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ORIGINAL RESEARCH

Research Participants' Preferences for Hypothetical Secondary Results from Genomic Research

Julia Wynn[1] · Josue Martinez[1] · Jimmy Duong[2] · Codruta Chiuzan[2] · Jo C. Phelan[3] · Abby Fyer[4] · Robert L. Klitzman[4] · Paul S. Appelbaum[4] · Wendy K. Chung[1,5]

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Abstract Secondary or incidental results can be identified in genomic research that increasingly uses whole exome/genome sequencing. Understanding research participants' preferences for secondary results and what influences these decisions is important for patient education, counseling, and consent, and for the development of policies regarding return of secondary results. Two hundred nineteen research participants enrolled in genomic studies were surveyed regarding hypothetical preferences for specific types of secondary results, and these preferences were correlated with demographic information and psychosocial data. The majority of research participants (73%) indicated a preference to learn about all results offered, with no clear pattern regarding which results were not desired by the remaining participants. Participants who reported greater interest in genetic privacy were less likely to indicate a preference to learn all results, as were individuals who self-identified as Jewish. Although most research participants preferred to receive all secondary results offered, a significant subset preferred to exclude some results, suggesting that an all-or-none policy would not be ideal for all participants. The correlations between preferences to receive secondary results, religious identification, and privacy concerns demonstrate the need for culturally sensitive counseling and educational materials accessible to all education levels to allow participants to make the best choices for themselves.

Keywords Genomics · Incidental findings · Incidental results · Return of results · Secondary findings · Secondary results · Whole exome sequencing

Introduction

Genomic sequencing is now routinely used in research and clinical testing, and secondary or incidental results (results unrelated to the primary indication for testing) are a well-recognized consequence. There is a growing consensus among researchers and clinicians that certain types of secondary results, including those related to highly penetrant disorders with impactful and potentially life-saving medical interventions, should be returned. However, there is less consensus about returning results that do not have effective medical interventions and results for adult-onset conditions in minors (Klitzman et al. 2013; Lemke et al. 2013; Townsend et al. 2012; Yu et al. 2014). The current American College of Medical Genetics and Genomics (ACMG) policy for clinical genomic testing is to return clearly pathogenic variants from a select set of 56 genes to all patients unless they opt out (Directors 2015). These guidelines have led to debate within the genomics community, including concern about effective ways to obtain informed consent, ethical and legal obligations to disclose potentially

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✉ Wendy K. Chung
wkc15@columbia.edu

[1] Department of Pediatrics, Columbia University Medical Center, 1150 St. Nicholas Ave., Russ Berrie Pavilion, 6th Fl, Rm 620, New York, NY 10032, USA

[2] Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA

[3] Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA

[4] Department of Psychiatry, Columbia University Medical Center and NY State Psychiatric Institute, New York, NY, USA

[5] Department of Medicine, Columbia University Medical Center, 1150 St. Nicholas Ave., Russ Berrie Pavilion, 6th Fl, Rm 620, New York, NY 10032, USA

life-saving secondary results, and resources required to identify and convey these findings (Appelbaum et al. 2014; Black et al. 2013; Klitzman et al. 2014).

The preferences and interests of numerous stakeholders including researchers and research participants must be considered as policies regarding secondary findings in research evolve. Most clinicians and researchers surveyed agree that the opinions of research participants should be considered in formulating these policies (Klitzman et al. 2013; Lemke et al. 2013; Yu et al. 2014). Studies examining participants' preferences for receiving secondary results consistently observe that the overwhelming majority wants to receive secondary results, regardless of clinical actionability, including results with no or unclear clinical utility and variants of uncertain significance (Bennette et al. 2013; Daack-Hirsch et al. 2013; Facio et al. 2013). However, preferences for specific secondary results vary among research participants. Specific attributes of the results important to some individuals include penetrance, treatability, severity, and family impact (Bennette et al. 2013; Regier et al. 2015). Individuals are motivated by curiosity, a desire to use the information to prevent future disease, wanting to contribute to research, and a belief in the intrinsic value of information (Gollust et al. 2012; Sanderson et al. 2015a).

We previously evaluated researchers' views on return of secondary results and observed correlations between increased willingness to return secondary findings and clinical training, active involvement in clinical care, and prior experience returning genomic research results (Wynn et al. 2015). In this study, we sought to understand research participants' perspectives and the relationship of demographic, medical, and psychological characteristics on the desire to receive secondary findings. Research participants' preferences to learn about secondary findings are likely complex, and thus we hypothesized that preferences may be affected by many different variables including current health status, healthcare practices, and feelings of control over their health. We also explored how genetics knowledge and numeracy, genetic essentialism, concerns for genetic stigma and secrecy, and knowledge of laws protecting against genetic discrimination might affect preferences. Finally, we examined demographic characteristics as well as family support, religiosity, and psychological state. Understanding these characteristics is important not only for the development of policies regarding the return of secondary results, but also to guide patient education and counseling in this era of genomic medicine.

Materials and Methods

Participants

Participants were recruited from a sample of English-speaking, adult research participants enrolled in parent studies using whole exome sequencing (WES) at Columbia University Medical Center (CUMC). Enrollment occurred from January 2012 to March 2015. Eligible participants received an invitation letter or email followed by up to five phone calls or emails from the research coordinator. If they indicated an interest in participating, they were sent a written consent form, which the research coordinator reviewed with them by telephone. Those who agreed to participate signed and returned the consent form. Participants completed the survey online or using a paper version, according to their preferences. They were compensated with a $25 gift card upon completion of the survey. The CUMC institutional review board approved this study. The participants came from three categories of research studies in which WES is used as a research method: 1) a study of probands with a history of breast cancer, 2) two studies of congenital heart defects (CHD) in which all but one participant, who was an adult affected proband, were unaffected parents of an affected child, and 3) studies of other birth defects including congenital diaphragmatic hernia (CDH), multiple congenital anomalies (MCA) developmental delay (DD), muscle weakness (MW) or other neurodevelopmental disorders for which WES was being done (WES). In this group all but one participant, who was an adult proband with diabetes, were unaffected parents of an affected child.

Focus Groups

Four focus groups, each comprising four participants eligible for the study, guided instrument development, as described below. The focus groups were moderated by a psychiatrist (RLK) and observed by a geneticist (WKC) or genetic counselor (JW). We reviewed the nature of the study and the vignettes and used TurningPoint polling software to allow participants to respond to questions anonymously by clicking buttons on a device. Participants were asked about the kinds of results in which they thought research participants would be interested, whether those results would impact their sense of self or their family relationships, whether they worried about discrimination, and how much they would be willing to pay for each result.

Instruments

Survey items included demographics, religiosity, medical history and several psychosocial measures. We adapted existing validated measures, including the Health Locus of Control Scale (Cronbach's α =0.78) (Wallston et al. 1976), Beck Anxiety Inventory (Cronbach's α =0.92) (Gech et al. 1988), Personal Health Questionnaire (PHQ–9) (depression; Cronbach's α =0.86–0.89) (Spitzer et al. 1999), General Self-Efficacy Scale (perceived ability to cope with stressors; Cronbach's α =0.76–0.90) (Schwarzer and Jerusalem 1995), a question from the General Sleep Disturbance Scale

(Cronbach's α =0.75) (Lee et al. 1991), and questions from the Genetic Knowledge Measure (Cronbach's α =0.92) (Erblich et al. 2005) with several of our own questions to assess general genetic knowledge rather than cancer-specific knowledge (Table SI). We developed novel scales based on the focus group responses, relevant literature, and experience of the investigators to address genetic stigma (Cronbach's α =0.74), genetic secrecy (Cronbach's α = 0.86), and health worry (Cronbach's α =0.71). We also asked questions about genetic essentialism, knowledge of the Genetic Information Nondiscrimination Act (GINA), social support, life changes, and numeracy.

Participants were asked to review vignettes about 11 types of genetic results to indicate the likelihood that, if given the choice at some point in the future, they would want each result (Table 1). These 11 vignettes represent a subset of all genetic results that are available through an exome and did not include polygenic risk scores or all monogenic diseases. Disorders were selected to be relatively identifiable conditions that vary by degree of risk; availability and effectiveness of screening, prevention, and treatment; and acceptability of screening, prevention, and treatment. Choices were hypothetical but participants were aware that in the future they might have the opportunity to meet with a genetic counselor to make actual decisions about preferences for secondary results.

All surveys were assessed for length and clarity by 15 medical professionals, including clinical geneticists, psychologists, psychiatrists, genetic counselors, and research coordinators. After gathering responses from the first 90 participants and doing a quality check, we removed some of the questions to reduce the length of the survey by 30% and decrease the time required to complete it to approximately 30 min. Among the redundant questions that were removed were items that provided further granularity about family composition, genetic essentialism, burden of medical conditions, planning for the future, and numeracy. A copy of the original survey with tracked changes to indicate the deletions is included in the supplementary materials.

Statistical Analysis

Data analyses only included responses from surveys over 50% complete. Descriptive statistics were used to summarize all variables of interest. The continuous variables were reported as mean (+/−standard deviation) or median (interquartile range). Categorical outcomes were summarized using frequencies (percentages). The study sample was categorized into two groups: those who indicated a preference to learn about all hypothetical results and those who indicated a preference not to learn about one or more hypothetical results. Two-tailed independent t-tests were used to compare differences in the two groups for continuous variables and chi-square tests were used for categorical variables. Additionally, a logistic regression model was fitted to assess the associations between desire to learn about genetic results and potential covariates such as age, gender, ethnicity, education level, religion, affected children and psychosocial measures. All statistical tests used a significance level set at 0.05, and were performed in R (Team 2012).

Results

Five hundred seventy-two eligible participants were identified and invited to join the study. Upon follow up by phone of 350 participants, 229 agreed, 36 did not respond to five follow up phone calls and were considered passive decliners, and 85 directly declined participation. In order of frequency of responses, decliners indicated they did not have time, were not interested in learning about additional genetic test results, did not provide a specific reason, or were concerned about privacy. The remaining 222 were not contacted for follow up after initial invitation because study enrollment was complete. The enrollment rate of individuals reached for follow up after initial invitation was 65% (229/350). The distributions of gender, age and parent study were not significantly different between

Table 1 Conditions included in the 11 vignettes participants reviewed to indicate preferences for learning about results

Condition	Description
Ancestry	No disease risk
Pharmacogenetics	No disease risk
Carrier Status	Risk for children
Hemochromatosis	Low risk, effective , acceptable treatment/ prevention
Breast/ ovarian cancer	High risk, effective treatment/ screening/ prevention of variable acceptability
Pancreatic cancer	Low risk, ineffective treatment/ screening/ prevention of low acceptability
Arrhythmia	Moderate risk, effective treatment/ screening/ prevention
Cardiomyopathy	Moderate risk, effective treatment/ screening/ prevention of variable acceptability
Depression	Hypothetical, low risk, variable effective treatment/ prevention
Alzheimer's	Moderate risk, no available treatment/ prevention
Huntington's	High risk, no available treatment/ prevention

the study participants and the people who declined participation or were not re-contacted after initial written invitation. After surveys that were less than 50% complete were excluded, 219 of the 229 surveys were included in the analysis.

The participants were predominately female, white non-Hispanic, married, college-educated and employed. The mean age was 45 (range 21–87) years. Nearly half of the participants self-identified as Christian (49%) and 28% as Jewish. Sixty-nine percent of participants had a physical examination within the past year. Across the study, 38% of the participants were personally affected, while over half had at least one child affected with the condition in the parent study, 36% had only unaffected children and 8% had no children. These categories were not mutually exclusive because many of the participants from the breast cancer study had children with breast or an associated cancer (Table 2).

Table 2 Sociodemographics of the participants (n = 219)

Demographics	N	%
Female	164	75%
Married	186	85%
Age		
Mean and SD (range 21–87)	48	14.3
Ethnicity and race		
White, Not-Hispanic	180	82%
White Hispanic	9	4%
Black	7	3%
Asian or Pacific Islander	7	3%
More than 1 race	2	1%
Other or not specified	14	6%
Education		
Up to HS or vocational training	30	14%
Some college/ Associate degree	43	20%
College degree	61	28%
Advanced degree	85	39%
Employed (full or part-time)	141	64%
Current Religion (n = 218)		
Christian	106	49%
Jewish	62	28%
Other (Buddhist, Taoist, Meditation) or >1 religion	9	4%
None	41	19%
Physical exam		
< 1 year ago	151	69%
> 1 year ago	68	31%
Insurance (n = 217)		
Private or Medicare	189	87%
Medicaid	28	13%
Parent study type		
Breast cancer	64	29%
CHD	94	43%
CDH, DD, D, MCA, MW, WES	61	28%
Personally affected	83	38%
Children		
Affected children	126	58%
Unaffected children only	78	36%
No children	17	8%

Abbreviations: congenital heart defect (CHD), congenital diaphragmatic hernia (CDH), developmental delay (DD), diabetes (D), multiple congenital anomalies (MCA), muscle weakness (MW), whole exome sequencing (WES), standard deviation (SD)

Psychosocial Measures

Twenty-eight percent of the participants had a BAI score (≥10) indicating increased anxiety, compared to the population frequency of 18.1% (Kessler et al. 2005). Seven percent had a PHQ-9 score (≥20) indicating moderate or severe depression, which is similar to the general population frequency of 6.7% (Kessler et al. 2005). All participants with depression also had elevated anxiety scores.

Genetic Knowledge, Numeracy, and Knowledge of GINA

Participants had good knowledge of genetics and high numeracy, with a mean score of 88% on the genetics knowledge scale and 92% on the numeracy scale. Knowledge of GINA was poorer: 80% correctly responded that GINA protects against health insurance discrimination but only 40% knew that GINA does not protect against life insurance discrimination. Only 25% answered both questions correctly.

Preferences for Return of Secondary Results

Seventy-three percent of participants indicated a preference to learn about all of the hypothetical results offered (Fig. 1). In general, more participants indicated a preference to receive results that conveyed no personal disease risk information (pharmacogenetics, carrier status, ancestry) or results for which there was effective treatment and intervention (breast and ovarian cancer, hemochromatosis, arrhythmia, cardiomyopathy) than other types of results. The categories for which 90% or fewer of participants indicated a preference to learn about results included depression, pancreatic cancer, Alzheimer's disease, and Huntington's disease (Fig. 1). Seventeen (8.5%) individuals elected to receive all results except Alzheimer's disease and/or Huntington's disease and an additional 4 (2%) individuals wanted all results except Alzheimer's disease, Huntington's disease, pancreatic cancer and depression. Sixteen percent indicated a preference not to learn about one or more results with available treatment or preventive intervention (hemochromatosis, breast cancer, pancreatic cancer, arrhythmias, cardiomyopathy or depression), and 8% indicted a preference not to learn about one or more conditions with an effective treatment

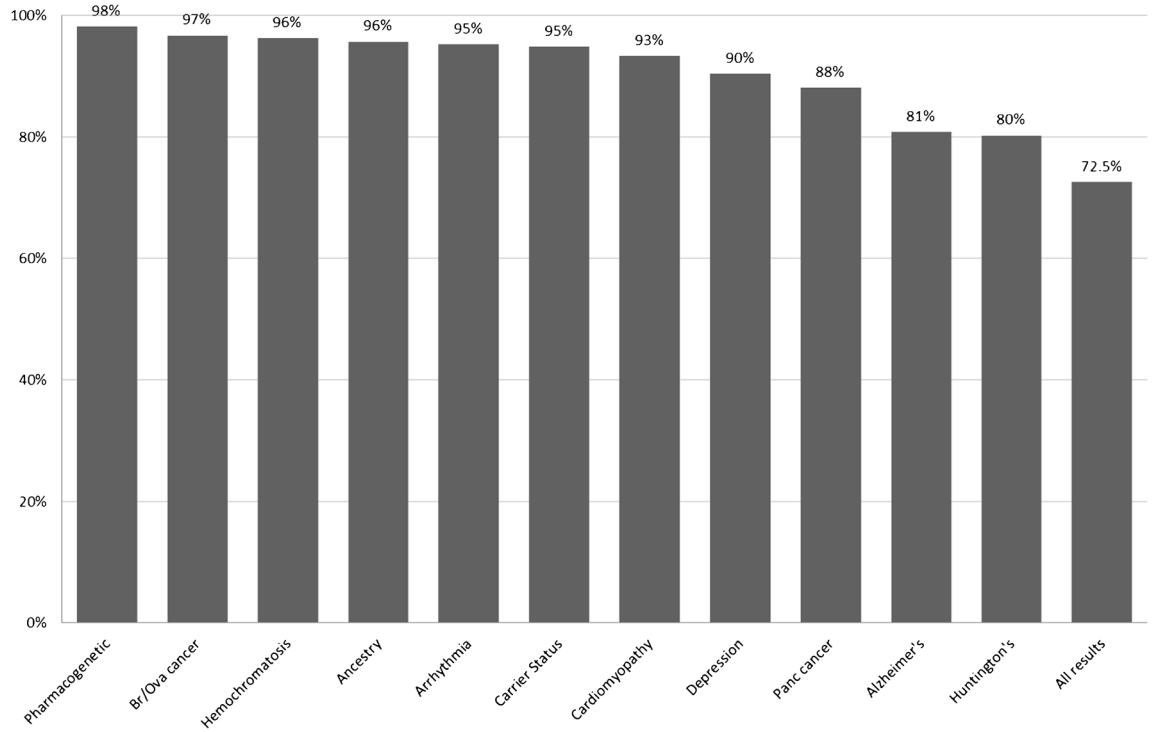

Fig. 1 Bar plot of the proportion of the participants who indicated they wanted to learn about each of the 11 types of genetic test results and all genetic test results

(hemochromatosis, breast cancer, arrhythmias, cardiomyopathy). There was no discernable pattern to the preferences of the remaining 35 (17.5%) individuals who elected to receive only some results (Fig. 2).

Relationship among Demographics Variables and Preferences for Return of Secondary Results

Examining the demographic characteristics of the 73% of participants who indicated a preference to receive all hypothetical results offered, compared to participants who preferred to receive only a subset of results, we observed a number of differences between these groups (Fig. 3). Participants who identified as having no religion were most inclined to receive all results (82%), followed by those who identified as Christians (78%) and Jews (55%) (p-value =0.01) (Fig. 3). Participants who self-identified as Christian reported the greatest degree of religiosity ("To what extent do you consider yourself a religious person"), which was statistically greater than participants who reported no religious identification (p-value <0.001) (data not shown) but not different from the other religion categories. Associations between participant self-identified religion and genetic secrecy and stigma measures were observed (Table SII). Pairwise comparisons showed participants who self-identified as Jewish on average had higher genetic secrecy scores (mean difference 0.39, 95% CI 0.17–0.61, p-value = 0.001) and higher stigma scores than participants who identified as Christian (mean difference 0.23, 95% CI 0.04–0.42, p-value = 0.019). There were no other statistically significant differences in the other pairwise comparisons of participant religion and genetic secrecy and stigma measures (Table SII). We did not observe any relationship between reported degree of religiosity and genetic stigma or genetic secrecy (data not shown).

Participants with no college education showed a trend toward being less inclined to receive results compared to individuals with more education (p-value =0.08) (Fig. 3). There was a trend for those with some college education but no bachelor's degree being most inclined to receive all results compared to the other levels of education. Individuals with Medicaid were less inclined to receive all results than individuals with other types of insurance (p-value =0.02) (Fig. 3). A correlation between lower education and having Medicaid insurance was observed (chi square, p-value =0.001) (data not shown). Individuals who indicated a preference to learn about all results offered did not differ significantly by type of parent study, age, gender, marital status, ethnicity, or whether the study participant was affected and or had a child affected with the condition under study (Fig. 3).

Genetic and GINA Knowledge and Preference for Secondary Results

There was no association between knowledge of GINA's protection from discrimination in health insurance or lack of protection from discrimination in life insurance and preference to

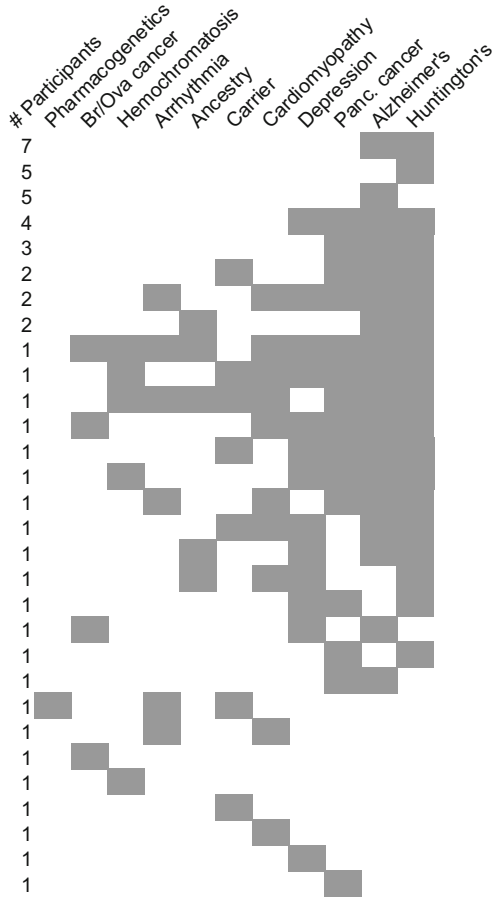

Fig. 2 Fifty-two participants who did not want all results but wanted some results. Grey boxes indicate results participants did not want to learn about

learn about all results (chi square *p*-value =0.93 and chi square *p*-value =0.43, respectively) (data not shown). There was also no significant correlation between genetic knowledge and results preferences (chi square *p*-value =0.92) (data not shown).

Relationship among Psychosocial Variables and Preferences for Secondary Results

Most psychosocial measures did not correlate with preferences to receive results, including ability to cope with stressors, perceived control over health, healthy behaviors, perceived quality of health, worry, sleep disturbances, family and social support, genetic stigma, and genetic essentialism (Table SIII). The exception was genetic secrecy, i.e., the perceived need to hide genetic information from family and employers and to exclude it from medical records. Individuals who did *not* want all hypothetical results offered on average had higher genetic secrecy scores than individuals who wanted all results (*p*-value =0.01) (Table SIII). To adjust for the possible effect of the type of parent study on genetic secrecy, a logistic regression model was fit with the genetic secrecy variable and type of parent study. Participants with higher genetic secrecy scores had an odds ratio of 0.5 (95% CI 0.31–0.98, *p*-value =0.04) (data not shown) for wanting all results compared to participants with lower genetic secrecy scores after adjusting for parent study. To adjust for the possible effect of knowledge of GINA's protection from discrimination in health insurance or lack of protection from discrimination in life insurance a logistic regression model was fit with genetic secrecy and response to these two questions about GINA. Participants with a higher genetic secrecy score had an odds ratio of 0.4 (95% CI 0.3–0.7, *p*-value =0.0012) (data not shown) for wanting all offered results, after adjusting for knowledge of GINA. Scales assessing genetic stigma and genetic essentialism were not associated with preferences to learn about results. A trend was observed for increased religiosity to be associated with lower interest in learning all results (*p*-value =0.06) (Table SIII).

Multiple Variable Regression Analysis of Preferences for Return of Secondary Results

A logistic regression model was fit based on the single variable analysis results and potential confounders, with desire to learn all results as the outcome variable (Table 3). A significant relationship remained between religion and preference to learn about all results after adjusting for age, gender, ethnicity, education level, secrecy, stigma and whether the participant or their child was affected by a disorder (Table 3). The odds ratio of self-identified Jews requesting all results was 0.20(95% CI: 0.07–0.58, *p*-value = 0.004) compared to self-identified Christians, after adjusting for other variables included in the model. Compared to participants with affected children the odds ratio of participants with no children requesting all results was 6.72 (95% CI: 0.94–48.05, *p*-value =0.06), after adjusting for other variables included in the model. There was also a modest association of participants greater than or equal to 45 years of age indicating a preference for all hypothetical results with an odds ratio of 1.04 (95% CI:1.00–1.08, *p*-value = 0.05) compared to participants less than 45 years, after adjusting for the other variables in the model. There were no significant associations between preferences to receive all results and level of education, parent study type, affected status, after adjusting for the other variables included in the model (Table 3).

Discussion

A large majority (73%) of our participants indicated their preferences to receive all hypothetical results offered, and only three participants indicated a preference not to learn about any results. The results of our study regarding research participants' preferences for secondary findings from genomic studies are consistent with previous studies (Bennette et al. 2013;

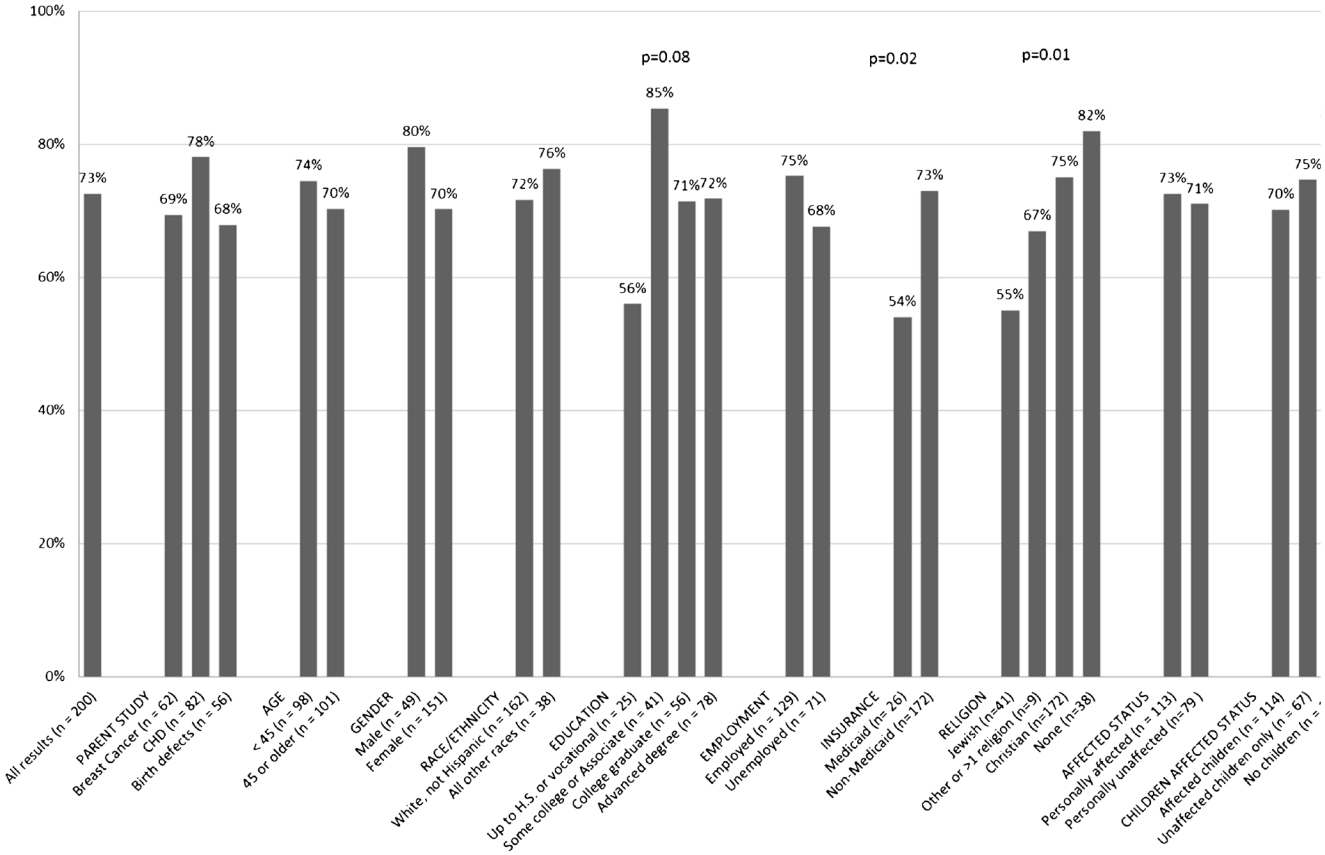

Fig. 3 Barplot of the proportions of participants with specific characteristics who indicated they wanted to learn all genetic test results. *P*-values generated from chi-square analysis

Daack-Hirsch et al. 2013; Facio et al. 2013; Regier et al. 2015; Sanderson et al. 2015a). Fewer participants had a preference to receive results related to conditions with no effective treatment or prevention, but at least 80% of participants indicated a preference to learn about genetic results related to pancreatic cancer, Alzheimer's disease, and Huntington disease, which are generally viewed as falling into this category. A small fraction (8%) of the participants indicated a preference not to learn about their risk for one or more conditions with effective treatment or prevention (hemochromatosis, breast cancer, arrhythmias, cardiomyopathy). There were eight participants with seemingly idiosyncratic preferences who requested results for Alzheimer's disease and Huntington's disease but declined at least one other type of result, such as pharmacogenetics or hemochromatosis. Thus, participants may have unique perspectives on the value of specific information, with factors other than disease treatment and severity influencing their preferences or may not have completely understood the information and implications of genetic testing for these conditions.

Demographic

This is the first study to examine the influence of participants' demographic and psychosocial characteristics on preferences for return of secondary results. In our sample, those who reported no religious observance or practice were most inclined to receive all results (82%), followed by participants who identified as Christian (78%) and Jewish (55%). The relationship between religion and genetic testing preference is complex. Pre-marital or pre-conception carrier screening are accepted practices in many Jewish communities but there is less consensus about genetic testing to inform disease risk (Hegwer et al. 2006; Warsch et al. 2014). In some parts of the Jewish community, there is substantial concern about stigmatization of families with genetic conditions and impact on subsequent marriage prospects for their children and therefore greater concern about keeping this type of information secret. This concern may have decreased interest in learning about these types of results in this study for these participants. In our study sample, Jewish participants had significantly higher levels of genetic stigma and secrecy compared to participants who identified as Christian. Despite the observing a relationship between religion and stigma and secrecy, the relationship between Jewish affiliation and preference not to want all results remained significant after adjusting for secrecy, stigma and other demographic variables, suggesting that there are other unknown factors influencing the relationship. Finally participants reported a greater degree of religiosity showed a

Table 3 Multiple logistic regression analysis of select demographic factors and desire to receive all genetic test results (primary outcome measure of interest). $N = 181$, AIC = 215.43, McFadden pseudo R squared = 0.1496

	OR	OR 95% CI L	OR 95% CI U	z-value	*p*-value	coefficient	SE
Secrecy	0.49	0.26	0.90	-2.29	0.022	-0.72	0.32
Stigma	1.73	0.89	3.34	1.63	0.104	0.55	0.34
Parent study							
Breast Cancer	ref						
Congenital Heart Defects	0.72	0.10	5.33	-0.32	0.747	-0.33	1.02
Birth Defects	1.30	0.22	7.75	0.29	0.770	0.27	0.91
Affected status							
Personally unaffected	ref						
Personally affected	0.26	0.06	1.26	-1.67	0.095	-1.33	0.80
Child status							
Affected children	ref						
Unaffected and affected children	4.90	0.91	26.32	1.85	0.064	1.59	0.86
Unaffected children only	6.72	0.94	48.05	1.90	0.058	1.91	1.00
Demographics							
Education							
Up to HS or vocational training	ref						
Some college/Associate degree	3.00	0.71	12.63	1.50	0.134	1.10	0.73
College degree	1.76	0.50	6.16	0.89	0.374	0.57	0.64
Advanced degree	2.77	0.81	9.44	1.63	0.104	1.02	0.63
Age							
< 45 years of age	ref						
≥ 45 years of age	1.04	1.00	1.08	1.93	0.054	0.04	0.02
Gender							
Male	ref						
Female	0.52	0.19	1.42	-1.28	0.202	-0.66	0.52
Ethnicity and Race							
White, Non-Hispanic	ref						
Not White, Non-Hispanic	0.79	0.25	2.52	-0.40	0.687	-0.24	0.59
Religion							
Christian	ref						
Jewish	0.20	0.07	0.58	-2.95	0.003	-1.62	0.55
Other* or >1 religion	0.38	0.06	2.65	-0.97	0.331	-0.96	0.99
None	0.80	0.26	2.42	-0.40	0.691	-0.22	0.56
Intercept				0.12	0.903	0.23	1.86

Abbreviations: Odds Ratio (OR), Ref (reference group for OR), Odds Ratio 95% Confidence Interval Upper, Lower(OR 95% CI U, OR 95% CI L), coefficient standard error (SE)

*Buddhist, Taoist, Meditation

tendency towards wanting fewer results. This is consistent with reports of lower uptake of *BRCA 1/2* testing for women reporting high levels of spiritual faith, who may be more inclined to rely on divine providence rather than medical interventions (Schwartz et al. 2000). Our observations illustrate the importance of approaches that are sensitive to religious and cultural differences, as well as the need for further research to understand the relationship between religion and attitudes toward predictive genetic testing.

The positive correlations between education level, genomic literacy, positive attitudes about genetic testing, and willingness to participate in genetics research are documented in the literature, but less is known about the relationship between education and preferences to learn about genetic results (Kaphingst et al. 2012; Rose et al. 2005; Sanderson et al. 2015b). We observed a trend towards an association between level of education and desire to learn all results. Individuals with a high school education or less were least likely to

indicate a preference for all results, while individuals with some college education but no bachelor's degree were most likely to indicate a preference to want all results. For those with a bachelor's degree or greater there was a modest trend toward weaker preferences for all results. Our modest sample size and generally highly educated cohort limits the conclusions that can be drawn from these findings. Further studies are needed to more closely examine the relationship between education and genetic testing choices, and to help identify methods and tools that can assist all participants to make informed decisions.

Participants with Medicaid were less inclined to request all results compared to individuals with other types of insurance. This difference may be related to the educational differences in these two groups rather than a direct impact of Medicaid status, as insurance type was correlated with education level in our cohort. A larger study sample would be needed to assess the impact of insurance, independent of education level.

There was a tendency in our cohort for participants who had no children or at least one unaffected child to have stronger preferences to learn about all results, compared to participants with only affected children. To our knowledge, this is the first time this possible relationship has been identified. We hypothesize that families with affected children have already experienced a heavy burden of disease to which they do not want to add by learning more information through testing. This may be especially true of a cohort like ours that includes children with serious and debilitating medical conditions. This finding warrants further exploration with qualitative methods to better understand the attitudes contributing to this relationship.

Psychosocial Measures

Our finding of a negative association between the perceived need to hide genetic test results from family, potential romantic partners, employers and insurers, and preference to learn all offered genetic test results was similar to the results of other studies that have observed genetic secrecy to be associated with decreased interest in genetic testing for some conditions, including hereditary cancer (Allain et al. 2012; Armstrong et al. 2000; Armstrong et al. 2012). However, we observed no association between concerns about genetic discrimination and preferences, while past studies have observed that concerns for insurance and job discrimination influence the decision to have predictive and diagnostic genetic testing (Allain et al. 2012; Armstrong et al. 2000; Armstrong et al. 2012; Sanderson et al. 2015a). This difference may be a reflection of a true difference in our study population compared to the published literature or may be a limitation of our study design in which we grouped social discrimination with job and insurance discrimination in our measure of genetic stigma. A concern was that the low knowledge in our sample that GINA protects against discrimination in health insurance but not life insurance might influence the relationship between secrecy and results preferences, but the relationship remained similar after adjusting for GINA knowledge; this indicates an association between secrecy and preference for results regardless of GINA knowledge. Similarly, because previous studies have demonstrated an association between higher genetic secrecy and lower preference for *BRCA1/2* gene testing and one of our parent studies included women with hereditary breast cancer, we examined the relationship between secrecy and results preferences after adjusting for parent study. Again, the relationship remained significant. Our findings support the need for more research on the relationship of genetic secrecy and perceived stigma and preferences for genetic testing, with stratification of the different types of discrimination.

In examining the other psychosocial measures, we observed no correlation between anxiety or depression and preferences for results; our participants were on average more anxious than the general population but this might have been a reflection of the disproportionate number of women in the study; women have higher anxiety levels then men (Kessler et al. 2005). We also observed no associations between participants' preferences and health attitudes and behaviors, social support, life planning, worry, ability to cope with stressors, or genetic essentialism.

Study Limitations

This study has several limitations. The modest, relatively homogeneous cohort is not representative of the general population of the U.S. The cohort disproportionately comprises older, well-educated women who are predominantly White, non-Hispanic. The lack of diversity as well as a self-selection bias for individuals who were more likely to want at least some genetic results limits the generalizability of these findings for population-based genetic screening. However, our observations are likely applicable to participants in genomic research, the target population this study was designed to address (Facio et al. 2013; Gollust et al. 2012). Although 38% of the initially invited population was included in the study, 65% of the participants who were contacted directly and given the opportunity to participate enrolled in the study. A proportion of the eligible participants declined because they were not interested in learning about secondary results or were concerned about privacy issues and therefore our results are likely biased towards participants with greater preferences to learn about results and fewer concerns about privacy and secrecy. Overall, the strong interest of the majority of the participants in receiving most results limited our ability to measure associations between participant characteristics and preferences. Our cohort had good genetic knowledge, likely related to their previous experience in genetic research, which may limit our ability to extend these observations to a population with more

diverse understandings of genetics. Additionally, the cohort had an overrepresentation of Jewish people compared to the US population, related to the composition of the parent studies and local referral patterns, which underscores the need to assess the impact of religion, including specific type of religion, in a more diverse population. The possible secondary results examined in this study represent a diverse group of conditions, but do not represent the full spectrum of possible secondary findings or all results that can be returned from an exome. This was a study of preferences in a hypothetical choice paradigm and there may be differences between expressed intentions and actual decisions to learn about secondary results. We are currently completing a study examining the responses of participants who were offered the opportunity to receive actual secondary results.

Practice Implications

Our observations are of particular importance for genetic counselors and other health care providers and researchers who are obtaining consent, providing counseling, and returning secondary findings. Guiding participants through these decisions is complex, and our findings highlight the importance of having qualified individuals trained in culturally sensitive counseling and use of effective educational tools. Preferences to receive secondary results from genetic research studies are varied, but the majority of research participants prefer having all results available. Although the characteristics of the disease risk identified (degree of risk and availability of effective medical treatment, screening and prevention)—which are often the focus of the medical community—influence participants' decisions, they are not the only factors participants consider. Participant characteristics, including religion, education, value placed on genetic privacy, and family history of a medical condition, also influence decisions.

Research Recommendations

Studies of participants who are making real-world choices about receiving secondary genomic results, rather than responding to hypothetical scenarios, will provide insight into how or if expressed preferences differ from actions, as well as illuminate the psychological effects and clinical utility of these types of results. Our future studies will also better address the diversity of possible secondary results and the complexities of informed consent and disclosure of select results according to participants' preferences. Additional research is needed on larger, more diverse cohorts to further understand the effects of cultural, demographic, and psychosocial factors on decisions regarding secondary results and genomic screening. Future research should target under-represented populations including minorities, younger people, and people of lower education level and socioeconomic status. Complete representation of the views and opinions of all stakeholders is vital to the ethical and responsible implementation of genomic and precision medicine.

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Compliance with Ethical Standards

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Conflict of Interest Julia Wynn, Josue Martinez, Jimmy Duong, Codruta Chiuzan, Jo C. Phelan, Abby Fyer, Robert L. Klitzman, Paul S. Appelbaum and Wendy K. Chung have no conflict of interests.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Human Studies and Informed Consent All procedures performed in this study were in accordance with the ethical standards of the CUCM and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants for being included in the study.

Animal Studies No animal studies were carried out by the authors for this article.

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