Assessing Usability and User Attitudes about an Educational Website: ConnectMyVariant

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Abstract

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Cascade testing for hereditary conditions such as cancer offers great potential for disease prevention, yet many challenges still exist for family communication and testing. ConnectMyVariant applies a unique combination of genealogy, direct-to-consumer (DTC) genetic testing, and social networking to the context of cascade screening for hereditary cancers. ConnectMyVariant is an educational website that offers information and resources for patients with pathogenic variants to connect with others who share the same pathogenic variant. This thesis describes the content development of the website and examines the usability and user perceptions of the website. Think-aloud and semi-structured interviews were conducted with potential users, and these interviews analyzed using qualitative methods. Usability issues included barriers to understanding, completing tasks, and navigation. However, many participants also made positive comments on many aspects of the website and expressed that they would share it with others, encouraging further development of the resource.

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I have been blessed beyond what I deserve, and I am so grateful to everyone who has helped me along this path.

DEDICATION

This is dedicated to my family, who never stopped supporting me and helped me get to where I am today.

1. INTRODUCTION

Over 200 hereditary cancer susceptibility syndromes have been identified. Although most cancer is sporadic, it is estimated that inherited cancer predisposition syndromes account for 5-10% of all cancer[1]. It is estimated that up to 10% of all breast cancer is caused by inherited mutations in breast cancer susceptibility genes[2]. For many hereditary cancer syndromes, there are medical management guidelines and recommendations to reduce cancer risk, such as prophylactic surgery or increased screening[3]. However, many people with hereditary cancer risk are undiagnosed[4].

Identifying at-risk individuals who carry pathogenic variants for hereditary cancer syndromes creates opportunities to intervene before cancer develops and also identify biologically related pathogenic variant carriers through cascade screening[3,5]. These hereditary cancer syndromes typically have an autosomal dominant inheritance pattern, so first-degree family members of affected individuals have a 50% chance of carrying the same pathogenic mutation. Cascade screening provides great potential for public health impact and has been shown to be cost-effective for hereditary conditions such as familial hypercholesterolemia[6]. The CDC Office of Public Health Genomics classifies Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome as Tier 1 Genomic applications. Tier 1 Genomic applications have significant potential public health benefit based on evidence-based guidelines and recommendations, such as early detection and intervention[7]. Currently, cascade screening is not widely implemented in the United States. Implementation of cascade screening has been impeded by obstacles such as limited access to genetic services and suboptimal communication between probands and family members[5]. Family communication of genetic risk and cancer prevention is a complex process, and this is a key area of interest for research to find ways to better implement cascade screening.

Many tools and techniques that are already being utilized have the potential to address the limitations that are currently inhibiting growth and implementation of cascade screening. In this introduction, I will discuss family studies in contrast to population screening as a way to identify individuals with hereditary cancer risk. I will then highlight several new technologies that may broaden and improve the reach of cascade testing: genealogy, direct-to-consumer (DTC) genetic testing, and social networking and online advocacy groups, which all have the potential to play a role in improving cascade screening. Finally, I will discuss how these diverse topics were combined into a novel website called ConnectMyVariant.

1.1 FAMILY STUDIES

Human geneticists have been leveraging the hereditary nature of genetics for decades. Family studies and linkage analysis are powerful tools for uncovering genetic contributions for diseases such as cancer[8]. Researchers have also been able to connect family trees of seemingly unrelated individuals based on genetic information, which has been helpful for identifying key genes connected to disease.[9,10] For example, the hereditary nature of some cancers had been identified as early as the 19th century, but large family studies were crucial to pinpointing how breast cancer is inherited[11]. To elucidate the model of inheritance for breast cancer, Newman et al. initially identified probands diagnosed with breast cancer to report family history of cancer diagnoses. For specific probands with multiple cases of cancer in their families, the researchers interviewed more family members, reviewing medical records and death certificates to identify all cases of cancer. The largest resulting family tree revealed 14 confirmed cases of breast cancer in a family of 252 individuals over 5 generations. Segregation analysis carried out with this data pointed to a dominant single-locus model of inheritance for breast cancer[12]. In addition to constructing family trees through traditional methods, geneticists have also been able to connect family trees based on DNA and shared haplotypes. Carbone et al. were able to find a common ancestor for four seemingly unrelated families with the same rare variant in *BAP1*, which causes an inherited cancer syndrome with high incidence of rare melanomas and mesotheliomas by age 55[10]. Despite multiple examples of connecting large families through shared genetic variants in the research setting, the principle of growing and connecting large families based on genetics has not been widely applied to public health.

1.2 POPULATION-BASED SCREENING

An alternative to family-based cascade testing that has been proposed is population-based screening for *BRCA1* and *BRCA2* [13,14]. However, population-based screening for hereditary cancer syndromes remains controversial, and there are both advantages and disadvantages to consider. Population-based screening could address shortcomings with current genetic screening for cancer prevention, as many carriers are not identified until they are diagnosed with cancer[4]. Modeling approaches have shown that population-based genetic screening for hereditary cancer syndromes is cost-effective in certain scenarios[15,16]. An additional advantage of population-based screening is identifying a subset of carriers who would not have otherwise been identified because their family history of cancer did not suggest genetic testing. Gabai-Kapara et al. carried out a population-based screening study of Ashkenazi Jews in Israel to assess cancer risk in carriers identified from the general population [13]. Of the families identified with *BRCA1* or *BRCA2* mutations, approximately half of the families had little to no family history of relevant cancers. Although population-based screening has many notable strengths, many barriers to implementation exist. Practical issues such as costs and implementation of large-scale screening and access to medical care need to be addressed[15]. Population-level genetic screening would take considerable time and resources before being able to reach the whole population[17]. Population-level screening also raises many ethical issues because patients should be sufficiently informed before doing genetic testing[18]. Additionally, King et al. argues against reporting variants of uncertain significance (VUS) results from population-based *BRCA1* and *BRCA2* testing, as VUS can create additional confusion or complicate medical management [14]. More ambiguity is introduced by the fact that variants that increase cancer risk have incomplete penetrance, and each person's medical management decisions to manage cancer risk have different motivations[14].

Population-based genetic screening for hereditary cancer has not been implemented in the United States. In contrast, family-based outreach to known relatives is widely accepted, and many insurance companies cover testing in at-risk relatives. A combined approach with aspects of both population-based screening and cascade testing may be the most effective and efficient to identifying all individuals with hereditary cancer risk[19]. Acknowledging that population-based screening may be useful, my thesis will focus on potential advances in cascade testing in families as a strategy improve hereditary cancer prevention.

1.3 GENEALOGY

Genealogy advances may help identify additional at-risk individuals in families with hereditary cancer risk. Genealogy has been increasing in popularity as a pastime, particularly in the United States. Genealogists compile family histories from a variety of sources, such as written histories, official documents, town records, and more[20]. With the internet, people can now connect to distantly related family members, connect family trees, and communicate more easily. Genealogy services like Ancestry.com facilitate genealogical research by compiling records from a variety of sources into a convenient, searchable online database[21]. Through these websites, professional and amateur genealogists now have more convenient access to records that may have been previously difficult to access. Companies such as Ancestry.com, MyHeritage, or Geni serve over 130 million users combined[22]. In addition to accessing records on these websites, users can also upload their own information from their family histories onto the websites[23]. As more users join genealogy websites, the amount of genealogical data on these websites grows larger, and many new uses for this data have emerged. Kaplanis et al. were able to build population-scale family trees from 86 million publicly available profiles downloaded from Geni.com. The average constructed family tree spanned 11 generations[24]. Building large-scale family trees using genealogy demonstrates the power and potential of online genealogical data, which could be leveraged in the context of genetics and hereditary cancer.

1.4 DIRECT-TO-CONSUMER GENETIC TESTING

Genetics and genealogy go hand-in-hand, and many genealogy companies also offer services to genotype customers' DNA and create family trees. Likewise, DTC genetic testing companies such as AncestryDNA.com and 23andMe offer services to provide genetic data to customers, provide ancestry reports, and connect with others in their databases[25].

Other third-party sites, such as GEDmatch, allow users to upload their own raw genetic data (typically generated in the course of DTC testing) in order to find others who may be related by comparing DNA sequences[26]. If two individuals share many long stretches of DNA, it is likely that the two individuals are relatively closely related or descended from a recent common ancestor. If two individuals share the same alleles along a stretch of DNA from a common ancestor, these haplotypes are identical-by-descent (IBD). Closely related individuals have longer segments of IBD because there have been fewer opportunities for recombination events[27]. Comparing DNA sequences to identifying matching sequences of DNA and find relatives also has applications beyond genealogy. GEDmatch has contributed to multiple criminal investigations, such as the Golden State Killer case. Law enforcement and investigators uploaded DNA from crime scenes onto GEDmatch, found distant relatives on the database, and traced the information back to the suspect[27,28]. Applications of DTC genetic testing and online genealogy could also be leveraged in the context of hereditary cancer to connect people who share haplotypes at loci that house pathogenic variants.

1.5 Social Networking and Online Advocacy Groups

The rise of social networks and online advocacy groups plays a role in cancer prevention. The internet allows people to connect with and share information much more rapidly and easily with others who are far away. Online advocacy groups offer resources, information, and support to people who share common experiences or diagnoses. Many cancer-specific groups exist, such as Facing Our Risk of Cancer Empowered (FORCE) which aims to serve people affected by hereditary breast and ovarian cancer[29]. Online forums create opportunities to build connections for people who might not otherwise connect. Cancer patients and survivors often use online forums and social media as resources for health information seeking, disease management, and social support[29]. In the context of hereditary cancer, cancer-specific advocacy groups also offer a unique resource called “variant specific forums” where carriers can connect with others who have the same variant. Users can post information about their genetic testing results or a specific variant, and other forum members can respond to their posts on the message boards or directly message the original author[30]. Online forums have been used to connect people with similar experiences or diagnoses, and now these variant-specific forums allow users to connect when they share individual genetic variants. These forums allow users to participate in and personally initiate connections through shared genetic variants, similar to the concept of connecting family trees through genealogy and genetics.

1.6 CONNECTMYVARIANT

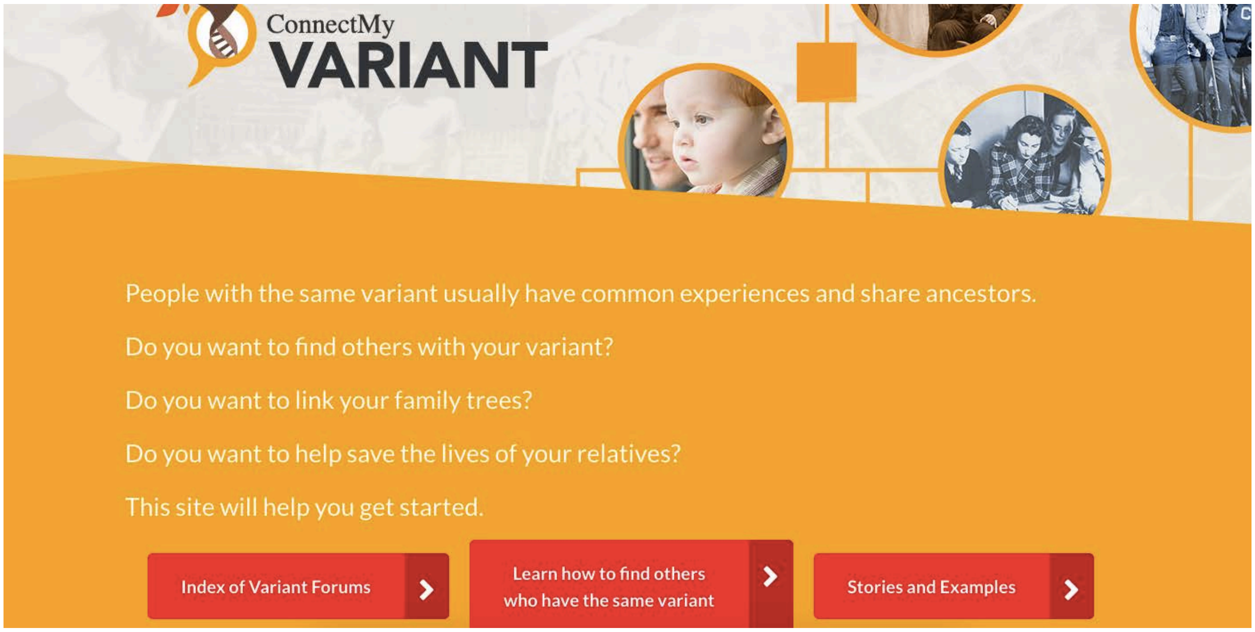
Cancer prevention has the potential to dramatically reduce the burden of disease, but there are many gaps in current cancer prevention practices, especially in the case of hereditary cancer. Research and recommendations to support cascade screening exist, however, many barriers to implementation remain. Familial communication about genetic testing and finding additional relatives to test are major areas that need improvement[31]. However, there are tools that are already being utilized in different contexts, such as genealogy, DTC genetic testing, and social networking, that could be applied to the context of cascade screening for hereditary cancers. Variant specific forums can be used to help connect people with the same variant, and then genealogy tools and DTC genetic testing could be used in tandem to help carriers identify more distantly related individuals who also carry the same variant. Identifying these relationships creates more complete and expansive family trees, which could also elucidate which relatives are at risk of inheriting the pathogenic variant by tracing it through the family tree. This approach of providing resources for pathogenic variant carriers to connect with relatives with the same variant has potential to reduce barriers to cascade screening and improve the efficiency of cancer prevention in the context of hereditary cancer.

Our research objectives for this project were 1) create an educational website to introduce resources and tools for pathogenic variant carriers to communicate genetic risk with relatives and connect with distant relatives, 2) assess the usability of this website by identifying any barriers for potential users to access and understand website content, and 3) gather feedback from potential users about how the information presented on the website would affect their communication with family members about genetic testing.

In order to address these objectives, we created an educational website called ConnectMyVariant to offer information and resources to facilitate communication about hereditary cancer risk and genetic testing. To assess usability of the website, we conducted an interview study using a think-aloud method [32]. In addition to the think-aloud study, we also conducted semi-structured interviews to ask participants about how they perceived ConnectMyVariant might affect how they communicate with family members about genetic testing. This thesis has a separate section discussing each of these objectives. I will discuss content development of ConnectMyVariant, the methods used to assess usability of the website, then the results from that assessment.

2. CONNECTMYVARIANT.ORG CONTENT DEVELOPMENT

The initial ConnectMyVariant content development team consisted of Brian Shirts, Ginger Tsai, and Carmen Ng. The format of the ConnectMyVariant website was planned to resemble the FindMyVariant website, a related educational website focused on variant reclassifications and family studies created by Dr. Shirts' team. To build the ConnectMyVariant website, we worked with Jenny Ross, a web developer. The website was coded in HTML with a PHP backend hosted on Amazon Web Services with code deployed and edited on GitHub. The homepage was designed with three buttons to lead to the three main parts of the website: "Index of Variant Forums", "Learn How to Find Others Who Have the Same Variant", and "Stories and Examples". Figure 2.1 shows the ConnectMyVariant homepage. The "Learn How to Find Others Who Have the Same Variant" button takes the user to the section of educational content and Frequently Asked Questions (FAQs). The homepage also included questions to guide users and explain the purpose of ConnectMyVariant.



People with the same variant usually have common experiences and share ancestors.

Do you want to find others with your variant?

Do you want to link your family trees?

Do you want to help save the lives of your relatives?

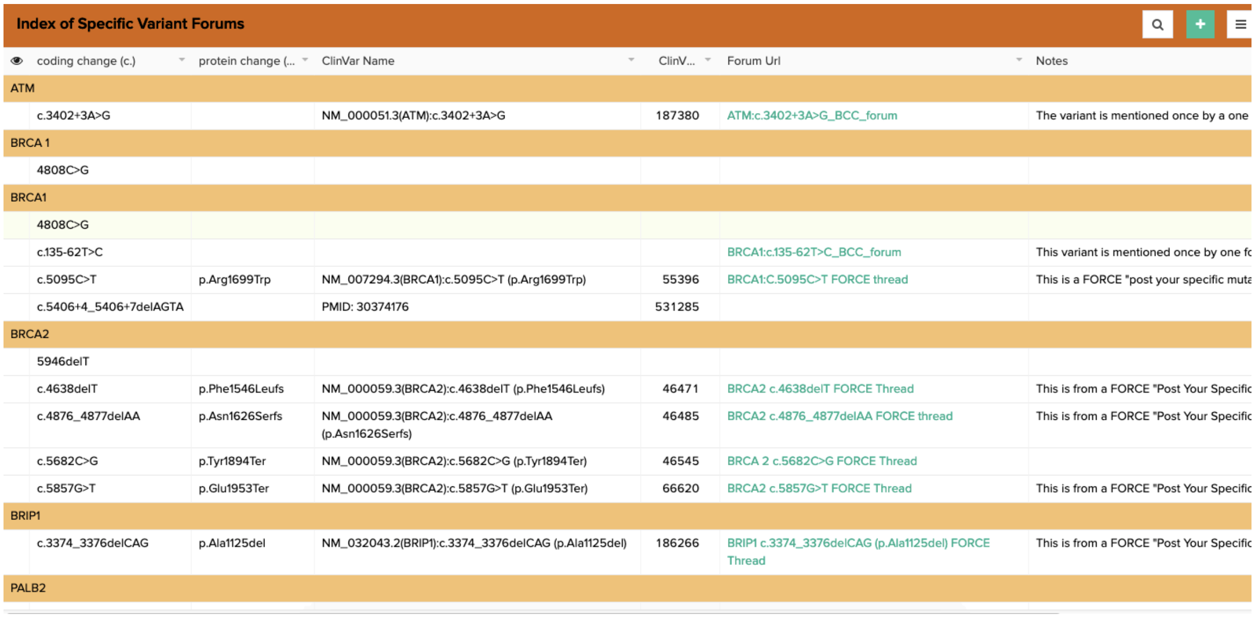
This site will help you get started.

Figure 2.1. Screenshot of ConnectMyVariant Homepage.

2.1 INDEX OF VARIANT FORUMS

The index of variant forums is an index for users to post links to a variant specific forum. Figure 2.2 shows a screenshot of the index of variant forums. Others can go to the index of variant forums to see if their variant has been posted on the index. This index was created to address barriers that prevent people from finding others with the same variant. Currently, variant specific forums hosted on message boards are not widely searchable, and there is no method for finding posts about the same variant if they are hosted on another message board or website. A key goal in creating the index was to create a central location where variant specific forums hosted on different websites could be collected in a single index so that users searching for a variant using a search engine, such as Google, could find the variant's entry on the index with a link to the variant specific forum. Another issue is inconsistent variant nomenclature since the forums are not regulated for these details when users make a post. After creating a variant specific forum on a message board such as the FORCE forums, a user can add an entry into the ConnectMyVariant index with information on the variant and a link to their variant specific forum. When adding a variant onto the index, a user can fill in fields for: gene, coding change (c.), protein change (p.), ClinVar Name, ClinVarID, genomic coordinates, and forum URL. Gene name and coding change are required fields, as these are the minimum requirements needed to identify a variant. The other fields were included so that searches for other names of the variant would lead to the same index entry. Each field includes a short description of what should be input and some examples, like "c.5857G>T" as an example of a coding change. There are also private fields for name, email, and notes. These fields allow the ConnectMyVariant team to contact the user who created the post for any follow-up, if necessary. Users can also contact the ConnectMyVariant team through a link if they need help adding variants. After a variant entry is added, anyone who visits the index on the ConnectMyVariant webpage can view the entry. When users click on an entry in the index, a pop-up appears on the right side of the screen that shows all the fields from the initial index page with additional fields, like “Forum Type” and “Forum Start Date”. This is shown in Figure 2.3.

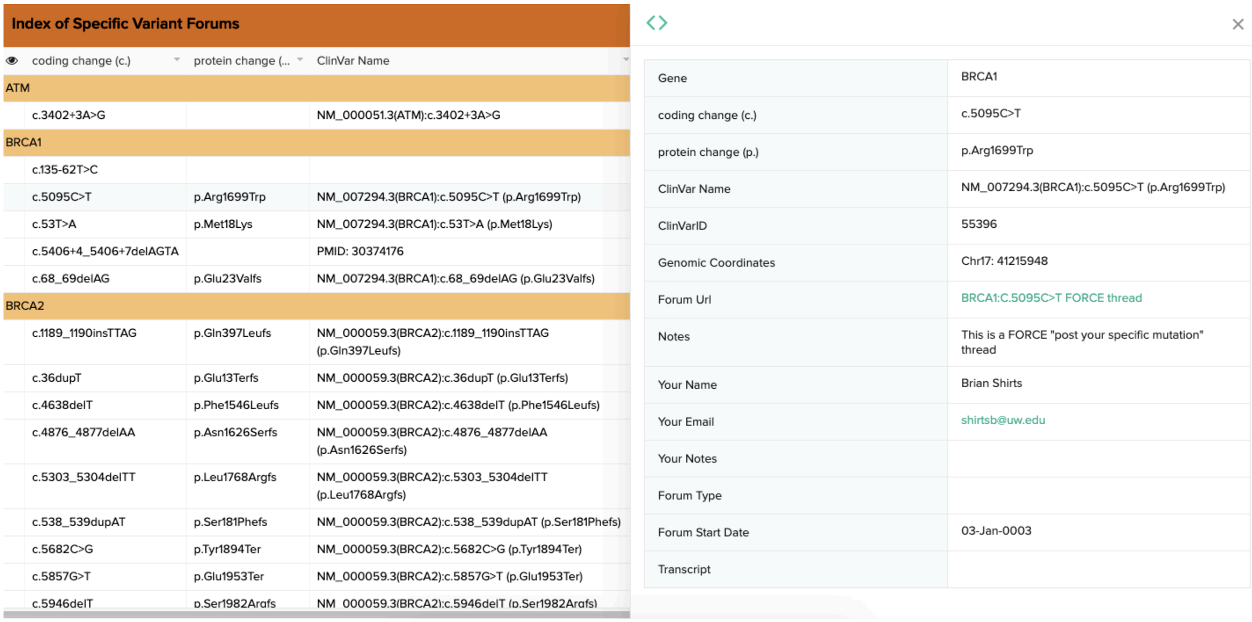
Dr. Shirts constructed the index of variant forums using Zoho Creator, an online custom app builder, and Jenny Ross embedded the index into the *ConnectMyVariant* website. The advantages of building the index on Zoho Creator were ease of both customization and initial set up. The fields and text of the index can be quickly and conveniently altered on the Zoho platform. One limitation is that the index is also not searchable with search engines, which was a failure of one key goal of creating the index of variant forums with the current implementation. The current index also requires curation from the *ConnectMyVariant* team or administrator, which has pros and cons. Curation allows the team to moderate the index and edit incorrect entries. The team can also fill in missing information, so users do not have to fill out all the fields before posting their variant. This addresses the current limitation of incomplete or incorrect variant information that is posted to variant specific forums. However, manual curation of the index may not be sustainable as the volume of indexed variants expands.



Index of Specific Variant Forums

coding change (c.)	protein change (...	ClinVar Name	ClinV...	Forum Url	Notes
ATM					
c.3402+3A>G		NM_000051.3(ATM):c.3402+3A>G	187380	ATM:c.3402+3A>G_BCC_forum	The variant is mentioned once by a one
BRCA 1					
4808C>G					
BRCA1					
4808C>G					
c.135-62T>C				BRCA1:c.135-62T>C_BCC_forum	This variant is mentioned once by one fo
c.5095C>T	p.Arg1699Trp	NM_007294.3(BRCA1):c.5095C>T (p.Arg1699Trp)	55396	BRCA1:C.5095C>T FORCE thread	This is a FORCE "post your specific muta
c.5406+4_5406+7delAGTA		PMID: 30374176	531285		
BRCA2					
5946delT					
c.4638delT	p.Phe1546Leufs	NM_000059.3(BRCA2):c.4638delT (p.Phe1546Leufs)	46471	BRCA2 c.4638delT FORCE Thread	This is from a FORCE "Post Your Specific
c.4876_4877delAA	p.Asn1626Serfs	NM_000059.3(BRCA2):c.4876_4877delAA (p.Asn1626Serfs)	46485	BRCA2 c.4876_4877delAA FORCE thread	This is from a FORCE "Post Your Specific
c.5682C>G	p.Tyr1894Ter	NM_000059.3(BRCA2):c.5682C>G (p.Tyr1894Ter)	46545	BRCA 2 c.5682C>G FORCE Thread	
c.5857G>T	p.Glu1953Ter	NM_000059.3(BRCA2):c.5857G>T (p.Glu1953Ter)	66620	BRCA2 c.5857G>T FORCE Thread	This is from a FORCE "Post Your Specific
BRIP1					
c.3374_3376delCAG	p.Ala1125del	NM_032043.2(BRIP1):c.3374_3376delCAG (p.Ala1125del)	186266	BRIP1 c.3374_3376delCAG (p.Ala1125del) FORCE Thread	This is from a FORCE "Post Your Specific
PALB2					

Figure 2.2. Screenshot of Index of Variant Forums.



Index of Specific Variant Forums

coding change (c.)	protein change (...	ClinVar Name
ATM		
c.3402+3A>G		NM_000051.3(ATM):c.3402+3A>G
BRCA1		
c.135-62T>C		
c.5095C>T	p.Arg1699Trp	NM_007294.3(BRCA1):c.5095C>T (p.Arg1699Trp)
c.53T>A	p.Met18Lys	NM_007294.3(BRCA1):c.53T>A (p.Met18Lys)
c.5406+4_5406+7delAGTA		PMID: 30374176
c.68_69delAG	p.Glu23Valfs	NM_007294.3(BRCA1):c.68_69delAG (p.Glu23Valfs)
BRCA2		
c.1189_1190insTTAG	p.Gln397Leufs	NM_000059.3(BRCA2):c.1189_1190insTTAG (p.Gln397Leufs)
c.36dupT	p.Glu13Terfs	NM_000059.3(BRCA2):c.36dupT (p.Glu13Terfs)
c.4638delT	p.Phe1546Leufs	NM_000059.3(BRCA2):c.4638delT (p.Phe1546Leufs)
c.4876_4877delAA	p.Asn1626Serfs	NM_000059.3(BRCA2):c.4876_4877delAA (p.Asn1626Serfs)
c.5303_5304delTT	p.Leu1768Argfs	NM_000059.3(BRCA2):c.5303_5304delTT (p.Leu1768Argfs)
c.538_539dupAT	p.Ser181Phefs	NM_000059.3(BRCA2):c.538_539dupAT (p.Ser181Phefs)
c.5682C>G	p.Tyr1894Ter	NM_000059.3(BRCA2):c.5682C>G (p.Tyr1894Ter)
c.5857G>T	p.Glu1953Ter	NM_000059.3(BRCA2):c.5857G>T (p.Glu1953Ter)
c.5946delT	p.Ser1982Argfs	NM_000059.3(BRCA2):c.5946delT (p.Ser1982Argfs)

Gene	BRCA1
coding change (c.)	c.5095C>T
protein change (p.)	p.Arg1699Trp
ClinVar Name	NM_007294.3(BRCA1):c.5095C>T (p.Arg1699Trp)
ClinVarID	55396
Genomic Coordinates	Chr17: 41215948
Forum Url	BRCA1:C.5095C>T FORCE thread
Notes	This is a FORCE "post your specific mutation" thread
Your Name	Brian Shirts
Your Email	shirtsb@uw.edu
Your Notes	
Forum Type	
Forum Start Date	03-Jan-0003
Transcript	

Figure 2.3. Screenshot of Index of Variant Forums with pop-up window.

2.2 LEARN HOW TO FIND OTHERS WHO HAVE THE SAME VARIANT - EDUCATIONAL CONTENT

When users click the “Learn How to Find Others Who Have the Same Variant” button, they are taken the educational content of the website. The educational content of the website is meant to educate and guide users on how to use the ConnectMyVariant tools. The educational portion of the website is split into 7 sections: Why Connect, Talking to Family about Cancer Risk, Helping Others Get Tested, Connecting with Distant Relatives, Familial Cancer and Non-Familial Cancer Risk, Finding Distant Relatives, and Finding Genetic Relatives Using DNA. Much of this content previously existed on FindMyVariant and was adapted for ConnectMyVariant, as noted above. Dr. Shirts and Ginger Tsai created a majority of the new content for ConnectMyVariant. My main role for the educational section was reviewing and editing content, and providing feedback. I also worked on adding useful links within and between sections and to outside resources.

The “Why Connect” section is the landing point for the “Learn how to find others who have the same variant” button. The “Why Connect” page has a short summary of the reasons patients might wish to connect with relatives and find others with the same variant. The summary also includes an overview of the website, with multiple links to other pages of ConnectMyVariant for users to jump to specific pages of the website that may be more relevant to them.

The “Familial and Non-Familial Cancer Risk” page is meant to teach basics of cancer risk and differentiate between familial and non-familial cancer risk. This page also provides brief descriptions about general cancer prevention and examples of risk-reducing options for pathogenic variant carriers.

The “Talking to Family about Cancer Risk” page provides users with resources for communicating cancer risk to family members, such as ideas for finding the best mode of communication, and tips for navigating difficult situations. The purpose of this page is to help users initiate talking to family members about a potential shared cancer risk. The content of this page is almost entirely identical to content from a similar page on FindMyVariant.

“Helping Others Get Tested” offers a step-by-step guide to genetic testing and recommendations for how to share genetic test results with relatives. If users need information on genetic testing to help relatives get tested, this provides comprehensive descriptions of the different aspects of genetic testing, like types of genetic testing, reading genetic testing reports, and more.

The “Connecting with Distant Relatives” page is meant for users who need ideas on how to start reaching out to more distant relatives or finding contact information. There are also scripts for reaching out to family members over social media about cancer, which are adapted from scripts created for FindMyVariant. The content of this page is also almost entirely identical to content from a similar page on FindMyVariant.

“Finding Distant Relatives” provides a general overview of genealogy techniques and provides users with links to genealogy tools to help them start compiling a family tree. “Finding Distant Relatives with DNA” gives more technical, specific directions about using data from DTC genetic testing and GEDmatch to find people who may be biologically related. This section also explains the concept of IBD and how genetics can be used to find others with the same variant. The text from this section is included in Appendix A as an example of website content.

2.3 STORIES AND EXAMPLES

The “Stories and Examples” page contains short, fictional vignettes that illustrate different kinds of situations that could happen for people who use ConnectMyVariant. The stories offer demonstrations of how to use the website to connect with others who share the same variant, with links to different pages of the website to illustrate main points. Users may also connect or relate to situations with the scenarios as they read through the stories. Each story was written to illustrate specific points to teach certain aspects of connecting with distant relatives or communicating with family members. Stories were designed to focus on different aspects of connecting with distant relatives because stories can illustrate concepts that may otherwise be difficult to grasp. Reading through the stories and examples could also provide ideas for users.

I developed three stories for this section: Linda’s story, Mary’s story, and Tom’s story, with Dr. Shirts. As developing these stories was a key component of thesis work, I will go over each of these in detail, with a bulleted list of the key components that each story was designed to teach. All 3 stories are fictional, but the stories were modeled after characteristics and experiences that could be relevant to real patients. The text of the stories was written by Dr. Shirts, Ginger Tsai, and myself after planning out the main teaching points. Table 2.1 describes the content of the stories in three main sections: Family, Process, and End Result. The “Family” section refers to the main character’s family history of cancer and genetic testing, which are generally described in the beginning of the story. The family history and structure can be used to teach about genetics, hereditary cancer, and inheritance. Patients may also relate with certain aspects of the main character’s family history, so a variety of family histories, cancers, and genes were included. The “Process” section includes the main points of how the character utilized ConnectMyVariant and other tools to try to find others with the same variant. We created examples using different avenues and tools of finding family members to illustrate the variety of methods that could be used. The "End Results" section includes the outcomes of each character's story, such as if they were able to find any distant relatives, connect family trees, or share information about their variant with them. We presented stories with a variety of outcomes to demonstrate both successful and unsuccessful examples. Individual stories can have multiple outcomes, just like real life.

Stories of experiences of patients will relate to many different skills related to identifying and communicating with relatives, so it is also more realistic to have stories illustrating many concepts. Stories and examples were a part of FindMyVariant and were one of the features that was noted to be most helpful by FindMyVariant study participants[33].

In addition to helping develop these stories, I also created a series of pedigree images with Proband software to accompany Linda and Mary's stories. The stories were created to show how specific individual efforts can help increase information about how a cancer risk variant can be traced through a family. Multiple pedigree images visually depict how the family tree grows as more information and family members are discovered. An example of these pedigree images is shown in Figure 2.4. Figure 2.5 shows how the pedigrees would be integrated into the text of the story using Mary's story.

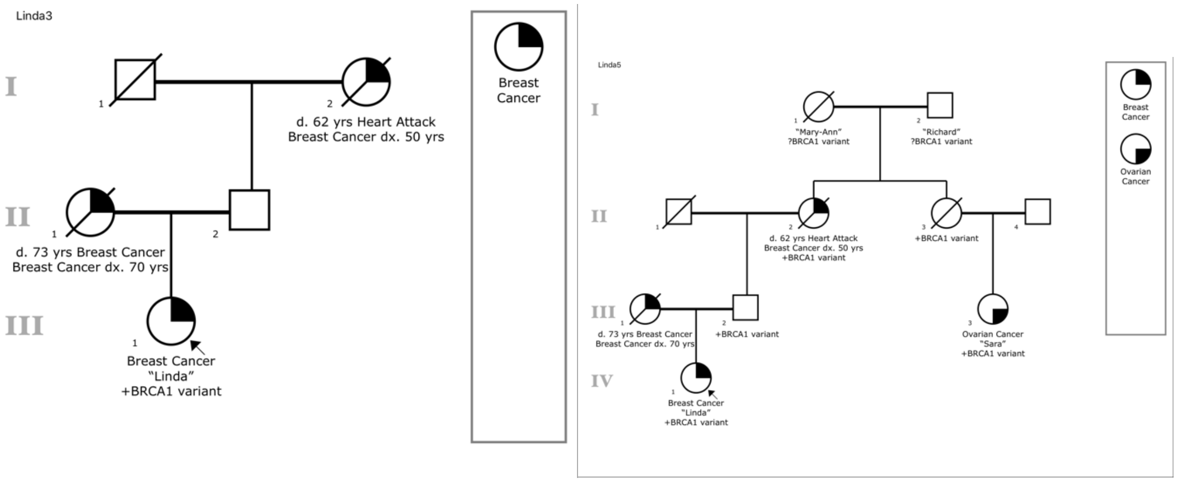
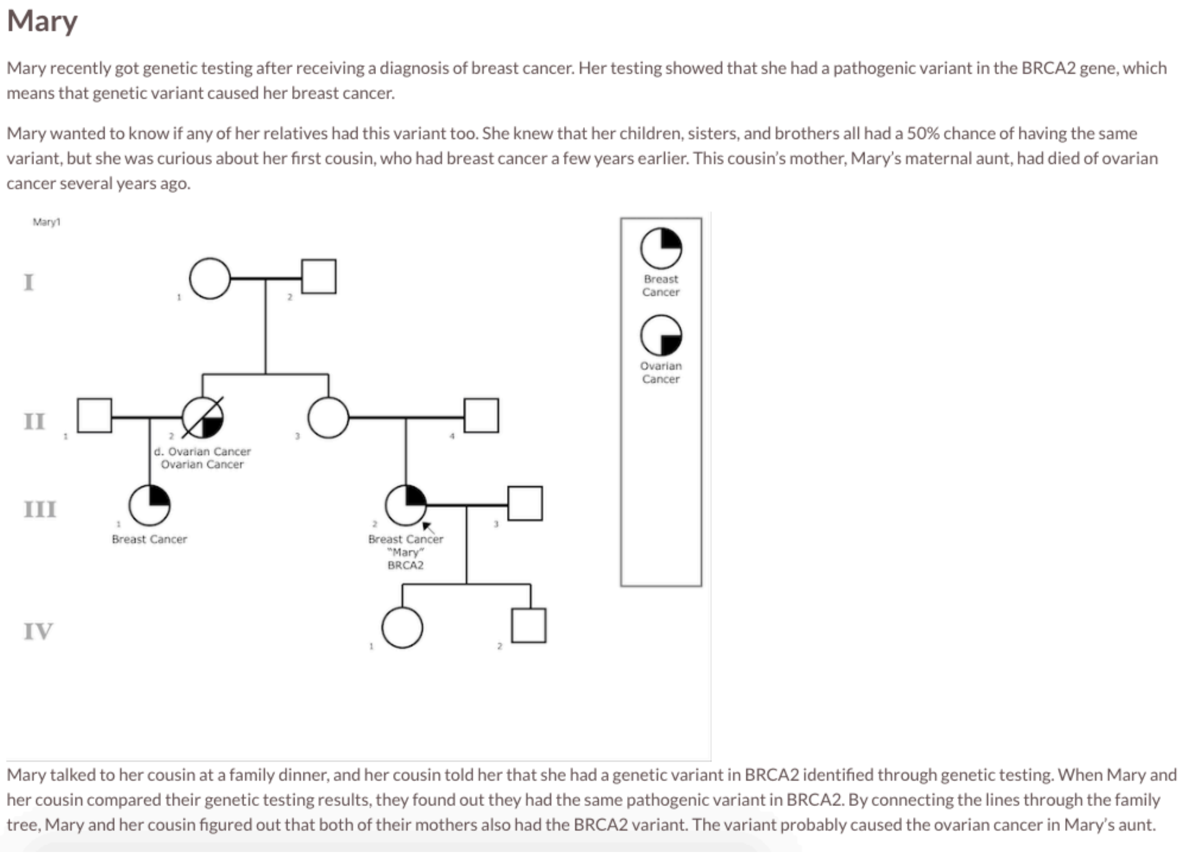


Figure 2.4. Examples of Pedigrees from Linda's Story.



Mary

Mary recently got genetic testing after receiving a diagnosis of breast cancer. Her testing showed that she had a pathogenic variant in the BRCA2 gene, which means that genetic variant caused her breast cancer.

Mary wanted to know if any of her relatives had this variant too. She knew that her children, sisters, and brothers all had a 50% chance of having the same variant, but she was curious about her first cousin, who had breast cancer a few years earlier. This cousin's mother, Mary's maternal aunt, had died of ovarian cancer several years ago.

Mary talked to her cousin at a family dinner, and her cousin told her that she had a genetic variant in BRCA2 identified through genetic testing. When Mary and her cousin compared their genetic testing results, they found out they had the same pathogenic variant in BRCA2. By connecting the lines through the family tree, Mary and her cousin figured out that both of their mothers also had the BRCA2 variant. The variant probably caused the ovarian cancer in Mary's aunt.

Figure 2.5. Screenshot of Mary's story from the website.

2.3.1 *Linda*

In Linda's story, she was described as having inherited a pathogenic *BRCA1* mutation from her father's side of the family, illustrating that a mutation associated with HBOC can be passed through either the mother or father. Linda finds another family member diagnosed with cancer who also carries the same pathogenic variant. Linda and her relative then go through the process of finding and reaching out to distant relatives to demonstrate each step in the process.

2.3.2 *Tom*

Tom's story was written as an example of someone who went through the process of trying to connect with others who had the same variant but was not able to find clear family connections with others that he found on the message board. To find others who shared his variant, Tom utilized genealogy techniques such as constructing family trees with names, birth dates, and death dates of family members. Tom was able to connect family trees with one forum member, but he was unable to find the exact link with another forum member who shared the same variant. This example was meant to demonstrate how a variety of outcomes could result from seeking to connect with others with the same variant.

2.3.3 *Mary*

Mary's story illustrates an example of a person who was able to connect with both closer and distant relatives who shared the same variant. After a close relative was also diagnosed with cancer and found out she was also a carrier, Mary was able to trace the variant back to a maternal common ancestor. Mary used an ancestry testing kit and found other relatives who shared the same common ancestor through the ancestry testing company. She was able to reach out to them through the website and share about her diagnosis, pathogenic variant, and hereditary cancer risk.

Table 2.1. Stories and Examples Highlights

	Linda	Tom	Mary
Family	• Mother died of breast cancer—no genetic testing • BRCA1 variant inherited from father's side ○ Paternal grandmother: diagnosed with breast cancer ○ Father's cousin Sara: diagnosed with ovarian cancer	• Parents passed away—did not do genetic testing • Brother died of colon cancer in 40's—did not do genetic testing • Paternal aunt with endometrial cancer—tested positive for variant	○ Family history of breast and ovarian cancer ○ Mary: tested positive for pathogenic variant ○ Cousin—tested positive for same variant
Process	• Asked family members about cancer diagnoses • Connected with another relative who had gotten genetic testing separately • Traced variant through family tree • Created forum on American Cancer Society Cancer Survivor Network ○ Added onto Index of Variant Forums ○ Emailed ConnectMyVariant team for help filling in fields • AncestryDNA ○ Connected family tree ○ Found matching segment with Sara • GEDmatch.com ○ Used Matching Segment search ○ Compared results that shared with both Linda and Sara	• Joined online forum • Shared variant and experiences through online forum • Created family trees with help from family members • Connected with other forum members to connect family tree	• Talked with cousin to connect family trees • Used ancestry testing kit • Reached out to individuals on website

	- Shared Cancer risk - Referral to genetic counselor		

End result	- Found relatives using GEDmatch
	  - One relative refused genetic testing
	  - One relative sought genetic testing and found a genetic counselor
		- Was able to connect with one member of message board
		- Was unable to connect with another member of message board--Couldn't find how they were related
			- Found ancestry site member also had the variant
			- Connected family trees
			- Ancestry site member: adopted
			  - referred to genetic counselor for testing

2.4 FREQUENTLY ASKED QUESTIONS (FAQS)

The FAQ section was meant to summarize key points from the website, answer questions, and supply information that may not fit into other sections of the website. I built an FAQ section, as a place to quickly answer questions that may come up from other sections. The answers were written to be short, simple explanations with links to other resources or other parts of the website for further reading and information, if applicable. In order to identify questions to answer on the FAQs, I asked friends and colleagues who were not experts in genetics or this project to casually browse the website and share questions that came up. I also tried to predict what common questions would come up from browsing the website, and I also wanted to include information that was not found in other parts of the website, such as the cost of genetic testing or recommended age range for genetic testing. The information I gathered from these questions and comments informed how I would approach the interviews and gather feedback from interview participants. A screenshot of the FAQ section is included in Appendix B.

3. WEBSITE USABILITY ASSESSMENT METHODS

As this project had multiple research objectives, we selected methods to meet our goals of gathering feedback on ConnectMyVariant. We chose the think-aloud method to assess the usability of this website and the semi-structured interview method to gather feedback from potential users about how the information presented on the website would affect their communication with family members.

3.1 RECRUITMENT

We sought to enroll five to seven participants in think-aloud assessments. This study was deemed not human subjects research by the University of Washington IRB (Study 00006849). Inclusion criteria for this project were adults 18 years and over and also be known to have a pathogenic or likely pathogenic genetic variant. Two groups of potential participants targeted were patient advocate collaborators of the research team and individuals who participated in past research with Dr. Brian Shirts who had indicated interest in participating in future research studies. These groups were chosen because there were several collaborators who are patient advocates who had expressed interest in providing feedback on ConnectMyVariant. The ConnectMyVariant site also addresses requests brought up by participants in the FindMyVariant study, who are another target audience.

Recruitment was performed by Dr. Shirts, Ginger Tsai, and myself. Initial email invitations were sent out to prospective interview participants by Dr. Shirts and Ginger Tsai, with follow-up emails sent by me. Interviews were scheduled and conducted between March 28 and April 17, 2019. A confirmation email with a pre-interview checklist was sent to participants to ensure the appropriate technology would be available during the interview. A link to join the Zoom meeting and the think-aloud task list were sent to participants by email approximately 30 minutes before the scheduled interview time (see Appendix C for materials sent to participants).

3.2 THINK-ALOUD

One of our goals was to assess the usability of ConnectMyVariant and pinpoint any major barriers to usability. With guidance from thesis committee Annie Chen and Malia Fullerton, we chose to use a think-aloud method to assess usability. Think-aloud is a method employed in usability research. Briefly, the researcher asks participants to "think aloud" as they are completing a set of tasks as requested by the researcher. Some recommend that the researcher should only give minimal cues when the participant stops talking. Researchers should also regularly acknowledge the interviewee with neutral prompts such as "mhmm" or "uh-huh" to invite the participant to continue speaking as they complete their tasks[32]. This ensures that the researcher does not influence the participant with too much or too little feedback during the think-aloud exercise[34].

At the beginning of the interview, we collected verbal consent from each participant, explained the format of the interview, and offered time for participants to ask questions. Then we collected and recorded select demographic information, such as age, gender, ethnicity, and highest level of education. Participants were next briefed on the think-aloud procedure. Then I demonstrated the think-aloud approach and shared my screen as I worked through an example task. Before starting the think-aloud, participants were also asked to share their screen while practicing thinking aloud.

We planned for the participants to complete three tasks related to the website. The goal of creating this task list was to direct participants to test or visit key pages of the website. The task list given to participants is included in Appendix C.

The first task on the list, "Browse the ConnectMyVariant Website," was left purposefully open-ended to allow participants to spend as much time browsing, reading, and commenting on different pages of the website as they were so inclined. After browsing the ConnectMyVariant website, participants were next asked to click the "Learn how to find others who have the same variant" button on the homepage, read through the "Why Connect" page, and explore any other links they wish to explore. The "Why Connect" page was targeted to ensure that participants read through the purpose of the website and see their reactions to it. Participants were then asked to read through the "Stories and Examples" page in order to see how the participants interacted with the stories and examples, gather feedback, and see if users found the examples helpful or relevant. The final task was to add a variant to the index of variant forums. Participants were told before the interview that they would have an opportunity to share information about their own variant, if they wanted to add a variant. However, they were also told that they did not need to do so and that an example variant would be provided for them if necessary. Since the index of variant forums was a novel aspect of the website, it was important to include this task to understand and assess any barriers that users might encounter with use of the index.

3.3 SEMI-STRUCTURED INTERVIEW

Another goal of this thesis project was to understand how the information presented on ConnectMyVariant might affect participants' willingness to communicate with family members about genetic risk. We chose to use the semi-structured interview method to ask open-ended questions, follow-up questions, and probes. The semi-structured interview was conducted immediately after the think-aloud activity. The interview guide is included in Appendix D. The interview guide was developed based on constructs from the Family Genetic Risk Communication (FGRC) Framework, developed by Wiens et al. based on the Theory of Planned Behavior (TPB)[31]. Wiens et al. selected the TPB as the guiding theory to develop their FGRC framework because it fulfilled their set of criteria relevant to family communication and genetic risk communication. Another reason they chose the TPB was because of its widespread use in healthcare settings and behaviors. They conducted a systematic literature review to identify important factors in family communication about genetic risk and found 12 themes which fell into the three major categories of the TPB: Attitude, Subjective Norm, and Perceived Behavioral Control. The Attitude construct deals with the individual's attitude towards the behavior, which is affected by factors such as perceptions of relevance of the genetic risk information for the relative. Pressure to share or withhold information about genetic risk from family members, health professionals, and society are all components of the Subjective Norm construct. The Perceived Behavioral Control construct is affected by beliefs about factors that either facilitate or inhibit communicating genetic risk, such as family dynamics, and whether the individual has the ability to understand complex genetic information. The specific constructs of Attitude and Perceived Behavioral Control were chosen as topics for questions in the interview guide because they were considered to be most relevant to the ConnectMyVariant project. We predicted that the educational material about the importance of communicating genetic risk to family members would potentially influencing an individual's perceptions of relevance and usefulness of communicating, which relate to the Attitude construct. Providing resources for connecting with others with the same variant could affect an individual's perception of communication skills or ability to understand information relevant to communicating genetic risk. The Subjective Norm construct was thought to be less relevant to this project because it deals with pressure that an individual feels from family members, society, and health care professionals about communicating genetic risk, which is not as directly related to the central goals or plans for ConnectMyVariant as the other constructs.

Other questions in the interview guide were meant to explore how participants would share the website with others and what parts of the website seemed most or least relevant, which would give insight into how participants understood the website and who they believed it would be relevant for. Specific questions on the interview guide were designed to inform these constructs and these topics supplied the overarching structure for the codebook. These were included in the codebook as: Sharing ConnectMyVariant, Potential Uses, Attitudes, and Perceived Behavioral Control.

A mock interview was conducted with Ginger Tsai to make final edits to the interview guide and test the interview recording. Interviews were conducted over the Zoom meeting platform. Audio and screen sharing were recorded with participants' verbal consent. Interview recordings were de-identified by Dr. Shirts and myself, and then sent to outside companies for transcription. Transcripts were edited by me to fill in parts that were deemed "inaudible" by the transcription company and ensure accuracy.

3.4 DATA ANALYSIS

Interview transcripts were coded using Atlas.ti8 software. An initial codebook was developed and revised throughout the data analysis process. The think-aloud data were inductively coded to find emergent themes related to usability and barriers [35]. The semi-structured interview data were coded with a combination inductive and deductive approach[36]. Because the interview guide was developed to address specific constructs of the FGRC framework, these constructs were used as the initial overarching code categories. The selected constructs from the FGRC framework included subcategories, such as communication skills under perceived behavioral control, which served to categorize the codes under the constructs from the FGRC framework. Subcodes under these categories were developed from emergent themes from the data to observe what participants brought up relating to these aspects of communicating genetic risk. The final codebook is included in Appendix E.

4. WEBSITE USABILITY ASSESSMENT RESULTS

4.1 PARTICIPANT CHARACTERISTICS

Email invitations were sent out to FindMyVariant participants and advocacy group collaborators. Ginger sent a total of six email invitations to past FindMyVariant study participants, and two participants were interviewed. Dr. Shirts sent emails to research collaborators from FORCE and BRCA Sisterhood, and three interviews were conducted with these contacts. A total of five interviews were conducted between March 28 and April 17, 2019. The interviews ranged in length from 38-80 minutes, and the median interview duration was 63 minutes.

All interview participants identified as female and White (n=5). A majority of participants had completed a bachelor's degree (n=4), and one participant had completed some graduate school. The median participant age was 38 years, and the range was 30-43 years.

4.2 USABILITY

We invited participants to do three specific tasks using the "think-aloud" method as an assessment of the usability of the ConnectMyVariant website. We were specifically trying to identify any barriers that would prevent users from being able to use and learn from the material presented. The think-aloud usability research revealed various barriers in two different categories: barriers to understanding information and barriers to completing tasks. Participants also provided feedback on what changes they felt should be made to the website. Another emergent theme from the think-aloud interviews was that the website content prompted participants to reflect on their own experiences with genetic testing and family communication.

In addition to articulating barriers to usability, participants also brought up which pieces of the website were helpful or impactful. Each of these will be discussed below.

4.2.1 *Barriers*

Barriers to understanding were generally attributed to feeling overwhelmed about complex genetic information. Although all participants had previously undergone genetic testing and tested positive for a pathogenic mutation, participants expressed varying levels of comfort with understanding genetics information. Self-reported genetics knowledge level was not collected beforehand during the demographic information and could not be accurately gauged. A majority of instances when participants expressed being overwhelmed with genetics information occurred when participants were accessing the Index of Variant Forums. Although four out of five participants brought their own personal genetic testing reports for the interview, many participants expressed confusion when trying to use it to complete the task of adding a variant to the index. While looking at a copy of her personal genetic testing report to add a variant to the index, one participant stated, "[The genetic testing report] just looks like a string of number and letters to me. It's a little overwhelming actually because I don't know what to do with it" (P2). Participants felt that they could not understand the content presented that dealt with complex genetics information.

Barriers to completing tasks were also closely related to familiarity with genetics knowledge. Four out of five participants were unable to successfully create a new entry for their variant. One participant stated, "I'm getting kind of confused on that part, putting it in…. not knowing really how it's laid out or how they code the genes or whatever, I would be confused a little bit on that" (P4). Other barriers included difficulties with website navigation, as some participants were unable to get to a desired page. While trying to navigate to the "Learn How to

Find Others Who Have the Same Variant" page, a participant struggled with the navigation buttons: "How do I get back to that? I can't find that button. I'm reading to where I connect, but I don't know where this…button is. I feel like I did that though before. Now I can't find it. How to find... is it back in this index?...I have no idea where that button is" (P1). Some navigated away from ConnectMyVariant by clicking a link to an outside website, while others could not find the correct link or button to get to other pages on ConnectMyVariant. Some links such as "Contact a Genetic Counselor" sent users to the FindMyVariant "Contact a Genetic Counselor" page because the FindMyVariant resources could function on ConnectMyVariant without any modifications. After going to the FindMyVariant website, some users could not find how to get back to ConnectMyVariant, and some required prompting to navigate back to ConnectMyVariant.

4.2.2 *Desired Features*

Participants also expressed many potential solutions to their own perceived barriers and brought up desired features and information while browsing the website. There were a variety of suggestions. Three out of five participants expressed desire for more links to outside websites. One participant stated, "I wish it had more links to outside sources or things it was talking about that it could link to" (P1). Other suggestions included more interactive features like videos, and a section on finding social support and resources after genetic testing.

Interesting variation emerged with regard to the preferred volume of website content. Some participants suggested adding more information, while others suggested simplifying the website and removing information. One participant stated that she thought the website had too much detail: "It's a lot to take in…it's a really good way to learn and understand, but it's very in depth. To me, it's a little bit too much detail at first. My first time into the site….I don't know.

There’s just a lot of detail to take in.” (P2) Another participant suggested adding more information and more pages: “It would be great to have a page that says these are the things that are the most recommended for people with a BRCA mutation….I think this page can be fleshed out a lot more.” (P1). The suggestions and proposed changes to the website reflected interest from the participants to improving the website.

4.2.3 *Reflection of Personal Experience*

During the think-aloud interviews, many participants brought up personal experiences related to content on the website, which impacted their perceptions of the utility of the website. For many participants, reading information on the website prompted them to bring up their own stories and experiences with genetic testing. One participant felt a connection with Linda’s story, which was a key goal in writing the stories: “I'm reading Linda's story...That's exactly what my genetic counselor did for me, that picture that is shown, is pretty much exactly what my own…my family tree looked like.” (P3)

Participants also reflected on how ConnectMyVariant might be personally useful to them, relating it to their past experiences with genetic testing and communicating with relatives. While reading the FAQ section, one participant stated, “I like these questions, because a lot of people did ask me these things when I asked them if they wanted to do the gene testing and stuff, like asking about how much it was going to cost and all these things. I didn't know the answers for those, so that's kind of nice.” (P4). When participants recalled relevant personal experiences related to the website content, they often offered generally positive comments about that section of the website, like the FAQ section mentioned above.

4.2.4 *Facilitators*

In addition to barriers and suggestions for enhanced ConnectMyVariant content, many participants brought up aspects of the website that they considered helpful or had positive reactions to. I will refer to these as “facilitators”.

Many participants commented on how they thought the links to outside resources were helpful. Participants expressed that these links gave them options if they wanted to get more background information. “I think that’s pretty awesome and I like that there’s links to ancestry. I like when there’s links to the outside things that might be helpful…” (P1). Other features that participants thought were useful were the structured scripts or step-by-step guides. These features gave them resources and direction to guide them through tasks that may be difficult, such as trying to connect with distant relatives or talk to family members about genetic risk. One person stated, “I like the step-by-step guide…I looked for a GEDMatch, use one-to-one tool…It's nice how it explains that, too. I like that.” (P4). When browsing the “Connecting With Distant Relatives” page, another participant commented, “The scripts on here are so great…because this is a very hard conversation to have, so having examples of scripts would be super cool...” (P3). A screenshot of the “Connecting With Distant Relatives” page with scripts is included in Appendix B. Participants make positive comments about wide variety of helpful features on the website, indicating that there were many pages and information that they felt were useful.

4.3 FAMILY COMMUNICATION

Information about the perceived impact of the website on family communication was mostly collected from the semi-structured interviews, with some overlap from the think-aloud portion. These results will be discussed as categories based on constructs and concepts that guided the development of the semi-structured interview guide, including selected constructs from Wiens et al.'s FGRC framework based on the TPB that were discussed earlier: Sharing ConnectMyVariant, Potential Uses, Attitudes, and Perceived Behavioral Control.

4.3.1 *Sharing ConnectMyVariant*

During the semi-structured interviews, participants were asked if they would consider sharing ConnectMyVariant with others and whom they would share it with if so. Participants responded that they would share the website with family members, but a number of participants also responded that they would share with non-family members as well. Many participants said that they would share the website with members of their cancer-related support groups or others who had previously undergone genetic testing. Three out of five participants mentioned that they would share ConnectMyVariant with both family members and non-family members.

4.3.2 *Potential Uses*

During the semi-structured interview portion, consistent potential uses emerged across the interviews. Many participants mentioned that they would share the website with their family members as a resource for them to independently browse because it would help answer potential questions that they might have. One participant said, "I think it would give a place that we could actually sit down and look at together and kind of answer some of the questions. Even if they have more questions, they can go back to it and always look at it and feel like they can always have information right there in front of them." (P4). Additionally, another participant anticipated that ConnectMyVariant could be used as a resource to give to her family members to understand more about genetic testing on their own: "When I'm having conversations with my family members, if they have something that they can look at in their own time and digest the request that I have for them [about genetic testing], they would be better able to get comfortable themselves with why they would say yes…" (P2). Overall, we saw that comments from multiple participants fell into these two main categories, using ConnectMyVariant as a resource for potential questions and using ConnectMyVariant as an informational resource.

4.3.3 *Attitudes*

Perceptions of the relevance of genetic risk information is one key factor that plays into the "Attitudes" construct of the FGRC framework because one goal of ConnectMyVariant was to educate users about how hereditary cancer risk affects their families. The perceptions of relevance fell into two different categories, depending on the relatives assumed: close relatives and distant relatives. All of the participants had already brought up genetic testing to their close family members, and some of those close relatives had already done genetic testing. As previously stated, many participants would want to share the website with close relatives who had not yet had genetic testing to try to convince them to consider genetic counseling and testing. However, perceptions related to distant relatives were different. Two out of five participants mentioned a change in how they thought about distant relatives as a result of interacting with the website and expressed interest in connecting with distant relatives. One participant said, "It's something I never thought about…thinking of distant relatives…Now I kind of want to go on my Ancestry thing, and I want to see what I can do as far as that goes" (P3). However, three out of five participants did not mention any increased interest in connecting with distant relatives. When asked if there were any less relevant parts of the website, the participant answered, “Probably finding distant relatives. I think it's cool. Maybe something I would do for fun eventually one day, but we came from Russia and I feel like other than it just being fun fact, I don't really see it... how it impacts my day to day” (P1). The participants’ perceptions of relevance of the genetic risk for their family members was a key construct that ConnectMyVariant sought to impact with information about hereditary cancer information and the importance of testing at-risk relatives, so mixed feedback about interest in connecting with distant relatives after browsing the website was an important finding.

4.3.4 *Perceived Behavioral Control*

The perceived behavioral control construct of the FGRC framework was a crucial construct to examine features of the interviews. In the FGRC framework, perceived behavioral control refers to how the proband perceives his or her control over the behavior of talking to family members about genetic risk. The questions touched on three different parts of the perceived behavioral control construct: Family Dynamics and Relationships, Communication Skills, and Ability to Understand.

4.3.4.1 Family Dynamics and Relationships

All the participants brought up difficulties with convincing family members to pursue genetic testing. Some mentioned barriers such as specific family dynamics and situations, and fear. One participant cited trauma from her family’s past as a reason for resistance to genetic testing: “In my extended family, there's been denial as a barrier and when people don't want to hear things or remember back to traumatic experiences from the cancer in our family's past, it's hard to face” (P5). Some participants brought up how ConnectMyVariant might be a helpful resource to convince family members to get tested because it could help answer questions and provide more information, while others felt that sharing the website would not change how their family members viewed genetic testing. In the case where the participant felt that fear was the main barrier for genetic testing for her family, she stated:

> “I honestly don't think [ConnectMyVariant] would [change how I communicate about genetic testing with family members] and I think the thing that people need in order to get through that first stage of grief isn't an understanding of how genetic variants work or the forums. It's an understanding that they're not going to have the same pain that our family experienced in the past and the hard part about that is you can't even guarantee that” (P5).

As family dynamics are very complex, the types of barriers to family communication about genetic testing will be equally complex. Although ConnectMyVariant was created to reduce barriers to cascade testing, participants perceived that it could only address some barriers, especially those related to information gathering and learning facts about genetic testing.

4.3.4.2 Communication Skills and Ability to Understand

Participants also felt that having a resource like ConnectMyVariant would affect the way they communicated with their family members because it would affect how they themselves understood genetic testing, thus affecting how they could explain it to their family members. Participants also felt that having the website as a resource would help them understand more about genetic risk, so that they could also help their family members understand. When asked if ConnectMyVariant would change how she would communicate with her family, one participant said, “I do because so much of the information that I was able to convey [to my family members] had to be just talked about in person or on the phone or just with my translation of what experts had told me. Since I don’t have a background in science, it was hard to answer a lot of questions” (P2). Additionally, she also said that it filled a need for “a family member who is considering being tested or wants somebody else to be tested to really delve into what it is and what it means to be tested” (P2). One main goal of ConnectMyVariant was to give participants resources, such as scripts, stories, and information to equip them to talk to their family members about genetic testing, and four of five participants expressed that they thought that a website like ConnectMyVariant would change how they spoke to their families about genetic risk.

5. DISCUSSION

A website like ConnectMyVariant with resources for pathogenic variant carriers that provides information about genetic testing and support for connecting with distant relatives is a novel tool in promoting cascade testing. We created this website to provide information about new tools from genealogy, DTC genetic testing, and social networking in order to fill a gap in communicating the importance of cascade testing to pathogenic variant carriers and their family members. We wanted to assess our initial efforts at meeting this perceived need and find out more information about family communication of genetic risk. In order to do this, we conducted think-aloud and semi-structured interviews with participants from a pool of potential users of ConnectMyVariant. From this feedback, we identified usability barriers and gathered many suggestions on how to improve ConnectMyVariant for these and future users. In addition to suggestions for improvement, we were pleased to find that participants thought many aspects of the website were helpful, achieving some key goals of the development of ConnectMyVariant. There were many positive comments and enthusiasm from participants encouraging further work to pursue and develop this resource, reflecting participants' excitement towards filling this gap as well.

However, many participants focused on the general hereditary cancer information provided on the website rather than on connecting with distant relatives and cascade testing, which was the novel portion of the website. Some participants expressed that they wanted more information and resources on the website because they viewed it as a "one-stop-shop" for people who tested positive for a pathogenic variant. This perception of the purpose of the website may have emerged if participants felt that it was difficult to engage with resources that they did not expect to use going forward, such as resources for connecting with distant relatives. Another manifestation of the confusion is that multiple participants connected the ConnectMyVariant website with variants of uncertain significance (VUS) and variant reclassification. This bias may have come from the recruitment, as many participants had previously worked with the FindMyVariant team on other projects dealing with VUS reclassification.

5.1 LIMITATIONS

One limitation of the study is the small number of interviews. There were only five participants. Some participants offered opposing comments and sentiments, so more interviews would give the ability to distinguish between a few outliers and a trend. This was intended to be a pilot study with an alpha-testing group, so this limitation was expected.

The group was also demographically homogenous. The FGRC framework includes “outside factors” such as culture, gender, and past experience, which influence constructs of the framework. This study did not allow us to explore how these outside factors affected communication of genetic risk. Interviewing more potential users with different backgrounds could clarify how other factors affect genetic risk communication and also reveal more usability barriers.

5.2 FUTURE CHANGES

The results of the study provided many areas to change in order to improve the usability of the ConnectMyVariant website and meet the needs of future users. These will be discussed as smaller website changes and larger content changes.

Website changes include relatively small changes to the website, requiring only minor changes to the code. Users experienced some difficulty with navigation, such as finding the right links. And even when provided with the task list, many users went to the index of variant forums first, without reading the pages that provide the background information about the index and variant-specific forums, because the “Index of Variant Forums” button is the left-most button on the homepage, as seen in Figure 2.1. This caused additional confusion because users did not yet have adequate background to understand the index of variant forums and how to use it. A simple adjustment that may reduce the confusion is to put the link to educational content as the left-most button so that users would be more likely to go to that page and read the necessary background before exploring other pages. Reorganization of the website sections in the sidebar and having clearer labels on navigational links and buttons could help users access relevant information. Another potential change to navigation would be adding guides to lead users through the website. In the think-aloud interviews, users were given specific tasks to guide their exploration of the website, so we were not able to see how would browse the website unprompted.

Many participants did not focus on key topics like connecting with distant relatives, but rather focused on hereditary cancer and genetic testing information. The discrepancy between big take-away points from ConnectMyVariant may highlight a larger underlying difference between the goals of the team and the needs of these participants. A key goal in creating the website was to improve cascade testing by offering resources to connect people with the same variants. However, many users suggested adding resources, information, and outside links to provide people with more information about genetic testing, which was only one part of connecting with others with the same variant. The consistent theme of sharing ConnectMyVariant with close family members may reflect a need for informational resources that people can share with family members when talking about genetic testing. Although this was not a central goal when creating the website, it was consistently brought up by participants during interviews. However, all the participants had already asked close relatives to get genetic testing, and they also all encountered some resistance from family members about genetic testing. This may have influenced responses from this pool of participants. One potential method of addressing this concern is to add in more links to outside resources that address and explain information about hereditary cancer and genetic testing. By providing outside resources for additional information that could be shared with participants' family members, the website can remain focused on providing resources related to connecting relatives with the same variant.

Further changes could be made to make website's content more approachable to a larger audience. Various suggestions included videos and interactive content to make the website more accessible. Many usability barriers centered on issues with understanding complex genetic information, so adjusting content to adapt for all levels of genetics knowledge and creating new content to fill in gaps are crucial changes. Larger changes to the content will require thorough curation of current content to address issues that participants brought up. Further investigation to identify specific dimensions of the perceived barriers, such as readability, understandability, or usability issues, would help to target specific problem areas of the website content that were too complex for participants[35]. After making the changes to the website that are clearly indicated from the talk-aloud and interview feedback described, follow-up will be necessary to assess the success in addressing barriers.

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APPENDIX A: TEXT FROM "FINDING GENETIC RELATIVES WITH DNA" WEBPAGE

Finding Genetic Relatives that Have Your Variant Using AncestryDNA, MyHeritageDNA, or 23andMe Data

There are several companies that do ancestry DNA testing. **AncestryDNA**, **MyHeritageDNA**, and **23andMe** are among the largest and best known. These tests usually do not directly test family-specific disease variants, instead they look at common genetic variants called single nucleotide polymorphisms (SNPs) that are spread across the whole human genome. Even though they do not directly test for your specific variants, the DNA results can help identify relatives who have the same family-specific risk variant.

Because these common SNPs are spread across genome, they can show who inherited the same large blocks of DNA a common ancestor. We say that there is **identity by descent** (IBD) for DNA that you share with your relatives, because you have inherited the same identical stretch of DNA from same ancestor. If you share the block of DNA surrounding your variant with a relative, it is much more likely that the relative has the same variant as you. All close relatives share at least some DNA with each other. Finding out who might share a specific variant can be challenging though, as relatives get more distant the chances that they share a specific piece of DNA with you gets smaller and smaller.

DNA testing companies can show which genetic segments you share with different relatives in different ways. Detailed instructions on how to find this information from different companies is listed below.

It is possible that someone shares a segment that looks like it has your variant, but does not. This is because you have two copies of each chromosome, one from your mom and one from your dad. Everyone in your family that has the same variant will be connected to the same parent.

It is always important to recommend confirmatory medical testing if you suspect someone has your variant. People can share a segment of DNA without having the same risk variant. In most cases, if someone shares a segment where your variant is they have about a 50% chance of having your variant. This is because you have two copies of each gene, one from your mom and one from our dad. If the variant came from your mom, the relative may be sharing the copy of the gene that you got from your dad. In rare cases the connecting ancestor lived before the mutation that caused the variant happened. In this rare case shared genomic segments do not necessarily mean that a relative has the variant.

- **Step by Step Guide to Check for finding relatives using DNA**
- Find out the genomic location of your variant. Sometimes this is on your report. If it is not, one way to find genomic location is to look for your variant on **ClinVar**. ClinVar with have 2 genomic locations (Assembly GRCh38 and GRCh37). GRCh37 is the one that is used most often and will be closest to GEDMatch location. If you can not find the genomic location of our variant contact us, and we may be able to help.
- Remember, if someone looks like they share the segment where your variant is, they have about a 50% chance of having your variant. You have two copies of each gene, and they may be sharing the other copy of the gene.

- If someone share a DNA segment with you and also shares the same segment with other people who you know have your variant, the probability that person has the variant is higher.
- **Step by Step Guide to Check for Shared DNA with GEDMatch**

For an overview, **here** is a guide about how genetic matching with DNA SNP kits works.

- You will need to have ancestry genetic data from some company. GEDMatch does not do testing itself. It was built to DNA results from many sources to help people find each other through shared DNA.
- If you have received ancestry genetic data, both you and the other person who has your variant should download DNA data. Instructions for downloading raw data files can be found at **Ancestry**, **MyHeritage**, and **23andMe**.
- Sign up for **GEDMatch**. Use the **"'one-to-one' compare" tool** (**video tutorial about how to use this tool**). Look for matches that span the genomic location of your variant. On the 2D viewer, the numbers on the bottom are in millions of bases, so chr3: 37,042,537 would be on chromosome 3 at about 37M. In general, ignore pink and blue segments, as these are more likely to be background relatedness from very distant relatives.
- If there is match that is larger than 20 cM at the coordinates of your variant, then it is very likely that you inherited the variant from the same ancestor.
- If you want to look for more relatives you can pay $10 and try the one-to-many comparison tool. This allows you to look for anyone in the GEDMatch database shares a specific segment of DNA.
- Remember people can share a segment of DNA without having the same risk variant. In most cases, if someone share a segment where your variant is they have about a 50% chance of having your variant. **It is always important to recommend confirmatory medical testing** if you suspect someone has your variant.
- **Step by Step Guide to Check for Shared DNA with MyHeritageDNA**
    - If you were tested using a different company, like AncestryDNA or 23andMe you may be able to **upload your DNA data** and find people who have done MyHeritageDNA testing.
    - After you have your DNA data in the MyHeritage system, on the DNA page click “Tools.”
    - One of the tools is “Chromosome Browser.” Select this tool.
    - You will now see a list of all genetic relatives in the MyHeritage system.
    - You can compare your chromosomes to up to seven other relatives.
- **Step by Step Guide to Check for Shared DNA with 23andMe**
    - After you have your DNA data in the 23andMe system, on the 23andMe ancestry page click “Find your matches” in the DNA Relatives section.
    - You will need to decide what to share and opt in to sharing DNA information with relatives.
    - In the page that shows DNA relatives, select a relative. Below the place where you see the shared DNA you have you will see a link to “View DNA Comparison” – Click that link.
    - You will now see a list of all genetic relatives. You can select up to 5 additional relatives to compare in addition to the initial relative you selected. Make sure to select yourself as one of the relatives.

  - You will get a plot that shows which DNA segments you share with each of these relatives mapped on each of 23 chromosomes. Below the shared segment there are details of the start and end positions of the shared segments. You can go through your relatives 5 at a time looking for people who share the segment with your variant.

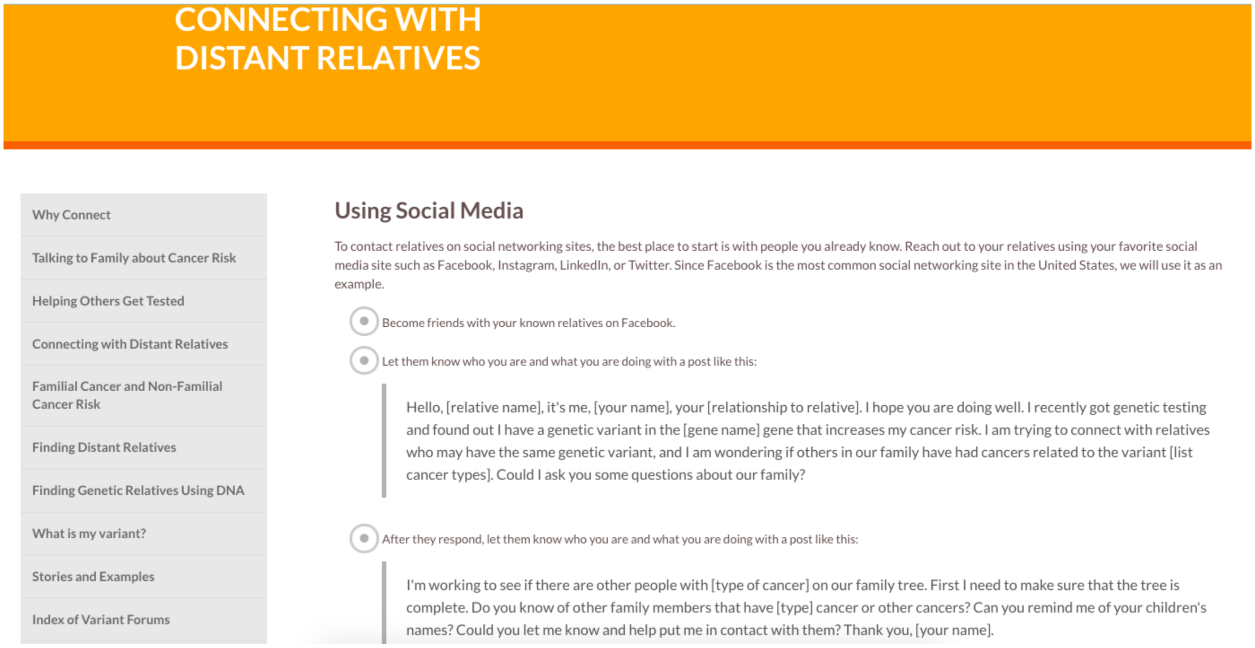
- **Step by Step Guide to Check for Shared DNA with AncestryDNA**

Ancestry DNA does not have a feature that lets users find out which individual segments of DNA they share with relatives yet. If you want to try this you can**download your AncestryDNA raw data file** and upload it to GEDMatch or MyHeritageDNA. (See the step by step guide to GEDMatch and MyHeritageDNA above for more instructions on what to do after that).

If you want to use AncestryDNA to find relatives with your variant, the information that it gives you about relationships can help.

  - Look for the ThruLines tool in the DNA menu. This will show people who share DNA with different specific ancestors.
  - If you already know which parent, grandparent, or great-grandparent had your variant, you can look for others who are descended from the same ancestor.
  - If you know someone else who shares your variant and also has AncestryDNA results, you can find them on ThruLines by looking for a common ancestor. If you click o that person ThruLines will list common relatives that both of you share DNA with. This is not all of your common relatives, just those that you both share some DNA with. However, the people listed could share any DNA segment, not necessarily the DNA segment with your variant.
  - In order to find if people have the segment with your variant using ThruLines, you would need compare lists and look for people that share DNA with two or three other relatives that you know have the your variant.

APPENDIX B: ADDITIONAL SCREENSHOTS OF CONNECTMYVARIANT WEBPAGES



CONNECTING WITH DISTANT RELATIVES

Using Social Media

To contact relatives on social networking sites, the best place to start is with people you already know. Reach out to your relatives using your favorite social media site such as Facebook, Instagram, LinkedIn, or Twitter. Since Facebook is the most common social networking site in the United States, we will use it as an example.

● Become friends with your known relatives on Facebook.

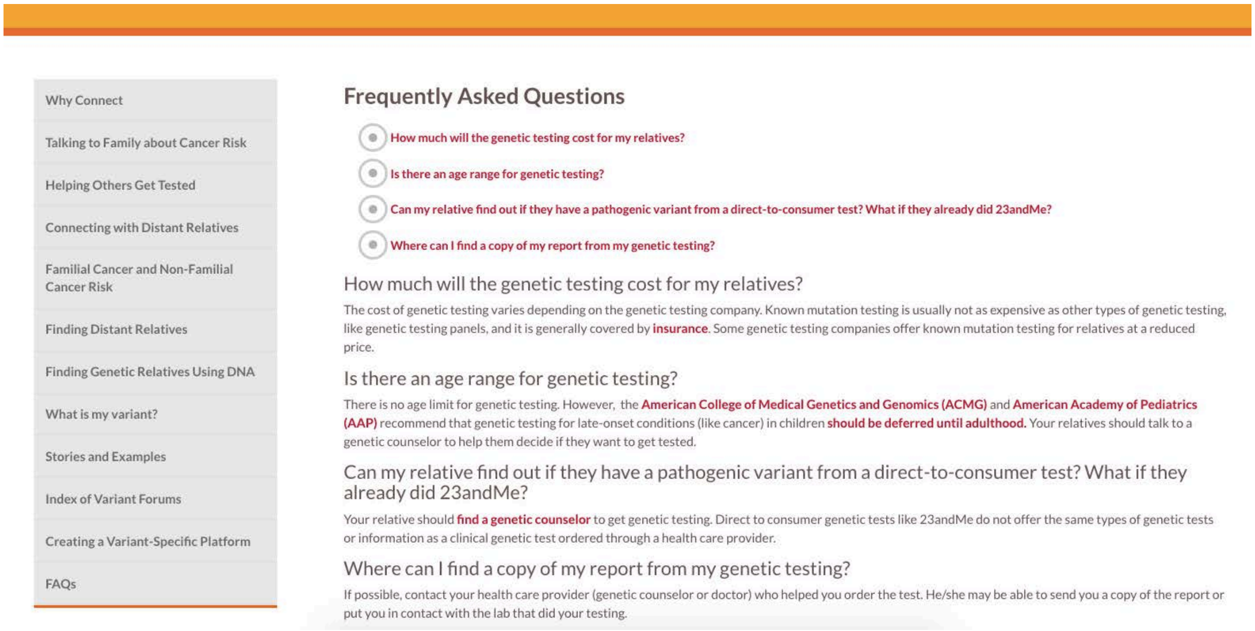
● Let them know who you are and what you are doing with a post like this:

> Hello, [relative name], it's me, [your name], your [relationship to relative]. I hope you are doing well. I recently got genetic testing and found out I have a genetic variant in the [gene name] gene that increases my cancer risk. I am trying to connect with relatives who may have the same genetic variant, and I am wondering if others in our family have had cancers related to the variant [list cancer types]. Could I ask you some questions about our family?

● After they respond, let them know who you are and what you are doing with a post like this:

> I'm working to see if there are other people with [type of cancer] on our family tree. First I need to make sure that the tree is complete. Do you know of other family members that have [type] cancer or other cancers? Can you remind me of your children's names? Could you let me know and help put me in contact with them? Thank you, [your name].

Screenshot of "Connecting with Distant Relatives" page



Frequently Asked Questions

● How much will the genetic testing cost for my relatives?

● Is there an age range for genetic testing?

● Can my relative find out if they have a pathogenic variant from a direct-to-consumer test? What if they already did 23andMe?

● Where can I find a copy of my report from my genetic testing?

How much will the genetic testing cost for my relatives?

The cost of genetic testing varies depending on the genetic testing company. Known mutation testing is usually not as expensive as other types of genetic testing, like genetic testing panels, and it is generally covered by **insurance**. Some genetic testing companies offer known mutation testing for relatives at a reduced price.

Is there an age range for genetic testing?

There is no age limit for genetic testing. However, the **American College of Medical Genetics and Genomics (ACMG)** and **American Academy of Pediatrics (AAP)** recommend that genetic testing for late-onset conditions (like cancer) in children **should be deferred until adulthood.** Your relatives should talk to a genetic counselor to help them decide if they want to get tested.

Can my relative find out if they have a pathogenic variant from a direct-to-consumer test? What if they already did 23andMe?

Your relative should **find a genetic counselor** to get genetic testing. Direct to consumer genetic tests like 23andMe do not offer the same types of genetic tests or information as a clinical genetic test ordered through a health care provider.

Where can I find a copy of my report from my genetic testing?

If possible, contact your health care provider (genetic counselor or doctor) who helped you order the test. He/she may be able to send you a copy of the report or put you in contact with the lab that did your testing.

Screenshot of FAQ section

APPENDIX C: PRE-INTERVIEW MATERIALS

Follow up Email Invitation

Hello,

Thank you for being willing to participate in the interview.

Shortly before the arranged time, I will send you a Zoom link. We will be audio recording the interview, and only video recording the screen sharing portion of the interview. A webcam is not necessary. In that email, I will also send you a list of tasks for the interview.

Pre-Interview Checklist
  Computer:
    Internet access
    Compatible with Zoom meeting software
    Ability to share screen
Optional
  Copy of clinical genetic testing report: there is an optional portion of the interview where you can try inputting your variant into a function of the website
    From FindMyVariant
    From genetic counselor or provider

Please let me know if you have any questions.

Best,
Carmen Ng

ConnectMyVariant Interview Task List
These will be the tasks assigned in the first section of the interview. We will ask you to think aloud as you complete these tasks. This will help us find out more about the usability of the website.
<u>Think Aloud Practice</u>

1. Go to the ConnectMyVariant homepage (http://connectmyvariant.org/) on your web browser
2. Share Screen (in Zoom Desktop Application)
    a. Go to the Zoom window
    b. Click the green "Share" button on the bottom center
    c. Find the "ConnectMyVariant" option on the menu
    d. Your screen should be shared

<u>After recording has started:</u>

3. Browse the ConnectMyVariant Website
    a. Visit and read through whatever pages you would like
4. Click the "Learn how to find others who have the same variant" button on the homepage

  a. Read through "Why Connect"
  b. Explore any other links that you want to explore. Take as much time as you want.
5. Click on the "Stories and examples" button
   a. Read through as many of the examples as you want
6. Try to add a variant to the "Index of variant forums"
   a. If you'd like to, you can add your own variant. We can delete if afterwards, if you want.
   b. If you'd like an example variant to add, we will provide one for you.

APPENDIX D: INTERVIEW GUIDE

Introduction

OPENING STATEMENT

Hello, my name is Carmen. Today, we are conducting this interview to see how it is to use the ConnectMyVariant website and whether it may be helpful to people who have pathogenic variants. I appreciate you taking the time to help us with this work.

Participation in this is purely voluntary. At any time, you may choose to stop the interview or decline to answer any questions. The entire interview should take between 40-75 minutes; will you be available for the whole time? We can reschedule, if this time does not work for you.

In the first portion of this interview, I will be asking you to go to the ConnectMyVariant website and complete some tasks while talking out loud about your thought process. We are testing the website; we are not testing you. In the second portion of the interview, I will ask you questions about your experience with the content presented on the website.

With your permission, we would like to audio and video record this interview. We will be recording audio and the computer screen as you browse ConnectMyVariant and complete a set of tasks. We will also be audio recording your responses to the interview questions. I will also be taking notes, but the recordings will help us capture all of your feedback. Again, this is purely voluntary, and you can ask to stop the recording at any time.

Do you have any questions before I begin?

First, I am going to ask you a few demographic questions. We will only report this information in aggregate form, meaning you won't be singled out or identified with this information.
Age:
Race/ethnicity:
Highest degree received or highest level of school completed:
Sex:

CONSENT DOCUMENTATION

If you are not interested in continuing this interview, you may stop at this time.

THINK ALOUD PORTION

We will now begin the think-aloud portion of the interview. I will ask you to speak your thoughts out loud as you complete the tasks. I want you to tell me everything you are thinking from when you are given the task until you complete the task. Again, we are testing the website and not you, so it is important that you keep speaking what you are thinking, like speaking to yourself. If you stop talking, I will ask you to keep talking.

As you are doing the tasks, I won't be able to answer any questions. But if you do have questions, go ahead and ask them anyway so I can learn more about what kinds of questions the ConnectMyVariant website brings up. We will try to answer any questions after the session. I also won't be talking or giving directions. You can take as much or as little time as you want on each task, and you may move on whenever you want.

Do you understand what I want you to do? Good. So now I will demonstrate the screen sharing and think aloud as I complete this task.

PRACTICE THINKING ALOUD WITH AN EXAMPLE

Now let's move onto the tasks that I sent you earlier. We will go over them together and see if you have any questions before we start.

Please open up the task list document from the email. Why don't you read it aloud just so you can get comfortable with speaking your thoughts? Do you have any questions about the tasks?

You may begin. I will now start the recorder.

START RECORDING

TASKS TO ASSIGN

Please complete the first task: browse the homepage, and then please refer to the task list for your next tasks.

First, please go to the ConnectMyVariant homepage (http://connectmyvariant.org/).

7. Go the ConnectMyVariant website
    a. Browse the homepage and visit any pages

8. Click the "Learn how to find others who have the same variant" button
    a. Read through "Why Connect"
    b. Explore any other links that you want to explore. Take as much time as you want.

9. Click on the "Stories and examples" button
    a. Read through as many of the examples as you want

10. Add a variant to the index of variant forums
    a. If you'd like to, you can add your own variant. We can delete if afterwards, if you want.
    b. If you'd like an example variant to add, we will provide one for you.
        i. I will send you the example variant through the Zoom chat function

RECOMMENDED PROMPTS

1. Mmhmm
2. Uh-huh
3. Please keep talking

This concludes the think-aloud portion of the interview. Do you have any questions or comments before we move on?

SEMI-STRUCTURED INTERVIEW PORTION

Now I will ask you some questions about what you thought about the content of the website and how it might help pathogenic variant carriers and their families.

ATTITUDES: PERCEPTION OF RELEVANCE

1. If you were given the option to use a website like ConnectMyVariant, do you think you would choose to use it? What makes you answer that way?
    a. What were there any parts that's seemed most relevant and meaningful to you? Can you tell me more about why?
    b. Were there any parts that you thought were less relevant to you? Can you tell me why?
2. I'm now going to move away from asking specifically about the website and ask a few questions about your experience receiving genetic test results. When you initially got your genetic test results from your doctor, did you talk to your family members about your genetic variant?
    a. Can you tell me more about that?
    b. What were the reasons for your decision at that time?
    c. Did you have any different experiences talking with other family members? Please explain.
3. How do you think a website like ConnectMyVariant might change the way you speak to family members about genetic testing? What makes you answer as you do?
    a. Can you share more about that?
    b. If so, what part of the website motivated you?
4. Suppose you wanted to find additional relatives and help them get genetic testing, do you feel that the website has enough information to help you?
    a. What concerns, if any, might you have about connecting with relatives after going through the website?
    b. What information or resources from ConnectMyVariant might help you overcome those concerns?
5. Would you share this information or website with others?
    a. With whom would you share this information?
    b. Why?
6. Is there anything else that you would like to add?

CLOSING STATEMENT
That concludes this interview. Do you have any other questions or comments to share? Thank you again for your participation

If you think of other comments or concerns, you can contact me by email at carmenng@uw.edu.

APPENDIX E: CODEBOOK

Usability codes: Think-aloud and parts of semi-structured interview

Primary Code	Description/Definitions
Desired feature or information	Participants bring up information or features that they think would be helpful or would like to see on the website.
Reflection of Personal Experience	Participants bring up personal experiences in response to content presented on the website
Inability to complete tasks	Participant cannot navigate website effectively to complete their desired task or describe obstacles that would prevent them from completing tasks
Inability to understand	Participant expresses confusion or does not understand the information on the website
Perception of usefulness	Participant perceives that the information/content presented on the website is useful or informative Subcodes: • Personal: Information is helpful or useful to participant • General: Information would be helpful to others or potential users
Positive Comments	Participants make general, positive comments about the website content Examples: • “I like that” • “That’s cool”

Family communication codes: Mostly semi-structured interview

Construct/Category	Code	Description/Definitions
Attitude	**Desire to Protect**	Participant expresses desire for family members to get tested in order to prevent potential cancers
	Perceptions of relevance	Participant mentions how ConnectMyVariant impact relevance of family communication Subcodes: • Desire to connect with distant relatives: Participants describe their level of interest in connecting with distant relatives
Perceived Behavioral Control	**Communication skills**	Participant mentions how ConnectMyVariant would affect communication with family members.
	Ability to understand	Participant mentions how information presented on ConnectMyVariant helps increase personal understanding about hereditary cancer risk Subcodes:

Construct/Category	Code	Description/Definitions
		- ConnectMyVariant as an information source about hereditary cancer risk - Helpful links to other resources on the website
	Family Dynamics & Relationships	Participants describe family dynamics and family reactions to hearing about genetic testing results Subcodes: - Barriers for family members getting tested
Sharing ConnectMyVariant	**Sharing with non-family member**	Participant expresses desire to share ConnectMyVariant website with non-family members, such as support group members
	Sharing with family member	Participant expresses desire to share ConnectMyVariant website with family members
Potential uses for ConnectMyVariant	**Potential uses for Connectmyvariant**	Participant describes how they could use ConnectMyVariant or discusses Examples: - Information resource/reference for family members to independently browse - Resource for people who just received initial genetic test results - Answering potential questions of viewers and family members