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ORIGINAL ARTICLE

A survey of aortic disease biorepository participants' preferences for return of research genetic results

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Abstract

There is ongoing debate on whether and what research genetic results to return to study participants. To date, no study in this area has focused on aortopathy populations despite known genes that are clinically actionable. Participants (n = 225, 79% male, mean age = 61 years) with an aortopathy were surveyed to assess preferences for receiving research genetic results. Participants were 'very' or 'extremely likely' to want results for pathogenic variants in aortopathy genes with implications for family members (81%) or that would change medical management (76%). Similarly, participants were 'very' or 'extremely likely' to want actionable secondary findings related to cancer (75%) or other cardiac diseases (70%). Significantly lower interest was observed for non-actionable findings—pathogenic variants in aortopathy genes that would not change medical management (51%) and variants of uncertain significance (38%) ($p < .0001$). Higher health and genomic literacy were positively associated with interest in actionable findings. Most participants (>63%) were accepting of any means of return; however, a substantial minority (18%–38%) deemed certain technological means unacceptable (e.g., patient portal). Over 90% of participants reported that a range of health professionals, including cardiovascular specialists, genetics specialists, and primary care providers, were acceptable to return results. Participants with aortopathies are highly interested in research genetic results perceived to be medically actionable for themselves or family members. Participants are accepting of a variety of means for returning results. Findings suggest that research participants should be asked what results are preferred at time of informed consent and that genetic counseling may clarify implications of results that are not personally medically actionable.

KEYWORDS

aortic disease, biobank, research genetic results, service delivery models, variants of uncertain significance

1 | INTRODUCTION

The ethical responsibilities to disclose actionable findings are increasingly debated within genomic research (Beskow & Burke, 2010; Cassa et al., 2012; Fernandez & Weijer, 2006; Jarvik et al., 2014) as well as methods for return of research genetic results to study participants (Fullerton et al., 2012; Jarvik et al., 2014; National Heart, Lung, and Blood Institute working group et al., 2010). Some experts

argue that return of research results is beyond the scope of the research enterprise and may unnecessarily blur the lines between research and clinical care (Viberg et al., 2013), particularly given that research is not regulated by the Clinical Laboratory Improvement Act [CLIA]. However, recommendations supporting the return of results have been issued by multiple institutions and advisory boards, and there is emerging consensus that researchers should, when feasible, return results that are medically actionable (Gliwa & Berkman, 2013; National Heart, Lung, and Blood Institute working group et al., 2010; Weiner, 2014). The Presidential Commission on the Study of Bioethical Issues recommends that researchers move toward returning genetic results, including clinically significant secondary findings (Weiner, 2014). The National Heart, Lung, and Blood Institute also endorses that research studies return genetic results to participants when the test is analytically valid, the results are actionable, and the participant has opted to receive results (National Heart, Lung, and Blood Institute working group et al., 2010). In 2018, the National Academies of Sciences, Engineering, and Medicine Workshop released guidance advocating for potential return of results to benefit participants and advance research. This report highlights the needs of assessing participant, clinician, and researcher preferences around return of results in a variety of populations in order to sufficiently address participant needs, diversity, and equity (Addie et al., 2018). Finally, in 2019, the American Society of Human Genetics released a position statement on duty to recontact research participants delineating scenarios in which researchers should recontact study participants when reinterpretation of genomic research results may impact participants' medical management (Bombard et al., 2019).

The American College of Medical Genetics and Genomics (ACMG) recommends that when clinical genomic testing is performed, pathogenic variants from 59 genes deemed clinically actionable be disclosed given the patient's consent (Kalia et al., 2016). Identification of a pathogenic variant aids in diagnosis, informs clinical management and, importantly, allows for informative, predictive cascade screening for family members. The majority of genes on the ACMG list are associated with hereditary cardiovascular disease or cancer predisposition. Seven genes are specifically associated with thoracic aortic aneurysms, dissections, or rupture. Up to 25% of all patients presenting with a thoracic aortic aneurysm and dissection have an identifiable genetic predisposition (Renard et al., 2018). When features such as Marfan syndrome or Loeys-Dietz syndrome are present, the genetic testing yield is up to 92% (Baetens et al., 2011). Other genetic etiologies are not associated with syndromic features, as with *ACTA2*, *MYLK*, and *MYH11* pathogenic variants (Brownstein et al., 2017). At least 30 genes have been shown to be associated with aortic disease and genetic aortopathies although evidence is limited regarding clinical actionability for some genetic etiologies (Renard et al., 2018). Given acute morbidity and mortality in aortopathies and the ability to identify genes associated with these conditions, there are clear clinical benefits of receiving genetic results for both patients and at-risk family members.

As clinical guidance has become more robust, so has evidence for return of results in the research setting; however, many institutions and researchers are still in the process of defining what results and how results should be returned. When returning results to research participants, the type and actionability of results, as well as participant preferences, are important considerations. To date, research on participant preferences for return of results has largely been limited to cancer (Lerman et al., 1996), pediatric (Fernandez et al., 2014), and general populations (Fullerton et al., 2012; Lewis et al., 2015) with these studies demonstrating that participants are broadly interested in receiving their individual research genetic results. (Goodman et al., 2018). Few return of results studies have been conducted in cardiac populations. These cardiac studies have shown that cardiac populations—including early adopters of genetic testing (Facio et al., 2013) and individuals with heart disease (Joffe et al., 2019)—are highly interested in broad results. In a feasibility return of result study of a pediatric biorepository of early-onset heart disease, 86% of families who received actionable findings opted to pursue clinical follow-up with clinical genetics (Papaz et al., 2019). The primary objective of this study was to determine a) whether and what type of results participants with aortic disease would like to receive, and b) participant preferences for how results should be returned.

What is known about this topic

There is ongoing debate on whether and what research genetic results to return to study participants. In previous research, research participants have expressed broad interest in return of results.

What this paper adds to the topic

This study adds perspective of an aortopathy population who expressed higher interest in return of actionable results. The study also found that participants were accepting of return by a variety of health professionals and by various modalities (e.g., in-person, phone).

2 | METHODS

2.1 | Participants and procedures

Participants were recruited to the Michigan Medicine, Cardiovascular Health Improvement Project (CHIP) biorepository between December 2016 and June 2017. All participants had a clinical diagnosis of an aortopathy, which was defined as a thoracic aortic aneurysm, abdominal aortic aneurysm, bicuspid aortic valve with or without aneurysm, aortic dissection or rupture, or a molecular or clinical diagnosis of a connective tissue disorder such as Marfan syndrome or familial aortopathy (Yang et al., 2017). Participants had not routinely received genetic counseling prior to enrollment. Participants provided informed consent for a one-time research blood draw for research genetic testing, access to medical

records, questionnaires, recontact for future unspecified research, and potential receipt of research genetic results via active choice (initialing their choice rather than opt-in or opt-out) for primary and secondary findings. DNA was isolated from peripheral blood lymphocytes and prepared for genotyping via sequencing and molecular inversion probes for gene and variant discovery. Study procedures were approved by the Michigan Medicine Institutional Review Board (HUM00052866).

2.2 | Instrumentation

The survey was developed by a multidisciplinary team with expertise in genetic testing, cardiovascular genetics, genetic counseling, and health behavior survey research. Survey items included validated instruments on genomic literacy, health literacy, and perceptions of causes of aortic disease. Novel questions were also developed by the research team based on literature review of previously demonstrated predictors (e.g., health literacy and educational attainment) of return of result preferences (Goodman et al., 2018; Lewis et al., 2015). A full version of the survey may be found in the supplement.

2.3 | Demographics and health history

Demographic characteristics were collected via participant report and electronic medical record review. Educational attainment was used as a proxy for socioeconomic status due to ease of measurement, stability as compared to income, and because it has been shown to be an effective metric of socioeconomic status in health research (Adler et al., 1994; Shavers, 2007). Electronic medical record review was utilized to determine whether the participant was diagnosed with aortic disease. For participants with multiple aortic diagnoses, the more significant, earlier onset condition was selected as the primary indication. For instance, an individual diagnosed with both bicuspid aortic valve and thoracic aortic aneurysm was classified as bicuspid aortic valve as that is likely the primary cause of aortopathy (Go et al., 2014).

2.4 | Genetic literacy, perceptions, and knowledge

The Short Test of Functional Health Literacy in Adults (STOHFLA), a validated three item measure (Chew et al., 2004), was used to assess health literacy. Possible scores ranged from three to 15, with a score of 10 as the standard cutoff score indicating higher levels of health literacy. The Genome Sequencing Knowledge Scale, a 10-item validated measure adapted from previous genetic literacy measures (Kaphingst et al., 2012), was used to assess knowledge of sequencing limitations and benefits. Possible scores ranged from 10 to 50, with higher scores with standard cutoff of 20 indicating higher levels of sequencing knowledge. Both scales were analyzed as continuous variables. Finally, 14 items from the validated Revised Illness Perception Questionnaire (IPQ-R) were used to assess participant perceptions of causes of their aortic disease, both genetic and otherwise (Moss-Morris et al., 2002). Two differentiating items from the IPQ-R, 'Perception due to aging' and 'Perception due to genetics', were used in analysis.

2.5 | Types of genetic results to return

Novel brief scenarios were developed by the study team that described different types of research genetic results. Questions after each scenario assessed participants' interest in receiving the result (1 = extremely unlikely to want test results to 6 = extremely likely, with no neutral option). Scenarios addressed the following types of possible research genetic results and were asked in the following order:

1. Actionable aortic: Pathogenic variants in well classified aortic disease genes that would change medical management.
2. Non-actionable aortic: Pathogenic variants in aortic disease genes that would not change the participant's own medical management.
3. Variant of uncertain significance (VUS) in an aortic disease gene: A VUS was defined as a variant that is not yet known to be pathogenic or not. A VUS is not medically actionable and would not be used for testing of at-risk family members.
4. Secondary—cardiac: ACMG secondary finding genes related to other cardiac conditions (e.g., cardiomyopathy) (Kalia et al., 2016).
5. Secondary—cancer: ACMG secondary finding genes related to cancer predisposition syndromes (e.g., Hereditary Breast and Ovarian Cancer) (Kalia et al., 2016).
6. Family information: Aortic disease variants that have implications for family members' risk determination and medical management irrespective of impact on the patient's own medical management.

Following each of the first five scenarios, participants were asked to write in the amount that they would be willing to pay to clinically validate the particular genetic result. The monetary value ranged from $0 to $3,000, with the upper bound chosen based on self-pay cost of clinical exome sequencing at the time of survey development. The participants' willingness to pay for clinical validation served as a proxy for the participants' value of the type of result they preferred to receive (primary, secondary, and VUS) (Scenarios are provided in Supplemental Material) (Kopits et al., 2011; Olsen & Smith, 2001).

The complete survey was reviewed for face and content validity by the team's experts in cardiovascular genetics and health survey research. Prior to implementation, the survey was piloted with CHIP biorepository participants (n = 10) for face and content validity of self-administration among biorepository participants. Small wording revisions were made following piloting (e.g., changing 'cardiologist' to 'cardiovascular specialist' to include participants' cardiovascular surgeons). Scale reliability of responses across the above six scenarios

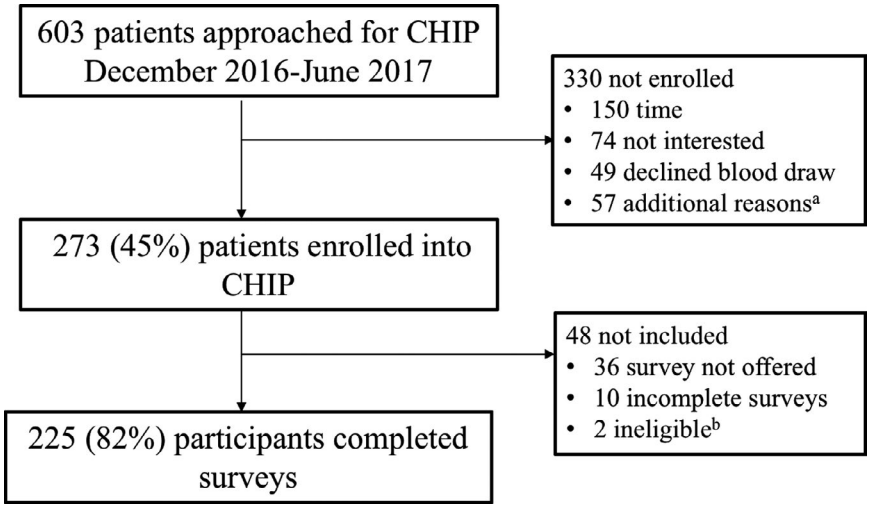

FIGURE 1 CONSORT study flow diagram. [a] Additional reasons include patient was overwhelmed (31), concerns about privacy (17), health limitations such as frailty (9). [b] 2 participants were excluded due to diagnoses of Hypermobile Ehlers-Danlos syndrome in absence of an aortic indication

was assessed following administration with the full sample, and the novel scale was found to have high internal consistency (Cronbach's $\alpha = 0.85$ [CI 0.82–0.88]).

2.6 | How and by whom results should be returned

Participants were asked their preferences for mode of genetic results delivery (e.g., telephone, in-person) and by whom (e.g., genetics professional, cardiovascular specialist). Both questions were on a 4-point scale of 'Highly acceptable' to 'Highly unacceptable' and were adapted from previously validated return of results survey research (Fernandez et al., 2014). Participants were then asked to indicate their most preferred mode of delivery, as well as their most preferred healthcare professional for disclosing results.

2.7 | Data Analysis

Descriptive statistics were used to characterize the sample in terms of its demographics, genetics perceptions, family history of aortopathy, health history, responses across scenarios willingness to pay, and perceptions and acceptability of research genetic testing questions. Internal consistency of scenario responses was evaluated using Cronbach's alpha.

For the primary outcome of what results to return and how to return results, ANOVA and Tukey HSD post hoc tests were conducted to assess differences in responses between scenarios. Tukey HSD was chosen as the post hoc test in order for conservative correction of multiple comparisons. Non-responses were excluded from analysis. For 'how to return' questions, participants were given the option of 'N/A, I do not use', which were re-coded in data analyses as 'Highly unacceptable'. Given results of ANOVA testing and multicollinearity identified between scenarios on what results to return, a factor analysis was pursued. Exploratory and confirmatory factor analyses with the manifest six return of results scenarios were conducted with an orthogonal rotation, and data were visualized with a latent component analysis.

Primary analysis of data was then conducted with linear regressions predicting the actionable and non-actionable factor scores. Variables were standardized, and standardized beta coefficients and p values were reported. The covariates for the regression model were added stepwise as follows: a) demographics—age, sex, race, educational attainment; b) health history—type of aortic disease diagnosis, time since diagnosis, family history of aortic disease; and c) knowledge and perceptions—genomic literacy, health literacy, perception disease is due to genetics, perception disease is due to aging, and willingness to pay for genetic confirmation. AIC was used to assess model fit. Supplemental analysis was conducted via a mixed-effects linear regression to evaluate for multiple outcomes per individual. The referent scenario category (scenario to which remaining scenarios were statistically compared) was VUS due to participant lower interest, and standardized beta coefficients and 95% confidence intervals were reported. All data analysis was performed in RStudio (RStudio Team, 2015).

3 | RESULTS

3.1 | Demographics

43% of pre-screened patients approached for enrollment consented to participation and response rate to the survey was 82% (Figure 1). The mean participant age was 61 years (range: 22 to 97 years) with the majority being male (79%), white (95%), and non-Hispanic (99%). Participants' levels of educational attainment were evenly distributed from high school or less through an advanced degree. The most common diagnosis was bicuspid aortic valve (34%), while known molecular or clinical syndromes (4%) encompassed the smallest portion of diagnoses (Table 1, Figure 1).

TABLE 1 Participant characteristics ($n = 225$)

Participant characteristics	% (*n*) or *mean (SD)*
Age (years)	*60.7 (13.3)*
Range (years):	22.4–97.3
Male	78.9 (179)
Race	
White	94.5 (207)
Black/African American	5.0 (11)
Asian	0.5 (1)
Non-Hispanic Ethnicity	98.6 (217)
Highest educational attainment	
Advanced degree	20.2 (45)
4-year college degree	21.1 (47)
Some college/ 2-year degree	22.0 (49)
High school or less	36.7 (82)
Clinical diagnosis[a]	
Bicuspid aortic valve	33.3 (75)
Thoracic aortic aneurysm	30.2 (68)
Abdominal aortic aneurysm	16.5 (37)
Aortic dissection	14.2 (32)
Genetic etiology[b]	5.8 (13)
Age at diagnosis	*54.7 (16.0)*
Range (years):	Birth–82
Time since diagnosis (years)	*6.1 (8.8)*
Family history of aortic disease	
None	70.2 (158)
1 family member	16.0 (36)
2–6 family members	13.8 (31)
Health literacy (3- to 15-point scale)[c]	*11.8 (2.7)*
Genomic literacy (10- to 50-point scale)[d]	*38.9 (4.5)*

Note: Missing data: Race (6), Ethnicity (7), Educational attainment (4), Health literacy (7), Genomic literacy (15)

[a]Clinical diagnosis is categorized by most known underlying etiology of the condition (e.g., a participant with a bicuspid aortic value and thoracic aortic aneurysm is categorized as thoracic aortic aneurysm).

[b]Genetic etiology includes individuals with clinical Marfan syndrome diagnosis (7), PRGK1 pathogenic variants (3), Ehlers Danlos Syndrome Vascular Type (1), and Loeys-Dietz Syndrome (1), Turner Syndrome (1).

[c]Higher health literacy is standardly defined as a score ≥ 10 on the 3- to 15-point scale

[d]Higher genomic literacy is standardly defined as a score ≥ 20 on a 10- to 50-point scale

3.2 | What types of research genetic results to return

Across the six scenarios of possible genetic results, most participants endorsed 'Extremely likely' or 'Very likely' to want to receive results that would have implications for family members (81%), medically actionable aortic disease variants (75%), cancer-related secondary findings (75%), and cardiac-related secondary findings (70%, Figure 2). Fewer participants were interested in return of results for non-actionable aortic disease variants (51%) and VUS related to aortic disease genes (38%).

Participants had a significantly stronger interest in actionable results (familial implications, actionable aortic, and cardiac and cancer secondary findings) compared to non-actionable results (non-actionable aortic and VUS) (F (5, 1,321) =31.48, p»0.0001). Results of the ANOVA led the authors to pursue a factor analysis, and a confirmatory factor analysis demonstrated that a two-factor solution explained the most variance between scenarios. These factors conceptually align with the results of the ANOVA with the two factors representing actionable and non-actionable scenarios (Figure S1, $p = .006$, AIC = 3,211.03).

Stepwise regressions predicting interest in the actionable results factor from confirmatory factor analysis demonstrated that participants who had higher health literacy and higher genomic literacy were significantly more likely to want actionable results. Additional demographic variables and diagnostic experiences did not significantly influence participants' likelihood to want results (Table S1). A mixed-effects linear regression model utilizing the five return of results scenarios demonstrated that 38% of variance in participants' responses was due to individual-level differences (ICC = 0.383). Individual-level differences describe that participants answer differently across scenarios rather than providing consistent responses that can be predicted between individuals. The mixed-effect regression model also demonstrated that individuals diagnosed at a younger age were more likely to want research genetic test results. No other demographic or diagnostic variables significantly impacted participants' likelihood to want results (Table S2).

3.3 | Willingness to pay for validation of research genetic results

A majority of participants were willing to pay at least some amount of money for clinical validation of actionable scenarios—actionable aortic (57%), secondary—cardiac (55%), and secondary—cancer (56%). The median amount for each scenario was $100, $50, and $100, respectively (Table 2). Participants were significantly less willing to pay for clinical validation of VUS (39%) compared to actionable aortic (57%, $p = .0029$) and secondary—cancer (56%, $p = .018$) findings. Additionally, while a majority of participants were willing to pay for all actionable scenarios, there was a substantial subset of participants who were 'very' or 'extremely' likely to want research genetic results but were nevertheless not willing to pay for clinical validation (up to 19%).

3.4 | Perceptions and acceptability of research genetic testing

When asked if research testing was the same as clinical testing, 71% of respondents agreed or were neutral (25% agreed, 46% neutral).

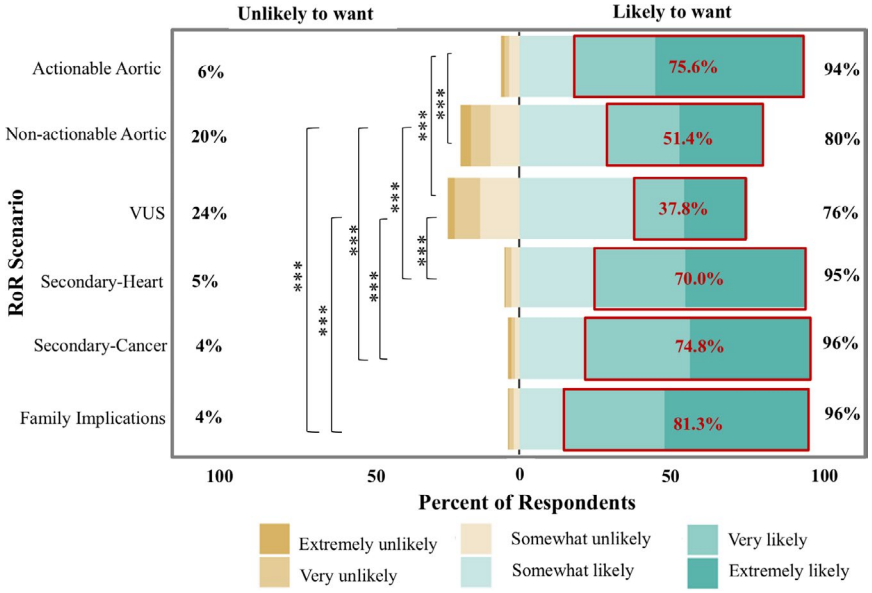

FIGURE 2 Participant responses to what types of results they would like returned (F (5, 1,321) = 31.48, $p > .0001$). The percentages along the y-axis represent likely and unlikely percentages of respondents to want results by scenario. The percentages in red boxes represent the percent 'likely' and 'extremely likely' to want each given type of results. A majority of participants wanted all types of results. Participants were significantly more likely to want actionable result categories (actionable aortic, secondary—heart, secondary—cancer, and primary results with family implications) than non-actionable results (VUS, non-actionable aortic). Brackets indicate significant differences assessed by one-way ANOVA with a Tukey HSD post hoc test (*$p < .05$, ***$p < .0001$)

16% of respondents perceived research genetic testing to be more error prone than clinical testing. 78% of individuals responded that the error (i.e., sample swap or incorrect genotype) rate needed to be less than one percent for research genetic testing results to be disclosed.

3.5 | How to return research level results

A majority of participants (>63%) were accepting of any means of return of results (Figure 3a); however, a number of participants do not use a patient portal (11%) or email (9%) and/or found technological means unacceptable (7% for patient portal, 27% for email). All other approaches of return were preferred over email. An in-person appointment (88% acceptable) was preferred over a phone call (75% acceptable) ($p < .01*10^{-16}$). 90% of participants reported that any of the healthcare or research professionals listed were acceptable for return of results (Figure 3b). A one-way ANOVA with Tukey HSD post hoc test demonstrated a preference for the participant's cardiovascular specialist compared to a researcher or the participant's primary care provider (PCP) ($p = 1.4x10^{-4}$).

4 | DISCUSSION

This is the first study to examine preferences for return of research genetic results within an aortopathy population. We found that most participants prefer to receive any type of genetic research results but feel most strongly about receiving medically actionable results. This higher interest in actionable results reflects that genetic testing for various aortopathies can inform effective, potentially even life-saving clinical management and intervention for patients and family members. Our findings reinforce that researchers should prioritize medically actionable primary findings followed by secondary findings; study results also clarify participant reticence around uncertain results, which has been explored in several prior return of results studies (Facio et al., 2013; Goodman et al., 2018; Middleton et al., 2016; Murphy et al., 2008; Wendler & Emanuel, 2002). We add to the existing knowledge by showing that aortopathy patients desire actionable genetic test results and are interested in results with implications for family members. We conclude that because of significantly higher interest in primary results with implications for family members over non-actionable aortic results, participants may not fully recognize the implications of cascade screening of family members even for non-actionable genetic results.

Our finding via stepwise linear regression (Table S1) of a high interest in actionable results may in part be due to higher health and genomic literacy. Other demographic and diagnostic factors did not significantly affect participants' interest in results, suggesting that within our sample health and genomic literacy were the most important variables impacting interest in results. The association between literacy and interest in actionable results reinforces assessing and addressing health and genomic literacy as a part of informed consent and genetics education. One-third of American adults have low health literacy (Kutner et al., 2006) and likely even more have low genomic literacy which can affect one's understanding of personal genomic risk (Lea et al., 2011). Further, previous studies have also suggested a need for targeted genetics

TABLE 2 Participant report of amount they would be willing to pay to clinically validate a research genetic finding in US Dollars. Range was bounded from $0 to $3,000

Scenario	Willing to pay (any amount) % (*n*)	Median	Mean (*SD*)
Actionable aortic	56.6 (107)	100	556.5 (898.4)
Secondary—cancer	56.1 (106)	100	512.3 (860.7)
Secondary—cardiac	54.8 (103)	50	459.0 (813.0)
Non-actionable aortic	42.2 (79)	0	356.0 (758.9)
VUS—aortic	38.6 (73)	0	258.2 (638.2)

Note: Missing data: A) Actionable aortic (36), B) Non-actionable aortic (38), C) VUS (36), D) Secondary—cardiac (37), E) Secondary—cancer (36)

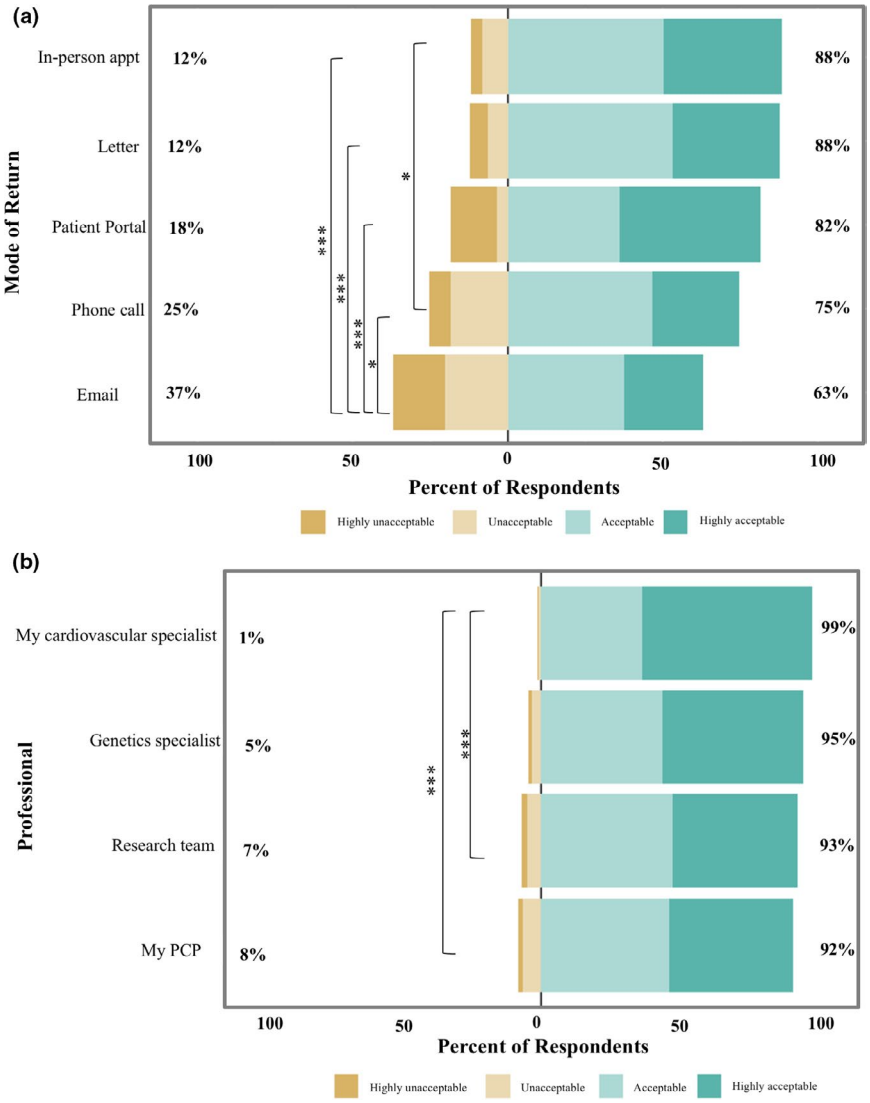

FIGURE 3 A) Participant responses to how they would prefer these results be returned (F (4, 1,076) =10.69, p»0.0001). The percentages along the y-axes represent percent acceptable and unacceptable. Participants found in-person return to be the most acceptable form of result return and significantly preferred over email or phone call. There was no significant difference in acceptability between in-person appointment and letter. Brackets indicate significant differences assessed by one-way ANOVA with a Tukey HSD post hoc test (*$p < .05$, ***$p < .0001$). B) Participant responses to by whom they would like the results returned (F (3,851) = 31.48, $p = .00014$). The percentages along the y-axes represent percent acceptable and unacceptable. Brackets indicate significant differences assessed by one-way ANOVA with a Tukey HSD post hoc test (*$p < .05$, ***$p < .0001$)

education based on literacy level (Lachance et al., 2010; Sheridan et al., 2011). Additional studies have found that genetic knowledge and education are predictors of undergoing clinical genetic testing (Butrick et al., 2015; Hall et al., 2012). Additionally, the high proportion of individual-level variation (38%) observed in the mixed-effects regression model demonstrates that individuals do not answer in a consistent pattern as to what types of results they would like returned. This variability of responses taken into account with influence of genomic and health literacy further supports the need for genetic education and counseling to allow participants the opportunity to opt-in/out of return of results at the time of consent to genetic research.

There was a lower rate of interest to receive VUS among this aortopathy population, adding clarification to the developing literature around uncertain results. One large US population-based study (n = 4,659) demonstrated that 91% of participants were

likely to want research genetic results, even if there was nothing to be done about them (Kaufman et al., 2008). When studies have asked specifically about VUS, however, the reported interest in this type of research result varies widely (Facio et al., 2013; Middleton et al., 2016; Wendler & Emanuel, 2002). Return of results preferences for uncertain results may be influenced by how these types of results are described in survey questions, and the relatively low level of interest in VUS found in this study may be due to the more thorough definition offered in our survey scenarios. Participant differentiation between actionable variants and VUS also demonstrates individual differences in what information the participant finds personally valuable. For some individuals, only actionable results may be valuable, but for others such as early adopters, they may want all information for information's sake, independent of actionability (Lewis et al., 2015).

Given that our participants have manifesting disease, genetic testing may or may not change their own medical management. Regardless, a known familial pathogenic variant is necessary for genetic cascade screening of at-risk family members. Genetic cascade screening would provide informative positives and negatives for family members on their monogenic risk for aortopathy (Brownstein et al., 2017). This is a notable improvement over clinical cascade screening via echocardiogram or CAT scan, where costly scans may be done repeatedly over time since it is not known if an individual is at higher or lower risk (Ahmad et al., 2019). Based on the striking and significant discordance in responses between the non-actionable aortic and family information scenarios, we postulate that individuals do not fully understand the utility and necessity of identifying a familial variant to trigger cascade screening. Genetic counseling may help to clarify the importance of the cascade screening process for identifying at-risk family members.

Further, we observed a significantly higher interest and willingness to pay for validation of actionable research genetic results compared to non-actionable results. However, our finding that approximately 1 in 5 of participants who were 'very' or 'extremely' likely to want to receive actionable results were not willing to pay for clinical validation suggests a need for funding—insurance, institutional, or grant—to cover this cost. A variety of modalities for returning results appear to be acceptable to this study population. Preferences for specific modes have been previously explored in only a few studies. A study of pediatric cancer patients, similar to ours, found that participants rated several types of providers as acceptable for returning results, with primary care provider viewed as acceptable as specialists (Fernandez et al., 2009). Our results demonstrate that—while a primary care provider was still acceptable to a vast majority of participants—a primary care provider was the least preferred professional overall. These findings suggest a preference for specialist involvement in the return of results process. Additionally, in our adult population, a substantial subset of participants did not use technological platforms (email and patient portal). These technological limitations should be considered in a return pipeline, particularly when working with older populations who may not commonly use these communication technologies. Though our participants significantly preferred in-person result return, 75% of participants found phone calls acceptable suggesting return via phone a viable option. Acceptance of return of results via telephone could increase reach for return of results, especially given that studies have found comparable satisfaction and comprehension of results with phone genetic counseling compared with in-person counseling (Christensen et al., 2018; Lewis et al., 2015).

4.1 | Limitations

There are important limitations to consider when interpreting the results of this study. The survey was administered to a predominantly white and non-Hispanic sample; however, the sex ratio of participants is representative of the aortopathy population and educational attainment is representative of the general population. The scenarios were novel and—while validated for face, content validity, and internal consistency—external validity with another sample and criterion validity were not assessed. There was also a notable minority (n = 36–38) of participants who did not respond to the willingness to pay scenarios and so these data should be interpreted with caution. Additionally, while aortic dissection was sufficiently represented, participants with emergent disease were not recruited. Therefore, responses in our sample may not be representative of emergent cases with more severe and acute presentations. The study assessed participant preferences and expectations around return of results, but not their perceptions regarding the limitations and challenges that return of results would pose for the research enterprise. Last, the study was a cross-sectional study using hypothetical scenarios, and so may not predict participants' actual responses if given the choice to have different types of results to return. Further research should include assessment of participant experiences following return of different types of genetic testing results and through different return of results pipelines in order to establish best practices.

4.2 | Practice Implications

As has been seen across prior return of results studies, this aortopathy population demonstrates interest in receiving research genetic results, which reinforces the need to prioritize the return of actionable primary and secondary findings. Because a variety of modalities of return of results was acceptable to participants, the study supports researcher and institution flexibility around who returns and how results are returned. Given potential lack of participant understanding of utility of genetic testing results, genetic education and counseling around personal and family utility is also a necessary component of results disclosure in order to effectively reduce morbidity and mortality within this population. In summary, consistent with recent recommendations from the National Academies of Sciences, Engineering and Medicine, (Addie et al., 2018) these findings support a need for institutional and funding support to establish an infrastructure for return of actionable research findings, without compromising primary aims of genetic biorepository research.

AUTHOR CONTRIBUTIONS

Jamie Love-Nichols (Jamie.love-nichols@childrens.harvard.edu) principally developed survey, managed data, performed data analysis, drafted the work, and provided final approval for publication. Wendy Uhlmann (wuhlmann@med.umich.edu) provided oversight in survey development, statistical analysis, drafting and revision of work, and provided final approval for publication. Patricia Arscott (parscott@med.umich.edu) provided oversight in survey development, statistical analysis, drafting and revision of work, and provided final approval for publication. Cristen J. Willer (cristen@med.umich.edu) provided conception for design of work, oversight in survey development, data collection, statistical analysis, drafting and revision of work, and provided final approval for publication. Whitney E. Hornsby (whornsby@med.umich.edu) provided conception for design of work, oversight in survey development, data collection, statistical analysis, drafting and revision of work, and provided final approval for publication. J. Scott Roberts (jscottr@umich.edu) provided oversight in survey development, statistical analysis, drafting and revision of work, served as primary advisor for this work, and provided final approval for publication.

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST

Jamie Love-Nichols (Jamie.love-nichols@childrens.harvard.edu) has no conflicts of interest to disclose.

Wendy Uhlmann (wuhlmann@med.umich.edu) has no conflicts of interest to disclose.

Patricia Arscott (parscott@med.umich.edu) has no conflicts of interest to disclose.

Cristen J. Willer (cristen@med.umich.edu) spouse works for Regeneron Pharmaceuticals, which has no relationship to this study.

Whitney E. Hornsby (whornsby@med.umich.edu) has no conflicts of interest to disclose.

J. Scott Roberts (jscottr@umich.edu) has no conflicts of interest to disclose.

HUMAN STUDIES AND INFORMED CONSENT

Michigan Medicine IRB Initial Approval Date: 05/23/2013.

Protocol Number: HUM00052866.

ClinicalTrials.Gov registration: NCT02306200.

All study participants provided informed consent prior to enrolling in this research study.

ANIMAL STUDIES

No non-human animal studies were carried out by the authors for this article.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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