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ConnectMyVariant: An Innovative Use of Technology and Social Networks to Realize the Benefits of Cascade Screening

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Hereditary Cancer Prevention and Family Outreach

The technology exists to prevent nearly all hereditary cancer. If genetic risk is known, death from almost all common, hereditary cancers is preventable [1]. The current challenge is identifying people who would benefit and helping them get the appropriate interventions before they get cancer. In this article, I will describe a new strategy to identify individuals with hereditary cancer risk by expanding the scope and scale of family outreach, and then detail my group's efforts to implement this new strategy.

Discovering the Public Health Potential of Modern Family History Tools

In 2016, as part of the Ohio Colorectal Cancer Prevention Initiative, Rachel Pearlman, a cancer genetic counselor at the Ohio State University, noticed that two individuals with mismatch repair-deficient colon and endometrial cancer both had the *MSH6* p.Leu370Ser variant. At the time, this *MSH6* variant had not been reported in public databases and was classified as a variant of uncertain significance (VUS). Rachel was intrigued that the two individuals with this rare variant lived near each other and wondered if they could be related. The OCCPI included broad provisions for genetic counselors to help with family outreach and cascade testing. Rachel took the pedigrees that she had gathered and used records available through Ancestry.com to find possible connections. After substantial genealogy work, Rachel found that the two individuals were 3rd cousins with a common ancestor who migrated to the area in the 1800s. With this extensive pedigree data, the variant could be clearly classified as pathogenic. Identifying the ancestral relationship then allowed Rachel to provide genetic counseling and testing to about 150 at-risk relatives and diagnose 50 individuals with Lynch syndrome.

Rachel Pearlman's experience illustrated to me how modern genealogy tools can provide novel pathways to advance disease risk identification. Mary Clair King, an established hereditary cancer researcher with an extensive family cohort, also found that connecting 2nd or 3rd cousins and testing descendants of their common ancestor revealed dozens of new carriers (personal communication). Hearing about these research stories

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prompted me to ask if connecting individuals with the same variant using family history tools had been implemented to benefit public health.

There has been extensive research on cascade outreach in families with preventable hereditary disease. Cascade outreach for hereditary cancer has been consistently found to be cost-effective or even cost-saving [2, 3]. The modeling work of Kenneth Offit's group has shown that if cascade outreach were optimal, it would be possible to identify all 3.9 million individuals with hereditary risk cancer in the USA in about 10 years [4]. The modeling defined optimal outreach as cascading to 1st and 2nd cousins, which sometimes involves leaping over deceased relatives. The Offit group's modeling does not align with current practice, as family outreach rarely cascades optimally to relatives and almost never bypasses deceased relatives [5–7]. However, if individuals knew which ancestor their variant came from, it could allow outreach to 2nd cousins regardless of whether their ancestors are alive. Connecting with distant relatives is easier than it has ever been with billons of family history documents available online, often for free, and millions of individuals participating in direct-to-consumer (DTC) DNA testing to find genetic relatives. In theory, connecting relatives could be incredibly beneficial, but theory is different from reality.

Developing a Program to Realize the Potential of Modern Family History Tools

We realized that the innovation of connecting people with the same variant needed to be coupled with data-driven strategies to help patients communicate with both close and distant relatives. The remainder of this article will describe how we implemented this process. We modified existing family outreach strategies to be used with both close and distant relatives and created a platform to connect putative relatives based on their specific variant while addressing potential privacy and information security concerns. These efforts are predicated on the observation that over 90% of the time people in the Ohio Colorectal Cancer Prevention Initiative who had the exact same rare disease variant shared the same haplotype (i.e., linked variants) surrounding the variant, indicating a presumably shared common ancestor [8]. Our initial pilot study, which was designed primarily to assess the acceptability and demand, was called the ConnectMyVariant study. In the last 4 years, ConnectMyVariant has grown into an educational health-focused 501(c)3 nonprofit organization. Today, there are over 700 individuals seeking to find others with their variant and being assisted by over 20 volunteer family outreach navigators.

Provider- or Patient-Led Family Outreach?

One initial challenge when developing an outreach program was whether to focus on patients or have providers lead outreach efforts. There is growing literature on strategies to overcome barriers to family outreach [9–11]. In this literature, there is an apparent tension between patient-driven and provider-driven methods. Frey shows that expert-driven outreach is more effective, if there are resources for a provider mediated strategy [9]. Clearly, genetic experts who have time dedicated to family outreach can have a large beneficial impact on family outreach. On the other hand, relatives appreciate communication coming from people they already know [9]. Patient-driven methods can be very effective if patients are given the resources and training to be successful.

In the end, it was decided that a patient-driven approach made most sense. Our work with family outreach to gather VUS classification information found that patient-mediated outreach was much more effective than institution-centered outreach [12]. The patient-driven strategy yielded 6.7 relatives invited per family with 67% of those invited participating, which is a 9-fold increase over the 0.48 reported by the only other study that has reported this metric [12, 13]. The high participation rate contributed to reclassification of 62% of VUS to likely benign or likely pathogenic classification for participants enrolled for at least 1 year. The improvement that we saw in family outreach was at least partly due to the participatory nature of the process [14–16].

One challenge with patient and family-centric work is losing some control over messaging. I have found that this should be embraced. People generally know how to communicate within their own families better than we do. When families talk, there is built-in micro-cultural harmonization. For example, while on a Zoom call talking about family outreach with a community leader who has a pathogenic *BRCA2* variant, the conversation was paused to call a cousin and coax that cousin to commit to getting genetic testing on the spot. It was not the approach I would have advised, but it worked perfectly in that family context.

Exploring the Uptake of New Resources for Extended Family Outreach

Our initial study assessed the acceptability and demand for using social media and networks created by DTC genomic genealogy sites, such as AncestryDNA or 23andMe, to help people with family outreach. ConnectMyVariant study participants could engage in

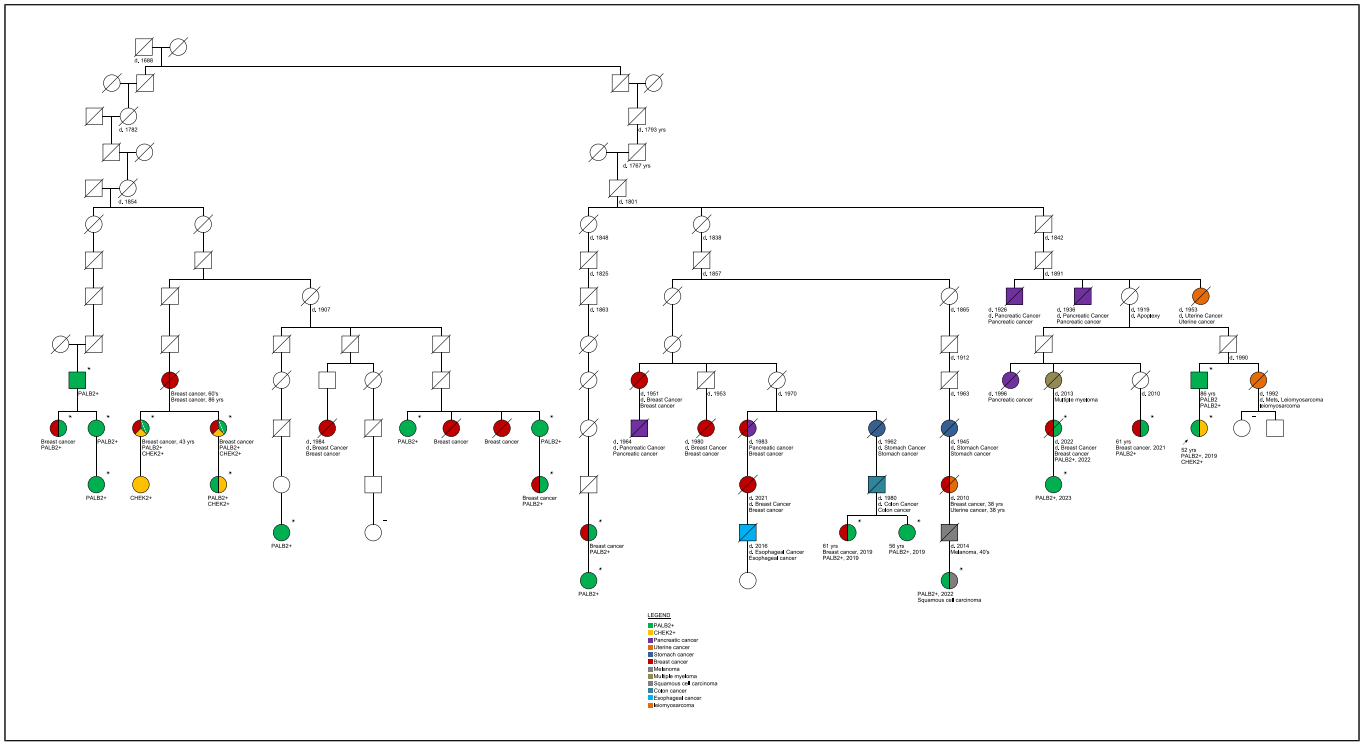

Fig. 1. Large de-identified pedigree showing links between several individuals with a pathogenic PALB2 variant created by a ConnectMyVariant participant (published with permission). Individuals with green shading are known to have the variant of interest. Other colors indicate types of cancer or other variants.

several outreach activities [17]. Many of these activities, such as sharing results with close relatives, would be considered traditional cascade outreach. Other activities such as genealogy research, DTC genomic testing analysis, contacting distant relatives, and creating Facebook groups for specific variants expanded beyond traditional cascade outreach. Every family was different. Some participants wanted to help others prevent cancer, but others were motivated primarily by finding out more about their family history [17]. The pilot study found that connecting an individual with someone else who has the same variant increased participation in family outreach activities 2.5-fold [17]. We initially focused on DTC genetic testing, but we found that other factors such as documentary genealogy sharing, encouragement from putative relatives, and simple reminders contributed more to outreach efforts for most families. We were surprised at the extent to which forming connections with others and the possibility of extending family trees motivated participants to revisit cascade outreach to their close relatives. Many participants used the free documentary genealogy resources that have been made publicly available through FamilySearch or extensive resources available online through Ancestry, MyHeritage, or other organizations. After the study ended, we found that DTC genetic information was most useful in groups where more than a dozen people with the same variant are working together to triangulate common ancestors.

We performed semi-structured interviews with both primary participants and distant relatives who were contacted by those participants. Several questions explored the ethics and acceptability of extended family outreach activities. Although participants reported social, emotional, and logistics challenges, no one reported concerns with the ethics of family members reaching out to their own distant relatives [17]. Similarly, participants see the potential to identify biological relatives that are at risk as a unique feature of this strategy. Several current participants have had positive experiences discovering or disambiguating biological and adoptive relatives. In the initial study, several close and distant relatives were reluctant to commit to genetic testing, but no interviewees expressed concerns about the ethics of being contacted "out of the blue" by their relatives about genetic risk in their family. Almost all relatives expressed gratitude for being informed.

How the ConnectMyVariant Model Works Now

ConnectMyVariant brings many potential family outreach resources together to make them available to anyone, particularly people less likely to have access to those resources. These resources include: (1) individual assistance to design and implement personalized family outreach plans through family outreach navigators, (2) connecting people with the same variant so that they can share prevention stories, find putative ancestral connections, and plan outreach to cousins, (3) interactive educational workshops, (4) genealogy assistance to help connect individuals with the same variant, and (5) micro-grants to families in demographic groups that have been historically underrepresented in genetic testing.

When someone signs up on the ConnectMyVariant website, they are asked if they want to share their contact information (usually first name and email) with others who have the exact same variant in their family. This addresses HIPAA issues by asking permission to share, defining what information is shared, and who it is shared with. If two or more individuals have the same variant, we send an email introduction and encourage people to connect in the way and at a time that works best for them. Volunteer family outreach navigators ask all ConnectMyVariant members, regardless of whether someone else has their variant, if they want assistance communicating with relatives. Family outreach navigators also help members make plans to talk to relatives, schedule meetings with groups of people who have the same variant, give basic family history assistance, and provide encouragement. Professional genealogists at the Brigham Young University Center for Family History and Genealogy are available for more complicated genealogy, usually working with variant groups of more than a dozen individuals trying to triangulate common ancestors. Free educational workshops on family outreach and prevention-directed family history are available to all members.

Again and again, I have been amazed at what individual patients and families can do. For example, with the help of ConnectMyVariant, one family built a tree connecting a dozen others with the same variant (Fig. 1). The connections illustrated by this tree have been key to extended family outreach efforts of at least six individuals with this variant and have helped dozens of distant and very distant cousins find out about their risk and access gene-specific cancer prevention. This is amazing! For comparison, the work that this one individual organized within her family group is similar in scale to work published in a paper with 9 co-authors listing funding from multiple NIH grants [18]. The patient-built pedigree in Figure 1 is not an isolated event; many other families are engaged in similar pedigree building and extended family outreach. We have found a surprising number of people who intuitively understand the importance of extended family outreach and are energized to find resources and others who appreciate those efforts and are sincerely willing to help.

Playing the Outcomes Long Game

The full clinical outcomes of ConnectMyVariant will not be realized for many years and it will be scientifically challenging to quantify those outcomes. Each person faces different family communication challenges and decides on their own strategies to address those challenges. Family outreach is a multi-year, multi-participant, extended conversation; and the downstream consequences of such complex conversations are not easily quantified. One participant's email after the pilot study ended, used with permission, illustrates both the dramatic impact of this outreach and the extent of challenges in measuring outcomes:

> "I wanted to follow-up on some amazing news. I no longer participate in the study, but when I did, I messaged a potential relative on Ancestry about my family history. She didn't get back to me for an entire year, but [she]. . . passed on the info to a family member . . . and that person followed up with me.. . . Her mother passed away from ovarian cancer and her grandmother passed away from breast cancer. She decided to undergo genetic testing, and sure enough, she has the same mutation as me! She is now planning preventative surgery and alerting other relatives. . .. I'm grateful for the tools and resources you provided with this task!"

We have seen many times that such positive outcomes often come months or years after initial outreach and may be realized in individuals who are several steps removed from the people we work with. Similarly, we have seen that addressing genomic inequities may be more effectively achieved but less easily measured by focusing efforts on individual families in underrepresented groups rather than through generalizable solutions or scalable automations. Our experience with families that span international borders has been a revelation. Extended families working together naturally bring genomic resources to underserved communities in innovative ways. This was seen most clearly in a family with cousins in both the USA and Trinidad and Tobago. Discussions within the family have expanded organically exploring exactly who has access to which testing and treatment resources in which country and how those specific relatives can help other specific relatives by searching for resources, making introductions to providers, or mailing test kits. The benefits from family outreach can snowball quickly or can take years to materialize, depending

on the family. Each person that connects with another and finds a common ancestor makes it easier for the next person who joins that variant group. We have seen the benefits of extended family communication reach across national borders and span multiple continents. The full benefits of extended family outreach may simply be impossible to measure accurately as they multiply beyond our limited field of view.

Overcoming Barriers: From Theory to Reality

ConnectMyVariant's core innovation is extending the concept of cascade testing by growing and connecting families. This innovation is grounded in core genomic principles. Systematic barriers to optimal family communication for cascade prevention have been well documented; these include misconceptions about HIPAA [19, 20] and lack of effective family communication training [21]. Genomics is inherently centered on families, but healthcare systems are usually not structured for genomic prevention or family-centered care [22]. Similarly, insurance coverage for health services is tied to individual need rather than family or public health benefit.

Extending family outreach to distant relatives does not address systemic issues that deprioritize prevention; what it does is maximally empower motivated individuals to help a much larger number of relatives. The related innovations of leveraging DTC technology and genealogy informed social networks have made this extended outreach feasible. The major barriers to ending preventable hereditary cancer in the next 10 years are social, not technological.

Despite the challenges mentioned here, I believe that overcoming barriers is not only possible but is now in process. My experience with ConnectMyVariant members is that patients are perfectly capable of cascade outreach to both close and distant relatives, if given appropriate resources and training. Many families are already involved in these efforts. Online networking and communication platforms currently allow families to find others with the same variant, to meet with each other (in person or online), and to work together asynchronously to help relatives receive genetic testing and appropriate follow-on prevention. Family outreach that is inherently culturally appropriate is already crossing international borders. Genealogy and DTC genomic technology are allowing people to find and connect with distant genetic relatives now.

We have just begun to realize the potential power of combining genetics and modern family history tools for hereditary disease prevention. For me, the clear potential of the ConnectMyVariant community to positively impact population health is the brightest point on the near horizon for public health genomics.

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Author Contributions

Brian Shirts is responsible for the conceptualization, drafting, and final approval of this manuscript.

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