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Factors influencing NCGENES research participants' requests for non–medically actionable secondary findings

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Purpose: Genomic sequencing can reveal variants with limited to no medical actionability. Previous research has assessed individuals' *intentions* to learn this information, but few report the *decisions* they made and why.

Methods: The North Carolina Clinical Genomic Evaluation by Next Generation Exome Sequencing (NCGENES) project evaluated adult patients randomized to learn up to six types of non–medically actionable secondary findings (NMASF). We previously found that most participants intended to request NMASF and intentions were strongly predicted by anticipated regret. Here we examine discrepancies between intentions and decisions to request NMASF, hypothesizing that anticipated regret would predict requests but that this association would be mediated by participants' intentions.

Results: Of the 76% who expressed intentions to learn results, only 42% made one or more requests. Overall, only 32% of the 155 eligible participants requested NMASF. Analyses support a plausible causal link between anticipated regret, intentions, and requests.

Conclusions: The discordance between participants' expressed intentions and their actions provides insight into factors that influence patients' preferences for genomic information that has little to no actionability. These findings have implications for the timing and methods of eliciting preferences for NMASF and suggest that decisions to learn this information have cognitive and emotional components.

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INTRODUCTION

Genome-scale sequencing detects a wide range of variants unrelated to a patient's phenotype that are termed "incidental" or "secondary" findings. In 2013, the American College of Medical Genetics and Genomics (ACMG) advocated for the analysis and disclosure of pathogenic variants in a group of gene–disease pairs considered to have a high degree of medical actionability regardless of the indication for testing.[1, 2] With opt-out provisions, medical genetics professionals support this approach.[3–7]

No such consensus exists, however, regarding how to handle the much larger group of variants that fail to meet a high threshold of medical actionability, despite providing potentially relevant information. These variants include those that (1) provide information of an association to disease rather than being predictive, (2) determine carrier status for recessive conditions, and (3) are causative of conditions for which effective presymptomatic treatment is not available, or some combination of these factors. There is currently little agreement about how these "non–medically actionable" secondary findings (NMASF) should be categorized and described, which types should be offered for disclosure, and how individuals can be helped to make informed decisions about learning them.

At present, individuals are typically asked to state their preferences for secondary findings (SF) when consenting for diagnostic genomic sequencing. This timing requires them to make decisions about learning information with varying degrees of health implications. Alternatively, clinicians could disclose diagnostic and medically actionable SF results before

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discussing optional NMASF. A staged consent process would allow individuals to learn diagnostic results relevant to their clinical indication for sequencing and any SF result that necessitates immediate disclosure before deciding about less urgent information.[8]

Previous research has assessed attitudes and hypothetical intentions about NMASF[9, 10] but few studies report the decisions people make and why. Despite broadly expressed interest,[10] people's stated intentions may not correspond with their subsequent behavior, thus making it critical to study behaviors in light of intentions.

Three studies that described patients' or parents' decisions about learning SF[11–13] reported that the majority (93.5%, 76.1%, and 83.4% respectively) chose to learn some types offered. Preferences for SF, a mixture of medically actionable and NMASF, were elicited following consent for diagnostic sequencing. However, 15% of the parents in the Shahmirzadi study requested results from categories for which their children were ineligible implying some were confused.[11] Similarly, the Fiallos study revealed that participants' focus on diagnostic results prevented their understanding of the implications of learning a secondary result.[13] People's intentions prior to their decisions were not assessed.

The North Carolina Clinical Genomic Evaluation by Next Generation Exome Sequencing (NCGENES) project was part of the Clinical Sequence Exploratory Research (CSER) consortium that investigated the performance of exome sequencing for diagnosing patients with suspected genetic disorders. The study collected empirical evidence of the intentions and subsequent decisions made by individuals offered NMASF. A diverse population of adult participants was randomized to be eligible to request this information, which was categorized into six types. In this paper, we describe the categorizations and a staged education, consent, and disclosure model designed for this study. We also describe decisions that participants made about NMASF, including the types they requested and whether they chose to place clinically confirmed results into their electronic health record (EHR).

We also extend our prior analysis[14] of how participants' stated intentions to learn NMASF relate to the decisions they ultimately made, and identify factors associated with these decisions. Previously, we found that anticipated regret for their decision was an important predictor of participants' intentions to request NMASF.[14] Moreover, although 76% of NCGENES participants expressed intentions to learn at least some categories, 24% intended to learn none. Thus, intentions are likely an important predictor of subsequent behavior.

In this study, we hypothesized a causal pathway whereby the association between anticipated regret and requests for NMASF is mediated by participants' stated intentions to request this information. Because the disclosure of some results required an in-person visit, we also hypothesized that barriers such as distance from the study site and employment status would weaken the proposed mediated association, resulting in fewer requests. Finally, to investigate why, in many cases, intentions to request NMASF were incongruent with subsequent behavior, we report how participants who had not made any requests responded to a question asking them why they had not done so. Study findings are expected to inform guidelines for helping patients make informed decisions about learning information that currently has little to no medical actionability but may, nonetheless, be perceived as valuable.

MATERIALS AND METHODS

Study overview

We defined three categories of disclosable exome sequencing results: (1) diagnostic information (positive/uncertain/negative), (2) medically actionable SF, or (3) NMASF. For category 2, we developed a semiquantitative approach to evaluate actionability and chose 165 highly actionable gene–disease pairs, some of which overlap with the ACMG list.[2, 5] Our categorizations of NMASF are described below.

Participants

Study recruitment and enrollment procedures have previously been described.[14] Following sequencing and analyses of diagnostic and highly actionable variants, we randomized eligible adult participants in a 1:1 ratio to either a decision group that received education about NMASF, or to a control group that did not receive this education and was not eligible to request NMASF. This study focuses on adult participants randomized to the decision group.

At enrollment, 247 of 622 participants were ineligible for randomization because they were either the parents of a child participant or a cognitively impaired adult. Thirteen participants' sequences revealed medically actionable SF, making them ineligible for randomization. Of 362 remaining participants, 27 were ineligible because we could not contact them for a disclosure visit. Thus, 335 participants were randomized: 171 to the control group and 164 to the decision group. Nine participants randomized to the decision group failed to attend the disclosure visit, did not receive education about NMASF, and were excluded leaving 155 participants in the decision group.

Categories of non–medically actionable secondary findings

To facilitate participant education and decision-making about NMASF, we applied a classification scheme developed through expert consensus of genetics professionals on the study team. This process resulted in six categories that differed in the types of information provided and by the range of risks of harm to participants upon their disclosure. These risks were defined as the potential to (1) cause the participant distress and/or (2) be misinterpreted and misused by health-care professionals. As shown in Table 1, the six categories were (A) single-nucleotide polymorphisms for risk assessment of common diseases, (B) pharmacogenomic variants, (C) heterozygous variants indicating carrier status, (D) specific alleles of the *APOE* gene (E2, E3, and E4) associated with risks for Alzheimer disease, (E) variants associated with rare

Table 1 Descriptions of NMASF and methods of disclosure of results in NCGENES

Type	Description of risk	Examples	The result you are most likely to learn	Medical management	How to learn results
A	Common diseases	Typical forms of heart disease, cancer, and diabetes	Average or slightly different risk compared with the general population	Routine recommendations such as eating right and getting exercise	Telephone
B	Differences in response to some medications	Response to the blood thinner, Coumadin	Average or slightly different risk compared with the general population	Possible change in the amount of medicine or avoidance of other medicine	Telephone
C	Carrier status	Cystic fibrosis, sickle cell anemia, many others	Everyone is expected to have 4–8 positive results	No personal health problems	One in-person visit
D	Common form of Alzheimer disease	Typical form of Alzheimer disease	Average or slightly different risk compared with the general population	Routine recommendations such as eating right and getting exercise	One in-person visit
E	Rare genetic diseases	Adult polycystic kidney disease, factor V Leiden; many others	Normal	For some conditions, some symptoms can be treated	One in-person visit
F	Rare, severe, progressive diseases of the brain and nervous system	Lou Gehrig disease (ALS); others	Normal	No prevention; no treatment	Two in-person visits

ALS amyotrophic lateral sclerosis, *NCGENES* North Carolina Clinical Genomic Evaluation by Next Generation Exome Sequencing project, *NMASF* non–medically actionable secondary findings.

Mendelian diseases for which no effective presymptomatic interventions exist, and (F) variants associated with rare, highly penetrant, progressive, neurodegenerative Mendelian diseases that cannot be prevented or effectively treated. Participants could request some types of NMASF without having to request them all permitting investigation of participant preferences.

Procedures

The study protocol is illustrated in Fig. 1. Randomization occurred approximately 10 months after consent was obtained. Participants randomized to the decision group were mailed a brochure that (1) described the six categories of NMASF, (2) presented our rationale for the categorizations, and (3) provided examples of associated health conditions or predicted impact on health. The brochure stated that results in these categories did not meet the study criteria for being "medically actionable" and explained why.

After disclosing diagnostic results, a medical geneticist and certified genetic counselor spent approximately 20 minutes describing the NMASF categories. They restated the kinds of conditions or impacts on health using the same terms and examples as in the brochure. They described how each category could be requested and how results would be disclosed and emphasized that the value of learning this information was controversial. Immediately after the visit, a study interviewer surveyed participants' intentions about learning any of these results.

The disclosure methods for each type of NMASF are shown in Table 1. Disclosure of categories A and B could be by a scheduled telephone call, while categories C, D, and E required an in-person visit. All results from categories A–E could be disclosed at that visit (visit 3). For participants interested in category F, the clinicians discussed potential risks associated with this information at visit 3. Interested participants were instructed to call the study office again to request analysis of this category and results were disclosed at a second in-person visit.

Our institutional review board (IRB) required that participants' consent be obtained before placing clinically confirmed results into the University of North Carolina (UNC) Hospitals' EHR. Participants made separate decisions for diagnostic, medically actionable, and NMASF categories and for each clinically confirmed result. Only *APOE* results and pathogenic or likely pathogenic variants in categories E and F were clinically confirmed before dislosure and thus eligible for placement. All procedures were approved by the IRB of the University of North Carolina–Chapel Hill.

Measures

Sociodemographic and clinical variables were obtained from health records or from the intake questionnaire. Sociodemographic variables included sex, age, race/ethnicity, educational attainment (has completed at least 4 years of college versus has not), annual household income, marital status, health insurance status, distance in miles from study

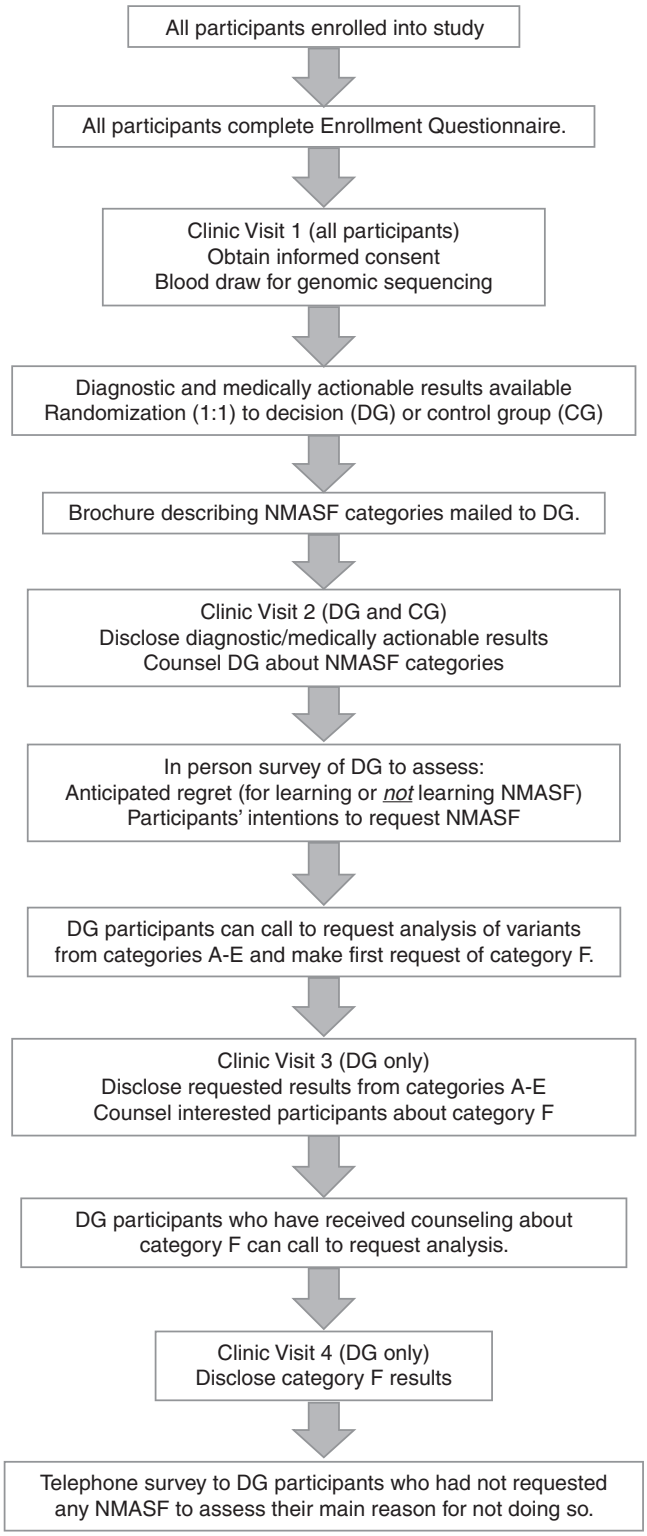

Fig. 1 North Carolina Clinical Genomic Evaluation by Next Generation Exome Sequencing (NCGENES) study protocol. *NMASF* non–medically actionable secondary findings.

site, and employment status (working full or part time versus not working). Clinical variables included physical functioning, measured using a self-report version of the Karnofsky Performance Status scale,[15] generalized distress, using the Hospital Anxiety and Depression Scale (HADS)[16] and self-reported prior genetic testing, coded as yes (=1) or no (=0). To account for multiple results in an individual, each possible diagnostic result (positive, uncertain, negative) was coded as either present (=1) or absent (=0).

We also assessed general health literacy with the Rapid Estimate of Adult Literacy in Medicine (REALM)[17] and objective numeracy with a validated measure that included three math problems;[18] scores ranged from 0 to 3.

Immediately following the disclosure of diagnostic results, we also assessed (1) anticipated regret for not learning and for learning each NMASF category, reported on a scale from 1 (not at all) to 5 (very much),[14] averaging scores across categories ($\alpha = 0.91$ and 0.90, respectively); and (2) intention to learn NMASF, asking participants to rate their intention to learn at least some NMASF on a scale from "definitely will not" (1) to "definitely will" (5). Participants who answered "4" or "5" reported their interest in learning each category (interested = 1, and not interested = 0). Secondary findings knowledge was assessed with a 12-item questionnaire created for this study (Cronbach's $\alpha = 0.69$) administered after participants reported their intentions.

Analytic approach

First, we computed descriptive statistics and the psychometric properties of study measures. Then, we examined correlations of all variables with the dichotomous requesting outcome (requesting one or more category versus requesting none). Next, we identified predictors to be entered in the models, selecting those correlated with the outcome at $p < 0.1$. Then, we conducted a hierarchical logistic regression analysis, entering variables in several steps: race/ethnicity, work status, generalized distress, and knowledge of NMASF (step 1); anticipated regret for learning and not learning NMASF (step 2); and intentions to request NMASF (step 3).

To test the hypothesis that the association between anticipated regret and actual requests would be mediated by intentions to request these findings, we conducted bootstrap mediation analyses.[19] We tested two mediation models, first one with anticipated regret for learning NMASF as the focal predictor and then one with anticipated regret for not learning NMASF as the focal predictor. The covariates in both mediation models were race/ethnicity, work status, generalized distress, and knowledge of NMASF. We also tested two moderation models to assess whether the association between intentions to request NMASF and actual requests was moderated by distance from study site or work status. The models included the same variables and steps as the hierarchical logistic regression described above, except that in a subsequent step we added the main effect of the moderator being tested (distance from study site or employment status) and, in a final step, the interaction term for intentions and the moderator.

Finally, we used content analysis[20] to understand why some participants who stated probable or definite intentions to request NMASF had not requested any categories by the

time of the final survey, 6 months later. Participants were asked, "In your own words, can you tell me ONE MAIN reason that you have **not** requested any of these incidental findings at this time?" Two authors (I.G. and G.H.) coded the 36 responses independently, agreed on four categories, and resolved a small number of coding differences.

RESULTS

Descriptive statistics

The descriptive statistics for this adult sample have been previously reported.[14] Briefly, the sample was moderately ethnically diverse (21% were Hispanic and/or nonwhite), 57% held less than a 4-year college degree, and mean income was between $45,000 and $59,999. Approximately 75% were female and the average participant age was 47 years.

Requests for NMASF

When asked about their intentions immediately after their diagnostic disclosure visit,[14] 76% of eligible participants expressed intentions to request NMASF, however, only 32% (50 of 155) requested one or more categories. Of those who expressed intentions to learn results, only 42% made a request. Therefore, under the study conditions present in NCGENES, there was a substantial discrepancy between participants' stated intentions to request information and their actual requests for it. Of participants who stated that they did not intend to make a request, none changed their minds.

Of the 50 participants who requested results from at least one category, 27 (54%) requested all six categories, 11 (22%) requested all but category F, and 12 (24%) requested other combinations with no apparent pattern. The most common request was for *APOE* results (44 of 50 or 88%). Eighty-nine percent (24 of 27 participants) who requested category F results contacted us a second time to initiate the analysis.

Forty-six participants learned results from every category they requested. Four participants did not learn their results either because we could not contact them ($n = 3$) or they declined to learn their results ($n = 1$). All participants who learned category F results had previously requested and learned results in every other category (A–E).

Of 40 participants who learned confirmed NMASF results, only 28% consented to their EHR placement. This rate was much lower than the 95% of all study participants who consented to placement of diagnostic and medically actionable results. Consent was obtained from 9/40 for *APOE* results and 4/7 for category E results.

Logistic regression

Correlations among study variables are shown in Table 2. The hierarchical logistic regression analysis was significant, $\chi^2(7) = 51.8$, $p < 0.001$. Results are shown in Table 3. In step 2 of the model, participants who reported greater anticipated regret for learning NMASF were less likely to request those results, after controlling for race/ethnicity, work status, distress, and NMASF knowledge (odds ratio [OR] = 0.60, 95% confidence interval [CI]: 0.39–0.92; $p = 0.019$). Participants who reported greater anticipated regret for not learning NMASF were more likely to make a request, after controlling for covariates (OR = 1.62, 95% CI: 11.11–2.37; $p = 0.013$). However, these associations became nonsignificant when the intention variable was added to the model in step 3. Intention to request any category (versus none) was associated with a 3.15 increase in the odds of making a request for any category, controlling for covariates and the anticipated regret variable (95% CI: 1.57, 6.31; $p = 0.001$).

Next, we conducted bootstrap mediation analyses to assess whether intention to request any category mediated the relationship between anticipated regret and requesting any of the categories. We tested a separate mediation model for each of the two anticipated regret variables. Intention mediated the relationship between anticipated regret and making requests in both mediation models. In the first model, anticipated regret for learning NMASF was negatively associated with intentions to learn them ($\beta = -0.422$, SE = 0.078, $p < 0.001$), and participants' intentions were positively associated with making a request ($\beta = 1.381$, SE = 0.337), $p < 0.001$). Thus, participants who had higher anticipated regret for learning NMASF were less likely to state intentions to request them, and in turn, were less likely to make a request. The bootstrap estimation of indirect effects revealed significant results ($\beta = -0.582$, SE = 0.219), $p = 0.008$). In the second model, anticipated regret for not learning NMASF was positively associated with intentions to learn them ($\beta = 0.355$, SE = 0.072, $p < 0.001$), and participants' intentions were positively associated with making a request ($\beta = 1.381$, SE = 0.337), $p < 0.001$). The indirect effect was significant ($\beta = 0.490$, SE = 0.196, $p = 0.012$). Thus, participants who reported greater anticipated regret for not learning NMASF were more likely to report intentions to learn them, and in turn, also more likely to make a request.

In the moderation models investigating whether distance from study site and work status would attenuate the association between intention to request NMASF and making a request, we found that neither distance (OR = 1.00; 95% CI: 0.99–1.01; $p = 0.880$) nor work status (OR = 1.37; 95% CI: 0.35–5.32; $p = 0.654$) moderated this association.

Content analysis

Using content analysis, we studied the responses of 70 participants stating "probable" or "definite" intentions to request NMASF after the disclosure of their diagnostic results but who had not made a request 6 months later. The open-ended question asked participants to state one main reason for not making a request. Of the 70 participants who stated intentions to make a request but did not do so, 34 did not answer the open-ended question either because they did not complete the survey ($n = 24$) or were inadvertently not asked this question ($n = 10$). Among the remaining 36 respondents, we identified four reasons: (1) misunderstanding how to request ($n = 7$), (2) being too busy or forgetting ($n = 9$), (3) rethinking the value/utility of these findings ($n = 15$), and (4) concern that this information would be an emotional burden ($n = 5$).

Table 2 Correlations among study variables ($N = 155$)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Mean (SD)	Range
1. Requested any NMASF	—																						
2. Age	0.12	—																				47.35 (13.98)	17–77
3. Sex (female)	0.03	−0.00	—																				
4. Race/ethnicity (non-Hispanic white)	0.26[a]	−0.19[b]	0.00	—																			
5. Educational attainment (4-year college degree or higher)	0.10	0.11	0.002	0.26[a]	—																		
6. Annual household income	0.13	0.20[b]	−0.11	0.27[a]	0.53[c]	—																$45,000–$59,999 (3.03)	Less than $15,000–$135,000 or more
7. Marital status (married)	0.04	0.18[b]	−0.12	0.12	0.29[c]	0.52[c]	—																
8. Health insurance status (insured)	0.07	0.04	0.06	−0.19[b]	0.25[a]	0.31[c]	0.05	—															
9. Physical functioning	−0.06	0.02	0.06	−0.08	−0.29[c]	−0.22[a]	0.05	−0.00	—													2.74 (1.44)	1–7
10. Prior genetic testing (yes)	0.11	0.02	0.26[a]	0.28[a>]	0.33[c]	0.24[a]	0.13	0.21[b]	−0.10	—													
11. Positive diagnostic results	−0.03	−0.13[d]	−0.01	−0.00	−0.04	−0.16[d]	−0.14[d]	−0.13	0.01	−0.18[b]	—												
12. Negative diagnostic results	0.12	−0.03	0.04	−0.01	−0.00	0.04	0.03	0.04	−0.06	0.15[d]	—	—											
13. Uncertain diagnostic results	−0.11	0.16[b]	−0.04	0.02	0.04	0.10	0.09	0.08	0.06	−0.01	—	—	—										
14. General health literacy (≥9th grade reading level)	0.09	0.04	0.01	0.23[a]	0.25[a]	0.34[c]	0.11	0.00	−0.30[c]	0.10	−0.16[d]	0.14[d]	−0.03	—									
15. Objective numeracy	0.09	−0.01	−0.11	0.39[c]	0.041[c]	0.45[c]	0.09	0.21[b]	−0.22[a]	0.19[b]	1.04	−0.01	0.05	0.39[c]	—							1.68 (1.11)	0–3
16. NMASF knowledge	0.17[b]	0.18[b]	0.11	0.22[a]	0.44[c]	0.48[c]	0.24[a]	0.21[b]	−0.21[b]	0.24[a]	−0.10	0.08	0.00	0.49[c]	0.40[c]	—						8.45 (2.39)	1–12
17. Generalized distress	−0.18[b]	−0.10	0.04	−0.19[b]	−0.20[b]	−0.28[a]	−0.09	−0.22[a]	0.47[c]	−0.13	−0.00	−0.13	0.15[d]	−0.26[a]	−0.20[b]	−0.31[c]	—					11.71 (7.18)	0–30
18. Distance in miles from study site	0.09	0.11	0.13	0.15	−0.24[d]	−0.18	−0.03	−0.13	0.03	0.00	−0.01	0.05	−0.05	−0.03	0.01	−0.00	−0.06	—				71.02 (113.84)	1.41–1026.67
19. Employment status (working full or part time)	0.14[d]	−0.11	−0.21[b]	0.14[d]	0.33[c]	0.27[a]	0.17[b]	0.01	−0.49[c]	0.07	0.01	0.06	−0.08	0.22[a]	0.15[d]	0.20[b]	−0.24[a]	−0.08	—				
20. Anticipated regret for learning NMASF	−0.31[c]	0.00	−0.03	0.09	−0.03	−0.06	−0.11	0.03	−0.04	−0.04	0.01	−0.06	0.06	−0.20[b]	−0.04	−0.28[c]	0.09	−0.10	−0.02	—		2.27 (1.15)	1–5
21. Anticipated regret for not learning NMASF	0.30[c]	−0.06	−0.13	−0.03	−0.20[b]	−0.17[b]	−0.06	−0.07	0.08	−0.05	−0.10	0.10	−0.02	−0.14	−0.15[d]	−0.15[d]	0.06	0.20	−0.04	−0.36[c]	—	3.65 (1.23)	1–5
22. Intention to learn NMASF	0.43[c]	−0.13	−0.11	0.16[d]	−0.04	0.08	−0.03	0.07	−0.04	0.02	−0.06	0.04	0.01	0.23[a]	0.06	0.05	−0.05	−0.04	0.06	−0.42[c]	0.37[c]	4.05 (1.16)	1–5

Correlations between a continuous variable and dichotomous variable are point biserial correlations. Correlations between two dichotomous variables are phi coefficients.
NMASF non–medically actionable secondary findings.
[a]$p < 0.01$.
[b]$p < 0.05$.
[c]$p < 0.001$.
[d]$p < 0.10$.

Table 3 Hierarchical logistic regression model (step 3) predicting requested (versus did not request) NMASF

	Odds ratio	Lower 95% CI	Upper 95% CI	*p* value
Non-Hispanic white	3.87	0.92	16.23	0.064
Working full or part time	1.39	0.59	3.26	0.449
Distress	0.96	0.91	1.03	0.259
NMASF knowledge	1.08	0.87	1.34	0.482
Anticipated regret for learning NMASF	0.78	0.49	1.22	0.271
Anticipated regret for NOT learning NMASF	1.37	0.91	2.06	0.127
Intentions to request any NMASF	3.15	1.57	6.31	0.001

CI confidence interval, *NMASF* non–medically actionable secondary findings.

DISCUSSION

We investigated the behavior of 155 adult participants who were eligible to request up to six categories of NMASF after learning their diagnostic results from exome sequencing. Overall, the number of participants who requested results demonstrated a much lower interest than reported in prior studies and was lower than their previously stated intentions would have predicted. Specifically, immediately after learning their diagnostic results, 76% stated intentions to request one or more categories. In these analyses we found that only 32% of eligible participants requested any category and, of those who expressed intentions to learn results, only 42% made a request. To understand the discrepancy between participants' intentions and behaviors, we examined predictors of requests for NMASF and sought explanations for why many individuals who initially expressed interest did not make any requests. Our results provide new insights for clinicians and researchers who offer NMASF with implications for informed decision-making.

Our results contrast with previous studies that have offered SF with a range of medical actionability to adult research participants.[13, 21, 22] We found that NCGENES participants who reported no intentions to learn any NMASF did not change their minds; rather, many who expressed an initial interest in them did not subsequently make a request. The relatively lower percentage of participants who expressed intentions to request NMASF, and the even lower percentage who made a request, may have been influenced by the deliberate design of the study protocol that sought to mimic a real-world scenario, and to gauge actual interest as opposed to hypothetical intentions. Such results imply that how and when preferences for disclosure of NMASF from genomic sequencing are obtained may influence participants' decisions.

Several factors in our study likely contributed to the lower percentages of participants who expressed interest in NMASF and who made a request for them. First, randomized participants had already learned diagnostic results and negative results from the analysis of highly actionable gene–disease pairs before being asked to state their preferences for NMASF. Thus these findings may not generalize to situations in which requests for secondary findings include results with a wider range of actionability. Second, we conveyed to participants why we had classified this information as "non–medically actionable," that requesting it was voluntary, and that learning it had both potential benefits and risks. We also used the term *decision* rather than the value-laden word *choice* to convey our expectation they consider both the pros and cons of their decisions.

Our staged consent process delayed decisions about NMASF until after the disclosure of their diagnostic results. Participants made requests by telephone thereby preventing them from having to decline information in front of study clinicians. Instead, they could passively decline simply by their inaction. We assured them that any decision they made would contribute equally to the research and that only their specific requests would trigger the variant analysis of relevant genes. The latter was meant to counter the assumption that these results had already been generated. Finally, the disclosure methods were consistent with our stratification by potential harms associated with each category, meaning that some types required additional visits while others could be obtained by telephone. Although we hypothesized that practical barriers would influence the likelihood of making a request, this was not supported by our findings. Content analysis of 36 participants' responses suggested that, while these explained some of the discordance between intentions and requests, other factors played important roles including a loss of interest, a reevaluation of value, or simple forgetting.

Analyses examining predictors of requests identified a robust association between anticipated regret and requests for NMASF. Anticipated regret is an emotionally focused factor that indicates the extent to which people are motivated to reduce uncertainty and to avoid feared and/or unpleasant outcomes.[23] In our prior analysis of participants' intentions to request NMASF,[14] those who anticipated that they would regret not learning this information expressed a stronger intention to learn them, whereas those who anticipated that they would regret learning them had a weaker intention to learn them, even after controlling for sociodemographic, clinical, and literacy-related confounds. Findings from this study indicate that these associations all extended to the decision to make a request including the strong associations involving anticipated regret. We identified a plausible causal pathway explaining the association between anticipated regret and requests for NMASF. Specifically, analyses showed that this association was mediated by intentions. For instance, participants who anticipated that they would regret not learning their NMASF also reported stronger intentions to request them and were, in turn, more likely to actually request them. These findings underscore the important role that emotional processes, such as anticipated regret, play in affecting participants' preferences for information. Clinicians who explicitly address these emotional components may help patients better recognize the reasons underlying their decisions. Along with both sufficient information and time,

this recognition can help patients make thoughtful decisions about their preferences for learning genetic information.

Although the study protocol was designed to learn which types of NMASF individuals preferred, our categorizations may have been too complex to enable participants to distinguish between them; most requested all categories or all except category F. Apart from Alzheimer disease, many conditions were unfamiliar to participants, making them difficult to distinguish. Assessing patient preferences for heterogeneous genetic information remains challenging.

Content analysis of the responses of 36 participants who stated intentions to request NMASF but who did not do so identified a minority who were unsure how to make a request. This confusion may have also deterred participants who did not answer this question from making a request, thus contributing to our relatively lower rate. However, more respondents reported that they had reevaluated the potential value of the information or had become worried about its potential impact as their main reasons for not making a request. Because most studies only assess initial preferences for learning secondary genomic information, it will be important for future research to investigate whether these change over time.

Our results indicate that even when participants express intentions to learn genomic information that fails to meet a high threshold of medical actionability, initial intentions do not necessarily translate into the actions needed to obtain it. Our results have implications for assessing the degree to which individuals value nonactionable results, as defined by the NCGENES project, as well as the timing and methods of eliciting preferences for NMASF. Our findings can also guide the development of educational and counseling strategies to help people weigh critical information and recognize the emotional components of making these decisions. Empirical results from studies with diverse participants, such as this study, provide realistic insight into factors influencing how patients determine their preferences for genetic information.

ELECTRONIC SUPPLEMENTARY MATERIAL

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DISCLOSURE

The authors declare no conflicts of interest.

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