Preferences Regarding Return of Genomic Results to Relatives of Research Participants, Including after Participant Death: Empirical Results from a Cancer Biobank

Carmen Radecki Breitkopf, Gloria M. Petersen, Susan M. Wolf, Kari G. Chaffee, Marguerite E. Robinson, Deborah R. Gordon, Noralane M. Lindor, and Barbara A. Koenig

Introduction

Biobank data and samples frequently endure beyond the life of the individual who provided the sample; this is particularly true for biorepositories that archive data and samples from cancer patients. Those data and samples may be used for research, including after the death of the individual. When the research produces genetic research results (a term used here to include incidental findings and individual research results) that have potential health or reproductive importance for the individual who provided the sample, the results may also have importance for blood relatives. This raises the question of whether the research results should be shared with relatives, at their request or at the initiative of the researchers. The issues are complex even when the research participant is alive, but are particularly challenging after the death of the individual whose data and sample are archived, as the individual may not have been asked their preferences about sharing with family, including after death. Even if the individual's preferences on sharing have been elicited, investigators and biobank directors may be concerned about withholding genetic research results from relatives that are of potential health significance.

A literature has begun to emerge offering policy and legal perspectives as well as ethical arguments on return of an individual's results to relatives and the balance of interests between the deceased research participant and the decedent's family.[1] However, few studies report data on the attitudes of cancer biobank participants toward return of genetic research results to relatives, including after death of the participant.[2] Empirical data are needed to inform and shape emerging policy and practice. In one recent exploratory study of preferences for disclosure of genetic research results in participants in the OurGenes, OurHealth, OurCommunity biobank, more than half of the individuals surveyed indicated they would want post-mortem return of their own results to a biological relative.[3] Other reports, including two qualitative studies addressing public preferences and one population-based study in the Netherlands, have shown that individuals recognize and value learning genetic research information in principle, due to its meaningfulness and potential benefit to family members.[4] While these studies provide an important first step in understanding views on return of genetic research results to family, additional research is needed that directly assesses the attitudes and preferences of biobank participants and their family members. To fill this gap, we conducted a survey of perspectives on offering genetic research results to family members. This survey was undertaken as part of a project funded by the National Institutes of

Health (NIH) on return of results to relatives, producing empirical research as well as consensus guidance.[5] Our study examined the attitudes and preferences of individuals participating in a pancreatic cancer biobank, a family member registry on pancreatic cancer, and generally healthy individuals receiving a general medical exam; all three groups were recruited at Mayo Clinic in Rochester, Minnesota. Biobank participants were those with a diagnosis of pancreatic cancer (probands/affected individuals) who participated in Mayo Clinic's National Cancer Institute (NCI)-funded pancreatic cancer Specialized Program of Research Excellence (SPORE). Family members, including blood relatives and spouses/partners, were participants in a related pancreatic cancer family registry. The question of return of results to relatives is an important one for individuals with pancreatic cancer and their family members, as pancreatic cancer is difficult to detect early and is rapidly fatal, and approximately 10% of pancreatic cancers may be due to susceptibility genes.[6] Genetic and genomic research on pancreatic cancer is likely to uncover mutations in genes (e.g., *BRCA1* and *BRCA2*) of participants that may increase risk for other cancers, such as breast and ovarian cancers.[7] Genetic and genomic research may additionally discover incidental findings of further potential health importance.[8]

Our study examined the attitudes and preferences of individuals participating in a pancreatic cancer biobank, a family member registry on pancreatic cancer, and generally healthy individuals receiving a general medical exam; all three groups were recruited at Mayo Clinic in Rochester, Minnesota. Biobank participants were those with a diagnosis of pancreatic cancer (probands/affected individuals) who participated in Mayo Clinic's National Cancer Institute (NCI)-funded pancreatic cancer Specialized Program of Research Excellence (SPORE). Family members, including blood relatives and spouses/partners, were participants in a related pancreatic cancer family registry.

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I. Methods

A. Study Population and Survey Methodology

The sampling frame was comprised of a total of 6,103 individuals: 840 probands in a pancreatic cancer biobank who had a diagnosis of pancreatic adenocarcinoma, 2,471 family members in the pancreatic cancer family registry (reflecting 1,781 blood relatives and 690 spouses/partners), and 2,792 healthy individuals who were patients attending a general medical exam at Mayo Clinic (referred to as "controls" in this study). Controls consented to provide data for pancreatic cancer research and were frequency-matched to pancreatic cancer biobank probands on sex, residence (neighboring five-state area: MN, WI, IA, SD, ND), race/ethnicity, and age (in 5-year increments).[9]

Survey packets were mailed in three waves between July and September 2013, with two follow-up mailings sent to non-responders at 30-day intervals. Packets included an invitation letter containing a description of the purpose of the study and the voluntary nature of participation, a survey booklet, a postage-paid return envelope, and a toll-free telephone number to allow those not wishing to participate to call, in order to opt out of receiving additional survey mailings. Permission to use responses for research purposes was implied by survey completion and return. The research was approved by the Mayo Clinic Institutional Review Board under expedited review procedures for minimal risk research.

B. Survey Development

The content of the survey was developed by our team and guided by qualitative work consisting of 51 in-depth interviews with pancreatic cancer patients and family members sampled from the biobank.[10] Interview participants were subsequently excluded from participation in the survey portion of the study. Survey development was also aided by general discussion among members of the NIH-supported Clinical Sequencing Exploratory Research (CSER) Consortium Outcomes and Measures Working Group.[11]

Initial survey questions underwent pilot testing among 36 individuals at an educational symposium on pancreatic cancer for understandability and to determine the adequacy of response options. Items were revised based on the results obtained during pilot-testing. The revised survey was presented to a 5-member pancreatic cancer patient advocacy group associated with the biobank who considered face validity and clarity of the items and provided feedback on the survey design and appropriateness of the response metrics. Further refinement led to a final survey booklet containing the following nine sections: "Research Participation and Opinions," "About Your Family," "Views on Genes and Health," "Genetic Testing Experience," "An Example from Genetic Research," "Practical Considerations in Genetic Research," "How to Return Genetic Research Results," "Genetic Research Results and Privacy," and "About You." The full content of the survey can be viewed on the website for the University of Minnesota's Consortium on Law and Values in Health, Environment & the Life Sciences (http://consortium.umn.edu/).

Survey questions were primarily close-ended items with Likert response scales. Questions with "yes" or "no" response options also included "not sure" or "I don't know" options where applicable; for these items, "yes" responses are reported, with "no," "not sure" or "I don't know" collapsed to create a dichotomous variable to reflect absence of endorsement. To assess attitudes across a variety of items, a 5-point Likert rating scale was used with the descriptors "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree." To reduce reporting complexity, responses were dichotomized; the responses "agree" and "strongly agree" were combined to reflect agreement, while "strongly disagree," "disagree," and "neither agree nor disagree" were combined to reflect absence of agreement.

The first four sections of the survey assessed general expectations about participating in genetic research and experience with genetic testing. They also captured the vital status (living or deceased) of selected first-degree blood relatives including biological parents, biological siblings, and biological children.

The fifth section of the survey, "An Example from Genetic Research," was designed to access perceptions about return of an individual's genetic research results to relatives for three types of results: (1) a new gene related to pancreatic cancer risk, (2) the *BRCA2* mutation which has potential health implications, and (3) a gene indicating carrier-status for the *CFTR* gene (cystic fibrosis) which thus has potential implications for offspring. The particular gene mutations included in the hypothetical scenarios reflected actual results (incidental findings) that were obtained from testing samples in the pancreatic cancer biobank at Mayo Clinic. Based on the formative interviews, preferences regarding offering these results to relatives were examined using the example of a hypothetical participant named "Pat." "Pat," a name chosen purposefully to be gender neutral, was presented alternatively as being: (1) alive at the time of the genetic discovery, or, as the scenario unfolded, (2) deceased at the time the discovery is made, with or without having stated prior wishes about offering genetic results to family. The hypothetical scenarios were presented as "Pat's Story," with Pat being described as a 58-year-old individual diagnosed

with pancreatic cancer in 2009 who enrolled in a cancer biobank and provided a blood sample for research. Pat has a spouse and two biological children: a daughter age 22 and a son age 24. In Part 1 of the story, a new gene related to pancreatic cancer risk is discovered and found to be present in Pat's blood sample. In Part 2 of the story, researchers find a mutation in the *BRCA2* gene in Pat's sample in 2012, and the implications for Pat's children are described. In Part 3 of the story, Pat's blood sample tests positive for the cystic fibrosis mutation, although Pat does not have the disease; carrier status and risk of inheritance in Pat's children and future potential grandchildren are outlined. After each part of the story, a series of eight statements were presented with a 5-point "strongly disagree" to "strongly agree" rating scale. The statements were prefaced with the following: "Please remember that 'offering' results means that the person is given the option of saying 'yes' or 'no' to actually learning the result. The result is not provided unless the person says 'yes' to the offer" (emphases in the original). The statements addressed return of results to Pat, privacy and dissemination of information within the family, offering results when Pat's wishes are unknown, and honoring Pat's wishes when known, before and after death. After reading the Pat scenarios, respondents were asked to consider their attitudes toward sharing or keeping private *their own* genetic research results (assuming they were medically useful).

The section on "Practical Considerations in Genetic Research" addressed two key policy-related issues in genetic research — the right not to know genetic results and the tension that may arise between respecting the source individual's wishes concerning sharing with family and the potential for family health benefit. This section included forced-choice items that instructed respondents to "select only ONE of the following two statements that best reflects your opinion about offering results" (emphasis in original). The first of these addressed protecting the right not to know ("Not offering results to any research participants, in order to protect those who do not want to know genetic research results, is the right thing to do," or "Offering genetic research results to all research participants, even at the risk of upsetting those who may not want to be offered results, is the right thing to do."). The second addressed the potential tension between respecting the individual wishes of the participant on sharing and family benefit ("The most important factor to consider in returning genetic research results is the wishes of the person who provided the sample," or "The most important factor to consider in returning genetic research results is whether blood relatives will benefit."). Additional items captured preferences regarding who should make decisions about offering genetic information after a research participant dies, if the participant's wishes about return to family were not documented before death; whose responsibility it is to initiate consideration of return of genetic research results (the research participant or the researcher who makes the discovery); and at what cost to the research.

The following section, "How to Return Genetic Results," queried the types or characteristics of genetic research results that "should," "could," or "definitely should not" be offered to research participants or family members. These items reflected result characteristics such as actionability, disease severity, and result certainty. The last two sections in the survey addressed concerns regarding the privacy of genetic research results within and outside the family and captured respondent demographic information.

C. Statistical Analyses

Statistical analyses were performed using SPSS, version 21 (IBM Corp.). Descriptive data are presented as frequencies (n) and percentages (%) based on the denominator of those responding to the item (excluding missing data). For ease of presentation, Likert-scale responses are dichotomized as described above, and percent agreement is reported. For selected variables, group differences between pancreatic cancer biobank participants (including affected probands, spouses/partners, and biological relatives) and controls were evaluated to examine patterns in the data. Group differences in categorical variables (such as agreement vs. absence of agreement) were evaluated using z test of proportions, chi-square, or Fisher's Exact tests where appropriate; P values are reported in conjunction with the evaluation of group differences. In light of the multiple comparisons performed, we considered P values ≤ 0.01 statistically significant and performed a modified Bonferroni adjustment[12] to control for inflated error rates due to performing multiple comparisons on the data where appropriate. Preliminary results were presented at the 2014 Annual Meetings of the American Society of Human Genetics and the American Society for Bioethics and Humanities.[13]

II. Results

A total of 3,630 surveys were returned, reflecting an overall response rate of 59.5%, using the standard definition of response rate involving mail surveys of specifically named persons.[14] A lower survey response rate was observed for cancer biobank and family registry participants as compared with controls (57.5% vs. 61.9%, $P<0.001$), a difference driven primarily by a 55.2% response rate among probands/affected individuals who may have found it difficult

Table 1

Characteristics of Survey Respondents (N=3,630)

Characteristic	All Respondents N=3630 n (%)	Controls n=1727 n (%)	Pancreatic Cancer Biobank Participants (Proband/ Affected) n=464 n (%)	Family Registry Participants (n=1439)	
				Blood Relative n=1040 n (%)	Spouse/Partner n=399 n (%)
Sex					
Male	1566 (43.1)	859 (49.7)	231 (49.8)	339 (32.6)	137 (34.3)
Female	**2064 (56.9)**	**868 (50.3)**	**233 (50.2)**	**701 (67.4)**	**262 (65.7)**
Age, years					
Mean (SD)	66.2 (12.2)	69.0 (10.8)	66.4 (11.3)	60.3 (13.4)	69.1 (10.4)
Range	23-99	32-96	29-94	23-99	38-94
Median	67	69	66	61	70
Race					
White	**3512 (98.2)**	**1671 (98.4)**	**444 (97.4)**	**1012 (98.4)**	**385 (98.0)**
Black/African American	13 (0.4)	5 (0.3)	4 (0.9)	4 (0.4)	0 (0)
Asian	18 (0.5)	8 (0.5)	3 (0.7)	4 (0.4)	3 (0.8)
Hawaiian/Pacific Islander	2 (0.1)	0 (0)	0 (0)	0 (0)	2 (0.5)
American Indian/AK Native	18 (0.5)	8 (0.5)	3 (0.7)	5 (0.5)	2 (0.5)
Other	12 (0.3)	6 (0.3)	2 (0.4)	3 (0.3)	1 (0.3)
Missing	55	29	8	12	6
Hispanic Ethnicity					
Yes	30 (0.8)	12 (0.7)	6 (1.3)	8 (0.8)	4 (1.0)
No	**3540 (99.2)**	**1686 (99.3)**	**446 (98.7)**	**1020 (99.2)**	**388 (99.0)**
Missing	60	29	12	12	7
Marital status					
Married/Life partner	**2687 (75.5)**	**1408 (83.2)**	**377 (83.2)**	**797 (78.0)**	105 (26.9)
Separated/Divorced	194 (5.5)	79 (4.7)	37 (8.2)	78 (7.6)	0 (0)
Widowed	538 (15.1)	143 (8.4)	27 (6.0)	82 (8.0)	**286 (73.1)**
Single/never married	140 (3.9)	63 (3.7)	12 (2.6)	65 (6.4)	0 (0)
Missing	71	34	11	18	8
Education					
High school or less	688 (19.2)	338 (19.9)	111 (24.4)	157 (15.2)	82 (20.9)
2 year college/technical school	1142 (31.9)	515 (30.3)	140 (30.8)	343 (33.3)	144 (36.6)
4 year college or greater	**1748 (48.9)**	**848 (49.9)**	**203 (44.7)**	**530 (51.5)**	**167 (42.5)**
Missing	52	26	10	10	6
Employment[†]					
Not employed	229 (6.4)	87 (5.1)	62 (13.7)	67 (6.5)	13 (3.3)
Employed	1405 (39.4)	572 (33.7)	141 (31.2)	**577 (56.2)**	115 (29.4)
Retired	**1931 (54.2)**	**1037 (61.1)**	**249 (55.1)**	382 (37.2)	**263 (67.3)**
Missing	65	31	12	14	8
Health insurance coverage					
No	43 (1.2)	12 (0.7)	3 (0.7)	22 (2.1)	6 (1.5)
Yes (private, employer, public)	**3530 (98.8)**	**1686 (99.3)**	**451 (99.3)**	**1006 (97.9)**	**387 (98.5)**
Missing	57	29	10	12	6
Prior experience with genetic counseling					
Yes	324 (9.1)	78 (4.6)	56 (12.3)	158 (15.4)	32 (8.2)
No/Unsure	**3239 (90.9)**	**1614 (95.4)**	**398 (87.7)**	**871 (84.6)**	**356 (91.8)**
Missing	67	35	10	11	11

[†]Not employed = full-time or part-time student, unemployed, homemaker, unable to work due to disability; Employed = full-time or part-time employment, employed but on medical leave; Retired = retired, or retired but working part-time.

to respond due to disease burden. A lower response rate was observed among males as compared with females (56.5% vs. 62.3%, $P<0.001$). Missing data were minimal, ranging from <1% to 3% across survey items. Missing data were closer to 3% for forced-choice type items and closer to 1% for Likert-scale responses. No other patterns were observed with regard to missing data.

Survey respondents were predominantly white, non-Hispanic, highly educated individuals (nearly half with 4 years of college or more) with health insurance coverage (Table 1). A greater proportion of cancer biobank and family registry participants (13.1% across probands, blood relatives, and spouse/partners) reported prior experience with genetic counseling as compared with controls (4.6%) ($P<0.001$). Overall, 85.1% (n=3,044) of respondents had biologically-related children who were still living, suggesting personal relevance of the survey questions; this proportion did not differ between cancer biobank and family registry participants *versus* controls (84.4% *vs.* 85.8%, P=0.26). When compared with controls, however, cancer biobank and family registry participants reported higher proportions of living, biologically-related family members: 89.2% of cancer biobank and family registry participants reported one or more biologically-related siblings who were still living (*vs.* 85.5% controls, $P<0.001$), 27.5% of cancer biobank and family registry participants reported their biological mother was still living (*vs.* 23.5% of controls, P=0.007), and 14.5% of cancer biobank and family registry participants reported their biological father was still living (*vs.* 11.5% of controls, P=0.009). After adjusting the alpha level for multiple comparisons, only the group difference in biological siblings remained statistically significant.

A. Expectations and Attitudes Regarding Return of Genetic Research Results to Participants

Overall, 62.1% (n=2,192) of respondents "expected to learn something about their own genetic results" as a research participant (63.3% of cancer biobank and family registry respondents and 60.8% of controls, P=0.12). Of those who did expect to learn something, 98.8% (99.3% of cancer biobank and family registry respondents and 98.2% of controls, P=0.03) expected to be told "if researchers found something bad (a health risk)" in their blood sample, while 84.6% (88.3% of cancer biobank and family registry respondents and 80.2% of controls, $P<0.001$) expected to be told "if researchers found something good (I did NOT have a particular health risk)" (emphasis in original) in their blood sample. When asked to assume that the results would be medically useful, 96.2% (n=3,462) of the sample would want to know their genetic research results, and 77.7% (n=2,792) would want researchers to inform their health care provider about their genetic results.

Overall, only 5.4% (n=193) of the sample agreed that they would want genetic research results to be kept private, even after their death (6.5% of controls *vs* 4.4% cancer biobank and family registry participants, P=0.01). Only 1.8% (n=67) of the sample (1.7% of cancer biobank and family registry respondents and 2.0% of controls, P=0.62) indicated that they "would NEVER want to be offered genetic research results from their sample or a family member's sample" (emphasis in original). When forced to weigh "offering results to all research participants" (at the risk of upsetting some) against "not offering results to any participants" (protecting the participants' right not know), 86.5% (n=3,038) of survey respondents chose offering results to all, while 13.5% (n=473) chose not offering results to any in order to protect those who do not want to know genetic research results. These proportions did not differ significantly between cancer biobank and family registry participants as compared with controls (P=0.03) based on our threshold of significance.

Over three-fourths (76.7%, n=2,750) of the sample indicated it was the researcher's responsibility to offer genetic research results to research participants, with the remainder (23.3%, n=835) indicating that the responsibility should rest with the research participant to ask for genetic research results found in the sample. Two additional items probed researchers' duty to offer results as it relates to cost and their job responsibilities. Overall, 68.5% (n=2,459) agreed that researchers should offer results to participants, no matter how much money it costs. Only 14.2% (n=512) agreed with the statement, "Researchers should NOT be required to offer genetic results because it's not their job" (emphasis in original).

B. Responses to the Hypothetical "Pat" Scenarios

The responses to the statements addressing return of genetic research results were quite similar across the three "Pat" scenarios depicting different genetic findings: a new gene discovery related to pancreatic cancer risk, a *BRCA2* mutation, and a *CFTR* gene mutation, although the responses for the known gene mutations (*BRCA2* and *CFTR*) were more similar to each other than to the responses for the scenario depicting the new gene related to pancreatic cancer risk. The statements and responses for each of the genetic findings are shown in Table 2. A large majority of respondents (>90%) favored returning genetic research results to Pat while Pat was still

Table 2

Percent Agreement across All Respondents to Offering Results across 3 Hypothetical Scenarios Involving the Following Findings: A New Gene Related to Pancreatic Cancer Risk, a Known Cancer Risk Factor Gene Mutation (*BRCA2*), and a Mutation Revealing Carrier Status (*CFTR*) and Involving Reproductive Implications

Pat's Vital Status	Statement (emphases in original survey)	Percent Agreement when [finding] is:		
		Pancreatic cancer gene	*BRCA2* gene mutation	*CFTR* gene mutation
ALIVE	Researchers should offer Pat the information about the [*finding*] discovered in Pat's sample	94.6 %	98.2 %	98.1%
	Pat should be able to keep information about the [*finding*] private from others in the family	34.8 %	32.7 %	31.8%
	Pat, not the researchers, is responsible for sharing the information about the [*finding*] with blood relatives (biologically-related family members)	67.8 %	59.0 %	59.3 %
DECEASED	Researchers should ONLY offer Pat's information about the [*finding*] to blood relatives if Pat has given EXPLICIT PERMISSION to share genetic results	72.6 %	61.7 %	60.0%
	If the new discovery is made AFTER PAT'S DEATH, the information about the [*finding*] should be offered to Pat's spouse	88.9 %	92.0 %	92.8%
	If Pat's spouse REFUSES the offer of information about the [*finding*], researchers should offer the results directly to Pat's children	69.5 %	76.7 %	76.9%
	If the new discovery is made AFTER PAT'S DEATH, and Pat's wishes about sharing genetic information are UNKNOWN, the information about the [*finding*] should be offered to Pat's blood relatives	83.4 %	87.1 %	86.8%
	If the new discovery is made AFTER PAT'S DEATH, and Pat previously said NOT TO SHARE genetic information, the information about the [*finding*] should NOT be offered to Pat's blood relatives	37.7 %	32.2 %	31.2%

alive (98% in the *BRCA2* and *CFTR* gene mutation scenarios and 95% in the new pancreatic cancer gene scenario). Only about one-third of respondents agreed that Pat should be able to keep the genetic result private from others in the family (32-33% in the *BRCA2* and *CFTR* gene mutation scenarios and 35% in the new pancreatic cancer gene scenario). After Pat's death, a considerable majority (around 90%) agreed that genetic research results should be offered to Pat's spouse, and many (77% in the *BRCA2* and *CFTR* mutation scenarios and 70% in the new pancreatic cancer gene scenario) agreed with offering the results directly to Pat's adult, biological children if Pat's spouse refused the offer of information. When Pat was deceased and Pat's wishes about sharing genetic results were unknown, greater than 80% of respondents agreed that the information should be offered to Pat's blood relatives. Finally, after Pat's death in the scenarios, if Pat previously stated wishes not to share genetic information with blood relatives, only about one-third of respondents (31-32% in the *BRCA2* and *CFTR* scenarios and 38% in the new pancreatic cancer gene scenario) agreed that

Pat's wishes should be honored, with a majority of responses reflecting lack of agreement.

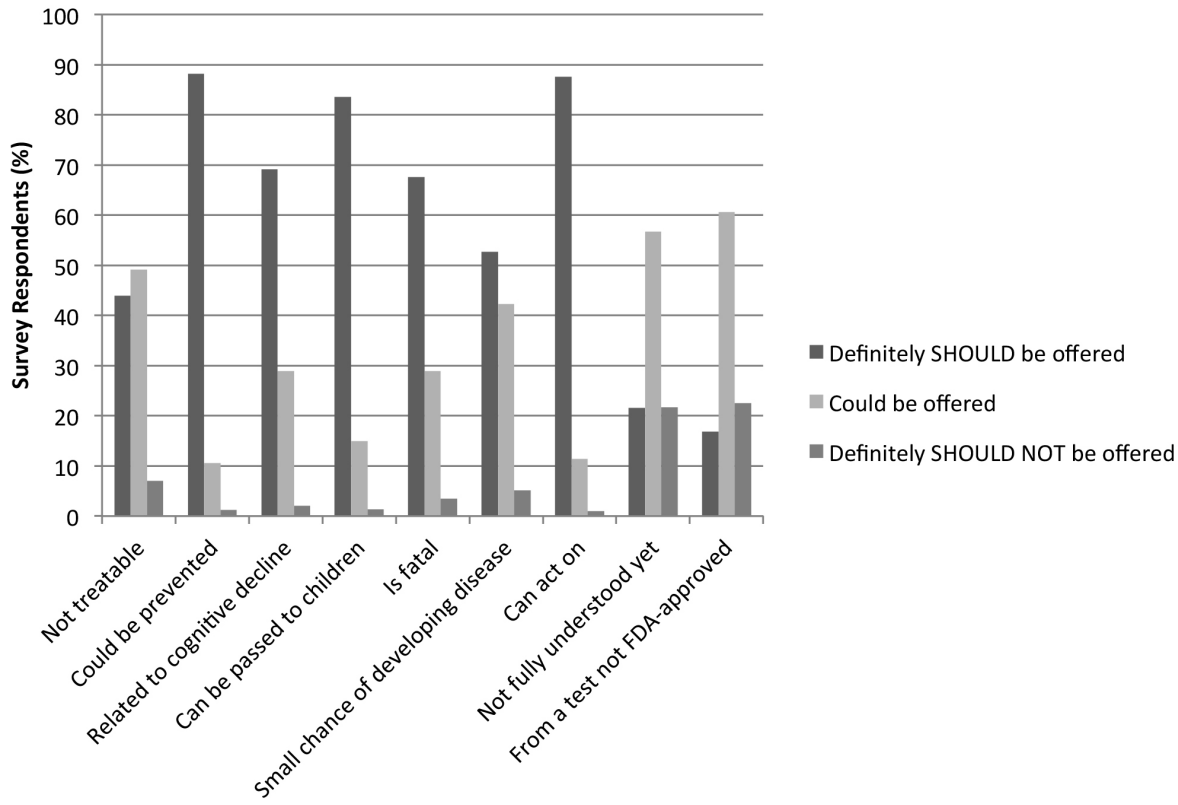
C. Attitudes Regarding the Type of Genetic Research Results that Should Be Shared and Who Should Decide

Figure 1 presents respondents' attitudes (i.e., definitely SHOULD be offered, could be offered, or definitely SHOULD NOT be offered (emphases in original)) toward offering genetic research results to participants or family members when the result has specified characteristics (e.g., can act on it, is related to a disease that is fatal, etc.). Over 80% of respondents indicated that genetic research results showing an increased risk for a disease that could be prevented or passed to children and a result providing information a person can act on definitely should be offered. These results are internally consistent with the pattern and proportion of responses observed in the Pat scenarios for sharing *BRCA2* and *CFTR* gene mutation results with blood relatives.

Respondents were presented with the item, "What if a research participant dies without saying whether his/her genetic information can be offered to family members? Who should make decisions about return of genetic information obtained from the blood sample?" with instructions to mark only one of the following options in response: (1) the research participant's spouse/partner, (2) blood relatives, (3) personal representative/executor of estate whether or not a blood relative, (4) primary care physician, (5) the researcher, or (6) other. Of the 93.4% (n=3,390) of respondents who adhered to the instructions (checked only one option), three-fourths chose a relative (with 39% choosing the spouse/partner and 36% choosing a blood relative), 8% chose "primary care provider," 7% chose "personal representative," 7% chose "researcher," and 3% selected "other." Importantly, the remaining 6.6% (n=240) of the sample either checked multiple options (2.4%) or did not check any of the options provided (4.2%), suggesting an unwillingness or inability to identify a single individual to make decisions about their sample after their death.

Figure 1

Attitudes Regarding Offering Genetic Research Results to Participants or Family Members by Characteristics of the Result



D. Expectations Regarding Privacy and Sharing Genetic Research Results with Relatives

We evaluated individuals' expectations about balancing proband privacy against sharing with relatives. This series of items was prefaced by the phrase, "assuming the results would be medically useful." Responses to these items were internally consistent (when phrased either in terms of privacy or in terms of sharing) and favored sharing within families overall, particularly when the respondents were cancer biobank or family registry participants rather than controls (Table 3). After adjusting for multiple comparisons, significant differences between cancer biobank and family registry participants versus controls remained for the items, "I would NOT want my blood relatives to know about my genetic research results" (greater proportion of controls favored privacy) and "I would feel OBLIGATED to share my genetic research results with my blood relatives" (greater proportion of cancer biobank and family registry participants felt an obligation to share with family) (emphases in original). In addition, 60.5% (n=2,162) of the sample indicated agreement with the statement, "Genetic information belongs to all blood relatives, not just the person who gave the blood sample." Specifically, agreement was 66.2% among probands, 66.0% among spouse/partners, 59.7% among blood relatives, and 58.3% among controls, reflecting a higher proportion of agreement among cancer biobank and family registry participants as compared with controls (62.6% vs. 58.3%, P=0.009).

Acknowledging that families are comprised of individuals who may not share the same opinions and that *offering* results is not the same as *actually learning* them, we queried participant's beliefs about agreement within their own families. Overall, 67.4% (n=2,422) of respondents agreed that all of their blood relatives would probably have the same opinion about *being offered* genetic research results. Specifically, agreement was 69.8% among probands, 69.5% among spouse/partners, 69.2% among blood relatives, and 65.2% among controls, reflecting a higher proportion of agreement among cancer biobank and family registry participants as compared with controls (69.4% *vs.* 65.2%, P=0.007). A somewhat lower proportion, 60.8% (n=2,182), agreed that all of their blood relatives would probably have the same opinion about *actually learning* genetic research results. Specifically, agreement was 65.2% among probands, 63.0% among spouse/partners, 59.7% among blood relatives, and 59.7% among controls, with no statistically significant difference observed between cancer biobank and family registry participants as compared with controls (61.7% *vs.* 59.7%, P=0.23).

Our study findings indicate that a majority of participants expected to learn their own genetic research results, would feel obligated to share their results with blood relatives while alive, and would want genetic research results to be shared with relatives after their death. Consistent with other reports on return of genetic research results, most respondents desired their own results and expected that researchers would extend an offer to learn them.

A forced-choice format was used to ascertain the more important factor to consider in returning genetic research results – the wishes of the person who provided the sample or whether blood relatives would benefit. Among controls, the two options were fairly evenly divided, with 48% (n=816) choosing the wishes of the individual and 52% (n=884) choosing whether blood relatives would benefit. Among cancer biobank and family registry participants, these options were more split, with 34.6% (n=158) of probands and 34.2% (n=134) of spouse/partners choosing individual wishes and 65.4% (n=299) of probands and 65.8% (n=258) of spouse/partners choosing relatives' benefit. Among blood relatives, 41.8% (n=427) chose the individual wishes of the person who provided the blood sample as being more important to consider in returning genetic research results over whether blood relatives would benefit (58.2%, n=594). The results of between-group comparisons using the z test of proportions demonstrate that controls significantly differed from probands (z=5.12), spouses/partners (z=4.95), and blood relatives (z=3.13) (all P<0.01).

III. Discussion

Our study findings indicate that a majority of participants expected to learn their own genetic research results, would feel obligated to share their results with blood relatives while alive, and would want

Table 3

Preferences Regarding Privacy and Sharing of Genetic Research Results with Blood Relatives. All Data Are Percentage Agreement % (*n*) with Each Statement, Where Agreement Includes the Responses "Agree" and "Strongly Agree"

Statement (emphases in original survey)	All Respondents	Pancreatic Cancer Biobank and Family Registry Participants	Controls	*P*[a]
I would NOT want my blood relatives to know about my genetic research results	9.0% (324)	7.5% (142)	10.7% (182)	0.001[b]
I would want my genetic results to be kept PRIVATE, even after my death	5.4% (193)	4.4% (82)	6.5% (111)	0.005
I would be OK with sharing my genetic research results with blood relatives who wanted to know them	93.8% (3371)	94.4% (1782)	93.0% (1589)	0.084
I would feel OBLIGATED to share my genetic research results with my blood relatives	85.9% (3090)	87.9% (1658)	83.8% (1432)	0.001[b]

[a]*P* value obtained when comparing pancreatic cancer biobank and family registry participants with controls using a 2-sided Fisher's Exact test.

[b]*P* value remained statistically significant after applying a modified Bonferroni adjustment.

genetic research results to be shared with relatives after their death. Consistent with other reports on return of genetic research results,[15] most respondents desired their own results and expected that researchers would extend an offer to learn them. When given a choice between protecting an individual's right not to know genetic results versus offering results to all, fewer than one in five respondents favored the former, even at the risk of upsetting some people by offering results.

On return to family, a consistent pattern emerged whereby the controls favored privacy and individual benefit proportionately more than the cancer biobank respondents and family registry participants, who favored family sharing and family benefit. The differences observed between groups warrants further investigation and replication in other research settings. These findings suggest that different populations (healthy patients presenting for medical examination *vs.* patients and blood relatives affected by a life-threatening cancer with potential heritability of genetic risk variants *vs.* spouses or partners of cancer patients) may differ in their perspective on the issue of return of results to relatives.

Our results were consistent with other reports suggesting that individuals recognize the potential value of genetic information to relatives[16] and highlight that for many research participants, there is a feeling of *obligation* to share their genetic results with blood relatives. Particularly when genetic research results show an increased risk of diseases that could be prevented or passed to children, or information a family member could act on, greater than 80% of respondents indicated the result definitely should be offered. This supports widening the scope of research and analysis on return of results beyond return to the participant, to the question of whether and how results should be offered to the family.

Through the use of a hypothetical scenario, we accessed attitudes toward post-mortem return to family that indicated a high level of support for sharing results with family members, *even if not authorized by the individual providing the sample or against the sample provider's wishes*. Our sample was split on honoring the previously expressed wishes of the (now deceased) research participant to not share results with family, with about two-thirds agreeing to go against the participant's expressed wishes to withhold information, particularly in the case of pathogenic and clinically actionable gene mutations, including results with reproductive implications (*BRCA2* and *CFTR*), and one-third expressing lack of agreement. These findings have potential ethical implications for researchers. Our results support the conclusion that the tension between participant control of dissemination of individual results after death and potential family benefit remains unresolved, calls for investigation in multiple populations, and requires a policy approach that considers differences of view.

As further evidence of support for sharing genetic research results with family members who may benefit, greater than 70% of respondents endorsed offering results directly to the sample provider's offspring in the case where a spouse refuses the offer of genetic results. This finding suggests that difficulties can arise when an individual designates a single gatekeeper of information within the family, particularly when that individual is not a blood relative, and the designated gatekeeper declines to share the information. Our observation that 6% of our sample was unable or unwilling to designate a single individual as the person responsible for decisions about sharing the participants' results after their death suggests that some participants may struggle with policies that necessitate such a selection/designation.

A number of survey strengths provide confidence in the data, including a favorable response rate resulting in a large sample size for all three groups of respondents (cancer biobank participants, family registry participants, as well as controls) and minimal missing data. We attribute these strengths to the careful pilot work that informed and shaped our survey design and methodology. Nevertheless, our study has some potential weaknesses including the socio-demographic homogeneity of the overall sample, and the fact that our sample may be biased toward well-educated individuals who were covered by some type of health insurance. These characteristics may limit the generalizability of our results. Lastly, it is possible that individuals who hold ambivalent or overly negative attitudes toward the topic of returning genetic research results may have been underrepresented among survey respondents. Although we are unable to assess this potential bias, we did attempt to minimize its impact by designing survey items and questions that included the ability to express negative, neutral, or unsure attitudes (as well as positive attitudes) regarding return of genetic research results to participants and family members.

The analyses presented in this paper offer primarily a descriptive presentation of our findings, with exploratory comparisons performed between controls and cancer biobank as well as family registry participants. To avoid capitalizing on our large sample size and potentially overstating the significance of our results, we took a conservative analytic approach by setting our initial alpha level at the more stringent $P<0.01$ versus the more traditional $P<0.05$, and by applying a modified Bonferroni correction when conducting multiple comparisons (statistical tests) on the data. In addition, we emphasize patterns of responses, de-emphasize statistical significance, and report the results of all comparisons performed to avoid over-interpreting what are sometimes modest observed differences between groups.

Conclusion

Our data demonstrate that a majority of individuals, but certainly not all, who provide blood samples for research prefer to be offered the opportunity to learn genetic research results generated from their sample. For many, this preference extends to offering their genetic research results to family members, particularly blood relatives, after their own death. In a scenario designed to avoid the inherent threat of directly considering *one's own* death, our data uncovered a split on whether to honor the proband's previously stated wishes to withhold genetic information from blood relatives, with about two-thirds favoring sharing with relatives (not honoring the proband's wishes) and one-third not agreeing to this. Finally, our data show that a number of factors are relevant to attitudes toward family return, including the type of genetic finding, characteristics of the disease associated with the genetic result, as well as the way in which the participant came into genetic research, that is, as a "healthy control," or as an individual affected by cancer directly (proband), or indirectly (family member of a proband).

Taken together, these findings suggest that biobanks and genomic research projects should consider the emerging policy and practice on whether and how a participant's research results may be shared within the family. In order to fully inform policy and guidelines about return of genetic research results to family, additional empirical studies are needed that assess the attitudes and preferences of more diverse populations across a variety of scenarios. Moreover, longitudinal studies are needed that investigate experiences with different models of return to family, with evaluation of psychological and behavioral outcomes in probands and family members.

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