm, where questions remain regarding who should pay for sequencing and for what purpose. For example, should an individual's health insurance pay for sequencing done for the benefit of family members?

Inclusion of older adults in research projects also requires researchers to consider working with clinicians to tailor discussions of clinical benefit to minimize risk of participants' misunderstanding clinical benefit and subsequent overtreatment. Enrollment of diverse participants requires consideration of how to tailor informed consent, pre-test education materials, and communication of return of results for individual circumstances. As found in GeneScreen, many older adults understood that they were unlikely to receive personal clinical benefit from results, but some overestimated the potential clinical benefits. Without thoughtful and tailored communications, older adults participating in genomic research may misunderstand the clinical benefits of the research and may undergo preventive screenings that increase risks of physical complications and overtreatment.

As preventive genomic screening enters clinical settings, will practice recommendations suggest upper age limits? GeneScreen researchers engaged in robust discussion about upper age limits, suggesting that this will likely be a point of contention for other preventive genomic screening programs going forward. Clinical evidence of the benefits and risks are traditionally based on chronological age. Our exploration of perceived benefits and risks introduces the social value of screening for older adults, a topic we argue also deserves attention.

There are currently no age guidelines for preventive genomic screening, but we can extrapolate from other types of screening programs to determine how upper age limits may come into play. Clinical screening guidelines often recommend against older adults undergoing preventive screenings because risks may outweigh potential benefits given their life expectancies and likelihood of comorbidities. For example, a survival benefit from breast or colon cancer screening is unlikely unless an individual is expected to live at least another 10 years.[31] The United States Preventive Services Task Force (USPSTF) considers age when making recommendations regarding screenings, recommending mammographies for women from 50 to 74 years of age, cervical cancer screenings for women from 21 to 65 years of age, and colorectal cancer screening for men and women from 50 to 75 years of age. The report for colorectal cancer for those 76 to 85 years of age recommends selective screening for this population noting, "[s]creening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy."[32]

Age cutoffs may serve population health in other clinical contexts, but it is not clear if this is the case for preventive genomic screening, which is associated with a familial cascade benefit. For example, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recently recommended that all individuals diagnosed with colon cancer should have their tumors sequenced for variants associated with Lynch Syndrome in part due to the potential for familial benefit.[33] As the concept of clinical utility expands to familial utility, it is likely that excluding older adults will be seen as antithetical to a screening program's goals.

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Table 1

Demographic Characteristics of GeneScreen Interviewees (N = 50)

	Variable	Frequency	Percentage
Gender	Male	24	48
	Female	26	52
Age	18 to 40	14	28
	41 to 60	16	32
	61 and over	20	40
Race	White	36	72
	African-American	6	12
	Asian-American	5	10
	Other	3	6
Hispanic	Yes	7	14
	No	43	86
Education	High school or some college	5	10
	Four-year college degree	16	32
	Graduate or professional degree	29	58
Income	Less than $24,999	2	4
	$25,000 to $49,999	5	10
	$50,000 to $74,999	11	22
	$75,000 to $99,999	6	12
	$100,000 to $124,999	3	6
	$125,000 to $149,999	4	8
	$150,000 to $174,999	5	10
	$175,000 to $199,999	3	6
	$200,000 or more	11	22

Table 2

Participants' Perceived Benefits of Participating in GeneScreen

Benefit	Representative Quote (age of respondent)
Prevention and Treatment	• The benefits for me are I can find out if I have one of these risk factors and hopefully work to prevent that disease. (28) • If it hadn't been the case that there was something that could be done for each of these [eleven] conditions, I wouldn't have been as interested. I don't want to walk around knowing something is wrong with me that I can't do anything about. (50) • I mean, if a truck is gonna hit me, I'd rather know. I'd rather have somebody yell at me 'Get out of the way!' (65)
Having Information and Peace of Mind	• It's peace of mind knowing that genetically I don't have to worry about X, Y, and Z. (27) • Interviewer: "So what made you decide to go ahead and join despite your reservations?" Respondent: "Hmm. I guess cause I think knowledge is key. So knowing is better…" (48) • Interviewer: "What do you hope to get out of participating in the GeneScreen study?" Respondent: "Knowledge…. Peace of mind hopefully." (76)
Pass information to family members	• I'm a mom. So if I have a chance that I've passed anything on…I absolutely want to know. (23) • If you have something, you'll be more informed to help your children, your siblings, that sort of thing. I just think it's a wonderful thing to relay that information. (59) • If there's something that I could do to give [my grandchildren] the potential information on future vulnerabilities that they or their offspring might have, I think that's a nice gift that I can give to them. (80)
Advance science/research	• I believe firmly in the importance of research, and I believe firmly that information is important to gather, and that in order to gather that information you require the participation of people. (27) • The more research we can get done…the better we can treat people and heal them. So that's why [I joined]. (44) • I'm a believer in science. I'm a believer in the more knowledge the better. (72)
Helping Others	• You can help other people by doing the study, and I mean that's important within itself. (26) • If anyone can benefit from my information that I am contributing, I think it would be a wonderful thing. (59) • I'm just happy to do a little bit that might help somebody in the future without truly any particular inconvenience to myself. (68)

Table 3

Participants' Perceived Risks of Participating in GeneScreen

Risk	Representative Quote (age of respondent)
Discrimination	• People [can use this] for billing or insurance purposes to say that 'Oh. You know he's got a pre-existing condition.' So it would be hard to find health insurance or find premiums that people can live with. So that's my biggest fear, and I kind of fear that more than the actual [positive] results that could come out of it cause like if you can't find healthcare and get yourself treated, then what's the point of doing the test? (34)
	• If it gets compromised or you know hacked into and exposed, or if at some point you know I did have to go out and find insurance on a marketplace. You know hopefully it wouldn't be an issue, but I suppose they could always find – a health insurance company could find another reason to deny. (48)
	• That file will be in my permanent record…I felt a little twinge possibly know[ing] that [it could] affect insurance company in any way… (61)
Worrying	• There's a chance I could find out you know I do have a gene mutation that I otherwise would not you know have known about until something went wrong. So I mean I think it gives people of course a little bit of anxiety until they receive their results. (23)
	• I am still a little concerned of if you know what the result is and how I will react to it and what – you know how it'll affect my daily and future thoughts and worries and all that kinda stuff. (48)
	• [My friends] said 'Do you really want to know?' I mean regardless. You know one of the things that I've been aware of by reading some articles is that sometimes what happens when you – like the old thing about if you gave everybody a full body MRI, you'd find something to work on, and I think that concerned me. I really don't want to poke around so much that I – I want to make a value judgment, and I don't want to like have somebody scare me half to death. (74)