A Randomized Trial of Two Remote Healthcare Delivery Models on the Uptake of Genetic Testing and Impact on Patient-Reported Psychological Outcomes in Families With Pancreatic Cancer: The Genetic Education, Risk Assessment, and Testing (GENERATE) Study

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Short Title: Remote Genetic Testing for Pancreatic Cancer

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Abbreviations:

Pathogenic germline variant (PGV)

Pancreatic ductal adenocarcinoma (PDAC)

Multi-gene panel testing (MGPT)

The GENetic Education, Risk Assessment, and TEsting (GENERATE) study

Known familial variant (KFV)

Research Electronic Data Capture (REDCap)

(Dana-Farber Cancer Institute (DFCI)

Rural-urban commuting area (RUCA) codes

The area deprivation index (ADI)

Ratio of uptake rate (RR)

Confidence interval (CI)

Adjusted ratio of uptake rate (aRR)

Direct-to-consumer (DTC)

Patient-reported psychological outcomes (PRPOs)

First-degree relatives (FDRs)

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Abstract:

Background and Aims: Genetic testing uptake for cancer susceptibility in family members of cancer patients is suboptimal. Among relatives of pancreatic ductal adenocarcinoma (PDAC) patients, The GENetic Education, Risk Assessment, and TEsting (GENERATE) study evaluated two online genetic education/testing delivery models and their impact on patient-reported psychological outcomes (PRPOs).

Methods: Eligible participants had ≥1 first-degree relative with PDAC, or ≥1 first-/second-degree relative with PDAC with a known pathogenic germline variant in one of thirteen PDAC predisposition genes. Participants were randomized by family, between 5/8/2019-6/1/2021. Arm 1 participants underwent a remote interactive telemedicine session and online genetic education. Arm 2 participants were offered online genetic education only. All participants were offered germline testing. The primary outcome was genetic testing uptake, compared by permutation tests and mixed-effects logistic regression models. We hypothesized that Arm 1 participants would have a higher genetic testing uptake than Arm 2. Validated surveys were administered to assess patient-reported anxiety, depression, and cancer worry at baseline and 3-months post-intervention.

Results: 424 families were randomized, including 601 participants (n=296 Arm 1; n=305 Arm 2), 90% of whom completed genetic testing (Arm 1 (87%); Arm 2 (93%), p=0.014). Arm 1 participants were significantly less likely to complete genetic testing compared to Arm 2 (adjusted ratio (Arm1/Arm2) 0.90, 95% confidence interval 0.78-0.98). Among participants who completed PRPO questionnaires (Arm 1 (n=194); Arm 2 (n=206)), the intervention did not impact mean anxiety, depression or cancer worry scores.

Conclusions: Remote genetic education and testing can be a successful and complementary option for delivering genetics care.

Key Words: Healthcare delivery; cascade genetic testing

Introduction:

Identification of inherited cancer risk facilitates cancer interception strategies that lead to decreased morbidity and mortality.[1,2] However, significant barriers limit the uptake of germline genetic testing, including competing medical demands, lack of communication regarding the diagnosis between the index case and family members, poor public understanding of inherited cancer risk, geographic access to providers trained in clinical genetics, out-of-pocket expenditures and insurance coverage, among others.[3]

Easy online accessibility, lowered costs, and broad genetic testing options, including whole genome sequencing, has sparked increased public interest in genetic testing for cancer susceptibility and led to the expansion of remote methods including telemedicine and direct-to-consumer (DTC) genetic testing.[4] The COVID-19 pandemic accelerated the widespread implementation of telemedicine care, expanding access to remote genetic services and virtual pre-/post-test genetic counseling.[5] DTC genetic testing, on the other hand, operates outside of the traditional healthcare setting and allows individuals to pursue genetic testing directly from a commercial laboratory. However, DTC cancer predisposition testing has been beset by concerns regarding inadequate pre-/post-test counseling, appropriate interpretation of testing results, and lack of patient awareness about insurance implications.[6]

An overarching hypothesis of this study was that remote healthcare delivery models for genetic education and testing, if appropriately implemented, could help overcome some barriers to testing, including provider availability, personal availability (i.e. primary caretaker to dependent, etc.), long wait times, geographic inaccessibility (i.e. distance, transport, etc.) and cost.[3,5,7] In addition, autonomy and convenience, including avoiding direct interaction with the healthcare system, are drivers towards developing patient-driven remote genetic education and testing strategies.[7] Although remote genetics care delivery models facilitate broader access to genetic

education and testing for hereditary cancer syndromes in family members of cancer patients, more data on the impact of these methods is needed.[5,7,8]

Up to 10% of patients with pancreatic ductal adenocarcinoma (PDAC) have a pathogenic germline variant (PGV) in a cancer susceptibility gene. National guidelines recommend germline testing for all individuals with PDAC regardless of age and personal and/or family history of cancer.[9-12] Whenever possible, timely genetic testing is imperative among patients with PDAC given its universally poor prognosis when detected in late stages.[13] Among individuals with a pathogenic germline variant in a PDAC risk gene, annual PDAC surveillance can lead to identification of earlier stage disease and longer-term survival.[14] However, given the generally poor prognosis among PDAC patients, the rates for genetic counseling and subsequent genetic testing are low, preventing many family members from understanding their genetic risk.[15,16] For this reason, guidelines now also recommend offering multigene panel testing (MGPT) to individuals with a family history of PDAC in a first-degree relative in situations where testing of the index PDAC case themselves is not feasible.

Through multi-site collaboration and the convergence of experts in the field of pancreatic cancer and identification of high-risk cohorts, we developed The GENetic Education, Risk Assessment, and TEsting (GENERATE) trial to evaluate the impact of two remote healthcare delivery models using online genetic education on the uptake of saliva-based genetic testing and their impact on patient-reported psychological outcomes (PRPOs) among relatives of patients with PDAC. The study's primary hypothesis was that participants at-risk for familial PDAC who were randomized to a live interactive telemedicine video-based genetic education session would have a higher genetic testing uptake compared to participants randomized to receive remote genetic education via online educational content alone. The study's secondary hypothesis was that participants who received genetic education through the interactive session would experience

less psychological distress, including anxiety, depression, and cancer worry, compared to participants offered online genetic education only.

Materials and Methods:

Eligible participants were aged ≥18 years, had a valid United States mailing address, access to a healthcare provider, and were willing to share genetic test results with that provider and the study team. At the outset of the study, participants were eligible if a family member had PDAC and a known pathogenic or likely pathogenic germline variant in one of 13 PDAC predisposition genes (*APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* or *TP53)*. Throughout this study we refer to these participants as having a known familial variant (KFV). Despite guidelines recommending germline genetic testing for index cases with PDAC, during study accrual it was evident that probands were obtaining testing at low rates, impacting the recruitment of KFV participants. Since the National Comprehensive Cancer Network guidelines include the stipulation that genetic testing of first-degree relatives of PDAC patients is recommended in cases where testing of the index case is not feasible, the decision was made to expand the eligibility criteria to this additional population of individuals at-risk for familial PDAC. Specifically, due to low recruitment and to align with guidelines, eligibility criteria were expanded to include first-degree relatives with PDAC but no KFV. Data were collected through REDCap (Research Electronic Data Capture), an electronic HIPAA-compliant application. Participants with a KFV provided a copy of the KFV report for the index carrier, which was verified by the study team.

Participants were ineligible if they had a known pathogenic or likely pathogenic germline variant in one of the PDAC susceptibility genes, had received genetic counseling for cancer risk within 3 years of the consent date, or were unwilling or unable to share genetic testing results with an identified healthcare provider or the study team.

Recruitment occurred through collaborating GENERATE study sites (Dana-Farber Cancer Institute (DFCI), Johns Hopkins University, Mayo Clinic, MD Anderson Cancer Center, the University of California San Diego, and Weill Cornell), social media advertisements, pancreatic cancer advocacy organizations, and The Stand Up To Cancer-Lustgarten Foundation. Collaborating sites referred eligible individuals in their clinics and familial cancer registries with PDAC to the GENERATE study via the study website (https://generatestudy.org/). The study website also included a four-minute video narrated by a medical oncologist (*MBY*) reviewing the GENERATE study, as well as generally discussing inherited PDAC risk, genetic testing and cancer prevention strategies (Supplemental Methods). This video was available online to all study participants and prospective participants. Informed consent was obtained from each participant prior to performing any study-related intervention. Additional details on study methodology are previously described.[17]

The intervention arms included specific information regarding *genetic education* and genetic testing. Traditional pre-test *genetic counseling* provides information and psychosocial support regarding genetic risk assessment and testing based on personal and family history. Alternatively, pre-test *genetic education* provides a generalized overview of the considerations regarding genetic testing including risks, benefits, and limitations. However, unlike *genetic counseling*, *genetic education* is not specifically tailored to an individual based on personal or family history and does not provide targeted psychosocial support. Although licensed genetic counselors provided *genetic education* in the GENERATE trial, *genetic education* can be delivered by trained personnel, such as a community health worker, and does not require delivery by a licensed genetic counselor.

Participants were randomized by family cluster into one of two arms in REDCap using an auto randomization hook created by the DFCI Research Computing Core.[17] Arm 1 included two parts. Part one consisted of a brief introduction by a genetic counselor that focused on reviewing the logistics of the study and explanation of what features of the communication platform would be utilized, including screen sharing. This brief introduction was followed by remote online genetic education through a video-based telemedicine platform (Doxy.me, Rochester/NY; Salt Lake City/UT; and Charleston/SC) with a 7-minute pre-recorded video (Supplemental Methods) narrated by a medical oncologist (*MBY*). Themes presented in the video included a broad overview of PDAC inherited cancer risk, utilizing knowledge regarding cancer risk for individual and familial cancer surveillance, and risk-reduction strategies as well as review of the eligibility criteria and the intervention arms. Part two involved an interactive 15-30-minute telemedicine genetic education session with a licensed GENERATE study genetic counselor (*AS, JS*) where participants could only ask generalized questions regarding the video they had viewed and/or discuss the risks, benefits, and limitations of genetic testing more broadly. Participants had the option of participating individually or alongside family members, whom could be geographically dispersed throughout the United States and join the online video-based genetic education session. All Arm 1 participants were required to complete the video based genetic education to qualify for genetic testing on the study. Arm 2 participants could review consumer friendly information regarding genetic testing on the commercial laboratory website before requesting genetic testing. Participants in both arms had access to the genetic education information available through the online commercial laboratory website, which included a five-minute animated video, reviewing the online content including genetic cancer risk as well as the risks, benefits, and limitations of genetic testing. Participants in both arms could request telephone-based pre- and post-testing consultation with a licensed genetic counselor from the commercial laboratory through the commercial laboratory's website, who would be licensed in the participant's state of residence.

Both arms offered participants the opportunity to request saliva-based MGPT at a commercial laboratory (Color Genomics, Inc., Burlingame, California, USA). Participants received a secure link by email embedded with a test code covering genetic testing costs, allowing them to initiate testing through the commercial laboratory. Participants who activated their testing code were sent a saliva-based genetic testing kit and returned the kit via mail to the commercial laboratory. Participants who received a genetic testing kit but did not return it, were considered genetic testing decliners. The commercial laboratory used a MGPT called the "Hereditary Cancer Test" that detects mutations in 30 genes linked to the most common hereditary cancers.[18]

All testing results were provided to participants by the commercial laboratory. Participants who had a pathogenic or likely pathogenic germline variant received their result disclosure through a telephone genetic counseling session with a licensed genetic counselor through the commercial laboratory. Participants with negative results could log onto a personal portal created at the time of requesting testing, to review their results and had the option to schedule a telephone genetic counseling session with a licensed genetic counselor through the commercial laboratory. After receipt of test results, only participants in Arm 1 were offered a video-based *genetic education* follow-up session with a GENERATE study genetic counselor to discuss general questions about their results. If participants solicited medical recommendations based on their genetic testing results, personal history, or family history, they were directed to have a personalized *genetic counseling* session by a licensed genetic counselor in their home state through the commercial laboratory, their primary care provider, or referral to a local genetics expert via their primary care office.

All participants completed baseline surveys that assessed demographics, personal and family cancer history, and PRPOs including cancer worry, anxiety, and depression.[17,19] Follow-up

questionnaires assessing PRPOs were also sent immediately post-intervention and 3-months post-intervention. In this manuscript we will focus on baseline and 3-month survey data, as the 3-month time point is the first post-intervention follow-up where participants had already received their genetic testing results. Cancer worry was assessed using an adapted Lerman Breast Cancer Worry Scale, which is an 8-item questionnaire that evaluates level of cancer worry.[20] This scale has also been implemented in pancreatic cancer surveillance populations.[21] The Hospital Anxiety and Depression Scale (HADS) is composed of two 7-question subscales that assess an individual's level of anxiety and depression over the last 7-days and has been utilized in clinical and investigative settings.[19,22]

Participants were also sent a socioeconomic status survey including health insurance coverage, education level, and annual household income post study completion.[23] Additionally, rural-urban commuting area (RUCA) codes and the area deprivation index (ADI) were utilized to extrapolate additional demographic data, based on street address reported in the eligibility form.[24-26] All participants will have ongoing follow-up for five years after study enrollment.

All participants received up to three email and phone call reminders about completing study steps. Reminders were sent approximately once per month. There were no specific reminders for genetic testing as participants could elect to not get tested. However, participants that did not mail in requested testing kits received up to two phone call reminders from the study team.

Descriptive statistics were used to summarize the uptake rate of genetic testing, participants' demographic characteristics, geographic factors, and PRPO scores (anxiety, depression, and cancer worry) by group. Between-group comparisons were performed by permutation tests with 10,000 iterations, taking account of within-cluster (i.e., family) correlation, where chi-square test statistic, two-sample Wilcoxon test statistic, and two-sample t-test statistic were used for

nominal categorical variables, ordered categorical variables, and continuous variables, respectively. Mixed-effects logistic regression models were used to assess the association of the uptake of genetic testing with the randomization arm, KFV status, age, sex, race, ethnicity, anxiety, depression, and cancer worry scores.[27] The degree of association was summarized by a ratio of uptake rate (RR) and corresponding 95% confidence intervals (CI), based on the resulting odds ratios and variance matrix from the mixed-effects logistic regression model and the estimated uptake rate in the entire study cohort.[28]

As a secondary analysis, we explored the bivariate association of the KFV status with the uptake rate of genetic testing, participants' demographic characteristics and geographic factors. The aforementioned permutation tests were used for statistical comparisons and two-sided p-values were calculated. A two-sided p-value <0.05 was considered statistically significant. All data analyses were conducted using R statistical software (version 4.0.3).

Initially, enrollment was planned for 1,000 unaffected family members from 200 PDAC families with an identified PDAC pathogenic germline variant, over 2.5 years. We estimated that 1,500 patients per year would be seen across all GENERATE study sites and that 10% of PDAC cases (150 patients) would carry a pathogenic germline variant .[10,11] Over 2.5 years (drawing from a total pool of 375 families) we expected to identify and recruit approximately 200 of the pool of 375 PDAC families with pathogenic germline variants. Based on this estimate, we planned to have a total of 100 families per arm and recruiting 5 relatives per family, for a total of 1,000 family members of PDAC cases (500 family members in each arm). Assuming that the online genetic education and healthcare team would lead to an uptake of genetic testing of 60%, and that online genetic education only would lead to an uptake of 40%, 80% power would be achieved with a total of 49 PDAC index mutation carriers who we estimated would be able to

enroll 5 family members in each arm at 0.05 two-sided alpha level. This calculation assumed an intraclass (within family) correlation of 0.4.

In November 2020, after randomization of 500 participants, a revised sample size was calculated in light of the aforementioned expanded eligibility criteria and because we observed a much higher overall genetic testing rate than previously anticipated (88%). We performed a sample size recalculation with the observed overall genetic testing rate and found that the study would achieve 80% power to detect a smaller absolute between-group difference (i.e., 81.55% vs. 94.45%), at 0.05 two-sided alpha level, with 500 participants. Consequently, the study investigators elected to stop accrual before 1,000 participants were randomized. The study was closed for accrual on the initially planned date of 6/1/2021 when there were sufficient randomized participants to ensure 80% power.

All authors had access to the study data and reviewed and approved the final manuscript. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (protocol number 18-222; Clinical Trial NCT03762590).

Results:

Among 815 participants who completed eligibility and initiated study procedures, 656 consented and 601 individuals from 424 families completed baseline questionnaires (Figure 1) and underwent randomization (Table 1). There were 296 participants randomized to Arm 1 and 305 to Arm 2. Study enrollment occurred from 5/8/2019-6/1/2021, and 514 (86%) study participants enrolled on or after March 11, 2020, the date the World Health Organization declared COVID-19 a global pandemic.[29]

Of 601 participants, 65% were female (N=388), 97% were White (N=583), 97% were non-

Hispanic (N=581), and mean age at enrollment was 52.4 years. Participants enrolled from 45 states (Figure 2) across urban and rural regions (Table 1). The study enrolled 55% of participants (N=329) from outside the GENERATE institutions, 46% (N=276) heard about the study from a family member, and 38% (N=227) heard from another source. Among 301 participants that completed the socioeconomic survey, the majority had a bachelor's degree or higher. There were no statistically significant differences in demographic factors across study arms (Table 1).

Overall MGPT uptake was 90% (541/601) among all randomized participants. MGPT uptake was significantly higher among participants randomized to Arm 2 (online genetic education only) compared to Arm 1 (online genetic education and a healthcare team) (93% vs. 87%, p=0.014) (Table 1).

At baseline, there were no statistically significant differences in mean anxiety, depression, or cancer worry scores across study arms (Supplemental Table 1). Among participants that completed both baseline and 3-month post-intervention PRPO questionnaires (n=400), there were also no statistically significant differences across study arms in mean anxiety, depression or cancer worry scores at baseline or 3-months post-intervention, after receipt of genetic testing results (Supplemental Table 2).

On multivariable analysis, the uptake of MGPT was significantly lower among participants randomized into Arm 1 compared to those in Arm 2 (adjusted ratio of uptake rate [aRR] 0.90, 95% CI: 0.78 to 0.98). There were no statistically significant differences in the uptake of MGPT based on age, sex, SES, RUCA code, ADI score, race, or PRPO scores (anxiety, depression, or cancer worry), but there was a significant difference across ethnicity, with uptake of genetic testing among Hispanic participants being lower compared to non-Hispanic participants (aRR

0.72, 95% CI: 0.34 to 0.98, Table 2). However, given the small number of Hispanic participants in the study (n=11), caution should be exercised in interpreting the statistical significance of the association.

Among all randomized participants, 31% (186/601) had a KFV with a mean 2.6 participants enrolled per family and mean age at time of enrollment of 45.2 years (Table 3). Secondary analyses performed based on KFV status showed that compared to non-KFV participants, participants with a KFV were younger (45.2y vs. 55.7y; p<0.001), had a higher number of participants enrolled per randomized family unit (2.6 vs. 1.7; p=0.002), and were more likely to be referred to the study by a GENERATE institution (64% vs. 37%; p<0.001), or family member (81% vs. 30%; p<0.001, Table 3). Additionally, the uptake of MGPT was not significantly different based on KFV status in both univariate (93% KFV vs. 89% Non-KFV; p=0.119, Table 3) and multivariable analysis (aRR 1.05, 95% CI: 0.99 to 1.08, Table 2).

Among 173 of 186 KFV participants who underwent MGPT, 51% (88/173) had PGVs. Among participants with a variant detected, 85 PGVs were identified in genes associated with PDAC susceptibility and the most detected pathogenic PDAC associated variants were *BRCA2*, *ATM*, *CDKN2A* and *PALB2* (Table 4). Five of 173 KFV participants were found to have PGVs distinct from the PGV known to be present in their family (*CHEK2*, *BRCA2*, *MITF*).

Among 368 of 415 participants without a KFV who underwent MGPT, 8% (30/368) had PGVs, 6 of which were PGVs in genes associated with PDAC susceptibility (*BRCA2*, *ATM*, *CDKN2A*). Seventeen of 368 participants without a KFV had a low-penetrance variant on MGPT that is not known to be associated with PDAC susceptibility (monoallelic *MUTYH*, *APC* p.Ile1307Lys, *CHEK2* p.Ile157Thr) (Table 4).

Discussion*:*

In this randomized study of 601 participants with familial/genetic risk of PDAC, 90% of study participants pursued MGPT through one of two remotely accessible methods of genetic testing delivery. Recent guidelines have created a need for MGPT among a new, large group of individuals with potential familial pancreatic cancer risk. Remote forms of genetic testing enable broad geographic diversity and allow for self-referral, with most referrals in this study occurring through family, friends, advocacy organizations, and social media. In addition, the GENERATE study demonstrated that these forms of remote online healthcare delivery models are acceptable and accessible to a subset of individuals at-risk for PDAC and can identify carriers of pathogenic/likely pathogenic germline variants who can benefit from early cancer prevention and detection strategies.

The GENERATE trial was designed as an entirely remote study prior to the COVID-19 pandemic and successfully enrolled geographically dispersed populations across 45 states, with the majority of participants being unaffiliated with the major cancer centers collaborating in the study. Coincidentally, during the study period, the COVID-19 pandemic led to a mainstreaming of telemedicine across U.S. healthcare, and specifically changed the landscape of cancer genetics care delivery, with a de-emphasis of traditional in-person genetic counseling models. During the pandemic, the use of telephone- and video-visits, which were already emerging as novel alternatives to traditional in-person visits, mostly replaced in-person pre-/post-genetic testing visits out of necessity.[30,31] The GENERATE study adds to the limited existing literature regarding this approach and provides evidence that online strategies for genetic education and testing are acceptable to individuals who are interested in pursuing genetic testing, results that can be leveraged not only in PDAC but other hereditary cancers.

Pathogenic germline variants were identified in approximately 50% of participants with a KFV

who underwent MGPT, reflecting Mendelian inheritance and 8% of participants without a KFV. These identified variants confer risk for PDAC and other cancers, which benefit from appropriate risk-reduction strategies[32] that are cost-effective and can increase life expectancy.[33,34] The most frequently detected pathogenic PDAC-associated variants in our study included *BRCA2*, *ATM*, *CDKN2A*, and *PALB2,* similar to other findings.[35] Importantly, pathogenic germline variants detected in these genes are also linked with breast, ovarian and other cancers[36] and have lifelong implications for pancreatic, breast, and ovarian cancer risk-reduction strategies. The GENERATE study demonstrates that interested individuals with a family history of cancer are willing to undergo remote genetic testing regardless of whether there is a known familial pathogenic germline variant.

To date, studies of remotely accessible online genetic education have been largely observational or non-randomized single-arm studies of various care delivery models. [37-40] These studies have demonstrated that among participants engaging in online genetic education, 68-79% underwent genetic testing.[37,38] Prior studies utilizing online video education also demonstrate that viewing a web-based educational tool significantly increases inherited cancer knowledge scores among affected and unaffected cancer patients.[39,41] The randomized controlled trial design of the GENERATE study further adds to this literature by demonstrating particularly high uptake of germline genetic testing in both of the care delivery models studied, across a geographically diverse cohort of self-referred individuals with potential familial PDAC risk.

In this highly motivated, self-referred cohort, in contrast to our primary hypothesis, the GENERATE study demonstrated a modest but statistically significant higher uptake of germline genetic testing among participants randomized to Arm 2 (online genetic education only) compared to Arm 1 (online education and a healthcare team). Possible reasons for this include

convenience, autonomy, and confidentiality.[7] Of note, however, the uptake of MGPT in both Arms was substantially higher than what was anticipated in the initial study design, suggesting that both healthcare delivery modalities were effective means of care delivery for this motivated population. Additionally, we would emphasize that the significantly higher uptake of germline testing among Arm 2 participants does not necessarily reflect this as being an inherently superior means of genetics care delivery. Indeed, one could argue that the slightly lower rate of germline testing uptake among Arm 1 participants may reflect more informed decision-making among these individuals, with some participants possibly opting to defer testing to a later time following their educational sessions with trained genetic counselors. Arm 2, on the other hand, was entirely participant-driven as individuals were able to proceed to genetic testing with only optional interfacing with the healthcare system.

Mean baseline anxiety, depression, and cancer worry scores were elevated across both arms of the study, the causes of which are likely multifactorial. Importantly, our study showed that among randomized study participants, the intervention did not impact PRPOs when measured after disclosure of genetic testing results. Our findings confirm and expand on those from the MAGENTA (MAking GENetic Testing Accessible) trial, which evaluated remote healthcare delivery models on the uptake of genetic testing in women at-risk for ovarian cancer.[42] Similar to the MAGENTA study, the GENERATE trial provides compelling supporting data that remote healthcare delivery models can be leveraged to provide genetic education and testing among both males and females, and may not negatively impact anxiety, depression, or cancer worry scores.[42] Through on-going follow-up over five years, we will explore the psychosocial impact of both healthcare delivery models in this study, including depression, anxiety, cancer worry, familial communication of genetic testing results, as well as the impact of this intervention on cancer surveillance and risk-reduction strategies.

Telemedicine care through telephone- and video-visits provides increased geographic access to providers trained in clinical genetics, evades direct interaction with the healthcare system, and provides personalized delivery of remote genetic education and testing. In comparison to DTC options, telemedicine genetics care includes an interactive visit with a provider trained in clinical genetics and can be embedded within existing telemedicine healthcare delivery models. A study across community oncology practices without integrated genetic counselors found that the uptake of genetic counseling and testing among individuals meeting genetic testing guidelines increased when implementing remote genetics care via telephone- or video-based visits.[43] Another study evaluating video-based genetic counseling, found that this type of healthcare delivery model increased geographic access to genetics providers, was cost-effective, and maintained patient satisfaction.[44]

While the expansion of genetics care services through video- and telephone- based modalities can increase access, they require specialists trained in clinical genetics, which may result in care delays due to lack of provider availability. Although the number of certified genetic counselors has increased, a shortage of genetics care providers remains and is unable to meet current patient demands.[45] Additional innovative healthcare delivery models including online strategies offer a promising method to increase access to care.[46] The GENERATE study provides compelling data that online genetic education and remote saliva-based testing can be utilized to overcome some barriers to care and should be considered as a complementary option for the delivery of genetics care.

The GENERATE study achieved significant geographic diversity and enrolled individuals across 45 states. However, despite its attempt to enroll a broad representation of the population using a variety of recruitment approaches including social media, participants electing to enroll in the GENERATE study were ultimately a largely homogenous White population that was less

disadvantaged and had a paucity of socioeconomic, racial, or ethnic diversity. Despite this, a prior study utilizing web-based video education for information on inherited breast cancer risk among Black females with breast cancer, demonstrated that this type of healthcare delivery model can increase knowledge scores among a socioeconomically diverse group of Black females, although genetic testing completion was not specifically assessed.[39] Moreover, sex, rural/urban location or socioeconomic status as extrapolated through the RUCA code and ADI score respectively, were not independent predictors for study enrollment, which may support utilization of remote methods of genetic education and testing to capture some difficult to reach populations. While we observed some interesting trends in uptake across ethnic groups, such as a lower genetic testing completion rate among Hispanic participants, the limited number of Hispanic individuals in our study limits our ability to examine these effects. Additional analysis of more diverse populations will be critical to understanding barriers and facilitators to genetic education and testing among historically marginalized racial and ethnic populations, as specific communities may have more barriers to remote genetics care and require additional resources or care navigation strategies.[47] To that end, multiple studies are working towards implementing sustainable, scalable, and acceptable approaches for cancer genetics care among historically marginalized racial/ethnic communities, including the REGENERATE study (Racial/ethnic Equity in GENetic Education, Risk Assessment, and TEsting study) inspired by the paucity of racial and ethnic diversity in the GENERATE study.[48]

We acknowledge that at the outset of the study there was low accrual of KFV participants as probands were obtaining MGPT at low rates. This in conjunction with wanting to align with current guidelines, led to eligibility criteria being expanded to include first-degree relatives of PDAC patients. Although this study is not a true cascade testing population, as the true number of at-risk relatives per family is not known, this change in eligibility criteria reflects a more comprehensive population of people for whom MGPT for potential familial PDAC risk was

recommended. Interestingly, although not a cascade testing study, most participants reported learning about the study via family members and the majority of KFV participants specifically, also learned about the study from family members as well.

We acknowledge several other limitations. The GENERATE study provided free genetic testing, which may have contributed to the high rate of uptake as cost can be a barrier.[3] Most participants had a bachelor's degree or higher, which although not reflective of the general US population is reasonably generalizable to the population of U.S. individuals who currently pursue germline genetic testing.[49] Participants were also required to have internet access and baseline internet literacy to access this online intervention. Although online genetics care may be more difficult to access among certain populations, it may be a viable modality for healthcare delivery if the appropriate supports are provided.[47] Study materials were offered only in English, which may have been a factor in the paucity of racial and ethnic diversity among study participants. This study specifically assessed genetic testing among a motivated group of individuals at-risk for PDAC, many of whom self-referred to the study. Furthermore, we do not have participant information among individuals who were eligible and viewed recruitment materials but did not consent to participate in the study.

In summary, the GENERATE study is a geographically diverse randomized trial of self-referred individuals with potential familial PDAC risk, which demonstrated high uptake of germline genetic testing via two forms of remotely accessible online education. We demonstrate that remote healthcare delivery methods have broad reach, are a successful and complementary modality to traditional in-person models and can increase the uptake of genetic testing to more than 90% among both KFV families and those whose families were naïve to genetic testing. Moreover, the GENERATE trial demonstrates that the two remote genetic education and testing healthcare delivery models evaluated may not negatively impact PRPOs including cancer worry,

anxiety or depression scores. It is also imperative that we continue to advocate for policy changes to ensure downstream coverage for ongoing telemedicine visits as well as surveillance and prevention strategies, as this is essential for genetic testing to have a long-term impact on healthcare outcomes. Lastly, it is critical that we continue to develop and implement additional strategies of care delivery and tailored approaches for historically marginalized racial and ethnic communities to advance equitable access to cancer genetics care and precision medicine efforts.

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Table 1. Characteristics and Uptake of Genetic Testing Among Randomized Participants

	Overall study cohort N = 601 (%)	Online genetic education and healthcare team Arm 1 N = 296 (%)	Online genetic education only Arm 2 N = 305 (%)	p-value
Age [year]				
Mean +/- SD	52.4 +/- 14.4	53.3 +/- 13.9	51.6 +/- 14.9	0.226
Range	18 - 90	19 - 85	18 – 90	
Sex				
Female	388 (65)	195 (66)	193 (63)	0.525
Education Level[a]				
Regular high school diploma or equivalent	10 (3)	6 (4)	4 (2)	0.993
Some college or less, including an associate's degree	52 (17)	30 (21)	22 (14)	
Bachelor's degree	106 (35)	52 (37)	54 (34)	
Master's degree	93 (31)	39 (28)	54 (34)	
Doctorate degree	40 (13)	14 (10)	26 (16)	
Racial background				
White/Caucasian	583 (97)	288 (97)	295 (97)	0.979
Black/African American	5 (0.8)	3 (1)	2 (0.7)	
American Indian/Alaskan Native	0	0	0	
Asian/Asian-American	4 (0.7)	2 (0.7)	2 (0.7)	
Native Hawaiian/Other Pacific Islander	1 (0.2)	0	1 (0.3)	
Two or more races	7 (1)	3 (1)	4 (1)	
Unknown	1 (0.2)	0	1 (0.3)	
Ethnic background				

Hispanic or Latino	11 (2)	7 (2)	4 (1)	0.154
Non-Hispanic or Latino	581 (97)	282 (95)	299 (98)	
Unknown	9 (1)	7 (2)	2 (1)	
Number of participants enrolled in family				
Mean +/- SD	2.0 +/- 1.4	1.9 +/- 1.2	2.1 +/- 1.5	0.272
Range	1 - 7	1 – 6	1 - 7	
Geographic location[b]				
Northeast	184 (31)	90 (30)	94 (31)	0.746
Midwest	156 (26)	71 (24)	85 (28)	
South	161 (27)	86 (29)	75 (25)	
West	100 (17)	49 (17)	51 (17)	
Mean Area Deprivation Index (ADI)[c]				
Mean +/- SD	29.0 +/- 21.7	30.4 +/- 22.5	27.6 +/- 20.9	0.163
Range	1 - 99	1 - 93	1 - 99	
Mean Rural-Urban Commuting Area Code (RUCA)				
Mean +/- SD	1.7 +/- 1.9	1.7 +/- 1.9	1.7 +/- 1.9	0.867
Range	1 - 10	1 - 10	1 - 10	
Referring institution				
GENERATE institution[d]	272 (45)	130 (44)	142 (47)	0.573
None of these institutions	329 (55)	166 (56)	163 (53)	
How did you hear about the study? [multiple choices]				
From a healthcare provider	128 (21)	65 (22)	63 (21)	0.719
From a family member	276 (46)	135 (46)	141 (46)	0.894
From other sources	227 (38)	112 (38)	115 (38)	0.951
Other sources include:				
From a friend	18	6	12	
From Stand Up To Cancer	3	2	1	
From a patient advocacy group	44	22	22	

In a magazine	3	2	1	
On television	2	2	0	
On the radio	0	0	0	
Through the internet	41	21	20	
Through social media	22	8	14	
None of the above	103	53	50	
Personal history of cancer				
Yes	75 (12)	38 (13)	37 (12)	0.799
Type of cancer: [e]				
Bladder cancer	2	0	2	
Breast cancer (including DCIS)	9	6	3	
Cervical cancer	2	2	0	
Colorectal cancer	2	1	1	
Esophageal cancer	1	1	0	
Head and neck cancer	1	1	0	
Hematologic malignancy	3	1	2	
Melanoma	10	3	7	
Non-melanoma skin cancer	27	14	13	
Ovarian cancer	1	0	1	
Prostate cancer	11	8	3	
Renal cell carcinoma	2	1	1	
Testicular cancer	3	2	1	
Thyroid cancer	5	4	1	
Uterine cancer	4	1	3	
Cancer, not otherwise specified	1	0	1	
Uptake of genetic testing				
Completed genetic testing	541 (90)	257 (87)	284 (93)	0.014

[a]An additional survey containing questions regarding socioeconomic status was distributed at a later date to participants therefore the response rate differed from baseline. Three hundred participants had missing values (155 in Arm 1 and 145 in Arm 2).

[b]Northeast=Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania; Midwest=North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Illinois, Missouri, Iowa, Wisconsin, Michigan, Ohio, Indiana; South= Tennessee, Kentucky, Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Georgia, Florida, South Carolina, North Carolina, West Virginia, Virginia, District of Columbia, Maryland, Delaware; West= Washington, Oregon, California, Nevada, Arizona, New Mexico, Colorado, Utah, Idaho, Wyoming, Montana, Hawaii, Alaska

[c]Six participants had missing values (two in Arm 1 and four in Arm 2). These missing ADI values were due to a census block group meeting one of the following two suppression criteria, suppression in the setting of low population and/or housing or suppression in the setting of a high group quarters population.

[d]Referring GENERATE sites include Dana-Farber Cancer Institute, Johns Hopkins University, Mayo Clinic, MD Anderson Cancer Center, University of California, San Diego, and Weill Cornell.

[e]Seven participants reported a personal history of two or more cancer types.

Table 2. Adjusted Ratio of Uptake Rate of Genetic Testing Among Randomized Study Participants

	Adjusted RR (95% CI)
Randomization arm (online genetic education and healthcare team vs. online genetic education only)	0.90 (0.78 to 0.98)
Known Familial Variant (KFV) status (KFV vs. Non-KFV)	1.05 (0.99 to 1.08)
Age, by decade	1.01 (0.99 to 1.03)
Sex (Female vs. Male)	1.04 (1.00 to 1.07)
Racial background (White/Caucasian vs. Others)	1.04 (0.84 to 1.09)
Ethnic background (Hispanic or Latino vs. Others)	0.72 (0.34 to 0.98)
Baseline Hospital Anxiety Scale	0.99 (0.98 to 1.00)
Baseline Hospital Depression Scale	1.00 (0.99 to 1.01)
Baseline Cancer Worry Scale	1.00 (1.00 to 1.01)

Table 3. Characteristics and Uptake of Genetic Testing Among Participants by Known Family Variant Status (KFV)

	KFV N = 186 (%)	Non-KFV N = 415 (%)	p-value
Age [year]			
Mean +/- SD	45.2 +/- 15.8	55.7 +/- 12.5	< 0.001
Range	18 – 90	20 – 86	
Sex			
Female	110 (59)	278 (67)	0.068
Education Level[a]			
Regular high school diploma or equivalent	6 (8)	4 (2)	0.663
Some college or less, including an associate's degree	17 (22)	35 (16)	
Bachelor's degree	24 (30)	82 (37)	
Master's degree	23 (29)	70 (32)	
Doctorate degree	9 (11)	31 (14)	
Racial Background			
White/Caucasian	181 (97)	402 (97)	0.478
Black/African American	1 (0.5)	4 (1)	
American Indian/Alaskan Native	0	0	
Asian/Asian-American	0	4 (1)	
Native Hawaiian/Other Pacific Islander	0	1 (0.2)	
Two or more races	3 (2)	4 (1)	
Unknown	1 (0.5)	0	
Ethnic Background			
Hispanic or Latino	3 (2)	8 (2)	0.843
Non-Hispanic or Latino	181 (97)	400 (96)	
Unknown	2 (1)	7 (2)	

Number of participants enrolled in family			
Mean +/- SD	2.6 +/- 1.5	1.7 +/- 1.3	0.002
Range	1 - 6	1 - 7	
Geographic Location[b]			
Northeast	61 (33)	123 (30)	0.026
Midwest	63 (34)	93 (22)	
South	33 (18)	128 (31)	
West	29 (16)	71 (17)	
Mean Area Deprivation Index (ADI)[c]			
Mean +/- SD	32.6 +/- 21.6	27.4 +/- 21.6	0.017
Range	1 - 97	1 - 99	
Mean Rural-Urban Commuting Area Code (RUCA)			
Mean +/- SD	1.9 +/- 2.2	1.6 +/- 1.8	0.205
Range	1 - 10	1 - 10	
Referring institution			
GENERATE institution[d]	119 (64)	153 (37)	< 0.001
None of these institutions	67 (36)	262 (63)	
How did you hear about the study? [multiple choices]			
From a healthcare provider	38 (20)	90 (22)	0.742
From a family member	150 (81)	126 (30)	< 0.001
From other sources	17 (9)	210 (51)	< 0.001
Other sources include:			
From a friend	0	18	
From Stand Up To Cancer	0	3	
From a patient advocacy group	3	41	
In a magazine	0	3	
On television	0	2	
On the radio	0	0	

Through the internet	3	38	
Through social media	1	21	
None of the above	10	93	
Personal history of cancer			
Yes	15 (8)	60 (14)	0.033
Type of cancer: [e]			
Bladder cancer	0	2	
Breast cancer (including DCIS)	1	8	
Cervical cancer	1	1	
Colorectal cancer	2	0	
Esophageal cancer	0	1	
Head and neck cancer	0	1	
Hematologic malignancy	0	3	
Melanoma	3	7	
Non-melanoma skin cancer	4	23	
Ovarian cancer	1	0	
Prostate cancer	1	10	
Renal cell carcinoma	0	2	
Testicular cancer	2	1	
Thyroid cancer	2	3	
Uterine cancer	1	3	
Cancer, not otherwise specified	0	1	
Uptake of genetic testing			
Completed genetic testing	173 (93)	368 (89)	0.119

[a]An additional survey containing questions regarding socioeconomic status was distributed at a later date to participants therefore the response rate differed from baseline. Three hundred participants had missing values (107 in Arm 1 and 193 in Arm 2).

[b]Northeast=Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania; Midwest=North Dakota, South Dakota, Nebraska, Kansas, Minnesota, Illinois, Missouri, Iowa,

Wisconsin, Michigan, Ohio, Indiana; South= Tennessee, Kentucky, Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Georgia, Florida, South Carolina, North Carolina, West Virginia, Virginia, District of Columbia, Maryland, Delaware; West= Washington, Oregon, California, Nevada, Arizona, New Mexico, Colorado, Utah, Idaho, Wyoming, Montana, Hawaii, Alaska

[c]Six participants had missing values (four in KFV and two in non-KFV). These missing ADI values were due to a census block group meeting one of the following two suppression criteria, suppression in the setting of low population and/or housing or suppression in the setting of a high group quarters population.

[d]Referring GENERATE sites include Dana-Farber Cancer Institute, Johns Hopkins University, Mayo Clinic, MD Anderson Cancer Center, University of California, San Diego, and Weill Cornell.

[e]Seven participants reported a personal history of two or more cancer types.

Table 4. Variants Detected Among Participants With a Known Familial Variant (KFV) and Without a Known Familial Variant (Non-KFV)

	KFV[a] N = 173 (%)	Non-KFV[b] N = 368 (%)
Participants with no variant detected	85 (49)	338 (92)
Participants with ≥1 PGV detected	88 (51)	30 (8)
Number of PGVs detected[d,e]	**93[d]**	**31[e]**
Pathogenic PDAC associated variant[c]	**85**	**6**
ATM	27	2
BRCA1	5	0
BRCA2	34	3
CDKN2A	6	1
MLH1	2	0
MSH2	2	0
PALB2	6	0
PMS2	2	0
STK11	1	0
Non-PDAC pathogenic variants	**5**	**8**
CHEK2	3	1
MITF	2	2
BARD1	0	1
BRIP1	0	3
RAD51D	0	1
Low penetrance variants	**3**	**17**
APC p.I1307K	1	3
CHEK2 p.I157T	1	3
Monoallelic *MUTYH*	1	11

a. Among 186 KFV participants, 173/186 completed genetic testing.

b. Among 415 non-KFV participants, 368/415 completed genetic testing.

c. There were no pathogenic variants detected in *APC, EPCAM, MSH6* and *TP53*

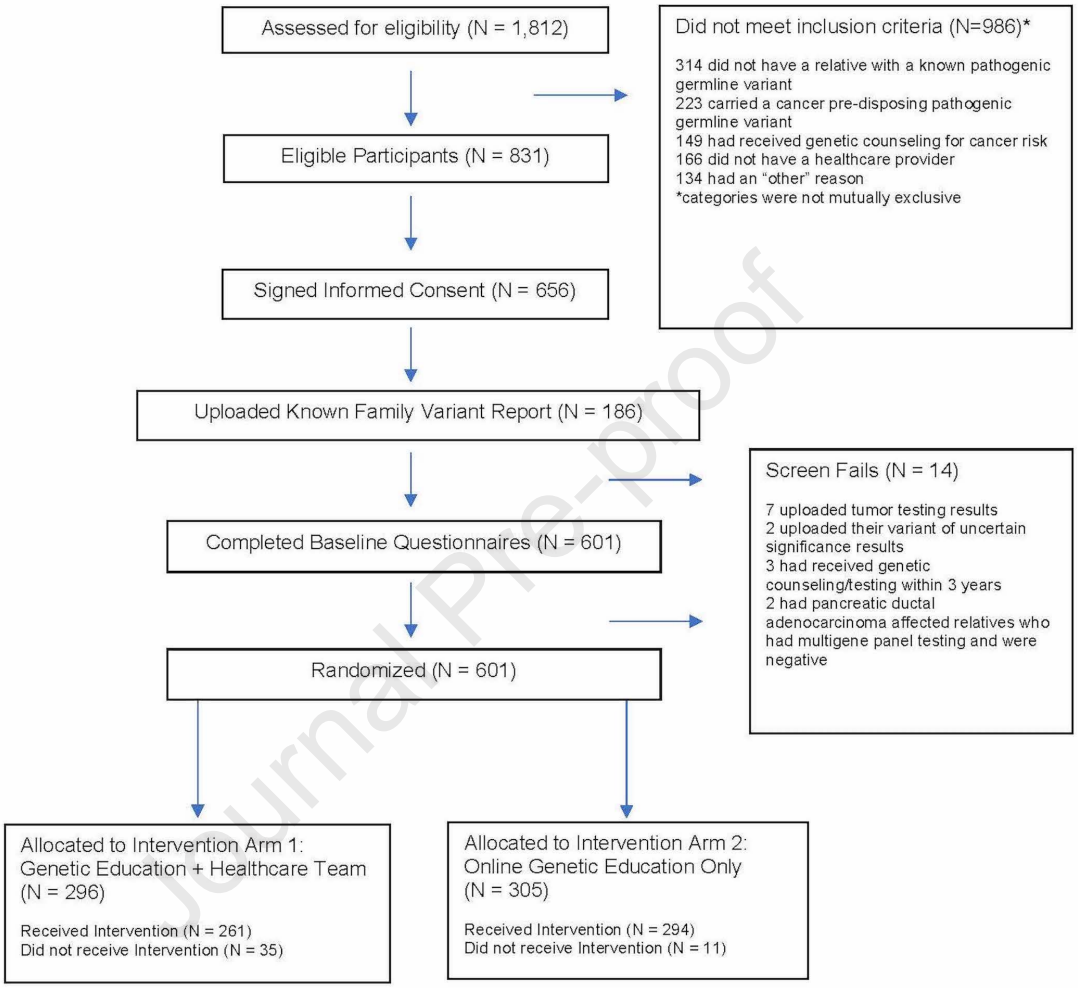
d. Double variant carriers include *1 ATM/BRCA2* carrier, 2 *ATM/CHEK2* carriers, 1 *BRCA1/CHEK2* carrier and *1 BRCA2/MITF* carrier. There were no disparities between identified variants and known pathogenic PDAC familial variants except for the identification of additional non-PDAC pathogenic variants in 2 *ATM* carriers (*CHEK2*), 1 *BRCA1* carrier (*CHEK2*) and 1 *BRCA2* carrier (*MITF*).

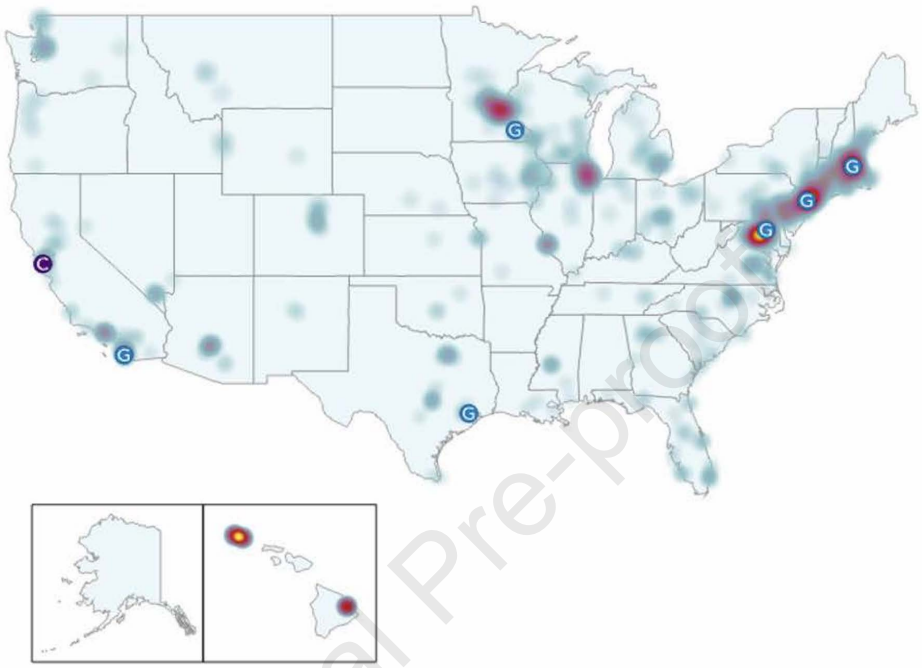
e. Double variant carrier includes 1 monoallelic *MUTYH/BRIP1* carrier.

Figure 1. Consort Diagram of the GENERATE Study

Figure 2. Heat Map of Randomized Study Participants

Figure 2. Legend





Supplemental Table 1. Patient-Reported Psychological Outcomes (Anxiety, Depression, and Cancer Worry) Among Randomized Participants at Baseline and 3-Months Post-Intervention (N=400)[a]

	Online genetic education and healthcare team (Arm 1) N=194	Online genetic education only (Arm 2) N=206	P-value[d]
Hospital Anxiety and Depression Scale[b]			
Baseline			
Anxiety Mean +/- SD	5.1 +/- 3.3	5.4 +/- 3.6	0.378
Depression Mean +/- SD	2.6 +/- 2.6	2.5 +/- 2.5	0.684
Total Score Mean +/- SD	7.7 +/- 5.2	7.9 +/- 5.6	0.732
3-months Post-Intervention			
Anxiety Mean +/- SD	4.9 +/- 3.4	5.5 +/- 3.7	0.119
Depression Mean +/- SD	2.7 +/- 2.9	3.0 +/- 3.1	0.299
Total Score Mean +/- SD	7.7 +/- 5.6	8.6 +/- 6.2	0.149
Cancer Worry Scale[c]			
Baseline			
Mean +/- SD	13.7 +/- 3.8	13.7 +/- 3.6	0.878
3-months Post-Intervention[e]			
Mean +/- SD	12.8 +/- 3.5	12.9 +/- 3.7	0.758

[a] Four hundred participants completed questionnaires at baseline and 3-months post-intervention.
[b] Hospital Anxiety and Depression Scale: Scoring 0-7 Normal; 8-10 Borderline abnormal (borderline case); 11-21 Abnormal (case).
[c] Cancer Worry Scale: Total Score ranges from 8-32; A score ≥14 indicates a moderate to high cancer worry score.
[d] Based on a permutation test with t-statistic. The number of iterations was 10,000.
[e] The number of subjects with missing information was two in Arm 1 and four in Arm 2.

Supplemental Table 2. Patient-Reported Psychological Outcomes (Anxiety, Depression, and Cancer Worry) Among Randomized Participants at Baseline (N=601)

	Online genetic education and healthcare team (Arm 1) N=296	Online genetic education only (Arm 2) N=305	P-value[c]
Hospital Anxiety and Depression Scale[a]			
Baseline			
Anxiety Mean +/- SD	5.4 +/- 3.6	5.4 +/- 3.5	0.839
Depression Mean +/- SD	2.7 +/- 2.8	2.5 +/- 2.4	0.242
Total Score Mean +/- SD	8.1 +/- 5.6	7.9 +/- 5.4	0.695
Cancer Worry Scale[b]			
Baseline			
Mean +/- SD	13.9 +/- 3.9	13.7 +/- 3.6	0.572

[a] Hospital Anxiety and Depression Scale: Scoring 0-7 Normal; 8-10 Borderline abnormal (borderline case); 11-21 Abnormal (case).
[b] Cancer Worry Scale: Total Score ranges from 8-32; A score ≥14 indicates a moderate to high cancer worry score.
[c] Based on a permutation test with t-statistic. The number of iterations was 10,000.

Supplemental Table 3. Patient-Reported Psychological Outcomes (Anxiety, Depression, and Cancer Worry) Among Study Participants at Baseline by Uptake of Genetic Testing (N=601)

	Obtained genetic testing N=541	Did not obtain genetic testing N=60	P-value[c]
Hospital Anxiety and Depression Scale[a]			
Baseline			
Anxiety Mean +/- SD	5.3 +/- 3.5	6.0 +/- 4.2	0.196
Depression Mean +/- SD	2.6 +/- 2.5	3.0 +/- 3.0	0.283
Total Score Mean +/- SD	7.9 +/- 5.3	9.0 +/- 6.7	0.192
Cancer Worry Scale[b]			
Baseline			
Mean +/- SD	13.8 +/- 3.7	13.7 +/- 3.8	0.838

[a] Hospital Anxiety and Depression Scale: Scoring 0-7 Normal; 8-10 Borderline abnormal (borderline case); 11-21 Abnormal (case).
[b] Cancer Worry Scale: Total Score ranges from 8-32; A score ≥14 indicates a moderate to high cancer worry score.
[c] Based on the generalized estimation equation analysis for correlated data, where the independent correlation structure was used as a working model.

What You Need To Know

- **Background and Context:**
    - Genetic testing for cancer susceptibility in family members of cancer patients is suboptimal. Remote genetics care among family members at-risk for pancreatic cancer may increase genetic testing rates.
- **New Findings:**
    - In this cluster-randomized controlled trial of families affected with pancreatic cancer, 90% of participants from across the United States who were unaffected by pancreatic cancer completed remote genetic testing using one of two online healthcare delivery models.
- **Limitations:**
    - Study participants were self-selected and predominantly White.
- **Clinical Research Relevance:**
    - Online genetic education/testing can be a successful and complementary healthcare delivery model that can overcome some barriers to care and does not negatively impact patient-reported psychological outcomes including anxiety, depression, or cancer worry.
- **Basic Research Relevance:**
    - Through remote genetic education and testing, the identification of likely pathogenic germline variants and pathogenic germline variants in pancreatic cancer susceptibility genes can advance precision medicine efforts.

Lay Summary:

- Online genetic education and genetic testing can be used to overcome some

healthcare delivery barriers without negatively impacting anxiety, depression, or cancer worry.

8.7 Script for Introductory Study Video for the GENERATE Website

GENERATE OVERVIEW VIDEO FOR WEBSITE

GENETIC EDUCATION RISK ASSESSMENT AND TESTING (GENERATE) STUDY

"Hi, I'm Matt Yurgelun, a medical oncologist at the Dana-Farber Cancer Institute.

Welcome to the GENERATE Study website.

The aim of this study is to improve access to genetic testing for families with pancreatic cancer.

About 10% of people with pancreatic cancer have inherited risk.

Knowing about inherited risk for pancreatic cancer can help you choose specialized screening to reduce your cancer risk and increase your chances for early diagnosis.

For you to be eligible for this study, a close relative of yours, such as a parent, sister, brother or child, has had pancreatic cancer. You are eligible to participate whether or not any of your relatives have had genetic testing. Having a close relative with genetic risk does not guarantee that you have it also, but you could share the inherited risk. Genetic testing can determine whether you carry this inherited risk or not. We hope that knowing about inherited risk for pancreatic cancer will allow participants to choose potentially life-saving strategies and improve their chances for good health.

The purpose of this study is to compare different strategies for helping people obtain genetic testing.

Participants will be randomly assigned to one of two study groups.

The first group will be referred directly to a lab called Color Genomics to arrange your genetic testing online at no cost through the study specific link provided to you. Participants in this group will be responsible for learning the information provided through the Color Genomics website.

The second group will participate in a brief interactive video conference session with a genetic counselor.

You can video conference with us using your smart phone, tablet or home computer.

All you'll need to do is click on a weblink provided to you to join the video conference.

Depending on your preference, your session can be set up individually, or with other family members at the same time (on the same video conference). You can do this from your own home or wherever you choose.

During this session, you'll have the opportunity to learn more, and to ask questions. Then, if interested, you will be directed to the GENERATE Study specific Color Genomics website to arrange your genetic testing online at no cost through the study specific link provided to you.

Your privacy is very important to us. We will not share your results with anyone outside the study without your permission.

Both groups will be asked to complete questionnaires at various points throughout the study.

Our goal is to help you understand why this testing is important, and how it could be helpful to you, and your family.

Also, we'd like to make the genetic testing process easier and more accessible for at-risk relatives. Through the GENERATE Study, we will help you understand the specific steps to take to arrange your own genetic testing, which can be done through the study at no cost.

This study will help inform you about how genetic counseling and testing might help you and your family. However, it is important to remember that specific medical recommendations for you should be made by your personal physician. If you are found to have a genetic mutation, you may benefit from following-up with a physician with cancer genetics expertise. If you have negative genetic testing, and there is no known mutation in your family, you may also benefit from special follow-up based on your family history of cancer. The study team is happy to connect you with cancer genetic specialists close to you.

We hope this study will lead to better care, and prevention, of pancreatic cancer. Thank you again, for your participation."

(2:24)

8.10 Script for Pre-recorded Genetic Education and Interactive Video Session in the Doxy.me plus Color Genomics Arm (ARM 1)

A. Pre-recorded education session

-Duration: 5:52 minutes
-Goal: Provide broad overview of inherited risk for pancreatic cancer and potential benefits of genetic testing
-Content: the session will provide information to at-risk relatives about:

1) How cancer risk can run in a family
2) Opportunities to ameliorate these risks through surveillance and possible participation in PDAC interception projects
3) Information about how to access genetic testing through Color Genomics to arrange their own testing

Script:

"Hi, I'm Matt Yurgelun, a medical oncologist at the Dana-Farber Cancer Institute.

Congratulations on taking the first step toward understanding more about genes, cancer risk, and ways to use this information to stay healthy. You were invited to watch this presentation because you have a family history of pancreatic cancer and might also have a family member with inherited cancer risk. Following this brief presentation, you will have a live interactive video session with a genetic counselor to answer your questions, and to help you understand how to make arrangements for your own genetic counseling and testing.

About 10% of people with pancreatic cancer have inherited a gene that makes them more likely than the average person to develop this cancer. There are a number of different genes that can increase the chance to develop pancreatic cancer.

Genes are inherited from our parents and are made up of a coiled substance called DNA. The DNA coil contains a genetic code made from a combination of letters.

A change in the letters of the genetic code, just like a spelling mistake in a word, may prevent that gene from working properly. A harmful spelling change in the genetic code is called a mutation.

We all have cancer risk genes. When these genes are working properly, they play a key role in repairing cells, controlling normal cell growth and keeping cancer from developing. If there is a mutation in a cancer risk gene, it leads to a higher than average cancer risk in a person's lifetime. It does not mean that person will develop cancer for sure, but he/she may have a higher chance than the average person. People who have a mutation in a cancer risk gene may be at risk for more than one type of cancer.

Different genes increase risk for different cancers. The amount of cancer risk will also vary from one gene to another. Genes that increase pancreatic cancer risk may also increase the risks of breast and prostate cancers, and some increase ovarian cancer risk as well.

A parent with a genetic mutation has a 50-50 chance of passing it along to each child. A father can pass a genetic mutation to a daughter or son, and a mother can pass a genetic mutation to a son or daughter. Mutations in cancer risk genes do not skip a generation, so if a person did not inherit it, they cannot pass it along to their children.

So why would anyone want to know if they have inherited a higher chance to develop pancreatic cancer?

People with inherited cancer risk are recommended to have special screening or other interventions to address their cancer risks. Pancreatic cancer screening, for instance, can include a yearly ultrasound or MRI of the pancreas.

These are not screening tests typically offered to those in the general population. By doing special screening, it's possible that a cancer might be found at its earliest and most curable stage. Depending on the genetic mutation present, other interventions, to target different types of cancer, may be available to reduce risks and improve the chance to stay healthy. Through this study, family members found to carry a cancer risk mutation will be offered a variety of novel interventions that we hope will be of benefit but are still learning about.

If a person with inherited risk develops pancreatic cancer, then they may benefit from specific cancer treatments based on the specific altered gene.

If there is a known gene mutation in your family, you could learn you did **not** inherit the known genetic mutation, or source of pancreatic cancer risk. In this case, the extra screening and follow-up is not needed.

You may be interested in your own genetic testing, even if no one in the family has had genetic testing yet. However, in this case, a result with no mutations identified may be less reassuring. Unless the reason for the family history of pancreatic cancer is known, because someone in the family has had a positive genetic test, your negative result could be due to the following reasons:

1. You did not inherit a familial mutation
2. The pancreatic cancer in your family may not be associated with an inherited risk
3. There may be a genetic cause of your family history of pancreatic cancer, but it cannot be found with our current lab testing

Unless there is a known gene mutation in the family, a negative result here is considered indeterminate. Special screening might still be offered based on your family history of cancer.

You are being offered genetic testing since you have a close relative with pancreatic cancer, and there may, or may not be a known mutation in your family.

The testing will look specifically for the mutation found in your relative's test, if one is present, in addition to other genes.

Rarely, there may be more than one altered cancer risk gene in the same family. It is also possible that a mutation may be found in your testing that may not explain the source of pancreatic cancer in your family, but still may provide information about other cancer risks.

Some people may worry that their test result may affect coverage for health insurance. A federal law called the Genetic Information Non-discrimination Act, or GINA, protects people from being treated differently by health insurers based on their genetic information.

GINA has some limitations. While it covers health insurance and employment, it does not offer protection for life insurance, or other types of insurance. Those protections will vary from state to state. You can ask questions about this topic during your video conference.

Your privacy is very important to us. We will not share your results with anyone outside the study without your permission.

The GENERATE Study has made arrangements for study participants to have genetic testing through an online genetic testing company called Color Genomics. In order to have study testing at no cost, you will need to use the specific Color Genomics link provided to you.

A saliva kit would be sent in the mail to you after you order the test.

After you mail back the saliva kit, Color Genomics will contact you about results within a few weeks.

Genetic counseling by phone with a licensed genetic counselor is available before and after testing at Color Genomics.

In addition, the study team is available to provide genetic education with certified genetic counselors to discuss the purpose, benefits, risks and limitations of genetic testing. This study will help inform you about how genetic counseling and testing might help you and your family. However, it is important to remember that specific medical recommendations for you should be made by your personal physician. If you are found to have a genetic mutation, you may benefit from following-up with a physician with cancer genetics expertise. The study team is happy to connect you with cancer genetic specialists close to you.

Color Genomics can also provide you with further information once your genetic test results are available. We encourage individuals who have been found to carry a mutation in a cancer risk gene to meet with a cancer genetic specialist - in person, if possible - and to consider the special follow-up opportunities offered through this study. The study team, as well as the Color Genomics genetic counselors, can help you identify a cancer genetics specialist closest to you.

Thanks for your time and thank you for being part of the GENERATE Study. Please remain online for a live session with a genetic counselor who will address questions you may have about the information you have learned in this video, including questions you may have about inherited cancer risk, examples of screenings that may be recommended based on having a genetic mutation and how to facilitate your genetic testing."

B. Interactive video session with genetic counselor

-Duration: 15-30 minutes (try to keep to 15)
- Goal: Answer questions that participants have after watching the pre-recorded genetic education session
-Content: Possible topics to address:

1) Discussion about specific gene and associated cancers
2) Discussion of risk for having mutation depending on relationship to proband
3) NCCN (National Comprehensive Cancer Network) recommended screening based on familial genetic mutation if asked
4) Logistics of accessing genetic testing through Color Genomics
5) GINA if asked
6) Teach back at end