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Research participant interest in primary, secondary, and incidental genomic findings

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Purpose: To define the frequency with which adult research participants consent to be offered clinically validated research genetic test results (RR) and incidental findings (IF).

Methods: Consents were obtained from 506 adults enrolled in one of three studies within the National Cancer Institute Clinical Genetics Branch's Familial Cancer Research Program. A cross-sectional analysis was performed involving the choices indicated on study consents regarding receipt of RR and IF.

Results: Ninety-seven percent opted to receive RR and IF. Participants who declined (n = 16) included two cancer survivors who were mutation-positive (1 = RR and 1 = both), eight who knew their primary mutation status (3 = RR; 4 = IF; 1 = both), three nonbloodline relatives (1 = RR; 2 = both), one untested but with the syndromic phenotype (1 = IF), and two parents of an affected child (2 = both). We speculate that these individuals either already had sufficient information, were not prepared to learn more, or felt that the information would not change their personal health-care decision making.

Conclusions: Adult research participants from families at high genetic risk for cancer overwhelmingly indicated their preference to receive both RR and IF. Future research will seek to identify the reasons for declining RR and IF and to study the impact of receipt of RR and IF on personal medical decision making.

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Key Words: familial cancer syndromes; genetic testing; incidental findings; intentions to receive research genetic results; whole genome/exome sequencing

INTRODUCTION

The use of next-generation sequencing technologies (most commonly, whole-exome sequencing (WES) and whole-genome sequencing (WGS)) in research into the etiology of familial cancer syndromes has led to the identification of rare, highly penetrant genetic variants responsible for the increased rates of cancers in highly selected families.[1] At the same time, this technology has resulted in the identification of incidental and secondary findings with uncertain or known clinical utility.[2] "Incidental findings" are generally understood to comprise findings unrelated to the primary intent of a specific test that are "stumbled upon" in the course of analyzing research data; they may be either "anticipatable" or "unanticipatable."[3] Secondary findings are defined as variants in genes that are not the primary focus of a specific test but are specifically and deliberately analyzed because they have been defined a priori as potentially medically actionable genetic loci (not necessarily related to the disorder undergoing study) that are unavoidably interrogated when using diagnostic WGS and WES.[3] There is a growing belief in the genetics and ethics communities that investigators must at least consider disclosing such abnormalities to those being tested because this information is potentially of great importance in their general medical care and that of their relatives.

Position statements from the American College of Medical Genetics and Genomics (ACMG) recommend that laboratories performing clinical sequencing: (i) obtain written informed consent regarding how these findings will be handled (after a discussion of the interpretive uncertainty, privacy, and the potential impact on other family members), (ii) seek out and report "pathogenic variants that may predispose to a severe but preventable outcome" to individuals being tested that are detected in specific classes or types of genes,[4] (iii) follow the same policy for children as for adults, and (iv) offer parents of tested children the option to decline disclosure of incidental and secondary findings.[5] EuroGenTest and the European Society of Human Genetics recently presented guidelines for diagnostic next-generation sequencing, including a rating system for diagnostic tests. The rating system provides information relevant to the coverage and diagnostic yield and aims to allow comparison of testing offered between different laboritories.[6]

The acquisition of next-generation sequencing clinical data and their interpretation have resulted in an active, unresolved debate as to whether there is a similar obligation to screen for

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and report incidental and secondary findings to research study participants. This is based on the idea that some specific results might be medically actionable; i.e., knowledge of their presence could significantly alter management and future health of the individual. The dominant view among genomic researchers, genomic health professionals, and the public supports the return of all genomic *research* results (i.e., when a causative gene is identified as the basis for the disorder being studied, as a secondary finding, or as an incidental finding) when there is perceived clinical utility and when the research result has been validated in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, even when these stakeholders did not expect researchers to deliberately screen for incidental and secondary findings in the research setting.[7]

Only limited data (primarily from small studies) exist regarding adult participants' interest in and intention to receive *research* genetic test results (RR), incidental findings (IF), and secondary findings obtained from WES and WGS for use by themselves and their relatives. A study among adults to determine motivations for participating in WGS research (n = 322) identified altruism and the expectation that the genetic research will improve the understanding of the etiology of disease, leading to the development of treatments for disease, as the main motivating factors.[8] Adult participants enrolled in the National Human Genome Research Institute's ClinSeq study expressed nearly universal intention (294/311; 95%) to receive all types of genetic test results, including carrier status and results with no known clinical utility, in the hope that this information would help either themselves or their relatives to improve their health outcomes.[9] As in previous reports, adults (n = 35) undergoing personal WGS/WES indicated that they would like to receive all WGS/WES results (94%), including the raw data (89%); however, at the same time, they expressed worry about the emotional impact and the privacy of the results.[10] On the other hand, among adults referred for clinical diagnostic sequencing, a greater number declined to consent to receipt of at least one category of secondary finding (e.g., a recessive trait, a cancer predisposition syndrome, an adult-onset disease predisposition, or an early-onset disease) for themselves (6/38; 16%) and for their children (7/162; 4%).[11] In a population-based study of sarcoma patients, their spouses, and selected family members (n = 1,200) evaluating attitudes toward genomic and incidental findings from genetic research,[12] approximately 60% thought favorably of genetic testing for an inherited condition, and virtually all the participants were receptive to receiving IF when there was clinical utility. In another study, adult patients (13/19; 68%) who were clinically diagnosed with Lynch syndrome and had previously received uninformative Lynch syndrome genetic results (i.e., high tumor microsatellite instability in the absence of mismatch repair protein expression by immunohistochemistry or a family history suggestive of Lynch syndrome, or uninformative comprehensive testing of the Lynch syndrome–associated genes) indicated that they would like to undergo WES testing and receive all possible results from WES, even variants of unknown significance.[13]

Findings related to parents' motivations and intentions to receive genetic research results for their children are somewhat more varied. In one study, parents (25/25; 100%) were interested in disclosure if the genetic abnormality was the cause of their child's condition and if that condition was treatable. They were interested in disclosure of secondary variants only when the associated condition was treatable or preventable. However, fewer (10/25; 40%) wanted to learn about secondary variants for untreatable conditions. Six parents did not want to learn any results, 9 were ambivalent or placed restraints on the type of information being disclosed, and 13 wanted to learn if they were carriers of an autosomal recessive trait.[14] In an online survey of parents' (n = 219) interest in obtaining multiplex genetic testing of their children for diverse common adult-onset diseases, all enrolled participants were inclined to have their children tested despite the lack of evidence of benefit for children.[15] Finally, parental uptake of genetic testing of *TP53*, the tumor-suppressor gene mutated in Li–Fraumeni syndrome, was high for children (159/172 families; 92%), with 137/144 (95%) families using diagnostic testing (to learn whether their family carried a pathogenic *TP53* variant) and 22/28 (79%) using predictive testing (to learn whether a family member carried the specific *TP53* variant already known to exist in their family).[16]

Study aims

We conducted a cross-sectional analysis of study subjects' responses to define the frequency with which adult clinical research participants consented to being offered clinically validated, research genetic test results (RR) and incidental findings (IF) among members of families at high genetic risk for cancer who were participants in a familial cancer research program. We developed the consents for each research study in 2012, before the distinction between "incidental" and "secondary" findings was clearly articulated in the literature.[3] Therefore, we defined two groups of research findings within the consents: (i) primary genetic research results (RR) (i.e., both new genes relevant to the condition being studied and genetic modifiers) and (ii) other genetic findings as incidental findings (IF). We assumed that adult participants who had enrolled in research studies designed to discover the underlying genetic basis of a rare hereditary syndrome or to improve cancer-detection methods in rare cancer syndromes would want to receive all types of genetic results, including clinically validated, incidental genetic findings that were not the primary focus of our research.

MATERIALS AND METHODS

Study population

The National Cancer Institute (NCI) Clinical Genetic Branch's Familial Cancer Research Program encompassed several studies actively accruing family members, including the Li–Fraumeni Syndrome Study (LFS; NCI Protocol 11-C-0255; NCT-01443468; http://lfs.cancer.gov); Inherited Bone Marrow Failure Syndromes (IBMFS; NCI Protocol 02-C-0052; NCT-00027274; http://marrowfailure.cancer.gov); and Familial Testicular Cancer (NCI Protocol 02-C-0178;NCT-00034424;

Box 1 Consent sample language: research results

Research Results from Genetic Research
In the course of this study, we might identify a genetic change that is felt to alter the cancer risk associated with XXX in such a way that may potentially change clinical management. If such a finding is found and a clinical test for it is available, we will send you a letter to inform you of the finding. The results will need to be confirmed in a clinical laboratory. You can choose to 1) not receive this information at that time, or 2) receive the information but not have clinical testing done, or 3) receive the information and have clinical testing done to determine whether you have this change. Please let us know your preference by initialing one of the following statements:

_[]____I DO NOT want to be contacted if genetic variants which could potentially alter cancer risk associated with XXX are discovered.
_[]____I DO want to be contacted if genetic variants which could potentially alter cancer risk associated with XXX are discovered.

Box 2 Consent sample language: incidental findings

Incidental findings from whole-genome or exome sequencing
One research focus of this study is to look for changes in genetic material (DNA) that could potentially alter cancer risk associated with XXX. In the process of looking for these changes, we might find changes that are not directly related to cancer risk or to XXX, but might be related to other illnesses. These are known as "incidental medical findings." If we found changes that are known to cause a certain medical condition, or if we found changes that we think are of clinical utility, we will plan to contact you with the information, unless you prefer not to be contacted for such information. Please let us know your preference by initialing one of the following statements:

_[]___I DO NOT want to be contacted if genetic changes with potential health implications unrelated to XXX or cancer risk are discovered.
_[]___I DO want to be contacted if genetic changes with potential health implications unrelated to XXX or cancer risk are discovered. You can choose to not receive the information when you are contacted.
If we find gene changes that are not known to be important at this time, we will not share that information with you.

http://familial-testicular-cancer.gov./CGB.html). Probands, spouses, and their relatives (either affected or unaffected with the relevant syndrome or cancer or other targeted disease) were participants in these institutional review board–approved longitudinal cohort studies at the NCI, and all subjects provided written informed consent in accordance with Department of Health and Human Services regulation 45 CFR 46. The Clinical Genetics Branch (CGB) integrated specific language soliciting the participants' preferences for receipt of research and incidental genetic findings into these three consent documents beginning in January 2012 (Boxes 1 and 2). Each study participant entered a field study cohort, and subsets of the field cohort entered the clinical cohort and were evaluated at the National Institutes of Health (NIH) Warren Magnuson Clinical Center. Members of the study team obtained consent from participants after a detailed discussion of the study, including its aims, benefits, and risks. Participants were offered a tiered approach to indicating whether they wished to receive primary genetic RR or IF.

The participants were also provided the opportunity to decline future re-contact, thereby limiting their direct participation in the initial visit. However, our research participants rarely declined future re-contact, and none of the participants in this analysis declined future re-contact. The consent document informed the participant that CGB's policy is to offer (but not require) return of RR and IF that have clinical utility after verifying the genetic alteration in a CLIA laboratory. Once those two conditions were met, the CGB research team would contact participants to inform them that a genetic finding that may be of clinical interest to them has been identified. Participants are offered the option to decline disclosure during initial consent and again at time of re-contact. If they agree to learn more about the RR or IF, then they are offered the opportunity to obtain genetic education, counseling, clinical testing, and disclosure. Research consent was obtained either during a clinical visit to the NIH Clinical Center or by telephone consent with study personnel. We obtained informed consent from 506 adult (age 18 years or older) participants enrolled in these three projects between January 2012 and March 2014.

Assessment of demographics and covariates

Participants completed self-administered questionnaires that captured data on factors that might influence their preference regarding receipt of RF and IF, including: age, race, education, marital status, children (yes/no), cancer-affected status, number of cancers diagnosed, and mutation status (carrier/noncarrier in a mutation-known family, unknown mutation status/untested). The study teams classified each family inheritance pattern (autosomal dominant/autosomal recessive/X-linked recessive, or unknown) after constructing a pedigree based on information from a family-history questionnaire completed by the proband or family contact in addition to information from medical records and from other relatives. If consented participants had not completed the self-administered questionnaire, then members of the study team reviewed the family pedigree to assess the

Table 1 Study-population demographics

	All studies	LFS	IBMFS	FTC
	n = 507	*n* = 220	*n* = 226	*n* = 21
Age	46 (18.0–90.3)	48 (18.19–90.0)	42 (18.0–90.3)	47 (21.2–89.1)
Gender				
Male	219 (43%)	90 (41%)	114 (43%)	15 (71%)
Female	288 (57%)	130 (59%)	152 (57%)	6 (29%)
Race				
White	475 (94%)	216 (98%)	238 (89%)	21 (100%)
Asian	8 (2%)	1 (0%)	7 (3%)	0 (0%)
Black	3 (1%)	2 (1%)	1 (0%)	0 (0%)
Other	8 (2%)	1 (0%)	7 (3%)	0 (0%)
Unknown	13 (3%)	0 (0%)	13 (5%)	0 (0%)
Education				
High school diploma or less	56 (11%)	17 (8%)	37 (14%)	2 (10%)
Any college or technical school	97 (19%)	43 (20%)	47 (18%)	7 (33%)
College graduate or professional degree	229 (45%)	141 (64%)	78 (29%)	10 (48%)
Unknown	125 (25%)	19 (9%)	104 (39%)	2 (10%)
Marital status				
Single	86 (17%)	21 (10%)	59 (22%)	6 (29%)
Married or long-term partner	380 (75%)	171 (78%)	197 (74%)	12 (57%)
Divorced/separated/widowed	41 (8%)	28 (13%)	10 (4%)	3 (14%)
Children				
No	126 (25%)	46 (21%)	64 (24%)	16 (76%)
Yes	381 (75%)	174 (79%)	202 (76%)	5 (24%)

FTC, familial testicular cancer; IBMFS, inherited bone marrow–failure syndrome; LFS, Li–Fraumeni syndrome.

demographics and covariates of individuals as reported in the family-history questionnaire.

Statistical analysis

We performed a cross-sectional analysis of the participants' choices as indicated on their study consent regarding receipt of RR and IF discovered through research. Descriptive statistics were used to summarize the participants' choices regarding receipt of RR and IF and participant characteristics. Bivariate comparisons were planned and stratified by choice, selected socio-demographic variables, affected status, variant status, and whether the participant had children.

Human-subjects protections: informed-consent documentation

The proposed analyses are fully consistent with the original research plan for the studies as described in the original protocols and related informed-consent documents.

RESULTS

The study population was primarily white, well educated, and married with children (Table 1). In addition, 74% of the individuals were unaffected with cancer and 32% were known or obligate mutation carriers of a known cancer-susceptibility gene, with the latter determined by pedigree analysis (Table 2). Of the 506 individuals who signed informed consent documents, only 16 (3%) indicated that they did not want to receive genetic RR and/or IF (Table 2). Because of the small number of participants who declined to receive RR and/or IF, no bivariate comparisons were conducted.

Participants who declined to receive both RR and IF ($n = 7$; Table 3) included one who survived testicular cancer at age 25, was currently disease-free at age 49, and was a Familial Testicular Cancer Study participant. A second participant was a 67-year-old woman who had been aware of her Fanconi anemia carrier status prior to study entry; she had one child affected with the disorder. A third participant was the spouse of a known *TP53* mutation carrier and had no personal or family history suggestive of a hereditary cancer-susceptibility syndrome. Two others were parents of a child with Diamond Blackfan anemia, an inherited bone marrow–failure syndrome in which up to 50% of new cases are caused by de novo dominant germ-line mutations. The last was a sibling (phenotypically unaffected/untested) of a participant with dyskeratosis congenita who was phenotypically affected but did not have a mutation in any of the known dyskeratosis congenita genes.

Four participants declined receipt of RR only (Table 3): one was the spouse of a known *TP53* mutation carrier, without a personal or family history of cancer suggestive of a hereditary cancer syndrome; two were unrelated participants who were aware of their Fanconi anemia carrier status prior to study entry; and one was a known *TP53* mutation carrier.

Table 2 Participant characteristics

	All studies	LFS	IBMFS	FTC
Cancer history				
Unaffected	375 (74%)	123 (56%)	241 (91%)	11 (52%)
One	63 (12%)	40 (18%)	16 (6%)	7 (33%)
Two	41 (8%)	32 (15%)	6 (2%)	3 (14%)
Three or more	28 (6%)	25 (11%)	3 (1%)	0 (0%)
Mutation status				
Negative	77 (15%)	51 (23%)	26 (10%)	0 (0%)
Positive (true or obligate)	162 (32%)	74 (34%)	88 (33%)	0 (0%)
Untested/unknown	260 (51%)	92 (42%)	147 (55%)	21 (100%)
VUS	8 (2%)	3 (1%)	5 (2%)	0 (0%)
Disorder (inheritance pattern, if known)				
Diamond–Blackfan anemia (AD)	69 (14%)	0 (0%)	69 (26%)	0 (0%)
Dyskeratosis congenita (AD, AR, XLR)	96 (19%)	0 (0%)	96 (36%)	0 (0%)
Fanconi anemia (AR)[a]	73 (14%)	0 (0%)	73 (27%)	0 (0%)
Shwachman–Diamond syndrome (AR)	16 (3%)	0 (0%)	16 (6%)	0 (0%)
LFS (AD)	128 (25%)	128 (58%)	0 (0%)	0 (0%)
LFL	81 (16%)	81 (37%)	0 (0%)	0 (0%)
Other LFS (multiple primaries)	9 (2%)	9 (4%)	0 (0%)	0 (0%)
Other IBMFS	12 (2%)	0 (0%)	12 (5%)	0 (0%)
Unknown	23 (5%)	2 (1%)	0 (0%)	21 (100%)
Optional studies				
Yes to research and/or incidental findings	491 (97%)	217 (99%)	254[b] (95%)	20 (95%)
Declined research findings	4 (1%)	2 (1%)	2 (1%)	0 (0%)
Declined incidental findings	5 (1%)	0 (0%)	5 (2%)	0 (0%)
Declined both research and incidental findings	7 (1%)	1 (0%)	5 (2%)	1 (5%)

AD, autosomal dominant; AR, autosomal recessive; FTC, familial testicular cancer; IBMFS, inherited bone marrow–failure syndrome; LFS, Li–Fraumeni syndrome; XLR, X-linked recessive.

[a]The majority of Fanconi anemia cases are due to autosomal recessive inheritance. There is one X-linked recessive gene (*FANCB*). [b]IBMFS study: one patient opted for the research but did not answer regarding incidental; four patients opted for the incidental and did not answer regarding research.

Finally, of the participants ($n = 5$) who declined receipt of IF only (Table 3), four were already aware of their mutation status (either true-positive or true-negative) and one had the dyskeratosis congenita clinical phenotype but had not been tested for the genes known to be associated with the disorder.

DISCUSSION

Nearly all the research participants enrolled in the CGB's family research studies of rare, hereditary cancer syndromes consented to be offered disclosure of RR and IF if discovered. This finding is consistent with other highly motivated persons who choose to enroll in a research study designed to discover the underlying genetic cause of disease in their families.[8] Of the few family members who declined either RR or IF, several already knew their personal underlying genetic risk or knew that they were not at risk (spouses of mutation-positive or mutation-negative family members). We can speculate that the known mutation carriers who declined RR or IF already had sufficient information relative to their family's genetic risk or were not interested in or prepared to receive additional information about themselves. One such individual was a cancer survivor in his late 40s without offspring who perhaps felt that the information would not be useful for personal health-care decision making. This analysis clearly demonstrates that the vast majority of individual participants in a family cancer research program are open to considering disclosure of both primary genetic RR and IF.

Our results are similar to observations in several adult study participant populations[8,9,11,13] in that participants profess to be eager for the return of RR and IF. Similarly, genetics professionals largely support the return of RR and IF when the findings have clinical utility for adult patients (85%),[17,18] support the return of pediatric RR and IF for adult-onset conditions (62%), and support disclosing the carrier status of children (62%).[17] The majority of genetics professionals also feel that individual patient preferences should guide whether and when to disclose results and that they should have the option to decline disclosure altogether.[18] For individual patients, the timing of when the results are offered, within the context of their lives, may influence whether they are receptive to the return of results.[19]

To date, most of what we know about intentions to receive RR and IF comes from highly selected research participants and small numbers of individuals undergoing clinical diagnostic genetic/genomic testing. We do not currently know whether these individuals are representative of the general population in

Table 3 Participants' intentions[a]

Study	Gender	Marital status	Age	Age at cancer	Mutation status/ inheritance pattern	Phenotypically affected	Familial syndrome	Children	Affected children
Declined both RR and IF									
FTC	M	S	49	25	UK/UK	Y	FTC	N	N/A
IBMFS	F	M	67	N/A	AR carrier	N	FA-A	Y	Y
IBMFS	M	M	62	N/A	NB/AD	N	DBA	Y	Y
IBMFS	M	M	60	N/A	UK/UK[b]	N	DBA	Y	Y
IBMFS	F	M	60	N/A	UK/UK[b]	N	DBA	Y	Y
IBMFS	M	S	36	N/A	UK/UK[b]	N	DC	N	N/A
LFS	M	M	60	N/A	NB	N	LFS	Y	N
Declined RR only									
IBMFS	F	M	86	N/A	AR carrier	No	FA-A	Yes	Y
IBMFS	F	M	39	N/A	AR carrier	No	FA-A	Yes	Y
LFS	M	M	58	42	*TP53*+/AD	Yes	LFS	Yes	N
LFS	F	M	61	N/A	NB/AD	No	LFS	Yes	N
Declined IF only									
IBMFS	F	S	25	N/A	+/AD	Yes	DBA	N	N/A
IBMFS	F	M	48	N/A	Untested/AD	Yes	DC	Y	Y
IBMFS	M	M	39	N/A	True negative/AD	No	DC	Y	Y
IBMFS	M	M	51	N/A	AR carrier	No	FA-A	Y	Y
IBMFS	F	S	23	N/A	+/XLR	Yes	DC	N	N/A

AR, autosomal recessive; DBA, Diamond Blackfan anemia; FA, Fanconi anemia; FTC, familial testicular cancer; IBMFS, inherited bone marrow–failure syndrome; LFS, Li–Fraumeni syndrome; NB, nonbloodline.

[a]All data at time of consent. [b]Family mutation unknown.

their understanding and acceptance of the results derived from their use of genetic and genomic technologies. Previous studies suggest that research participants are interested in receiving individual research results and believe that researchers have an obligation to return them, particularly if they are clinically "actionable."[12,20,21] However, it is unknown whether research participants and researchers interpret "actionable" in similar ways; this is an understudied issue. Research participants consider results with personal utility to be actionable, whereas researchers typically consider only findings with clinical utility actionable.[12,22]

The evolving legal obligations of the clinicians ordering the tests add to the complexity of the use of genomic technology in clinical care. Failure to disclose IF discovered in clinical genomic testing could potentially result in legal liability for the provider, for withholding information that might have been used to improve a health outcome.[23] Whether these standards will be applied to the research settings is actively being debated. The Presidential Bioethics Commission strongly recommended that all informed-consent documents related to WES and WGS data should clearly identify the intent of the research; enumerate the specific gene or genes being targeted for analysis; indicate what uses will be made of the data, including with whom it can be shared; and describe the plan for how RR, IF, and secondary findings will be managed. Currently, disclosure is not mandatory, but each institutional review board must decide for itself whether the proposed disclosure plan is equitable, given the specific study circumstances, and most research programs will probably require additional resources to support high-quality patient education, counseling, and disclosure.

Previous research has demonstrated that there was variable uptake of genetic test results and genetic counseling after patients were notified of the availability of test results.[19] Even in families who were well informed regarding the genetic risk associated with the disease in their family, the actual testing uptake was less than 50%. For individuals with scant information about genetic risk, the use of counseling and testing was even lower (21%).[19] The quantitative uptake of RR and IF in our study population is unknown at present, but it will be the subject of future analyses.

There are other complexities in the return of genetic RR and IF in a study population when compared with clinically identified genetic test results and IF. The timing of receipt of genetic RR and IF differs significantly when compared with clinically identified primary genetic RR and IF. Typically, when clinical WES or WGS is performed, the patient is notified within weeks to months about test results' availability for disclosure. At the time of the disclosure, both primary genetic test results and any IF that are identified are available. Although the interpretation of these results may be complex, and although variants of unknown significance may be identified, the patient will have the opportunity to discuss the findings with their health-care provider within a relatively short period of time. By contrast, when research-based WES or WGS is performed, frequently years elapse between initial consent of the individual and re-contact with them regarding results. In addition, the results

may not all be available at a given time. As research technologies advance, investigators will most likely "retest" the original biospecimen or reanalyze data using new information and seek to re-contact research participants over time.

Strengths of this analysis include the large number of participants who provided informed consent about their preferences regarding receipt of RR and IF. In addition, we used a consistent, uniform informed-consent process across all our studies that emphasized achieving high levels of comprehension of the risks and benefits involved in research participation and facilitated pooling of data from three different protocols. Finally, the eligibility evaluation prior to enrollment ensured that the research participants and their families were truly at high genetic risk for cancer or closely related to a high-risk family member.

One limitation of our findings is the inability to generalize these results beyond the family members who participated in our cancer-susceptibility cohorts. Additional limitations include a lack of access to all family members within each extended pedigree, which confines our findings to only the family members who chose to enroll and limits the generalization of these findings even within participating families. We also acknowledge that we have no measures of consent comprehension, reasons that study participants chose to receive or not receive RR and IF, or reasons that a few participants made one selection but not the other. One might speculate that participants who did not indicate an intention to receive RR or IF were undecided or may not have fully comprehended the question and chose not to respond rather than seek clarification; we have no data at present to support this possibility. In addition, the 260 participants categorized as having a mutation status "untested or unknown" comprised individuals who were nonbloodline (e.g., a spouse of a mutation carrier in a family with a known mutation), individuals who had not been tested for a known familial mutation, and individuals from families in which an underlying genetic etiology of the syndrome has not yet been identified. The potential implications of RR are vastly different for these groups, yet the majority of them chose to receive RR as well as IF. Finally, the consent documents informed participants that it is the policy of CGB to offer (but not require) return of RR and IF that have clinical utility after verifying the genetic alteration in a CLIA laboratory. By including this statement in the consent, and not providing an option to consider other RR without clinical utility, we may have inadvertently communicated to participants that this is a normative practice and thus potentially biased participants toward opting to receive RR and IF rather than decline.

Conclusion

In this well-defined population of individuals from families at high genetic risk for cancer, adult research participants overwhelmingly indicated their preference to be offered disclosure of genetic RR and IF. To date, none of these 506 individuals has opted out of future re-contact, which provides us the opportunity to evaluate the rate of use of RR and IF over time. Future research will seek to identify the underlying reasons for refusal of RR and IF by the small number of individuals who so declined and to study the impact of receipt of RR and IF in personal medical decision making among individuals from families at high genetic risk for cancer.

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DISCLOSURE

The authors declare no conflict of interest.

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