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Returning negative results from large-scale genomic screening: Experiences from the eMERGE III network

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AUTHOR CONTRIBUTIONS

All authors were involved in the conceptualization of this work, discussed the results, and provided critical feedback that shaped the final article. Kelsey Stuttgen Finn wrote the initial draft of the article, and John Lynch wrote portions of the second version of the article. Richard Sharp supervised this work.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Abstract

Population-based genomic screening has the potential to improve health outcomes by identifying genetic causes of disease before they occur. While much attention has been paid to supporting the needs of the small percentage of patients who will receive a life-altering positive genomic screening result that requires medical attention, little attention has been given to the communication of negative screening results. As there are currently no best practices for returning negative genomic screening results, we drew on experiences across the electronic medical records and genomics (eMERGE) III Network to highlight the diversity of reporting methods employed, challenges encountered in reporting negative test results, and "lessons learned" across institutions. A 60-item survey that consisted of both multiple choice and open-ended questions was created to gather data across institutions. Even though institutions independently developed procedures for reporting negative results, and had very different study populations, we identified several similarities of approach, including but not limited to: returning results by mail, placing results in the electronic health record via an automated process, reporting results to participants' primary care provider, and providing genetic counseling to interested patients at no cost. Differences in procedures for reporting negative results included: differences in terminology used to describe negative results, definitions of negative results, guidance regarding the meaning of negative results for participants and their family members, and recommendations for clinical follow up. Our findings highlight emerging practices for reporting negative genomic screening results and highlight the need to create patient education and clinical support tools for reporting negative screening results.

Keywords

genomic screening; negative results; return of results

1 | INTRODUCTION

Applications of precision medicine have been heralded for their capacity to identify previously undetected genetic risk factors that may be amenable to early intervention (Ginsburg & Phillips, 2018). Population-based genomic screening to identify individuals

at risk for preventable and treatable conditions has the potential to improve health outcomes by identifying genetic causes of disease before the diseases occur. While much attention has been paid to supporting the needs of the small percentage of individuals who will receive a positive genomic screening result for a condition that requires medical attention, comparatively little attention has been given to the communication of negative screening results, defined as the absence of known pathogenic or likely pathogenic variants in those genes. The vast majority of people who undergo genomic screening will have negative screening results, which may be considered uninformative. Additionally, the high number of people with negative results often prevent personalized return of those results, possibly impairing the participant's ability to fully understand the meaning and limitations of negative result.

Geneticists, genetic counselors, and primary care providers must address the fact that a negative result often is more complex to return than a positive result because of the absence of clinical findings and the incomplete assessment of all risk factors, genetic and non-genetic (Butterfield et al., 2019; Skinner, Raspberry, & King, 2016). Additionally, the many caveats that attend a negative result, including technology or knowledge limitations that might prevent recognition of a variant as pathogenic/likely pathogenic, can be challenging to explain. Therefore, the return of negative results requires planning to help patients, research participants, and providers understand the meaning and limitations of negative results. In addition, those receiving negative results might experience a range of problematic reactions to the results, bounded by two extremes. At one extreme, negative results may be met with skepticism that they are risk-free when the results are inconsistent with what patients believe their medical or family histories suggest. For instance, a person with a strong family history of breast and ovarian cancer may find it difficult to believe that pathogenic variants in breast and ovarian cancer syndromes were not identified in their genomic screen. At the other extreme, negative results may be met with unwarranted relief, prompting some people to believe that the absence of pathogenic variants in a genomic screen is an indicator of future good health.

Several challenges exist in returning negative population-based genomic screening results, including a limited workforce of genetic counselors, lack of effective communication materials that explain results to patients, and lack of protocols for contacting individuals who are lost to follow-up. Methods for returning negative results to very large numbers of patients are needed. Although different approaches to returning genomic screening results have been evaluated by others, these studies have focused primarily on returning positive results or variants of uncertain significance (VUS), not on methods of reporting negative screening results (Berg, Khoury, & Evans, 2011; Murray et al., 2018; Pacyna et al., 2019; Sapp et al., 2018; Sutton, Kullo, & Sharp, 2018).

The third phase of the electronic medical records and genomics (eMERGE) Network aimed to study processes for the delivery of clinical and research data, in a multi-site network, while providing genomic results to eMERGE III Network research participants and integrating genomic results into the electronic health record. Studies within the eMERGE III Network developed different genomic implementation studies, which provided a unique opportunity to study differences related to the reporting of negative genomic screening

results. Studies that returned negative results varied in how they operationalized the reporting process according to the individual needs of their study populations, study logistics or IRB requirements (Fossey et al., 2018) The large numbers of individuals involved across studies is consistent with the practical challenges that will be associated with reporting negative genomic screening results at the scale that is anticipated in the future (Murray et al., 2018).

The aim of this report is to draw on experiences across the eMERGE III Network to highlight the diversity of methods used to report negative genomic screening results, the challenges encountered in reporting negative test results, and share “lessons learned” across institutions. Sharing our collective experiences returning negative results may help inform research practices and contribute to the development of best practices.

2 | MATERIALS AND METHODS

This research was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was also approved by the Mayo Clinic Institutional Review Board (#19-006395).

As described previously (Zouk et al., 2019), the eMERGE III Network aimed to study the implementation of genomic medicine by conducting genomic sequencing of a panel of about 100 genes for conditions that are considered actionable in over 25,000 participants, providing results to research participants and their health care provides, and integrating those results into the electronic health record. Some studies enrolled participants with clinical indications, for example, colorectal cancer. Some studies enrolled biobank participants without clinical indications. Information about sequencing, including a list of genes evaluated, can be found in Zouk et al., 2019.

Each study in the eMERGE III Network made independent decisions regarding whether and how to return negative genomic sequencing results. In our study, a 60-item, investigator-developed survey that involved both multiple choice and open-ended questions was created to gather study-specific information about the return-of-results process. Survey items explored the decision to report negative results, the process used to report negative results, the development of materials to communicate results to participants, procedures for participants lost to follow-up, challenges encountered, and recommendations for improving the communication and process of returning negative results in the future. These data were collected from eMERGE III Network studies after decisions regarding return of negative results had been made and most negative results had been returned. Two studies were still in the process of reporting results at the time of data collection.

The survey was emailed to each study and was completed by the individual/s most familiar with the return of negative results processes at each study. Individuals who completed the surveys included research coordinators, research analysts, project managers, postdoctoral fellows, genetic counselors, and principal investigators.

Additionally, results letters and other written materials used to return negative results were collected to facilitate content analysis. Content analysis of written materials was informed

by previous work by Lynch et al., 2020 (Lynch et al., 2020). The content of these letters was examined with respect to nine elements: purpose of letter, reminder of study participation, confirmation that genomic testing was completed, reminder that participants consented to receive results, limitations of negative results, encouragement to speak with a genetic counselor and/or primary-care provider about screening results, encouragement to speak with family members about screening results, relevance of screening results for family members, and contact information for additional information. We coded negative results letters for these nine elements as well as for specific terminology used to define and describe negative results.

3 | RESULTS

Of the 11 institutions in the eMERGE III Network, 11 responded to our survey (100% response rate). Eight of the 11 institutions returned negative genomic screening results. Two institutions had more than one study cohort that received negative results, yielding 10 unique studies that returned negative results. The population of participants enrolled in each study can be found in Table 1.

3.1 | The process of returning negative results across studies

Given the aims of the eMERGE III Network, all studies placed some negative genomic screening results in the electronic health record (EHR). Most studies used automated processes to upload results into the EHR, except for two studies that manually entered results into the EHR. All but one study returned results to participants' primary care provider or referring physician/s either by sending results directly or providing notification the results had been placed in the participants' EHR. It should be noted that two studies reported results to participants' primary care providers only when requested by participants, this choice was given to participants at the time the results were disclosed. For other studies, participants had to agree to have their results shared with their primary care provider in order to participate in the study, and this was explained in the informed consent process.

The number of participants who received negative genomic screening results varied widely among studies, ranging from 123 to 2,130. (Table 2). Studies reported two situations where negative results were not returned: (a) participants did not consent to receive study results or did not consent to receive negative results and (b) participants were lost to follow-up or were deceased. Genetic counseling services were provided at no cost to participants at all but two studies, and a telephone number to access genetic counseling services was provided clearly in the results letter. Nonetheless, only a small proportion of participants utilized genetic counseling services (Table 2). It should be noted that at the time of consent, participants in one study selected the modality through which they wished to receive results, which included phone and in-person options. At that study, this approach resulted in higher utilization of genetic counseling services.

Multiple means of communication were used to return negative results, including U.S. postal mail, email, phone, online patient portal, and in-person (Table 3). All but one study used postal mail to return results to patients. When sending the result via postal mail to participants, all studies included a letter explaining the results, and all but one also included

the laboratory report. For the study that did not send the laboratory result, it was scanned and saved as a PDF in the EHR, but was not viewable in the patient portal. The study that did not use postal mail returned results through the patient portal. Four studies returned negative results using a combination of in-person and phone approaches.

In addition, four studies included ancillary educational materials in reporting negative screening results. These materials included a vignette which was sent via U.S. postal mail or email along with the result letter. The vignette consisted of an image with characters asking questions about negative results, followed by answers to those questions as part of the image. Links to online content was provided to participants at three study sites. At one study, participants were provided with two videos—one at the time of consent and another at the time results were returned. The first video explained basic genetics concepts and terms, how genetic testing works, and the kinds of conditions being evaluated. The second video explained what a negative result means and included limitations of testing, discussing residual risk and recommended actions. The impact of those ancillary materials is under investigation.

3.2 | Content of written communications used to describe negative results

Language used to describe negative results across studies is summarized in Table 4. Language used by studies to describe negative results included terminology that described the result as the absence of a positive or significant result (six studies), as “negative results” (three studies), and as “normal results” (one study).

A summary of the content of the written communications used to return negative results can be found in Table 5. These materials typically included five items: (a) the purpose of the letter, (b) a reminder of study participation, (c) confirmation that genomic testing was completed, (d) encouragement to speak to a genetic counselor or their primary care provider about their result, (e) limitations of negative results, and (f) contact information for the study team. Although a majority of studies included limitations of negative results in their letters, the language used, and thus the messages given, about limitations of negative results across studies were highly variable. Four studies reminded participants that they consented to receive negative results, and six encouraged them to speak to a genetic counselor or primary care provider about their result. Two studies encouraged participants to speak to family members about their results, and one study explained the relevance of negative results to family members. A further analysis of the language used across sites can be found in (Lynch et al., 2020).

3.3 | Logistical difficulties reporting negative results

Not all letters were delivered to participants, as some were returned to sender as nondeliverable. The follow-up process for participants who could not be reached differed across studies. Most studies made three phone contact attempts after receiving the “return to sender” mail. If contact was not made by the third phone contact attempt, the participant was marked as “lost to follow-up.” In addition to these steps, one study sent certified letters informing participants that their results were ready and resent negative results to participants who responded to the certified letter. Another study sent an email or letter to all participants

inviting them to complete a post-results survey. This invitation to complete a survey asked participants to contact the study team if they did not receive their results, which led to the identification of participants who had not received their results. Participants were then sent their results through an encrypted email. One study returned all results via certified mail after the initial mailing was returned to the sender, and three phone contact attempts had been made.

Studies unanimously reported that returning negative results was a labor-intensive process. Many studies experienced a large-volume of participants who reported they did not receive their results after they were mailed by studies and no “return to sender” mail was received. This was reported when participants were contacted for other reasons (e.g., inviting participants to complete a follow-up survey or participate in interview studies related to receiving their negative results). While some participants had moved without updating the study team with their new address, and the postal service may be to blame for others, some participants may not have remembered receiving their results.

Only two studies confirmed that participants received their results. One of these studies was able to track participants who viewed results electronically, and the other study called participants to confirm they had received results via mail. Upon calling participants to confirm receipt of results, the latter study reported: (a) many participants claimed never to have received their results by mail and (b) those who did receive their results had many questions about their results during the confirmation call. Studies that confirmed receipt of results via phone reported that this added significantly to the labor-intensiveness of the process of returning negative results. Several phone calls were often required to reach participants, and once participants were reached, several letters needed to be re-mailed (since many participants reported they never received their results), and re-mailed letters required additional follow-up phone calls to confirm they had been received. Although a small proportion of participants utilized genetic counseling services, eight studies reported receiving many questions from participants about their results when participants were invited to join interview or survey studies related to receiving negative results. One study collected data on the percentage of participants who reported they had questions about their results and these data are reported in Stuttgen, Pacyna, Beck, Kullo, & Sharp, 2020.

3.4 | Reasons for not returning negative results

Three institutions chose not to return negative results. Two studies chose not to return negative results because their samples came from biobank participants who agreed to be re-contacted for actionable results but not for other purposes. Additionally, one of these two studies reported that since their cohort had no clinical indications, if, at any time in the future, a participant presented with clinical symptoms of one of the conditions on the panel, re-testing would be indicated due to the evolving nature of genetic interpretation and technology. Therefore, they did not feel a negative result would be clinically useful in their cohort. A third study chose not to report negatives due to concerns that negative results might provide false reassurance or prevent clinical testing if there was an indication. Additionally, a prior, large-scale genomic screening study they conducted did not return negative results, and this study wanted to be consistent across projects.

4 | DISCUSSION

Our study examined the experiences of 10 eMERGE III Network studies, some of which had more than one study, that returned negative genomic screening results. Despite the diverse populations enrolled, and the independent development of return-of-results processes, we identified several similarities across studies, including but not limited to: returning results by mail, placing results in the electronic health record via an automated process, reporting results to participant's primary care provider, and providing genetic counseling to interested patients at no cost. However, significant differences were also identified and included but were not limited to: differences in the terminology used to describe negative results, differences in the language used to define and describe negative results, differences in describing the limitations of genomic screening, the meaning of the results for participant's family members, and recommendations for patients after receiving a negative result. Our data highlight the importance of future research to develop and evaluate standardized language and messages for returning negative results that can be utilized across institutions.

The eMERGE III Network experience shows that returning negative results did not burden genetic counselors as few participants requested follow-up with a genetic counselor after receiving negative results. Despite many questions study staff received from participants about their negative results when contacting participants to confirm receipt of results or invite participants to a related interview or survey study on receiving negative results, a very low proportion of participants utilized genetic counseling. This point is further emphasized by findings from a previous eMERGE III Network study (Stuttgen, Pacyna, Kullo, & Sharp, 2020) in which patient understanding of negative results returned was assessed, and data indicated that one third of participants were left with questions after receiving negative results. This suggests that merely providing a telephone number to access free genetic counseling services is not sufficient to provide support to individuals who have questions about their results. In reporting negative genomic screening results, it may be beneficial to provide additional explanation on the advantages of genetic counseling to participants. While providing a telephone number to assess genetic counseling services free of cost should not be eliminated, other mechanisms should be considered as additional resources to educate patients about negative results.

In addition, providing participants with ready resources (ranging from websites to videos to mailed/emailed FAQ documents) may be helpful in managing the inherent uncertainty of negative results and anticipating common questions those uncertainties may engender among screening participants. These alternative mechanisms should be easily accessible and patient-friendly, and might include interactive websites, online content, videos, and/or FAQs documents returned to patients along with negative results. Results letters might also include more directive language about accessing genetic counseling services, since the benefits and reasons to access genetic counseling services may be unclear to some participants. Future studies comparing the effectiveness of different modalities are required.

Overall, the language used by studies to describe negative results fell into three categories. The first category was terminology that described the result as the absence of a positive or significant result. This terminology has challenges, including complexity with explaining

the absence of something (Stuttgen, Pacyna, Beck, et al., 2020). The second category used the terminology “negative results.” Studies reported the results were negative and explained what that means. This differs from the first category in that there is a specific label “negative results,” which is then defined. While such labels might sidestep the challenge of describing an absence of clinical information, the terminology can be problematic if participants treat the label “negative” as indicating something deleterious or bad. Finally, the third category used the terminology “normal results” to indicate that their genetic variations are like the general population or a baseline reference group. While this framing could be reassuring, the language of normality may have potential eugenic implications, although a study (Adelsperger et al., 2017) showed that recipients of a single-gene test were able to interpret “normal” in non-eugenic ways.

The variability in language used to describe negative results across studies is concerning, not because of questions of accuracy, but rather because it may lead to participant confusion, especially if participants receive negative genomic screening results (a) at different points in time, (b) from different sources, or (c) using different screening techniques. The variability in language could also be a factor in other situations, including sharing of results among family members and patient-provider communication when patients and participants describe negative screening results to their healthcare providers. In both situations, a variety of terminology could complicate these communication efforts. Further research is needed to examine what terminology patients prefer for negative results, and what language patients most accurately understand.

The variability in language used to describe negative results may also contribute to lack of clarity about what a negative result means for a patient’s overall risk of disease. This may lead to an inaccurate downward shift in patient risk perception of disease, which is concerning for two reasons. First, it could lead to a decrease in health behaviors including a healthy diet, exercise, and medical care including yearly check-ups and screening behavior including mammograms and colonoscopies. Second, if this inaccurate risk perception is passed on to family members, it may, in turn, cause an inaccurate downward shift in family members’ risk perception of disease and/or a decrease in appropriate health behaviors (Gericke et al., 2017; Ransohoff & Khoury, 2010). Prior work has demonstrated a downward shift in patient risk perceptions after receiving a negative genomic screening result (Stuttgen, Pacyna, Beck, et al., 2020). Therefore, it is important that the impact negative results have on disease risk are clearly described to patients when returning negative results. The same holds true for recommended actions for patients to take after receiving a negative result and limitations of negative results—both must be clearly addressed when negative results are returned. Inconsistency regarding disease risk, limitations of negative genomic screening results, and recommended actions are places where more study is required.

A summary of challenges associated with returning negative results and suggested solutions is listed in Table 6. There are two caveats. The first is that the suggested solutions in Table 6 are both suggestions offered by the participating studies and suggestions developed by the authors. The second is that the contents of this table are not “best practices,” but rather lessoned learned by experiences so far, and further research is needed to establish best practices. Given the labor-intensiveness of returning negative results to study staff, allocation

for sufficient budget and resources should be considered not only for the return of positive results, but also for negative results. Although confirming receipt of results via phone was highly labor-intensive, and required even more labor when results needed to be resent, this approach ensured receipt by participants. One strategy to ameliorate the number of results not received by postal mail is to increase utilization of the EHR/patient portal. It will be important, however, to offer nonelectronic return options for those who do not have internet access or do not feel technologically comfortable. Another possible solution is to provide participants with an accurate timeline of the study and return of results process, as well as a sample copy of their results upfront, in order to appropriately set expectations. If participants have a timeline and know when to expect their results in the mail, it may decrease the number of participants who unknowingly throw out results letters. This, in turn, would decrease the labor required to return negative results by reducing the number of results requiring re-mail. Sending regular updates to participants about the study and the status of their results during the study may also be useful in maintaining participant engagement. It may also serve as an opportunity to collect updated contact information from participants and reduce the number of participants lost to follow-up.

It is also possible that the return of negative genomic screening results might serve as an opportunity for genetics education. In addition, it could serve as a tool for directing patients to other medical resources related to health promotion, disease prevention, and medical screening. Although none of the studies did this in this context, it may be something to consider in the future.

5 | LIMITATIONS

Data collected from each study was in the form of a questionnaire which was often completed by individuals serving different roles on the study teams across studies. Some of the more nuanced information about challenges of returning negative results and recommendations for the future may not include the views of all individuals in a particular study. It is possible our data reflect recall bias, especially in relation to the reasons the studies elected not to report negative results (as the decision may have occurred several years earlier).

Our data do not include participant understanding of negative results, nor does it compare the effectiveness of different methods of reporting such results. Our data also do not include whether participants followed recommendations that were contained in the letters, or how providers may have interpreted the meaning of the negative results. Additionally, we were not able to assess whether the reporting of negative results by the methods described here (largely by mail) was as effective as reporting those results in person, for example, at an in-person genetic counseling appointment.

Studies in the eMERGE III Network consortium all developed grants that included in their study designs a plan to include genomic results in the EHR. The fact that this was explicit at the outset might have influenced the content of the results letters. Similarly, the sheer size of these projects meant that results letters could not be tailored to the unique situation of each participant, for example, considering whether they may have a personal or family history

that might complicate the communication of the negative result. Thus, our data may not be applicable to other settings in which negative genomic results are reported.

6 | CONCLUSIONS

Given the immense diversity of language and messages that are given to participants across different institutions to describe negative genomic screening results, it is critical that we assess the efficacy of current materials and methods used to return negative genomic screening results in order develop best practices on processes, language, and messages used to return negative results for genomic health screening to participants. Accessible, participant-friendly educational materials must be provided to support patient understanding of negative results and promote engagement with healthcare providers who can address specific questions that participants may have after receiving their results. Additionally, it is important to share experiences across institutions in order to learn from each other and to encourage the sharing of educational resources in support of research participants.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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TABLE 1

Population enrolled by each study that returned negative results

Site	Population
1	Adults without clinical indication who had participated in prior pharmacogenomic sequencing
2	Adolescents without clinical indication
3	Three cohorts: **1** Adults without clinical indication who were members of the biobank **2** Asian adults without clinical indication who were members of the biobank **3** Adults with history of colorectal cancer and or familial polyposis who were members of the biobank
4	Latino or Ashkenazi Jewish adults without clinical indication
5	Adults who were outpatients of nephrology, liver, and oncology clinics
6	Adults without clinical indication who were participants of eMERGE II pharmacogenomic study
7	Adults with hyperlipidemia or colon polyps
8	Latino adults with hyperlipidemia or colon polyps
9	Adults with and without a family history for cancer, hyperlipidemia, and heart arrhythmia
10	African American patients who had breast, lung, colon, or prostate cancer, or were at-risk for cancer per NCCN guidelines for these four cancers

TABLE 2

Summary of results and genetic counseling encounters reported across sites participating in the eMERGE III Network that returned negative results

	1	2	3	4	5	6	7	8	9	10	TOTAL
Total number of results	2,453	251	2,500	341	1,120	2,998	2,535	500	1946	491	15,135
Total number of negative results generated (% of all results)	2,228 (90%)	136 (54%)	2,205 (88%)	123 (36%)	1,056 (94%)	2,719 (91%)	2,414 (95%)	490 (98%)	1775 (91%)	472 (96%)	13,618 (90%)
Total number of negative results reported (% of all negative results generated)	2,186 (89%)	123 (90%)	1,080 (43%)	107 (31%)	1,020 (91%)	2,130 (71%)	2,392 (94%)	490 (98%)	1774 (>99%)	472 (96%)	11,774 (86%)
Total number of negative results NOT reported because patients did not consent (% of all negative results generated)	0 (0%)	3 (2%)	1,125 (45%)	6 (2%)	0 (0%)	589 (20%)	4 (0.2%)	0 (0%)	0 (0%)	0 (0%)	1727 (13%)
Total number of negative results NOT reported because although patient consented to study they either actively chose to not learn any results, were lost to follow-up, deceased, etc. (% of all negative results generated)	58 (2%)	10 (7%)	0 (0%)	14 (4%)	36 (3%)	0 (0%)	22 (0.8%)	0 (0%)	1 (0%)	11 (2%)	152 (1%)
Total number of GC encounters associated with negative results (% of all negative results reported)	0 (0%)	0 (0%)	0 (0%	63 (18%)	0 (0%)	95 (4.5%)	4 (0.2%)	0 (0%)	22 (1%)	0 (0%)	184 (2%)

TABLE 3

Methods of reporting negative genomic screening results across studies participating in the eMERGE III Network

	1	2	3	4	5	6	7	8	9	10
Results placed in patient's EHR	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Negative results reported by mailed letter	✓		✓	✓	✓	✓	✓	✓	✓	✓
Laboratory report provided to patient	✓		✓	✓	✓	✓	✓	✓	✓	✓
Results reported to patient's PCP	✓	✓	✓	✓[a]	✓[a]		✓	✓	✓	✓
Results entered into EHR via automated process	✓		✓	✓	✓	✓	✓	✓	✓	
Genetic counseling available to interested patients at no cost		✓	✓	✓	✓	✓	✓	✓	✓	
Negative results returned by phone or in person				✓		✓		✓		✓
Patients given ancillary materials		✓		✓	✓	✓				
Confirmed patient received negative result		✓		✓	✓			✓		
Negative results returned by patient portal		✓				✓				

[a]Only when requested by participant.

TABLE 4

Term or phrase used to describe negative results to participants across studies

The tests that were done on your DNA as part of this research study did not identify any changes, also called mutations or variants, that are currently known to be associated with disease.
The results are considered negative. Negative means variants known to cause or significantly increase risk for the listed diseases were not found in the tested genes.
Your eMERGE report shows that you have normal results on the genes that we tested. The normal results mean that we did not find you have a genetic risk for the 68 genes we tested.
No genetic risks were found in the genes examined in this study. Your results indicate you DO NOT have a genetic risk for any of the diseases tested in the study, based upon the genes that we analyzed and the results you chose to receive.
No genetic risks were found in the genes examined in this study. Your results indicate you DO NOT have a genetic risk for any of the diseases tested in the study, based upon the genes that we analyzed and the results you chose to receive.
The results of your genetic testing are negative. A negative result means that for the genes we tested, we did not find any changes in your DNA that are thought to increase your risk of developing a disease or health condition based on today's knowledge.
No clinically significant genetic variants were found.
We did NOT find anything in the tested genes that needs to be treated.
Regarding disease causing variants, and based on your genetic test results, we did not identify any reportable findings that would put you at increased risk for a genetic disease. In other words, you have a normal risk for cancer, heart disease, and other conditions.
Your genetic testing shows a negative result which means there are no changes in the cancer-related genes tested for in this study.

TABLE 5

Content analysis of written communications used to return negative results to participants across studies

	1	2	3	4	5	6	7	8	9	10
Reminder of study participation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Purpose of letter	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Limitations of negative results	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Contact information for study team	✓		✓	✓	✓	✓	✓	✓	✓	✓
Confirmation that genomic testing was completed	✓	✓	✓	✓	✓		✓	✓		
Encouragement to speak with a genetic counselor and/or their PCP about their result	✓			✓	✓	✓		✓	✓	
Reminder that participants consented to receive result		✓	✓	✓			✓			
Encouragement to speak with family members about their result				✓	✓					
Relevance of their result for family member									✓	

Note: Written communications analyzed here include materials used to return results (letters and messages used to return results via the patient portal). Ancillary materials were not included in this analysis.

TABLE 6

A summary of challenges associated with returning negative results and suggested solutions

Challenges with returning negative results	Potential solutions
Logistical/organizational challenges	
Mailing letters was labor intensive to study staff	Allocation of sufficient budget and resources should be given for the return of negative results. Increase return of results by electronic health record/patient portal
Minimal use of genetic counseling services, but many questions about negative results	Development and dissemination of accessible, patient-friendly ancillary educational materials, such as interactive websites, videos, or FAQs documents
Many participants claimed they did not receive mailed results	Limit time from consent to return of results to minimize changes of address. Increase return of results by electronic health record/ patient portal
Participants were lost to follow-up	Limit time from consent to return of results to minimize changes of addresses. Maintain regular contact with participants and use contact as an opportunity to collect updated participant contact information
Language and participant comprehension challenges	
Diverse terminology used to describe “negative results”	Further research is needed to examine what terminology patients prefer for negative results and how patients prefer negative results to be described. Attempts to consistently use such terminology when returning negative results to patients should be made
Challenge of clarifying scope and limitations of negative results to patients	Improve explanations about the meaning and limitations of negative results when returning negative results to patients, especially when results are returned by mail. Possible mechanisms to improve explanations and limitations of results include ancillary education materials such as interactive websites, videos, or FAQs documents
Lack of clarity on what negative results mean for biological family members	Improved explanations about what negative results mean for biological family members are needed when returning negative results to patients
Participant confusion about how negative results affect their risk of conditions/diseases evaluated by genomic screen	Clear explanations about how negative results affect patients’ risk of conditions/ disease evaluated are needed when returning negative results to patients
Participant questions about the meaning of negative results when there is a known family history of disease	Improve explanations about what negative results mean for the participant when there is a known family history of disease. Possible mechanisms to improve explanations include ancillary education materials such as interactive websites, videos, or FAQs documents