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Preferences for Return of Incidental Findings from Genome Sequencing Among Women Diagnosed with Breast Cancer at a Young Age

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Abstract

While experts have made recommendations, information is needed regarding what genome sequencing results patients would like returned. We investigated what results women diagnosed with breast cancer at a young age would want returned and why. We conducted 60 semi-structured, in-person individual interviews with women diagnosed with breast cancer at age 40 or younger. We examined interest in six types of incidental findings and reasons for interest or disinterest in each type. Two coders independently coded interview transcripts; analysis was conducted using NVivo 10. Most participants were at least somewhat interested in all six result types, but strongest interest was in actionable results (i.e., variants affecting risk of a preventable or treatable disease and treatment response). Reasons for interest varied between different result types. Some participants were not interested or ambivalent about results not seen as currently actionable. Participants wanted to be able to choose what results are returned. Participants distinguished between types of individual genome sequencing results, with different reasons for wanting different types of information. The findings suggest that a focus on actionable results can be a common ground for all stakeholders in developing a policy for returning individual genome sequencing results.

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Conflicts of interest

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Keywords

genome sequencing; return of results; incidental findings; patient preferences; breast cancer

INTRODUCTION

Advances in sequencing technologies have the potential to alter health care through the availability of patients' individual genomic information (1,2). Whole genome and exome sequencing are already being used for clinical purposes (2,3), and sequencing is likely to become more important to patient care (4). This raises the critical communication challenge of returning incidental findings (IFs) (5), results not related to the indication for ordering sequencing (6). The issue of whether to return IFs has been actively debated; there is an emerging consensus among experts that researchers and clinicians should offer to disclose analytically valid, clinically actionable findings (6–9). In 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that when clinical sequencing is performed, a minimum list of 56 genes, selected based on penetrance, actionability, and pathogenicity (10), be evaluated and results returned to the ordering clinician (6). The ACMG did not recommend reporting other results (11).

The ACMG process did not include the views of a critical stakeholder group, patients (12), and the ACMG did not recommend offering patients a choice as to whether their clinicians would receive results (6), although the recommendations have been revised to include an opt-out option (13). Prior studies conducted with the general public have shown that individuals would like all individual results returned, regardless of certainty, disease type, or availability of treatment (14–16). In one study of families enrolled in a sequencing study, participants elected to receive all IFs (17), although this may not be true of all patients receiving clinical sequencing (18).

Young breast cancer patients are a key group in which to examine these issues (4,19). Women diagnosed with breast cancer at age 40 or younger are more likely to carry mutations in *BRCA1* and *BRCA2* (20,21), or other cancer susceptibility genes (22), and may be diagnosed at a later stage or have a more aggressive cancer (23). As such, sequencing has the potential to affect their clinical care by identifying cancer susceptibility alleles and mutations serving as treatment targets (4,19). However, prior studies have not focused on their preferences for return of IFs. We investigated what individual genome sequencing results women diagnosed with breast cancer at a young age would prefer to have returned and why.

METHODS

Participants

We recruited adult participants from an existing nationwide cohort of women diagnosed with breast cancer at age 40 or younger, the Young Women's Breast Cancer Program (YWBCP). This cohort is 91% Caucasian; mean age at diagnosis is 35 years and mean time since diagnosis is 10 years. Because we wanted to recruit a purposive sample of 60 women for in-

person interviews, only those YWBCP participants in the St. Louis region were contacted by e-mail, letter, and e-newsletter. Recruitment was stratified into four subgroups by family history of breast cancer, having received genetic testing for *BRCA1/2*, and *BRCA1/2* mutation status (Figure 1) in order to examine differences in themes by these variables. Family history of breast cancer was scored by an experienced genetic counselor and classified as strong (i.e., one 1st or 2nd-degree relative diagnosed <50; two relatives diagnosed at any age; or male relative diagnosed); moderate (i.e., one 1st or-2nd degree relative diagnosed ≥ 50); or no (i.e., no 1st or 2nd-degree relatives diagnosed).

Interview Procedures

We conducted qualitative semi-structured in-person interviews. We developed an interview guide based on existing literature, which was refined based on initial interviews (Supplement). Interviews began with an introduction to the topic of genome sequencing and a few general questions. Then, open-ended questions addressed interest in six possible types of IFs from genome sequencing, variants that: related to risk of a preventable or treatable disease; risk of an unpreventable or untreatable disease; affected treatment response; uncertain or unknown significance (VUS); carrier status; and no health meaning (i.e., ancestry, physical traits). Each type of result was described with examples before the interest questions. We investigated interest in receiving a result and reasons for interest or disinterest. At the end, we asked participants to rank their interest in the different result types. We asked the last 24 participants whether they would like a choice in results received.

Two trained master's-level staff conducted the interviews, which lasted about 90 minutes. Interviewers were encouraged to use follow-up questions to elicit more detail. All interviews were digitally recorded and transcribed verbatim. Each participant received a $50 gift card. Participants provided written consent. The university institutional review board approved this study.

Analysis

We conducted a directed thematic analysis of interview data (24). Initial thematic domains and a preliminary codebook were developed based on prior literature and the interview guide. The codebook was then revised by the research team to add inductively derived codes and thematic domains through an iterative, ongoing process that began after the first interviews. After the codebook was complete, all data were coded with the final codes. Two trained coders independently coded transcripts using NVivo 10, and then discussed discrepancies; remaining discrepancies were resolved by the research team. Analysis was based on consensus codes. Based on responses to open-ended questions, participants were categorized as interested (e.g., "very," "strongly," "somewhat" interested), disinterested (e.g., "not at all" interested, "wouldn't want to know that") or ambivalent (i.e., not clearly interested or disinterested) in receiving each result type. Memos summarizing each code were created and used to identify core themes. We first examined themes overall and then whether themes differed across subgroups.

RESULTS

Participants

Participants' current ages ranged between 33 and 64; 97% were Caucasian. About 73% had received prior genetic testing for *BRCA1/2*; of these, 14 (32%) carried at least one deleterious *BRCA1/2* mutation. Mean age at diagnosis was 37 years (range 27–40); mean time since diagnosis was 9 years. About 75% had a college degree or higher.

Interest in Result Types

Most participants were interested in receiving each of the six types of individual genome sequencing results (Table 1). When asked to rank their interest, 83% gave top ranking to variants affecting risk of a preventable or treatable disease and 15% to variants affecting treatment response (Table 2). Most gave lowest ranking to results without a health meaning (60%). There was more variability in rankings for VUS, variants affecting risk of an unpreventable or untreatable disease, and carrier status results. For example, interest in VUS received all rankings from 2nd to 6th.

Reasons for Interest

Major reasons for interest in each variant type are shown in Table 3, with illustrative quotes in the supplemental table. Results for variants that affect risk of preventable or treatable disease or treatment response were seen as currently useful or actionable. "Actionable" meant a range of potential actions to participants, including lifestyle changes, disease surveillance, medications, environmental changes, and discussions with doctors. In contrast, results for variants that affect risk of an unpreventable or untreatable disease and VUS were seen as having potential future meaning, for the participant or others, or use for life planning. Carrier results were seen as useful for family members or their own reproductive decision making. Participants were primarily interested in results without a health meaning for curiosity or fun.

These major reasons were similar across subgroups, but there were some differences. For example, quality of life emerged as a major reason for interest in variants that affect treatment response among women with a strong family history and no identified *BRCA1/2* mutation but not in the other subgroups: "*You wouldn't want to have a treatment that's gonna negatively affect your …quality of life*." *[Participant 57]* For VUS, research yielding new information in the future was the most important reason for interest among participants with no/moderate family history and no identified *BRCA1/2* mutation but not among the other subgroups. One participant from the former subgroup commented: "*They still don't fully understand it, but at some point, hopefully they will. … they would be able to go back and say okay, now we have something we can use with this information*." *[Participant 24]*

Reasons for Disinterest or Ambivalence

Among those not interested in receiving a type of result, major reasons were similar for variants affecting risk of an unpreventable or untreatable disease, VUS, and those without a health meaning (Table 4, supplemental table). Participants felt that these results were uninformative or not actionable, were unimportant or unnecessary, or might cause worry or

stress. Major reasons for disinterest were different for carrier status results, and related to not having children or feeling that the information might be overwhelming.

Major reasons for disinterest were similar across subgroups. However, there were a few differences, mainly between women with no/moderate family history of breast cancer who did not carry a *BRCA1/2* mutation and women in other subgroups. For example, among women in the former subgroup, a major theme was that they were not currently interested in receiving VUS, but might be in the future if the meaning became clear: *"What would be perfect is if I could get notified if the meaning of it became more clear over time. Because, an uncertain one … I'm not too interested." [Participant 9]* Also, among women in this subgroup who were not interested in receiving results for variants related to risk of an unpreventable or untreatable disease, a major theme was that these results would cause stress or worry: *"I probably would not wanna know about that… it'd probably just add a lot of stress in my life that I wouldn't really need. I would think I'd rather just live peacefully doin' what I like to do." [Participant 43]*

In addition to participants who were clearly interested or disinterested, we found that a few were ambivalent about receiving some types of results, weighing the possible benefits and concerns. One participant said for variants affecting risk of an unpreventable or untreatable disease: "*I'm torn. … I can set money aside for when I need it when the dementia comes then I can live an appropriate life, meanwhile I play…. On the other hand, does it create this gray cloud over my head going I forgot where my keys are does that mean—is that the early signs of dementia?*" [Participant 12] Another participant described her ambivalence about VUS as: *"I don't know; that could go either way. I could be worrying about something that might not happen for a long time… but at the same time, it would be interesting to know." [Participant 30]*

Importance of Patient Choice

Of those asked, all responded that it was important to them to be able to choose the results to receive. For some, this was related to having control or ownership over the information: "*It gives the patient a feeling of control… You're taking my blood, and you're sequencing my genomes, and give me the information in the order that I need it." [Participant 40]* Others wanted to receive only actionable information: *"That would be very important to me… Because I do feel strongly that there's some information that I would want and some information that I just would not want."[Participant 49]* The third major reason was based on ability to cope: *"I think the person has to know how they emotionally handle information and process it and how that's gonna affect their quality of life and I don't think a doctor really has enough information about a patient to know that. So, I think that kinda has to be a patient choice." [Participant 58]*

DISCUSSION

These findings show what individual genome sequencing IFs this sample of women diagnosed with breast cancer at a young age would want returned if their genome were sequenced. While the majority were interested in receiving all six types of results discussed, their reasons for interest varied between types. However, some were not interested or were

ambivalent about receiving results for four types of variants: affecting risk of an unpreventable or untreatable disease, VUS, carrier status results, and without a health meaning. When asked to rank their interest, participants identified results seen as actionable as of greatest interest.

These results are in contrast to some previous findings. Studies of the general public have generally shown strong interest in receiving all types of sequencing results (14–16), as have a number of studies with parents (25). One study with parents showed that 83% would want results predicting susceptibility to untreatable fatal conditions returned (26). Most participants in a family study of bipolar disorder wished to be informed about all health-related genetic risks, even for diseases without known prevention or treatment (27). This interest in receiving all results has also been observed among patients undergoing clinical diagnostic exome sequencing (28). Bergner et al. (2014) suggested that individuals living with a genetic condition may feel that they are adequately prepared for additional genetic risks (17). However, other studies have shown that some participants distinguish between different types of results (18). A focus group study with parents found most interest in actionable results (29). Among 19 Lynch syndrome patients who had received uninformative results from prior genetic testing, 63% wished to receive all results while 32% wanted only clinically relevant results (30).

Many young breast cancer patients have had experience making decisions about genetic testing and receiving these results. While some researchers have suggested that individuals pursuing genome sequencing may be more receptive to obtaining results than healthy individuals (28), it might also be that cancer patients with prior genetic testing experience are better able to make informed decisions about return of different types of results. In this study, we did not observe major differences across participant subgroups, suggesting that preferences for return of results might not be driven by *BRCA1/2* mutation status or family history of breast cancer. However, the subgroup that was most different from the others was women with no/moderate family history of breast cancer who did not carry a *BRCA1/2* mutation. It is possible that because these women do not feel that they have learned the cause of their cancer through *BRCA1/2* genetic testing or family history, they are interested in learning other types of genomic information that might provide answers.

Participants generally wanted return of a broader range of results than often recommended. The majority of participants in this study were interested in receiving all types of results, but with greatest interest in actionable results. Recent studies conducted among genetics professionals have shown greatest support for medically actionable results (31,32), with generally no support for return of VUS (33), and disagreement on return of carrier results for pediatric patients (34). One study found that 94% of genetics professionals would return results for a serious or treatable condition and 75% for pharmacogenomics results, in contrast to 29% who would return VUS (35). Even if professionals agree on policies for broad categories (i.e., actionable results), there still may be disagreement on specific variants (36).

Incorporating the views of all stakeholders, including genetics professionals, bioethicists, and patients, is critical to developing an effective, patient-centered policy for return of

individual sequencing results (35). Our results suggest that a focus on “actionable” results is a place to start in creating such a policy. Prior work to define actionable results could be examined (6,33), though others have highlighted the lack of consensus among genetics professionals (7,32), and patients may define the term more broadly (29), as in this study. However, a consensus-building process that includes all stakeholder groups could focus on what results are “actionable” and could be considered for return.

Our findings affirmed the importance of patient choice in developing policies for return of results (7). Consistent with other studies (25,30,37), participants felt that they should be able to choose what results are returned. While the ACMG recently recommended that patients have an opportunity to opt out (13), current practices vary (38). This situation highlights the importance of a more comprehensive opt-out approach and developing pre-test counseling approaches to determine what results patients would like to receive, as well as research to examine the implications of patients opting not to receive medically actionable results.

Our study adds to the understanding of reasons underlying cancer patients’ preferences for return of results. In interviews with patients with Lynch syndrome who had received uninformative genetic test results, major reasons for interest in individual genome sequencing results included making lifestyle changes, altering medical management and future planning (30), themes consistent with our results. Other studies have found that results might be used to enhance quality of life or for future planning (18,29). Interestingly, the theme of knowledge as power seen in other studies (18,30) was less common in our study; instead, the potential of information that is not meaningful now to become so in the future was important. Few studies have examined why participants might not want some results. In the study with Lynch syndrome patients, participants felt that some results might be difficult or scary (30), consistent with our finding. However, we also found that participants thought that some information would be uninformative or unnecessary, or might be overwhelming. Future research that assesses family characteristics (e.g., marital status, number of biological children) could examine whether and how these variables affect interest in receiving results. For example, the fear that information might be overwhelming could be related to having younger biological children at home. The concern that results might be inaccurate, expressed among focus groups conducted with the general public (29,39), was not observed in our data.

There are limitations that should be recognized. Most participants were a number of years past their cancer diagnosis. While they could then comment on what results would have been helpful after treatment, the actual decisions of young breast cancer patients at the time of diagnosis might differ. We do not know to what extent participants received prior genetic counseling, which could influence their preferences. Participant preferences may change over time (39), and our data only captures one point. Participants were mainly Caucasian and highly educated and had previously agreed to participate in the YWBCP. Preferences for receiving results may differ by race/ethnicity (29,40) and education (41).

Despite these limitations, we found that these women diagnosed with breast cancer at a young age value actionable individual genome sequencing results most highly and believe that it is important for women to have a choice in what information to receive. Participants

distinguished between different types of results, particularly in their reasons for wanting the information. These findings, together with prior studies, suggest that defining “actionable” is a place to start for all stakeholders to develop a policy for returning IFs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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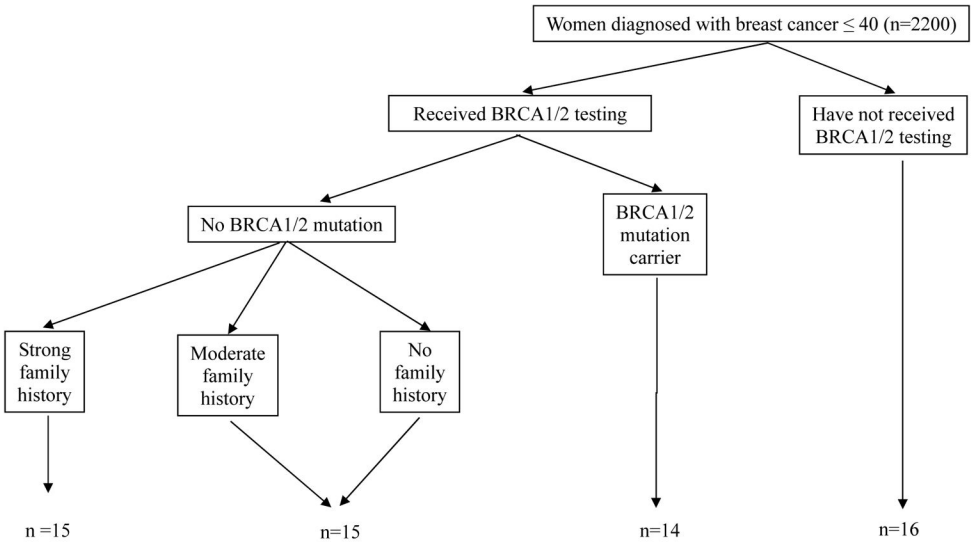

Figure 1.

Recruitment strata based on genetic testing, *BRCA1/2* mutation status, and family history of breast cancer.

Table 1

Participant level of interest in receiving each of six different types of individual genome sequencing results (n=60).

Variant type	Interested n (%)	Disinterested n (%)	Ambivalent n (%)
Affects risk of preventable or treatable disease	60 (100%)	0 (0%)	0 (0%)
Affects risk of an unpreventable or untreatable disease	35 (58%)	21 (35%)	4 (7%)
Affects response to a treatment	60 (100%)	0 (0%)	0 (0%)
Unknown/uncertain clinical significance	39 (65%)	16 (27%)	5 (8%)
Carrier result	52 (87%)	6 (10%)	2 (3%)
No health meaning (e.g., ancestry, physical traits)	46 (77%)	13 (22%)	1 (2%)

Table 2

Participant rankings of interest in different types of individual genome sequencing results (n=60).

Variant type	Ranking					
	1st (most interest) n (%)	2nd n (%)	3rd n (%)	4th n (%)	5th n (%)	6th (least interest) n (%)
Affects risk of preventable or treatable disease	50 (83%)	9 (15%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Affects risk of an unpreventable or untreatable disease	0 (0%)	2 (3%)	15 (25%)	18 (30%)	12 (20%)	13 (22%)
Affects response to a treatment	9 (15%)	40 (67%)	9 (15%)	2 (3%)	0 (0%)	0 (0%)
Unknown/uncertain clinical significance	0 (0%)	2 (3%)	5 (8%)	18 (30%)	25 (42%)	10 (17%)
Carrier result	1 (2%)	7 (12%)	28 (47%)	15 (25%)	8 (13%)	1 (2%)
No health meaning (e.g., ancestry, physical traits)	0 (0%)	0 (0%)	2 (3%)	7 (12%)	15 (25%)	36 (60%)

Table 3

Reasons for interest in different types of individual genome sequencing results.

Variant type	Major reasons for interest
Affects risk of preventable or treatable disease	• Actionable • Prevention possible
Affects risk of an unpreventable or untreatable disease	• Life planning • Future meaning
Affects response to a treatment	• Tailor effective treatments • Inform treatment decisions
Unknown/uncertain clinical significance	• Future meaning • Help research
Carrier result	• Benefit family members • Inform reproductive decisions
No health meaning (e.g., ancestry, physical traits)	• Fun/curiosity • Interested in ancestry

Table 4

Reasons for disinterest in different types of individual genome sequencing results.

Variant type	Major reasons for disinterest
Affects risk of preventable or treatable disease	None
Affects risk of an unpreventable or untreatable disease	• Worry or stress • Not actionable
Affects response to a treatment	None
Unknown/uncertain clinical significance	• Uninformative • Worry or stress
Carrier result	• No children • Information too overwhelming
No health meaning (e.g., ancestry, physical traits)	• Unimportant or unnecessary • Not actionable