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Descriptive Analysis of the Testing Outcome Populations of a Highly Facilitated Cascade Genetic Testing Framework for Cancer Predisposition

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Abstract

This research analyzes the demographic determinants of testing uptake in a highly facilitated cascade testing protocol pilot effort for families with inherited cancer-predisposing mutations. The program provided no-cost genetic testing to the family members of mutation carriers using direct contact, telephone genetic counseling, and mailed saliva kits. This facilitated intervention resulted in high uptake of testing for second degree relatives and reduced sex-based risk disclosure. Uptake rates were highest among females and older individuals. Young Caucasian males were most likely to decline testing. Contact was limited for non-Caucasian and international individuals with low English-language proficiency, resulting in lower uptake rates for these groups. Overall, uptake rates were comparable to traditional testing methods and conditional uptake rates were lower than expected. More work is needed to improve upon facilitated testing methods and to elucidate why some facilitation tools may lead to reduced testing uptake.

Introduction

For the majority of individuals who develop cancer, the causative mutations are somatic and random, induced by chance events during DNA replication or spurred on by exposure to environmental mutagens. However, mutations in genes that are critical for regulating the cell cycle can also be inherited. Currently recognized heritable mutations account for about 10% of cancer cases. An individual who inherits a genetic mutation is at an increased risk of developing cancer in their lifetime, typically at a much younger age than the general population. The exact cancer risks associated with these mutations vary by gene and tissue type. For example, individuals who have inherited mutations associated with Lynch syndrome have up to an 80% risk to develop colon cancer over their lifetime, markedly increased over the 5% risk in the general population (Vasen et al., 2007, Hampel 2016). For females with mutations associated with hereditary breast and ovarian cancer syndrome (HBOC), risk estimates range from about 40% to over an 80% lifetime risk of developing breast cancer and a 20-60% lifetime risk of developing ovarian cancer (Berliner et al., 2013; Rebbeck et al., 2015).

Knowing gene status has a great number of benefits. Morbidity and mortality can be reduced with proper surveillance (i.e. colonoscopies, mammograms, etc) to catch cancers at early stages when treatment is more successful (Nelson et al., 2016). In some cases, prophylactic surgeries are recommended to remove tissue before it develops malignancies (Barrow et al., 2015; Berliner et al., 2013; Rebbeck et al., 2015). Gene status also informs cancer treatment in individuals who have a cancer diagnosis. One of the most well-known examples is the success of PARP inhibitors for treating ovarian cancer in BRCA1/2 mutation carriers (Konecny & Kristeleit, 2016). Additionally, mutation carriers are at a higher risk for second

primaries, which can influence surgical treatment choices (Berliner et al., 2013). Mutation status is important for reproductive planning. In-vitro fertilization and preimplantation genetic diagnosis can be used to avoid transmission of a single mutation or, in rare cases, homozygous transmission which can lead to conditions like Fanconi anemia or ataxia telangiectasia (Woodson et al., 2014). Genetic information has a number of significant impacts on health management decisions as well as other life choices.

Targeted genetic counseling and testing is needed to identify individuals with cancer predisposing genetic variants. A patient may first be seen by a cancer genetics specialist due to a concerning family history or an uncommon personal diagnosis (i.e. early onset or rare cancer). If this person tests positive for a risk-elevating gene mutation, they are termed the index case for their family. Identification of their gene status provides more accurate risk assessment for close blood relations and opens the door for pre-symptomatic testing in first- and some second-degree relatives (FDR & SDR). This process is known as cascade testing and is currently the most efficient method for identifying mutation carriers before they develop cancer (Krawczak et al., 2001; Ademi et al., 2014).

Cascade testing is a multistep process that requires cooperation and communication between healthcare professionals, index patients, and other family members. Current practice relies heavily on the index patient to disseminate the information they learned during genetic counseling to their at-risk relatives, a process termed family contact. The index patient is also responsible for encouraging relevant family to seek out genetic counseling and testing for themselves (Landsbergen et al., 2005; Aktan-Collan et al., 2007; Barrow et al., 2015). This task is often an unwelcomed burden to the proband and its continued success is influenced by

characteristics of the index patient, including their motivations, health beliefs, and familial interactions (Landsbergen et al., 2005; Aktan-Collan et al., 2007; Barrow et al., 2015). Several studies have shown that family contact returns disappointing levels of testing uptake, often ranging from 20-45% (Suthers et al., 2006, Schlich-Bakker et al., 2007; Christiaans et al., 2008; Fehniger et al., 2013; Sharaf et al., 2013, Menko et al., 2019). A number of factors have been associated with these low levels. Index patients may be inhibited from informing any family members due to concurrence of their own cancer diagnosis and treatment (Sermijn et al. 2004; Barrow et al., 2015). If they are able to reach out, research on family communication of genetic risks and the process of family contact has shown there is a loss of accuracy as information originating from a genetic counselor is transferred and reinterpreted between family members (Landsbergen et al. 2005; Vos et al. 2011a; Vos et al. 2011b). This can result in lower perceived risks in relatives (Vos et al., 2011a). High proportions of index patients have reported that disclosure is an "emotionally distressing" experience and that they do not feel prepared or need additional guidance and support during the communication process (Gaff et al., 2005; Landsbergen et al. 2005; Finlay et al., 2008). Burns and colleagues suggest that genetic information, with its probabilistic nature and secondary findings, is too complex a subject to burden an index patient with conveying and they highlight that interpersonal dynamics variably influence how effective an index patient can be within their own family (2018). Some index patients may have inconsistent contact, estrangement, or emotionally distant relationships with some at-risk family members that impede difficult conversations about health maintenance (McGivern et al., 2004). As a result, index patients often inform only a subset of their at-risk family and studies have consistently identified preferential disclosure of

information to females and first-degree relatives (Aktan-Collan et al., 2000; McGivern et al., 2004; Landsbergen et al., 2005; Finlay et al., 2008; Stoffel et al., 2008).

It has been suggested for many years that medical providers, and genetics specialists in particular, do more to encourage cascade testing. Efforts to facilitate family contact have consisted largely of descriptive letters detailing the familial variant and other educational materials that index patients can provide to their family members (Sermijn et al., 2004; Suthers et al., 2006; Aktan-Collan et al., 2007). Others have attempted to increase the education and involvement of general practitioners (Barrow et al., 2013). However, these methods are still one step removed for the individual at risk. Genetics specialists, at the permission of the index patient, can contact family members directly. Ethical concerns have been raised regarding an individual's right not to be contacted by health professionals or to learn of their elevated genetic risk but empirical studies on attitudes toward direct contact are universally positive (Wright et al., 2002; Newson & Humphries, 2005; Suthers et al., 2006; Louter et al., 2017). Most direct contact efforts have involved mailing letters to at-risk family, detailing their specific risks and informing them about how to pursue testing. Other projects have employed genetics specialists to approach family members in person or over the phone (Louter et al., 2017). Regardless of the method, direct contact leads to higher levels of testing uptake (Suthers et al., 2006; Menko et al., 2019).

Once someone has been informed of their genetic risk there are a variety of characteristics and circumstances that have been associated with uptake of genetic testing. Attitudinal features of the index individual, such as familiarity with cancer surveillance practices, emotional preparedness, and satisfaction with their own testing experience are

known to influence cascade testing uptake rates for family members when family contact is employed (Blandy et al., 2003; Landsbergen et al., 2005). Traits of individuals that have positively correlated with uptake include high socioeconomic status and employment, higher education, female sex, and being a parent or planning a family in the near future (Lerman et al., 1996; Aktan-Collan et al., 2000; Hadley et al., 2003; Finlay et al., 2008; Cheung et al., 2010; Sharaf et al., 2013). Older ages and some ethnic backgrounds (Asian and African American) have corresponded to lower uptake across studies (Cheung et al., 2010; Fehniger et al., 2013). Some family characteristics predict greater uptake as well, including a greater number of affected first degree relatives and high levels of family support and knowledge about screening procedures (Blandy et al. 2003; Hadley et al., 2003; Irons et al., 2017). However, current research in this topic is inconsistent as some studies examining these same demographic and familial variables have reported no patterns predicting uptake of genetic testing (McGivern et al., 2004; Landsbergen et al., 2005; Christiaans et al., 2008; Fehniger et al., 2013). Individuals may opt out of testing at any stage of the cascade process, but once someone receives genetic counseling uptake rates tend to be very high, in excess of 90% by most reports (Hadley et al., 2003; Christiaans et al., 2008; Hafertepen et al., 2017).

Mechanisms exist today to further facilitate testing by eliminating logistical barriers that may prevent people from completing the process, like taking time off from work or traveling to a medical center. One such mechanism is telephone genetic counseling. Research efforts testing the effectiveness of telephone genetic counseling have repeatedly shown it to be noninferior to traditional counseling in all areas (Kinney et al., 2014; Kinney et al., 2016). There is a trend toward slightly lower uptake rates with telephone counseling (Butrick et al., 2015;

Schwartz et al., 2014). It is difficult to determine if this is because the additional individuals that are reached via telephone counseling are already less likely to test or if it is a consequence of the telephone counseling arrangement. Additionally, the advent of high throughput sequencing has allowed noninvasive DNA collection, like saliva and buccal swabs, to become an adequate source of DNA (Quinque et al., 2006; Pal et al., 2014). This allows for test kits to be sent and returned through the mail without the need for travel or a blood draw.

Most work on correlates with cascade genetic testing uptake has relied on family contact procedures or retrospective studies. Research supports the benefits of direct contact and facilitated genetic testing opportunities. From 2017-2019, Weill Cornell Medical Center piloted a highly facilitated cascade testing protocol for families with inherited cancer-predisposing mutations. This program provided no-cost genetic testing to the family members of mutation carriers using direct contact, telephone genetic counseling, and mailed saliva kits. This facilitated intervention design reduced many of the perceived barriers to genetic testing, providing the opportunity to make informed decisions to a large number of at-risk individuals. This project aims to identify variables that predict genetic testing uptake as well as variables associated with individuals who were lost to testing at various stages of the project. We hypothesize that the facilitated nature of this methodology will lead to high rates of testing uptake and reduce the impact of index patients and biased risk disclosure on genetic testing uptake. We predict that variables associated with the index patient, like degree of relation to the index patient, and variables previously associated with biased risk disclosure, like sex, will have limited impact on testing uptake due to direct contact through a health professional. We predict that variables associated with individual decision-making, like parenthood or personal

cancer history will best predict testing uptake. Knowing which variables characterize individuals who participate in cascade testing when logistical barriers are removed will help inform efforts to increase and tailor the cancer genetic testing process.

Methods

Enrollment of index patients:

Index patients were identified from a pool of patients currently receiving cancer care at Weill Cornell Medical Center (WCMC) during 2017/2018. Individuals who tested positive for a cancer-predisposing mutation as part of their regular cancer care were approached by an oncologist or study team member and offered enrollment in the study. The study team recruited 30 subjects, both male and female, over 18-years-old with any confirmed pathogenic mutation associated with an increased risk of cancer in any tissue(s). Subjects were contacted by phone 6-9 months after receiving their test results to assess for any additional relatives who pursued cascade testing outside of the study protocol.

Enrollment of at-risk family members:

Index patients worked with the study team to build a family pedigree and identify first and second degree relatives (FDR & SDR) at high risk of carrying the mutation. Individuals were considered “at-risk family members” if they met the following requirements:

- not already tested
- over 18-years-old
- a FDR to the index patient or any known mutation carrier in the family

- a SDR to the index patient if the intervening relative is deceased or has been contacted and unequivocally declined
- no intervening relative has tested negative

SDRs from the unaffected family lineage were not included if the lineage carrying the mutation was clear from the pedigree (i.e. strong preponderance of cancer on one side of the family and not the other). These criteria are fairly broad as they include SDRs and do not exclude family members on the basis of location or language barriers. Many studies assess only FDR uptake and discount geographically distant relatives due to the requirement of in-person genetic counseling and testing.

The number of at-risk family members changed after the first identified family members were contacted and tested. A number of FDRs of mutation carriers identified through study testing reached out to the study team to request testing. The project was able to accommodate all of these requests and so the number of at-risk family members was adjusted to include relatives of mutation carriers that were identified over the course of the project following the same rules listed above.

Index patients provided contact information for as many at-risk family members as they were able. The study team attempted to contact identified relatives to offer them enrollment. Efforts were made to contact international relations for whom contact information was available as well as non-English speaking relations using telephone interpretation services provided by WCMC. Contact was attempted a maximum of three times by any given modality – i.e. three phone calls or three emails. All efforts were made to provide family members with the

means to contact the study team, via voicemail or email, if direct contact was unsuccessful. Family members who were successfully contacted and agreed to participate in the study were provided with telephone genetic counseling by certified genetic counselors at Invitae Laboratories. Family members agreeing to genetic testing were mailed saliva kits by Invitae staff with directions for completion and return of the sample in a prepaid envelope. Test results were returned over the phone by the head oncologist on the study (MKF). Participants were considered to have successfully completed testing once they received results. All participants were contacted for follow-up at 6-9 months post genetic counseling session or results disclosure (whichever was later) to assess for any additional relatives who pursued cascade testing outside the study protocol. Follow-up contact was attempted a maximum of three times by phone or email and participants were provided with contact information to reach out to study staff if follow-up was unsuccessful.

Data analysis

Due to the loss of family members at various stages of the project, at-risk family members were stratified into three outcome categories.

No Contact Group: this category contains at-risk individuals who were identified during consultation with the index individual but contact with the study team was never accomplished, either due to a lack of contact information or failure to respond to the study team after efforts to reach out.

Informed Decline Group: this group includes individuals who spoke with the study team and either declined to participate before genetic counseling, opted not to continue after genetic

counseling, or who agreed to testing but never returned their saliva sample. At follow-up it was identified that most individuals who did not submit samples stated they had changed their minds regarding testing.

Uptake Group: the uptake group included family members who successfully complete genetic testing and received their results through the project or were identified on follow-up as having gotten genetic testing outside the study.

Potential predictive variables associated with placement in any of these groups were determined according to the data that was collected and these were classified into four basic groupings

Table 1: Background, health history, and predictive variables considered in statistical analyses

Demographics	Index traits	Family history [a]	Genetic factors
Age [b]	Index Age	Num. of family members with cancer	Penetrance [c]
Sex	Index Sex	Num. cancer deaths	
Parenthood	Index Education	Family participation [d]	
Race	Degree of Relationship [e]		
Education [f]			
Personal History Cancer			
Internationality			
English proficiency			

[a] First and second degree relatives only
[b] Binned value: 18-40, 41-60, 61+
[c] High penetrance genes: BRCA1/2, MSH2, MSH6, APC, PTEN
Moderate penetrance genes: ATM, BARD1, BRIP1, CHEK2, RAD51C/D, MUTYH
[d] Proportion of at-risk family + index case who completed testing, excluding the individual
[e] Degree of relationship to the index patient, defined as three groups: first degree, second degree, or third degree +
[f] Binned value: (1) high school or less, (2) college, (3) graduate school or more

Most data were logged as dichotomous categorical variables (yes/no) or by binning continuous values. Age was binned into approximate 20-year blocks which provided reasonably even distribution of the sample set across bins. Education was binned into three categories as high

school or less, college, and graduate school or above. Internationality was dichotomously defined as living within the United States or not. English proficiency was determined by those individuals who requested interpretation services when communicating with the genetic counselor or when receiving their results. Details of English proficiency for those individuals who were never contacted by study staff was collected from other family members whenever possible. When considering family history variables, only FDRs and SDRs to the individual in question were counted. The number of distinct family members with cancer, including typically environmental cancers like lung cancer in a known smoker, were included in this metric. The number of deaths in FDRs and SDRs that were a direct result of cancer, regardless of cancer type, was counted. Family participation was measured by calculating the proportion of at-risk individuals in the family (including the index patient) that successfully completed genetic testing with the exception of the individual in question. This retrospective measure was designed to capture the general acceptance of genetic testing that an individual may be observing in their family situation as well as to test for consistency of behavior within families. Penetrance was divided into high and moderately penetrant cancer predispositions. These divisions are considered somewhat arbitrary but penetrance has been determined for particular cancer types by the associated increase in relative risk as compared to the general population (Easton et al. 2015, Tung et al. 2017). Moderate penetrance has been loosely defined as an increase in average relative risk by 2-5 times over the general population and mutations are considered highly penetrant for relative risks above that (Easton et al. 2015, Tung et al. 2017). Mutations identified in the families in this project that are considered highly penetrant include:

BRCA1, BRCA2, PTEN, MSH6, MSH2, and *APC*. Mutations in the following genes have been classified as moderately penetrant: *ATM*, *BARD1, BRIP1, CHEK2, RAD51C*, and *MUTYH*.

Data was analyzed using SPSS (version 25.0). Some variables were considered but ultimately not included in data analysis due to sample size problems. The sex of the index individual was not included because only one index patient was male. Additionally, education was not a feasible metric for the *no contact* outcome group because this information was not reliably available for 66 of the 67 individuals in that group.

Descriptive statistics were run on at-risk relatives using frequency measures and means (Table 2). A subset of the sample was randomly chosen for chi-square analysis. Due to the confounding effects of family groups, the statistical assumption of independent sampling would not be met for the entire sample set. A random number generator was used to select one individual as a representative from each family to generate a subset for statistical analysis. Chi-square analyses were run on all dichotomous variables to test for association with the three outcome stratifications (no contact, informed decline, or uptake). Variables were also tested against the dichotomous outcome of completion of genetic testing or not. The continuous variables (number of family members with cancer, number of cancer deaths, and family participation) were analyzed in a single logistical regression model for both outcome group and dichotomous testing uptake.

Results

Thirty index patients were recruited into the study. According to our above criteria, 167 family members were identified to be at high-risk to be a mutation carrier, an average of 5.6 per index patient. The study team was provided with contact information for 101 family

members, an average of 3.4 per index patient. The study team attempted to contact all 101 and were unable to establish contact with 12. Of the 89 family members who spoke with the team, 5 declined genetic testing and 84 agreed to genetic testing. Of those that agreed, 19 received saliva test kits but never returned them and 64 returned their saliva kits and received their results (one individual did not get conclusive results after two attempts, this person was categorized in the *uptake* outcome group due to positive intention to test). On follow-up, an additional 11 individuals were found to have pursued cascade genetic testing independently, amounting to a total of 76 at-risk family members receiving cascade testing for the identified mutation in the family. Of the 30 families, no contact was successfully achieved for any family members in 6 families. In an additional 3 families, contact was made with at least a subset of at-risk family members but no one successfully completed testing. In 7 of the families, all of the initially identified at-risk family members completed testing. Fourteen of the thirty families had all members ultimately cluster within a single outcome group showing a consistency of behavior within these families.

The final testing uptake rate was 46% of the identified high-risk family members. Conditional uptake, defined as the proportion of individuals who pursued testing after contact by the study team, was higher at 76%. For the individuals whose mutation status is known (64 of the 76) there were 37 negative results returned and 27 positive results.

Table 2: Descriptive statistics of identified at-risk family members and separated by outcome group. All values are provided as number and percentage: n(%)

Characteristic	**At-risk Family Members (n=167)**	**No Contact Group (n=67)**	**Informed Decline Group (n=24)**	**Uptake Testing Group (n=76)**
Age				
18-40	51 (31)	24 (36)	10 (42)	17 (22)
41-60	65 (39)	24 (36)	11 (46)	30 (39)
61+	51 (31)	19 (28)	3 (13)	29 (38)
Sex				
M	91 (55)	38 (57)	17 (71)	36 (47)
F	76 (46)	29 (43)	7 (29)	40 (53)
Relationship to Index				
FDR	97 (58)	40 (60)	13 (54)	46 (61)
SDR	42 (25)	18 (27)	3 (13)	21 (28)
TDR+	28 (17)	9 (13)	8 (33)	9 (12)
Race				
Caucasian	110 (66)	37 (55)	21 (88)	52 (68)
Non-Caucasian	57 (34)	30 (45)	3 (13)	24 (32)
Parent				
Yes	88 (53)	20 (30)	13 (54)	55 (72)
No	65 (39)	33 (49)	11 (46)	21 (28)
Unknown	14 (8)	14 (21)		
Education				
High School or less	16 (10)		1 (4)	15 (20)
College	31 (19)	1 (1)	7 (29)	23 (30)
Graduate School +	39 (23)		16 (67)	23 (30)
Unknown	81 (49)	66 (99)		15 (20)
Personal History of Cancer				
Yes	70 (42)	5 (7)	1 (4)	64 (84)
No	89 (53)	54 (81)	23 (96)	12 (16)
Unknown	8 (5)	8 (12)		
International				
Yes	38 (23)	27 (40)		11 (14)
No	122 (73)	36 (54)	24 (100)	62 (82)
Unknown	7 (4)	4 (6)		3 (4)
English Proficiency				
High	126 (75)	36 (54)	23 (96)	67 (88)
Low	35 (21)	25 (37)	1 (4)	9 (12)
Unknown	6 (4)	6 (9)		
Penetrance				
High	125 (75)	45 (67)	20 (83)	60 (79)
Moderate	42 (25)	22 (33)	4 (17)	16 (21)
Family members with cancer (average)	3.3	3.0	3.3	3.4

Familial cancer deaths (average)	1.6	1.5	2.0	1.7
Familial participation rates (average)	0.53	0.29	0.53	0.74

with regard to testing outcome group for descriptive purposes.

Table 2 includes the demographic characteristics, family health history, and gene-specific information for the entire sample size as well as the three outcome groups. Table 3 reports the relevant characteristics assessed in the index patients from each family. Supplemental figures (S1-S11) graph the trends across the entire sample of at-risk family members

Table 2: Characteristics of Index Individuals. All values given in number and percentage: n(%)

Characteristic	**Index Group, n=30**
Sex	
M	1 (3)
F	29 (97)
Age	
18-40	6 (20)
41-60	14 (47)
61+	10 (33)
History of Cancer	
Yes	24 (80)
No	6 (20)
Education	
High School or less	2 (7)
College	14 (47)
Graduate school +	14 (47)

The *no contact* group showed a strong positive association with being located outside the USA, having low English language proficiency, being of non-Caucasian race, and a slightly higher rate of moderately penetrant mutations. The *informed decline* group showed positive association with younger age, male sex, and more distant degree of relationship to the index patient. A weaker trend was seen with Caucasian race and graduate level education. The *uptake testing* group was positively associated with increased family participation, older age, female

sex, living in the USA and proficiency with English. A weaker trend was seen with having a personal cancer history and parenthood.

Randomized family subsample

The randomized subsample exhibited similar patterns to the full sample and included 13 individuals in the *uptake testing* outcome group, 4 individuals from the *informed decline* group, and 13 individuals from the *no contact* group. Descriptive statistics on the subsample are shown in Table 4. Chi square analysis on the randomly sampled sub-set of family members did not support significant relationships between any demographic characteristics and testing outcome group or on the dichotomous result of testing uptake or no testing uptake. Table 5 displays the p-values for each variable.

Table 4: descriptive statistics on the 30-person subsample used for statistical analyses. n(%)

Characteristic	**Subset (n=30)**
Age	
18-40	8 (27)
41-60	13 (43)
61+	9 (30)
Sex	
M	19 (63)
F	11 (37)
Relationship to Index	
FDR	18 (60)
SDR	11 (37)
TDR+	1 (3)
Race	
Caucasian	22 (73)
Non-Caucasian	8 (27)
Parent	
Yes	20 (67)
No	8 (27)
Unknown	2 (7)
Education	
High School or less	3 (10)
College	6 (20)
Graduate School +	5 (17)
Unknown	16 (53)
Personal History of Cancer	
Yes	2 (6.5)
No	26 (87)
Unknown	2 (6.5)
International	
Yes	6 (20)
No	23 (77)
Unknown	1 (3)
English Proficiency	
High	24 (83)
Low	5 (17)
Unknown	1 (3)
Penetrance	
High	22 (73)
Moderate	8 (27)
Family members with cancer (average)	3.3
Familial cancer deaths (average)	1.3

Table 5: p-values from chi-squared analysis on the randomly chosen subset of at-risk family members. Testing predictive value of categorical descriptors with specific outcome group result as well as the completion of genetic testing generally. No significant associations were revealed

Variable	**Outcome Groups**	**Testing Uptake**
Age	0.08	0.08
Sex	0.63	0.35
Education	0.08	0.08
Race	0.99	0.70
Parenthood	0.33	0.28
Personal Hx Cancer	0.29	0.11
Internationality	0.30	0.52
English Proficiency	0.15	0.22
Degree of Relationship	0.25	0.46
Index Age	0.45	0.24
Index Education	0.42	0.63
Penetrance	0.90	0.70

Simple binary logistic regression model for the continuous variables (number of family members with cancer, number of cancer deaths, and family participation) on dichotomous testing uptake showed a significance influence from familial participation (p=0.014) but no significant

associations with the number of family members with cancer (p=0.166) or the number of cancer deaths in the family (p=0.215). A multinomial logistic regression was done to predict outcome group but the sample size was underpowered. No significant associations were found.

Discussion

This highly facilitated cascade testing design showed a level of genetic testing uptake (46%) similar to levels that have been reported by other cascade testing initiatives, most of which have ranged from 31-57% (Fehniger et al., 2013; Sharaf et al., 2013; Menko et al., 2019). Comparison of testing uptake rates across studies is complicated by important differences in methodologies. Studies vary in their methods for informing relatives of their risks, with some attempting pure family-contact, some employing direct-contact methods, and others using a blended approach (Suthers et al., 2006; Christiaans et al., 2008; Hafertepen et al., 2017). There is considerable variability in how studies define “at-risk” relatives, with some projects restricting this metric to FDRs only (Sharaf et al., 2013). Generally, testing uptake is found to be negatively related to degree of relationship with the index patient and this may be a direct consequence of the biased disclosure of risk to FDR during family contact (Blandy et al., 2003). The prediction that uptake would not be influenced by degree of relation to the proband was supported. In this protocol, testing uptake was not significantly different between first and

second degree relatives (p=0.25), as is so often seen in other research (McGivern et al., 2004; Christiaans et al., 2008; Barrow et al., 2015). This is likely a result of the facilitated nature of relative identification and direct contact by medical providers. There was a slightly increased proportion of more distant relatives (third degree or more) in the *informed decline* outcome group. Many of these relatives were contacted because of deceased intervening relatives, and so their risks to carry pathogenic variants would be estimated to be lower, which may have influenced the decision to decline testing.

Variables that did not display strong trends with any of the outcome groups include penetrance and features of the index patient like index age and education. Penetrance is a complicated concept and risk perceptions may be sufficiently elevated for all the genes considered in this study. While ultimately it does seem that the index patient impacted outcome grouping (detailed below particularly in reference to the *no contact* group) the demographic characteristics we analyzed, like age and education, do not appear to capture the relevant variability that may exist across index patients.

No Contact testing outcome

Several of the characteristics of the *no contact* testing outcome group are demographic and not associated with individual decision making based on risks. The *no contact* testing outcome group was more likely than other outcome groups to be non-Caucasian, live internationally, and have lower English language proficiency. They were also more likely to not be a parent and have no personal history of cancer. This group had the lowest levels of family participation in general. There was no pattern observed with regard to age, sex, or degree of

relationship. The majority of the *no contact* group is comprised of individuals for whom contact information was never obtained. The provision of contact information for at-risk relatives relied on the index patient and discrepancies appeared in the abilities or willingness of different index patients to reliably provide contact information. Index patients were far less likely to provide the means to contact relatives who lived internationally and did not speak English. This fact reinforces the importance of the index patient even in a highly facilitated testing framework. Cascade testing requires medical providers to reach out to people who are not in their medical system and so contact information can be difficult to acquire. It was at this early stage of the program that the largest proportion of at-risk family members were lost to testing. Contact was never attempted for 82% of this group; the remaining 18% did not return contact after it was attempted. It is unclear if index individuals informed family members in advance that they would be contacted by the study or how the levels of communication within families varied with relation to outcomes.

Research on individuals who are difficult to contact is expectedly slim. Hafertepen and colleagues were able to follow-up with a group of newly diagnosed breast cancer patients who were referred for genetic counseling but never made an appointment (2017). They found that these patients were under too much concurrent stress and did not feel like the genetic counseling appointment was sufficiently important. Other work on patients who decline testing prior to receiving genetic counseling has shown that these individuals feel this information is not relevant for them and have a low-perceived risk (Schlich-Bakker et al., 2007). Follow-up was not attempted with these individuals since consent was never acquired for participation in the study, making additional inference into their motivations impossible within this protocol.

Informed Decline outcome group

Most of the characteristics that make the informed decline testing outcome group stand out are associated with individual decision making and interpretation of risks. Informed decliners were more likely to be younger, male, Caucasian, and more distantly related to the index patient (third degree relatives or greater). They were also more highly educated on average than the uptake group. Only one individual in this group had a personal history of cancer and they were slightly less likely to be parents. Generally, these demographic patterns are not surprising based on what has been noted in the literature. Younger males have been reported to be less likely to participate in genetic testing (Barrow et al., 2015). Given the unbalanced risks for males and females inherent to some predisposing gene mutations, this pattern may reflect decreased perceived risks. Furthermore, upon follow-up many of the younger male participants stated that they would consider pursuing genetic testing independently in the future when they believed it would more directly impact their medical care. Similarly, parenthood has been associated with greater testing uptake and described by patients as a motivator for pursuing testing (Hadley et al., 2003; Finlay et al., 2008; Sharaf et al., 2013). Finding lower rates of parenthood in the *informed decline* group aligns with this pattern. The limited number of non-Caucasian individuals in this outcome group may suggest that telephone counseling and testing kits are well-received by non-Caucasian individuals and, once contact is successfully made, a facilitated protocol will lead to high rates of testing amongst these demographics. The trends in the literature between education and testing uptake are quite variable, with some research suggesting a positive relationship and other work finding either no correlation or less perceived benefit for highly educated people (Henneman et al.,

2013; Sharaf et al., 2013). This study population was generally very highly educated and education information was not available for a large portion of the at-risk family members which should be considered when interpreting this result.

The level of informed decline (24%) was somewhat higher in this project than other reported levels, which are typically below 10% (Christiaans et al., 2008). Much of the work on cascade testing uptake has been done in strictly a BRCA1/2 testing setting or in familial hypercholesterolemia (FH), a condition which can result in sudden death, and so motivations to test are slightly different across these populations (Fehniger et al., 2013, Finlay et al., 2008, Butrick et al., 2015, Christiaans et al., 2008; Sturm 2016). This pattern is further explored below.

Uptake Testing outcome group

This facilitated framework resulted in the highest uptake among demographics that have historically shown the highest uptake without facilitation. The *uptake testing* outcome group was generally older and more female. When compared to other outcome groups they were slightly more likely to be parents, more likely to have a personal diagnosis of cancer, and had the highest family participation rates. They were not more likely to be more closely related to the index patient. The association with female sex and parenthood mirrors the patterns seen in the informed decline outcome group and is supported by trends from other research (Aktan-Collan et al., 2000; Hadley et al., 2003; Finlay et al., 2008; Sharaf et al., 2013). Female sex has frequently been associated with greater testing uptake (Aktan-Collan et al., 2000; Finlay et al., 2008) and some have suggested that this is due to a feeling of responsibility as the family care-giver (d'Agincourt-Canning & Baird, 2006) but may also reflect the increased burden of several

mutations for female-specific tissues. Having a personal diagnosis of cancer logically increases someone's perceived risks of carrying the familial mutation and 8 of the 12 individuals with this history who received testing were positive. These individuals also came from families that exhibited higher rates of testing uptake on average. The familial participation variable was designed to capture the general positive or negative sentiments in a family toward genetic testing under the assumption that the decision of an individual to ultimately complete testing is indicative of a positive inclination toward genetic testing generally. Six families tested all at-risk relatives, and they comprise 30% of this outcome group.

Impacts of facilitation efforts on uptake

Although telephone genetic counseling has been shown to be non-inferior to traditional genetic counseling, it has been consistently documented to result in marginally lower uptake of genetic testing (Kinney et al., 2014; Kinney et al., 2016). The response to mailed, non-invasive sampling kits has not been well examined in the literature. One previous study used both telephone counseling and mailed buccal kits to test at-risk women with relatives who are known BRCA1/2 carriers (Kinney et al., 2016). This project differed in that it relied on family contact. Testing uptake rates were quite low (~28%) and significantly lower for the telephone counseling and buccal kit group than the in-person group (Kinney et al., 2016). The uptake rates we have documented are higher at 46%, suggesting that the addition of direct contact may have directly improved uptake in study participants. Conditional uptake with telephone genetic counseling has been documented between 84-87% (Butrick et al., 2015; Schwartz et al., 2014). We documented a lower than expected conditional uptake rate of 76%. It has been suggested that the separate step needed to obtain a sample, either traveling to a center for a blood draw

or completing and mailing a buccal kit, drives these lower uptake rates (Schwartz et al., 2014; Kinney et al., 2016). This inference is supported by another study. A public health effort to test family members for familial hypercholesterolemia in the Netherlands that employed traveling genetics field workers and could provide house calls exhibited very high rates of familial testing that plummeted by more than 80% once the project completed and the field workers were no longer active (Louter at el., 2017). It is also possible that people who are reached by telephone counseling include individuals who are less interested in genetic testing and would not have attended a traditional in-person counseling session and their inclusion reduces conditional uptake levels (Butrick et al., 2015).

It has been proposed that the gap in time between genetic counseling and testing allows patients in facilitated settings to second guess their decisions or be influenced by external opinions from family members (Kinney et al., 2016, Kanga-Parabia et al., 2018). We observed an interesting pattern among families with high rates of informed decline. The majority of the *informed decline* groups consists of individuals who did not return saliva kits after initially agreeing to testing. During follow-up discussions it became clear that conversations between family members had influenced decisions to withhold samples. These conversations involved one miscommunication regarding a financial obligation for testing and others who appeared to exhibit a decrease in perceived risk after discussing testing with relatives. The dynamics of inter-familial communication about genetic testing is known to have significant influence on uptake and other research has documented a similar change in decisions and reduction in perceived risks after consulting with family (Ramirez 2015, Kanga-Parabia et al, 2018). The number of families exhibiting complete assignment to a single outcome group and the

significant trend of increasing familial participation associated with individual uptake suggests that families are consistent in their behavior, which may imply that there is an important role for family communication in this highly facilitated testing framework.

Given our results and the patterns observed in other studies, more research is needed to examine the reasons for lower testing uptake when mailed sample kits and telephone counseling is employed. We encountered several issues with using these kits, including the need to resend kits due to user error and a high rate of non-return of kits (23% of kits sent were never returned). While mailed kits enabled the project to reach a large number of distant relations across the USA and internationally, it is unclear if this format had an overall positive impact on testing uptake.

Conclusions

While documenting statistically significant patterns was not possible for all variables aside from familial participation, some conclusions may be inferred from the findings observed here and comparisons made with other research. Cascade testing in its traditional form displays biases with regards to who is informed and who pursues testing. While this project was able to reach an array of distantly located family members, it was not able to eliminate the association with low uptake of testing in individuals that are non-white, have low English language proficiency, or live outside the USA. These patterns, when they have been addressed, have been seen in other projects (Cheung et al., 2010; Fehniger et al., 2013). However, once contact was established, uptake of testing among non-Caucasian individuals was high and so this

facilitated methodology may present a good option for these groups if the barrier of initial contact can be surmounted.

This testing framework eliminated the sex-based risk notification pattern that has been seen in family contact studies but still resulted in lower uptake of testing in males, a pattern previously observed (Barrow et al., 2015). The facilitated protocol and direct contact methods largely reduced any impact due to the degree of relationship to the index patient on either notification of risk or testing uptake rates. This testing effort also shed light on the consistency of behavior within families.

Taken as a whole, these results foster additional questions. Further investigation is needed to determine the impact that communication within families has on decision making and how this may lead to consistent behaviors within families during cascade testing. This may be particularly relevant when mailed sample kits are employed due to the additional time built in to the process and self-motivation required, which may promote indecision. Furthermore, testing may benefit from closely examining families with the highest uptake to determine what leads to the positive response to cascade testing in these groups. Lastly, this protocol improved testing uptake for distant relatives and ensured informed decision making for males and younger individuals who can be missed with traditional family contact but other demographic variables were in accord with traditional testing efforts. More work is needed to improve information gathering and contact of non-Caucasian, international, and non-English speaking families, potentially by focusing on engaging index patients.

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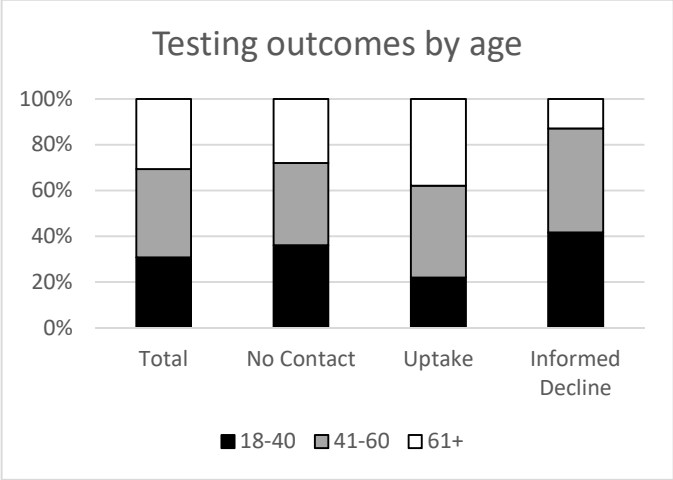
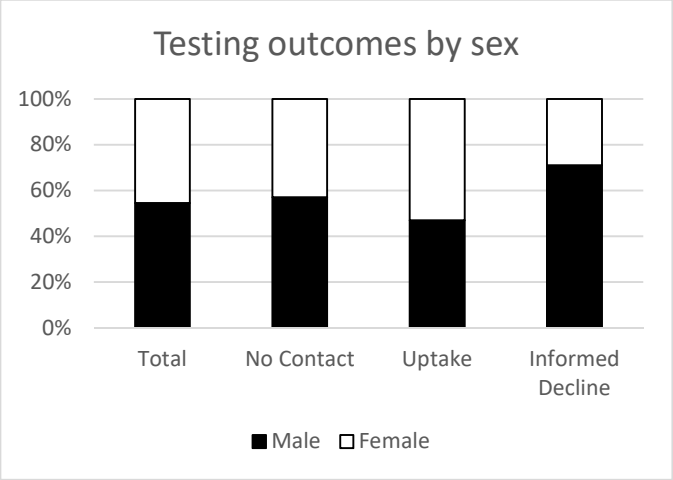
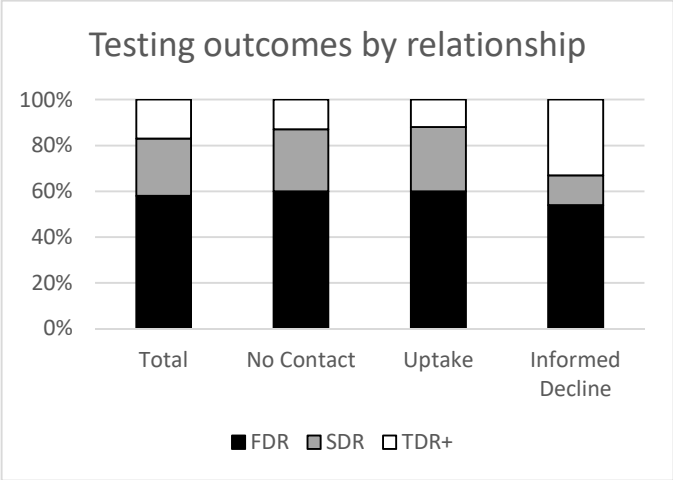
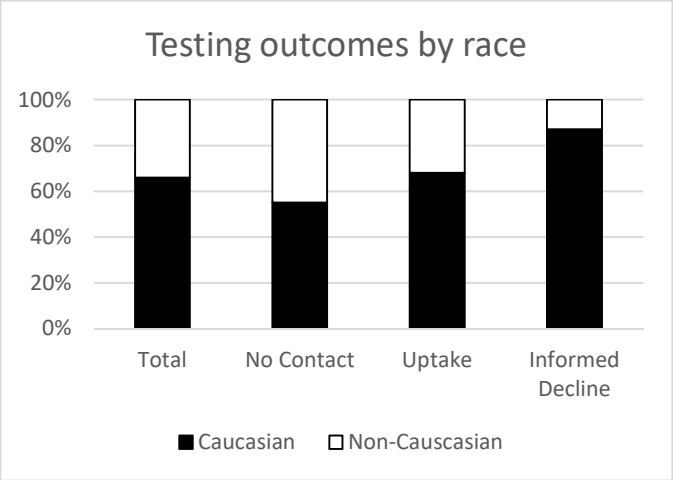
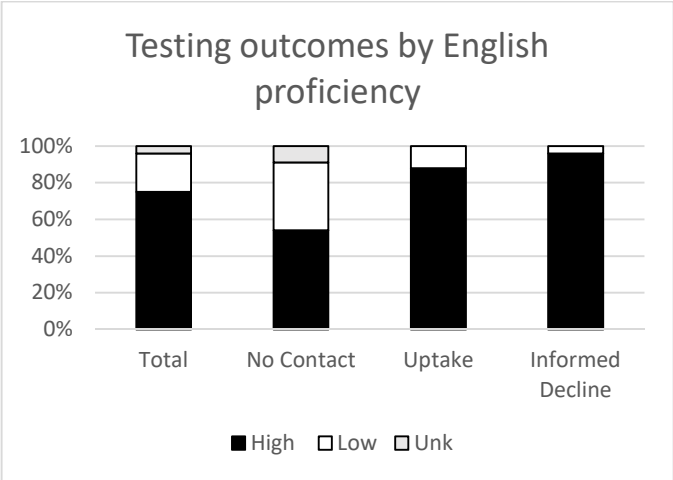
Supplemental Tables

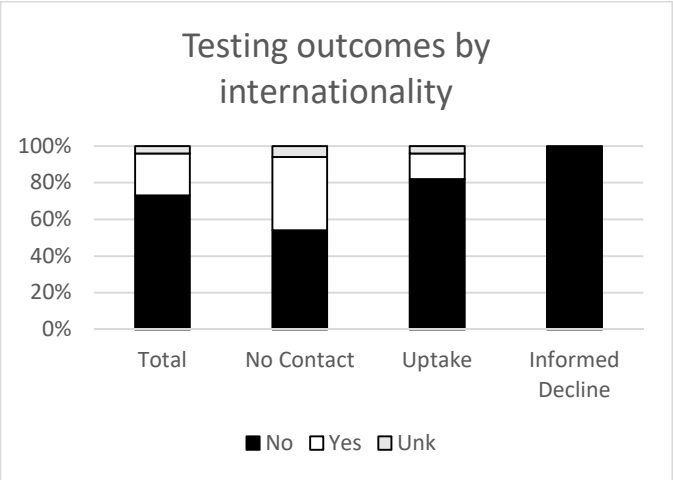


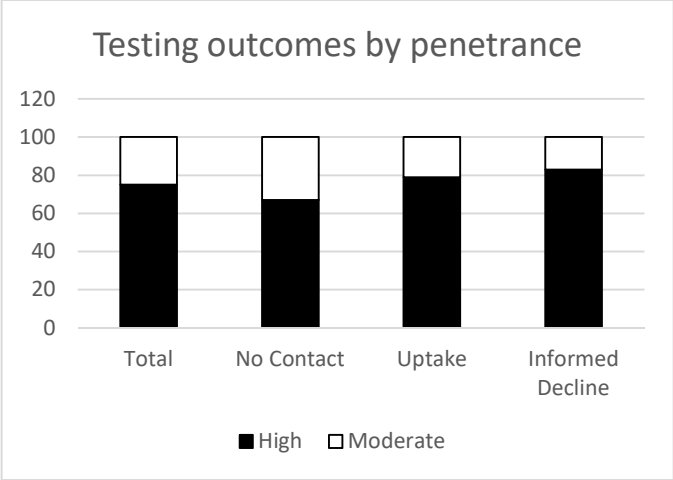











Testing outcomes by penetrance
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100
80
60
40
20
0
Total
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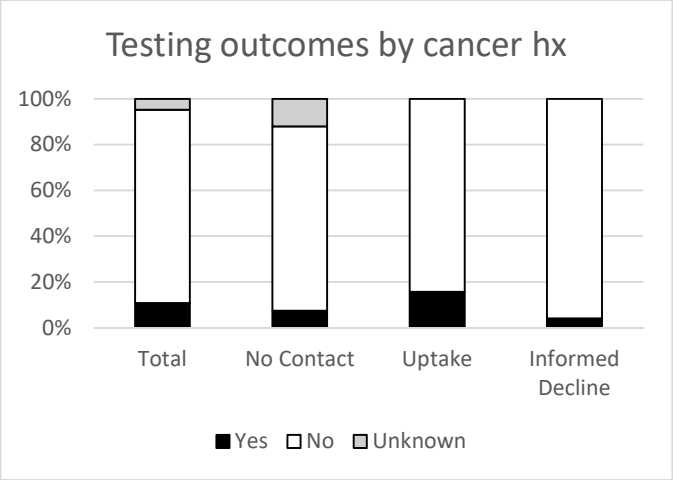
Uptake
Informed Decline
High
Moderate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Uptake
Informed Decline
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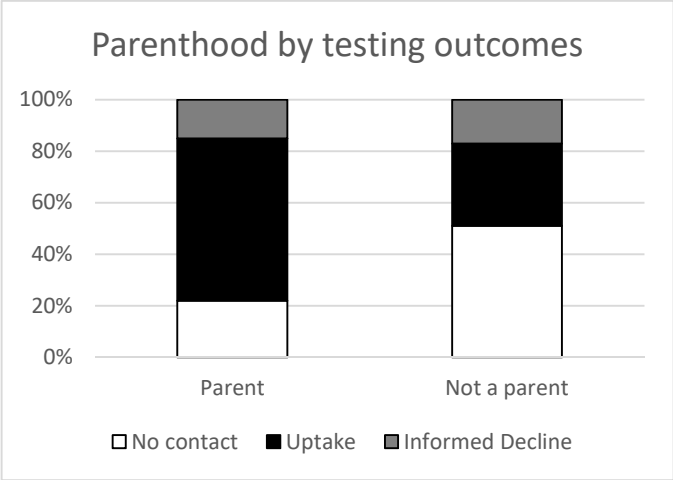
Parenthood by testing outcomes
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60%
40%
20%
0%
Parent
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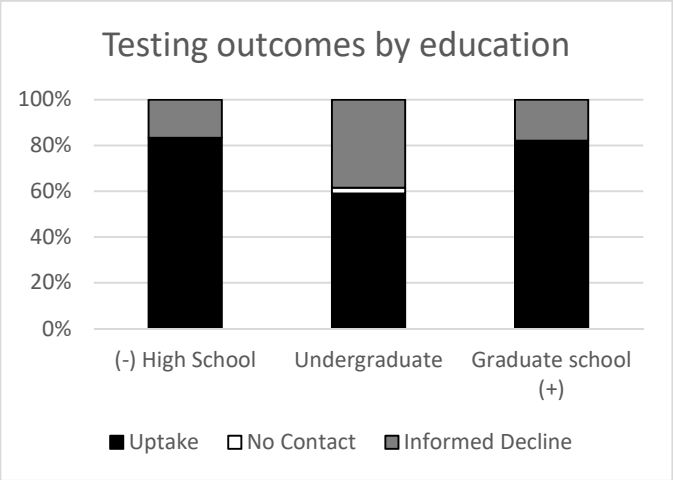
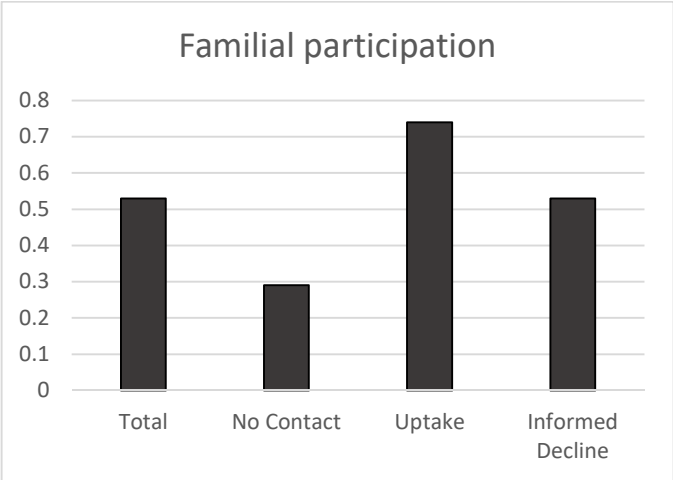
No contact
Uptake
Informed Decline


Testing outcomes by education
100%
80%
60%
40%
20%
0%
(-) High School
Undergraduate
Graduate school (+)
Uptake
No Contact
Informed Decline


Familial participation
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Total
No Contact
Uptake
Informed Decline