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ABSTRACT

Background: Identifying at-risk relatives of individuals with genetic conditions facilitates "cascade" genetic testing and cancer prevention. Although current standards of care give mutation-positive (index) patients the responsibility of sharing genetic risk information with relatives, the communication is suboptimal, limited largely to close relatives. We developed FamilyCONNECT, a provider-mediated, patient-navigated online tool to facilitate family outreach, and assessed its feasibility, usability and acceptability.

Methods: 1) Development of the FamilyCONNECT prototype; 2) Testing using online surveys of: a) members of Lynch Syndrome International (LSI); b) genetics service providers; and 3) Hands-on testing with LS patients.

Results: 1) FamilyCONNECT's features include introductory email to elicit participation, informational website/video, identity authentication/account creation, informed consent, sharing of genetic test results, pedigree expansion, and process to invite at-risk relatives. 2a) 33% of the 170 LSI participants completed the survey. FamilyCONNECT's features received favorable responses from at least 79% of respondents. Unfavorable responses were for length of the consent document and mistrust of opening emailed links. 2b) Thirty-five genetics professionals responded to the providers' survey. Key perceived barriers to FamilyCONNECT's usage were privacy/confidentiality (82%), a lack of institutional resources (76%), a defined process (66%), and time (69%). 3) Ten patients navigated data collection fields and provided feedback for improvements.

Conclusion: FamilyCONNECT tool's content and features were well-received among patients with LS as well as providers. The tool could be a viable alternative to increase family outreach among patients with LS. Future efforts will focus on refining FamilyCONNECT and assessing its uptake and utilization by LS patients.

INTRODUCTION

About 2-4% of common cancers are heritable, and most involve highly penetrant genes with autosomal dominant inheritance. When pathogenic variants in well-characterized genes are found, typically following a new cancer diagnosis in an index patient (IP), relatives of the IP can then undergo predictive genetic testing, and, if they have the same variant, can be offered surveillance and other risk-reducing interventions.[1-4]

Standard clinical practice and ethical guidance has supported an IP-mediated, rather than provider-mediated approach for communicating genetic risk to at-risk families and encouraging predictive genetic testing (i.e., cascade testing).[5 6] IPs are motivated to share information with family members to help reduce their cancer risks, typically emphasizing risk to their children, less often siblings, and less frequently to more distant relatives.[7 8] Reasons for limited communication may include less emotional closeness to and lack of regular communication with distant relatives or estrangement from at-risk kin, plus a perceived lack of relevance of this information to more distant relatives,[6 9 10] and perceived fears about insurance and employment discrimination.[11-16] Therefore, information about genetic risk may not extend very far into the families of patients with inherited cancer susceptibilities.[5 6 17-19] A large (n=1379) 2019 survey in the Netherlands, comprising a population-based sample and a sample of index patients and relatives with a known hereditary disease, found that a majority wished to be informed about their genetic risks, and most favored the involvement of both family members and health care providers in the disclosure of genetic risk information.[20]

Although healthcare providers may be considered well-suited to communicating genetic test results to at-risk relatives, many are unfamiliar with clinical practice guidelines for genetic counseling or testing, including cascade testing.[21] In addition, privacy (HIPAA) concerns often underlie providers' unwillingness to undertake outreach efforts to patients' relatives in routine clinical care. Furthermore, the traditional medical practice model focuses on one patient at a time and typically does not view risk to others as the individual practitioner's responsibility. A public-health based proactive approach to family

outreach, akin to testing those at risk for communicable disease, was shown by Suthers et al.[22] to significantly increase cascade screening and genetic testing. The success of the proactive approach of provider-mediated family outreach prompted us to develop FamilyCONNECT, a patient-driven, provider-facilitated digital intervention to increase awareness and communication of Lynch Syndrome risk in families, with the ultimate goal of improving cascade testing. Meanwhile, a recent online initiative, where family outreach and testing was mediated via a commercial genetic testing laboratory has shown promising results in increasing cascade testing.[23]

Such methods that utilize digital approaches have a strong potential for wide reach, adoption and diffusion across families: over 90% in the U.S. use the internet, 72% reported seeking health information online,[24] and the gap in technology adoption across generations continues to steadily decrease.[25] Additionally, interventions such as FamilyCONNECT have the potential to achieve efficiency and scalability in family outreach and communication regarding hereditary cancer risk, being largely self-directed in its use by patients and families. Potentially each new mutation carrier identified could easily contact additional at-risk relatives, thereby facilitating true dissemination or cascading of genetic knowledge within a given family. Finally, queries to respondents via FamilyCONNECT could allow for patients and relatives to opt-in to a virtual registry by expressing a willingness to be contacted for future initiatives.

The objective of this study was to develop and evaluate the acceptability, feasibility and usability of FamilyCONNECT in families with Lynch syndrome and among cancer genetics care providers.

MATERIALS AND METHODS

This research was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board (IRB). Following the development of an initial prototype of FamilyCONNECT, we assessed perceptions and feasibility of implementing in a sample recruited from a Lynch syndrome patient advocacy organization, and in a sample of health care providers and researchers recruited from a

professional organization focused on hereditary gastrointestinal cancers. A final version of the prototype was subsequently evaluated in structured, one-on-one user testing interviews.

Development of FamilyCONNECT

FamilyCONNECT was developed with active participation of compliance legal counsel and information technology (IT) security personnel. The software algorithm was developed by experts in IT, in liaison with developers at Progeny, and experts in REDCap (https://www.project-redcap.org/), to create a working prototype. Weekly meetings were held for designing, planning and troubleshooting, based on an iterative process of testing.

FamilyCONNECT includes a family history questionnaire (FHQ) that is the basic family history collection tool used by genetic counselors and a proprietary Progeny software (Progeny Genetics, Aliso Viejo, CA). The family history instrument used in our institutional electronic medical record, EPIC (Epic Systems Corporation, Verona, WI), can be migrated to Progeny and manipulated further within FamilyCONNECT. Process steps are described in the Results, with technical details provided as supplementary material.

Survey of Lynch Syndrome International members

Members of Lynch Syndrome International (LSI), a patient advocacy and education organization (https://lynchcancers.com/), were surveyed. The perceived benefit of surveying LSI members was that they are more diverse and representative of Lynch syndrome families than patients recruited locally from one hospital. The survey was coordinated with the LSI executive director, and the LSI board. The goals of the survey were to evaluate elements of the intervention prototype to broadly assess the acceptability of the FamilyCONNECT content and process, and to identify any concerns about our web-based intervention with the intent of making changes and enhancements as needed.

The self-administered online survey was developed using REDCap , and consisted of screenshots of FamilyCONNECT fields (Supplementary material - FamilyCONNECT feedback survey), a brief explanation of each field, and a series of questions about each feature of FamilyCONNECT. Additionally, data on demographics (e.g., sex, age, household income, educational level), type of cancer, type of mutation, and internet usage were collected. The survey was posted on the LSI website in August 2016 and remained open for 4 months. Participation was voluntary.

Survey of genetics service providers

The leadership of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC; http://www.cgaicc.com/) was approached to obtain permission to survey their members, most of whom are genetic counselors. The goal of the survey was to gauge interest in and enthusiasm about FamilyCONNECT and to identify perceived barriers to provider-mediated and online approaches for family outreach. The survey was anonymous.

In March 2017, a link to the 18-question online survey was emailed to all current CGA members; a second email was sent in June 2017. The online survey in RedCap collected data on demographics, genetic testing/family outreach practices, and perceived barriers to provider-mediated outreach; included a link to screenshots of FamilyCONNECT; and sought feedback regarding FamilyCONNECT's online approach and features.

Means and proportions for continuous and categorical variables were calculated to describe the data using STATA (version 14.0; Stata Corp, College Station, TX).

Usability testing of FamilyCONNECT with patients with LS

The FamilyCONNECT prototype was tested via interactive WebEx video conferencing (Cisco, San Jose, CA) with 10 LS patients. Informed consent was obtained, and a script developed by the research team was used to systematically guide testing. Participants were invited to view each feature of

FamilyCONNECT and asked to perform specific tasks on each screen to assess usability and navigability. If a participant encountered difficulties or sought guidance, the reasons were ascertained through additional questioning. Candid feedback about the overall user experience, including cosmetic appearance, ready access to information, and ease of navigation, was also sought. The usability testing sessions lasted 60-90 minutes and were recorded with the participants' permission. Testing was performed by 2 researchers (MP and SKP), and the content of the recordings was transcribed. Common themes emerging from the usability testing were reported to the information technology team so that improvements could be made iteratively.

RESULTS

Figure 1 depicts the sequences followed by patients and relatives, respectively, in FamilyCONNECT. Essentially, the IP can enroll in FamilyCONNECT, create a secure account to access their family pedigree and mutation test report, can expand the family pedigree and invite family members to FamilyCONNECT by providing their email address or phone number. Each invited family member can in turn create a secure account to access the pedigree and mutation report and can further expand the pedigree and invite additional family members, akin to the process followed by the IP.

Survey of LSI members

The demographic characteristics of the LSI participants (n=170) are listed in Supplementary Table 1. Most participants (89%) were women, reflecting the majority membership of the LSI. The median age of the participants was 50 years (range, 18-76 years). Participants had diverse income and educational levels. Eighty-four percent of them had a pathogenic mutation, 9% were never tested for mutations, 2% were true negatives, and the remaining patients were either diagnosed with a variant of unknown significance (2%) or were not sure of their test results (3%). A little more than half (53%) had a history of cancer.

LSI members' feedback on FamilyCONNECT's features is provided in Table 1. The median level of internet experience, on a scale of 0 to 100, was 68 (range, 5-100). Based on the content of the email invitation, 87.3% of participants indicated a willingness to participate in FamilyCONNECT, and 92.6% indicated that the authentication process would encourage them to create an account to access family risk information. Most respondents (98.3%) expressed a willingness for FamilyCONNECT to share their mutation test results and cancer information (with the consent of those contributing this information). As to the timing of FamilyCONNECT email invitations to relatives, 69.6% of the respondents were comfortable with allowing FamilyCONNECT to send invitations immediately. A smaller proportion, 30.4%, preferred the invitations to be sent after a waiting period of 1-3 months to allow time for personal communication, and the remaining 3.6% preferred a waiting period of 3 months. In a follow up question, about one-third of respondents (33.9%) preferred to talk to all their relatives before reaching out to them through FamilyCONNECT; 44.6% would talk to some relatives, while letting others be contacted directly by FamilyCONNECT; and a substantial proportion, 21.4%, preferred that all relatives be contacted up-front by FamilyCONNECT. The informed consent content received a median score of 34.5 on a scale of 0 to 100 for readability and comprehensibility; this was unsurprising given the length of the content and presence of many "boiler-plate" statements. Comments included "email invite looks professional but could be phishing or scam," "prefer that [FamilyCONNECT] identify the relative that provided my email/hear from relative first," and "informed consent too wordy, needs to be simplified/print too small."

Survey of genetics service providers

Survey responses from genetic service providers are listed in Table 2. Thirty-five genetics service providers consisting of 21 genetic counselors, 13 physicians, and one researcher responded to the survey. The participants were predominantly female (79%). When respondents were asked to indicate their current, customary means of achieving cascade testing, 91% reported that they provided the IP a "family letter," 6% reported contacting relatives at the request of the IP, and 3% reported that they do not pursue cascade testing for their patients. Of the respondents, 48.3% were satisfied that the approaches used at

their institutions met the needs of patients' immediate family members, but more than half were neutral (20.7%), disagreed (24.1%), or strongly disagreed (6.9%). Regarding barriers to contacting relatives on behalf of the IP, 83% of providers said that concern over privacy and confidentiality was the strongest barrier. This was followed by a lack of institutional resources (76%), time for family outreach (69%), or an identifiable structure or process for contacting relatives (66%).

Anticipating concerns about privacy and confidentiality, we asked whether these factors would still be viewed as barriers if the index patient provided an institutionally approved "consent to contact" form for contacting relatives. Fifty percent of respondents said that privacy and confidentiality would remain a concern even with patient consent. In a follow-up question regarding barriers that would persist if privacy and confidentiality were not concerns, respondents expressed concern about lacking time for contacting relatives (92%), an identifiable structure or process for contacting relatives (75%), and institutional resources (67%). When asked about preferred methods of contacting at-risk relatives, the respondents preferred email (55%), followed by conventional mail (38%) and telephone (7%).

Regarding potential approval and uptake of FamilyCONNECT at the providers' institutions, most providers (70%) believed that FamilyCONNECT would likely receive institutional approval. Importantly, when asked, "Having seen the features of FamilyCONNECT, and assuming its introduction met with institutional approval, do you think it would improve the proportion of relatives that would be identified as being at-risk and who would go somewhere for counseling and testing?", all providers who answered the question responded "yes".

Hands-on testing with LS patients

Ten LS patients participated in user-testing, 6 women and 4 men; mean age 44 years (range 30-68 years); 7 were IPs. Overall, the user experience of testing FamilyCONNECT was positive ("agree" or "strongly agree" responses to "ease of use" and "would like to use" questions). The patients' suggestions for improving the appearance of the screens and navigability or "user friendliness" were implemented where

feasible. We received important feedback regarding features that users considered desirable or essential, although some of these could not be implemented into the existing prototype.

Most of the participants recruited for user testing had proactively reached out to their relatives to share mutation test results and apprise family members of their risk for cancer. However, all participants saw value in using FamilyCONNECT to reach out to more distant family members like cousins and other family members who they were estranged from or not in touch with. One patient in particular emphasized that she saw great value in provider-mediated family outreach through FamilyCONNECT, because despite repeated attempts to inform her relatives about their genetic risk, she had not been taken seriously. She felt that this would change if the information came directly from a medical provider. Many participants expressed a desire to start using the prototype to reach out to relatives.

DISCUSSION

In our fourfold approach to developing and assessing FamilyCONNECT's usability and acceptability, we developed the software and processes according to input from our internal team, including compliance counsel and internet security personnel, then obtained feedback from affected LS patients and their relatives, genetics service providers, and hands-on users. Participants were self-selected but were diverse in terms of age, income, and education level.

Our results demonstrate a need for and interest in a web-based, provider-mediated tool for family communication, such as FamilyCONNECT. With it, the locus of control rests with patients and family members but under circumstances in which providers can facilitate and track family outreach. FamilyCONNECT provides a mechanism for initiating family outreach that is likely to be of particular value to IPs reticent about family interaction and relieves them of the heavy responsibility of reaching out directly to any/all at-risk relatives. All that is asked of the IP is contact information for and permission to contact such relatives. Beyond that, FamilyCONNECT provides a process for communicating essential information to relatives to aid them in their genetics referral and testing. To address the barriers of privacy

and confidentiality, the tool explicitly requires participant consent prior to provider-mediated outreach. Finally, to overcome the lack of provider resources for facilitating cascade outreach, FamilyCONNECT relies on patients and families to accomplish much of the work of creating and expanding the pedigree (freeing up time a genetics service provider would otherwise spend on this task). Incidentally, the Covid-19 pandemic is cited as a tipping point for digital health, with increasing provider-patient interactions via the internet, making such communication safer and more acceptable.

A recent review of the delivery methods for cascade screening for hereditary conditions found that, based on current evidence, IP–initiated cascade screening is suboptimal, supporting the notion that a provider-based approach to family outreach has potential value.[26] Methods by which IPs communicate genetic risk information are inconsistent[27], and communication may be incomplete or inaccurate. A recent systematic review reported IP-mediated approaches resulted in cascade testing uptake rate of 21% to 44% in hereditary breast ovarian cancer families and 41% to 62% in LS families[28]. In addition, two clinical trials focused on improving IP–initiated cascade screening by using education and telephone counseling to enhance patients' communication skills found that the approach was not associated with increased communication with or genetic screening among relatives.[29 30] Support for having clinical staff contact relatives directly for genetic testing comes from a study in which three-quarters of IPs found this method appropriate.[31] Authors of reports of low rates of cascade screening for IP–initiated family communication have also recommended that clinical staff contact family members directly with the IP's consent.[32 33] Taken together, these studies reinforce the need for a provider-mediated approach to optimizing cascade screening.

Obtaining a reliable and detailed family history is key for establishing the appropriate relatives at-risk who would benefit from cascade screening and testing. FamilyCONNECT leverages the ability of the IP and invited family members to update their information themselves, and to add/invite additional family members for extending outreach beyond the IP's immediate family. The ability for family members to collaboratively add or update family health history information, is a feature that has not typically been

included in online family history tools and one that may enhance interactivity and engagement. A recent review of 17 patient-facing electronic family history collection tools supported the value proposition of digitizing family history data collection.[34] Most tools were developed to enhance the clinician-patient encounter, with features such as interoperability with electronic health records and clinical decision support for risk assessment and recommendations; however, tools were limited in their ability to share family history within families and across families. An online initiative, in collaboration with a commercial genetic testing laboratory, directly offered low-cost predictive cancer genetic testing to first-degree relatives of IPs with a pathogenic germline mutation.[23] IPs provided relatives' email addresses to the laboratory, which in turn initiated email contact, resulting in 48% uptake of cascade testing; in addition, 12% of IPs' mutation-positive relatives, enabled contact with their first-degree relatives in the same manner, thus achieving the goal of true cascade testing. In fact, direct contact of at-risk relatives by trained health care providers has been proposed as a strategy to overcome barriers in IP-to-family communication; however, the feasibility of implementing this approach in the context of existing privacy policies has yet to be determined.[26] Finally, millions of people have used commercial ancestry programs such as 23andMe and Ancestry, suggesting that consumer acceptance of digitally sharing family history and genetic information has become more commonplace.[35] However, direct-to-consumer commercial testing labs like 23andMe and Ancestry do not systematically facilitate family outreach and communication about inherited cancer risk, the primary goal of FamilyCONNECT.

The provision of comprehensive educational content via FamilyCONNECT may reduce IPs' burden of relaying complex information to their relatives, which is consistent with relatives' desire to receive educational information from trusted health care sources.[19] Invited relatives can watch an explanatory video about Lynch syndrome, inherited cancer risk, risk management, and the importance of family outreach and genetic testing. More detailed information about each of these topics is also provided on the website, searchable via prominently placed tabs and headers. To encourage genetic testing, links are

provided to resources such as finding a genetic counselor by area of residence. A contact form is provided to access help from FamilyCONNECT staff.

Presently, most genetics service providers are not in a position to conduct family outreach because of having no knowledge of family members or their contact information, no outreach paradigm (no physician-patient relationship with relatives), a lack of resources/time for outreach, and a fear of violating the privacy and confidentiality of the IP and his or her relatives. FamilyCONNECT addresses and overcomes each of these barriers and implements a model of provider-mediated outreach. Coincidentally, it adopts most of the features of the program developed by Suthers et al. that demonstrated a 23% increase in uptake of genetic testing using a provider rather than IP-mediated approach.[22] In the Suthers model, newly identified mutation carriers are asked to provide contact information for their at-risk relatives and the provider sends letters to the relatives, relieving the IP of the responsibility to do so. Importantly, none of the relatives in the intervention cohort that were contacted directly by the clinical service (as opposed to relatives being contacted by the IP) complained of a breach of privacy or autonomy. The programs in Australia and New Zealand (https://www.nzfgcs.co.nz/) have been in place for more than 10 years as standard for clinical practice, however they are quasi-governmental, and thus similar to a public health model. In contrast, FamilyCONNECT can be used by providers operating in any setting.

Previous efforts, most notably the University of California, San Francisco's KinTalk (https://kintalk.org), have achieved some of the objectives of family outreach via an online tool. KinTalk takes a Facebook-like approach to family communication and links users to various educational materials and resources but it largely depends upon index-patient initiative for family outreach.

A key barrier to the proactive stance taken by FamilyCONNECT is the perception that genetic information requires special protections and that the provider-mediated approach in FamilyCONNECT may violate principles of confidentiality and privacy, including the Health Insurance Portability and Accountability Act (HIPAA). This overlooks the fact that the notions of confidentiality in HIPAA require only that a patient consent to divulging protected health information to others. FamilyCONNECT

explicitly provides for that consent. Accordingly, we are satisfied that the appropriate assurances of privacy and confidentiality are and will remain in place.

A major limitation of FamilyCONNECT is user friendliness of the software, especially when family trees expand as relatives add information. The clinical FHQ in Progeny was not designed to be patient-facing, nor was it developed with family outreach in mind, although some modifications have been implemented. Other limitations include the length and language of the informed consent that participants find difficult to comprehend. In addition, participants rightly suspect the authenticity of unsolicited emails and the fear of clicking on any links within them. Improving user friendliness and addressing these issues is a priority for the next iteration of FamilyCONNECT.

Future goals include measurement of uptake of cascade testing as a key metric of the success of FamilyCONNECT. Other planned assessments over time include rates of utilization of FamilyCONNECT, and evaluation of barriers and facilitators (e.g., psychosocial factors) associated with enrollment in FamilyCONNECT. These measures are anticipated to guide iterative evolution of FamilyCONNECT towards broader acceptability and increased usage.

Given similarities in risk identification and the utility of cascade testing across other autosomal dominant hereditary cancers, we anticipate that FamilyCONNECT may serve as a model for improving family communication for other hereditary conditions. If health care providers take a more active, direct role in communicating genetic risk information to family members—with or without the IPs' involvement—FamilyCONNECT can potentially be adapted for that use as well. Modifications may include originating email contact from a health care provider rather than the IP, with similar access to other features. This too supports the potential generalizability of FamilyCONNECT across different care models in cancer genetics.

In this study we have taken steps toward an approach to cascade testing of at-risk patients with pathogenic germline variants conferring cancer susceptibility. The workflow addresses the necessary elements

required to enable IPs to communicate to their relatives, by proxy, their test results and related risk information, followed by an opportunity for such relatives to identify and invite additional relatives. The intent is to make this process very patient-driven, but with guidance by providers. We obtained input from a variety of stakeholders, including patients themselves, genetic services providers, as well as legal, ethics, and IT professionals. The prototype that we have developed is a work in progress. It remains to be seen how much provider resources will need to be devoted to servicing FamilyCONNECT as it carries forward as a clinical tool. Nor do we yet know what the actual uptake by patients and their families will be. As a proof of principle, it should serve as an example to be improved upon, technologically and conceptually in the years to come.

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REFERENCES

1. Lynch HT, Snyder C, Casey MJ. Hereditary ovarian and breast cancer: what have we learned? *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2013;**24 Suppl 8**:viii83-viii95. doi: 10.1093/annonc/mdt313
2. Kwon JS, Sun CC, Peterson SK, White KG, Daniels MS, Boyd-Rogers SG, Lu KH. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. *Cancer* 2008;**113**(2):326-35. doi: 10.1002/cncr.23554
3. Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, Lynch P, Burke W, Press N. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA : the journal of the American Medical Association* 2006;**296**(12):1507-17. doi: 10.1001/jama.296.12.1507
4. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, Daniels MS, White KG, Boyd-Rogers SG, Conrad PG, Yang KY, Rubin MM, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *The New England journal of medicine* 2006;**354**(3):261-9. doi: 10.1056/NEJMoa052627
5. Petersen J, Koptiuch C, Wu YP, Mooney R, Elrick A, Szczotka K, Keener M, Pappas L, Kanth P, Soisson A, Kohlman W, Kaphingst KA. Patterns of family communication and preferred resources for sharing information among families with a Lynch syndrome diagnosis. *Patient Educ Couns* 2018;**101**(11):2011-17. doi: 10.1016/j.pec.2018.07.021 [published Online First: 2018/08/12]
6. Stoffel EM, Ford B, Mercado RC, Punglia D, Kohlmann W, Conrad P, Blanco A, Shannon KM, Powell M, Gruber SB, Terdiman J, Chung DC, Syngal S. Sharing genetic test results in Lynch syndrome: communication with close and distant relatives. *Clin Gastroenterol Hepatol* 2008;**6**(3):333-8. doi: 10.1016/j.cgh.2007.12.014
7. Peterson SK. The role of the family in genetic testing: theoretical perspectives, current knowledge, and future directions. *Health Educ Behav* 2005;**32**(5):627-39. doi: 10.1177/1090198105278751
8. Wilson BJ, Forrest K, van Teijlingen ER, McKee L, Haites N, Matthews E, Simpson SA. Family communication about genetic risk: the little that is known. *Community Genet* 2004;**7**(1):15-24. doi: 10.1159/000080300
9. Claes E, Evers-Kiebooms G, Boogaerts A, Decruyenaere M, Denayer L, Legius E. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. *Am J Med Genet A* 2003;**116A**(1):11-9. doi: 10.1002/ajmg.a.10868
10. van Oostrom I, Meijers-Heijboer H, Duivenvoorden HJ, Brocker-Vriends AH, van Asperen CJ, Sijmons RH, Seynaeve C, van Gool AR, Klijn JG, Tibben A. Family system characteristics and psychological adjustment to cancer susceptibility genetic testing: a prospective study. *Clinical genetics* 2007;**71**(1):35-42. doi: 10.1111/j.1399-0004.2007.00731.x
11. Allain DC, Friedman S, Senter L. Consumer awareness and attitudes about insurance discrimination post enactment of the Genetic Information Nondiscrimination Act. *Familial cancer* 2012;**11**(4):637-44. doi: 10.1007/s10689-012-9564-0
12. Surbone A. Social and ethical implications of BRCA testing. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2011;**22 Suppl** 1:i60-6. doi: 10.1093/annonc/mdq668
13. Lowstuter KJ, Sand S, Blazer KR, MacDonald DJ, Banks KC, Lee CA, Schwerin BU, Juarez M, Uman GC, Weitzel JN. Influence of genetic discrimination perceptions and knowledge on cancer genetics referral practice among clinicians. *Genetics in medicine : official journal of the American College of Medical Genetics* 2008;**10**(9):691-8. doi: 10.1097GIM.0b013e3181837246

14. Hampton T. Congress passes bill to ban discrimination based on individuals' genetic makeup. *JAMA : the journal of the American Medical Association* 2008;**299**(21):2493. doi: 10.1001/jama.299.21.2493
15. Billings PR, Kohn MA, de Cuevas M, MacDonald DJ, Banks KC, Lee CA, Schwerin BU, Juarez M, Uman GC, Weitzel JN. Discrimination as a consequence of genetic testing. *American journal of human genetics* 1992;**50**(3):476-82.
16. Rothstein MA. Discrimination based on genetic information. *Jurimetrics* 1992;**33**(1):13-8.
17. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. *Clin Gastroenterol Hepatol* 2013;**11**(9):1093-100. doi: 10.1016/j.cgh.2013.04.044 [published Online First: 2013/05/15]
18. Lynch HT, Snyder C, Stacey M, Olson B, Peterson SK, Buxbaum S, Shaw T, Lynch PM. Communication and technology in genetic counseling for familial cancer. *Clinical genetics* 2014;**85**(3):213-22. doi: 10.1111/cge.12317
19. van den Heuvel LM, Smets EMA, van Tintelen JP, Christiaans I. How to inform relatives at risk of hereditary diseases? A mixed-methods systematic review on patient attitudes. *J Genet Couns* 2019;**28**(5):1042-58. doi: 10.1002/jgc4.1143
20. Chivers Seymour K, Addington-Hall J, Lucassen AM, Foster CL. What facilitates or impedes family communication following genetic testing for cancer risk? A systematic review and meta-synthesis of primary qualitative research. *J Genet Couns* 2010;**19**(4):330-42. doi: 10.1007/s10897-010-9296-y
21. Vadaparampil ST, McIntyre J, Quinn GP. Awareness, perceptions, and provider recommendation related to genetic testing for hereditary breast cancer risk among at-risk Hispanic women: similarities and variations by sub-ethnicity. *Journal of genetic counseling* 2010;**19**(6):618-29. doi: 10.1007/s10897-010-9316-y
22. Suthers GK, Armstrong J, McCormack J, Trott D. Letting the family know: balancing ethics and effectiveness when notifying relatives about genetic testing for a familial disorder. *J Med Genet* 2006;**43**(8):665-70. doi: 10.1136/jmg.2005.039172 [published Online First: 2005/12/24]
23. Caswell-Jin JL, Zimmer AD, Stedden W, Kingham KE, Zhou AY, Kurian AW. Cascade Genetic Testing of Relatives for Hereditary Cancer Risk: Results of an Online Initiative. *J Natl Cancer Inst* 2019;**111**(1):95-98. doi: 10.1093/jnci/djy147
24. Fox S, Duggan M. Health Online 2013. Pew Research Center, Internet and Technology 2013 [Available from: https://www.pewresearch.org/internet/2013/01/15/health-online-2013/ accessed 11/11/2020.
25. Anderson M, Perrin A, Jiang J, Kumar M. 10% of Americans don't use the internet. Who are they? Pew Research Center 2019 [11/11/2020]. Available from: https://www.pewresearch.org/fact-tank/2019/04/22/some-americans-dont-use-the-internet-who-are-they/ accessed 11/11/2020.
26. Roberts MC, Dotson WD, DeVore CS, Bednar EM, Bowen DJ, Ganiats TG, Green RF, Hurst GM, Philp AR, Ricker CN, Atrum AC, Trepanier AM, Williams JL, Zierhut HA, Wilemon KA, Hampel H. Delivery Of Cascade Screening For Hereditary Conditions: A Scoping Review Of The Literature. *Health Aff (Millwood)* 2018;**37**(5):801-08. doi: 10.1377/hlthaff.2017.1630
27. Bowen DJ, Hyams T, Laurino M, Woolley T, Cohen S, Leppig KA, Jarvik G. Development of FamilyTalk: an Intervention to Support Communication and Educate Families About Colorectal Cancer Risk. *J Cancer Educ* 2019 doi: 10.1007/s13187-019-1484-3
28. Menko FH, Ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Ait Moha D, Bleiker EMA. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. *Fam Cancer* 2019;**18**(1):127-35. doi: 10.1007/s10689-018-0089-z

29. Hodgson J, Metcalfe S, Gaff C, Donath S, Delatycki MB, Winship I, Skene L, Aitken M, Halliday J. Outcomes of a randomised controlled trial of a complex genetic counselling intervention to improve family communication. *European journal of human genetics : EJHG* 2016;**24**(3):356-60. doi: 10.1038/ejhg.2015.122 [published Online First: 2015/07/02]
30. Montgomery SV, Barsevick AM, Egleston BL, Bingler R, Ruth K, Miller SM, Malick J, Cescon TP, Daly MB. Preparing individuals to communicate genetic test results to their relatives: report of a randomized control trial. *Familial cancer* 2013;**12**(3):537-46. doi: 10.1007/s10689-013-9609-z [published Online First: 2013/02/20]
31. Wright C, Kerzin-Storrar L, Williamson PR, Fryer A, Njindou A, Quarrell O, Donnai D, Craufurd D. Comparison of genetic services with and without genetic registers: knowledge, adjustment, and attitudes about genetic counselling among probands referred to three genetic clinics. *Journal of medical genetics* 2002;39(12):e84. doi: 10.1136/jmg.39.12.e84 [published Online First: 2002/12/10]
32. Schoeman M, Apffelstaedt JP, Baatjes K, Urban M. Implementation of a breast cancer genetic service in South Africa - lessons learned. *S Afr Med J* 2013;**103**(8):529-33. doi: 10.7196/samj.6814 [published Online First: 2013/07/28]
33. Sermijn E, Goelen G, Teugels E, Kaufman L, Bonduelle M, Neyns B, Poppe B, De Paepe A, De Greve J. The impact of proband mediated information dissemination in families with a BRCA1/2 gene mutation. *Journal of medical genetics* 2004;**41**(3):e23. doi: 10.1136/jmg.2003.011353 [published Online First: 2004/02/27]
34. Welch BM, Wiley K, Pflieger L, Achiangia R, Baker K, Hughes-Halbert C, Morrison H, Schiffman J, Doerr M. Review and Comparison of Electronic Patient-Facing Family Health History Tools. *J Genet Couns* 2018;**27**(2):381-91. doi: 10.1007/s10897-018-0235-7
35. Khan R, Mittelman D. Consumer genomics will change your life, whether you get tested or not. *Genome Biol* 2018;**19**(1):120. doi: 10.1186/s13059-018-1506-1

Table 1. Acceptability of features of FamilyCONNECT: results from survey of Lynch Syndrome International members

1. Internet experience on scale 0-100, median (range)	68	(5 – 100)
2. Response to content of invitation email and willingness to participate in registry (FamilyCONNECT), n (%)		
Yes	110	(87.3)
No	16	(12.7)
3. Impression of email content on scale 0-100, median (range)	71	(4 – 100)
4. Would authentication as shown encourage you to create an account to access family risk information? n (%)		
Yes	100	(92.6)
No	8	(7.4)
5. Are authentication instructions easy to follow? n (%)		
Yes	106	(96.3)
No	4	(3.7)
6. What do you think about the appearance of the authentication field? On scale of 0-100, median (range)	75	(0 – 100)
7. We have provided for the usual creation of an account that will enable entry of online data and for subjects to easily return to FamilyCONNECT on a recurring basis. Question: Does this field adequately explain the need for an "account field" and enable it to be easily used? n (%)		
Yes	95	(92.2)
No	8	(7.8)
8. Is the consent form generally readable, understandable and with content that helps you understand what you are being asked to do? On scale of 0-100, median (range)	34.5	(0 – 100)
9. Do you feel that inclusion of your relative's name on this report presents any potential for concern within your family? n (%)		
Yes	13	(21.3)
No	48	(78.7)
10. The information requested in these FHQ fields seems understandable and appropriate. n (%)		
Yes	57	(100)
No	0	
11. How likely are you to view and print your family tree? On scale of 0-100, median	86	(0 – 100)
12. If you saw this picture, would you know that it is a family tree? n (%)		
Yes	57	(100)
No	0	
13. The developers of FamilyCONNECT consider it desirable to have pedigrees show ALL useful information for the use of relatives. Although we, as providers, will have access to all of this information, we understand that it is sensitive when included in a pedigree available to all relatives that join FamilyCONNECT. Do you in general feel that it is OK to encourage family members to contribute their mutation and cancer information so that it can be viewed by other relatives? Keep in mind that this information is posted only with the consent of the person in question. n (%)		
Yes	57	(98.3)
No	1	(1.7)
14. The contact information field would enable us to identify and reach out to other relatives, some of whom may not have been known to the original index case (LS patient) in your family. Are you OK with the way in which this information is being requested? n (%)		
Yes	52	(96.3)
No	2	(3.7)
15. Given a choice, what would you consider the appropriate time to send the email invite to additional relatives that might be at risk? n (%)		
Immediately	39	(69.6)
After waiting a month	15	(26.8)

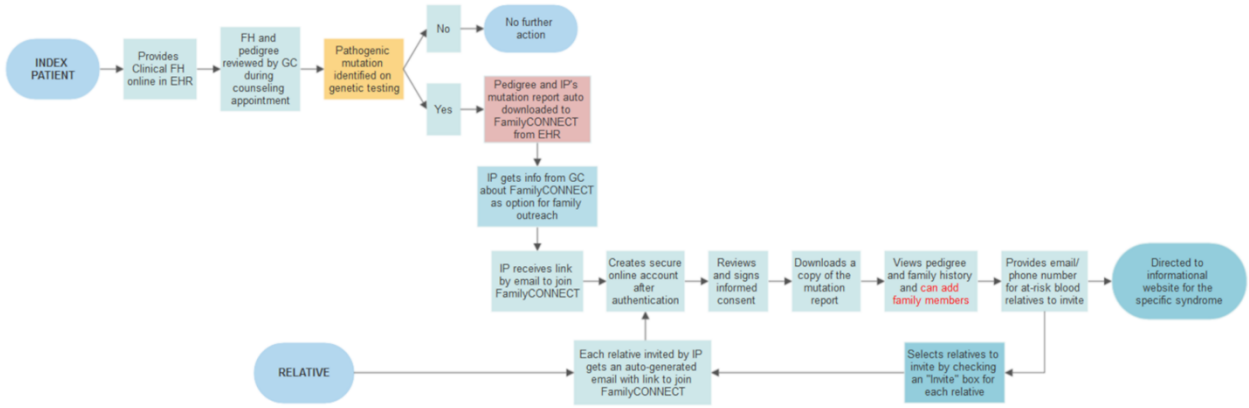
After waiting 3 months	2	(3.6)
16. Would you consider reaching out to your relatives and letting them know about the genetic mutation and cancer risk in the family BEFORE letting FamilyCONNECT do it on your behalf? n (%)		
Talk to ALL my relatives first	19	(33.9)
Talk to some relatives first and let the remaining be contacted by FamilyCONNECT	25	(44.6)
Let FamilyCONNECt reach out to all my relatives	12	(21.4)
17. Does the appearance of the FamilyCONNECT website have the look and feel of a website you would respond to if sent here by following a link in an email sent on behalf of a relative of yours? On scale of 0-100, median (range)	85.5	(36 – 100)

Table 2. Survey responses from genetics service providers

Variable/question	n	%
1. Proportion of patients in my practice seen for counseling that have a diagnosis of Colorectal or Breast cancer for whom initial testing for likely mismatch repair genes (HNPCC or Lynch syndrome) or BRCA gene mutations is being considered		
<10%	1	2.9
10-25%	4	11.8
25-50%	9	26.5
>50%	20	58.8
2. Proportion of patients in my practice referred for predictive testing for known cancer susceptibility gene mutation.		
<10%	10	29.4
10-25%	15	44.1
25-50%	4	11.8
>50%	5	14.7
3. Proportion of patients in my practice referred for predictive testing for known cancer susceptibility gene mutation (all that apply)		
we do not actively promote cascade testing	1	2.9
we provide patients with a "family letter"	31	91.2
we provide teaching materials we have developed or acquired for this purpose	4	11.8
we contact relatives upon request of index patient	2	5.9
4. I am satisfied that the approach used at our institution meets the needs of the immediate family of our mutation-positive index patients		
Strongly agree	0	
Agree	14	48.3
Neither agree nor disagree	6	20.7
Disagree	7	24.1
Strongly disagree	2	6.9
5. Assuming you do not routinely contact relatives on behalf of your mutation-positive index cases, which of the following best describes barriers to doing so		
there are no barriers, we simply don't do it	0	
concerns about privacy and confidentiality	24	82.8
lack of institutional resources	22	75.9
lack of a described structure or process for doing so	19	65.5
lack of time	20	69
6a. If your institution/practice had an agreed upon and valid "consent to contact" form from the patient, would privacy and confidentiality still be perceived as barriers?		
Yes	12	50
No	12	50
6b. Which of the following would still be a barrier?		
even without a privacy concern, we simply would not do it	1	8.3
lack of institutional resources	8	66.7
lack of described structure or process for doing so	9	75
lack of time	11	91.7
7. If all regulatory barriers (privacy, etc.) could be solved and you were able to get your patients to provide a list of their close and distant at-risk relatives with contact information, what do you think would be the easiest way to reach		
Phone	2	6.9
By regular mail (postal)	11	37.9
Email	16	55.2
8. If given the opportunity to contact at-risk relatives, what would be your preferred method to reach them?		
Phone	7	24.1
By regular mail (postal)	8	27.6
Email	14	48.3

9. At your institution, if direct contact of relatives were taken up, how many full time employees (FTE) would it require to contact relatives of your mutation-positive patients?			
	< or = 1	17	60.7
	2	9	32.1
	>2	2	7.1
10. If such a program were to be initiated, do you think enough new referral counseling and clinical services business would be generated by such relatives coming to your institution as to cover the FTE costs described above?			
	Yes	8	27.6
	No	21	72.4
11. Now that you have seen the features of FamilyCONNECT, if you could be assured that it had been approved at a major cancer center, do you think it would likely get approval at your institution?			
	Yes	16	69.6
	No	7	30.4
12a. What do you consider to be the barriers?			
	Privacy and confidentiality notwithstanding approval at another institution	6	85.7
	Unacceptability of some other specific feature of FamilyCONNECT	2	28.6
	I do not understand the features of FamilyCONNECT to venture an opinion	0	
13. Having seen the features of FamilyCONNECT, and assuming its introduction met with institutional approval, do you think it would improve the proportion of relatives that would be identified as being at-risk and who would go somewhere for counseling and testing?			
	Yes	22	100
	No	0	
14. If you could outsource the responsibility for contacting relatives and could be reassured that it was conducted ethically and appropriately, would you consider doing so?			
	Yes	20	87
	No	3	13
15. If outsourcing to a public health authority (for example a State Health Department) were possible, would you be in favor of doing so?			
	Yes	15	65.2
	No	8	34.8
16. If outsourcing to another institution were possible (again assuming no privacy, HIPAA, etc. issues), would you consider doing so even if it meant relatives might go to another institution for counseling and clinical services?			
	Yes	17	73.9
	No	6	26.1
17. If a program like FamilyCONNECT could be made available to you for your institutional use, including database and database support, but required a license, what do you think your institution would be willing to pay, as an alternative to outsourcing?			
	We would not be interested even if it were free	6	27.3
	up to $25,000/year	16	72.7
	$25,000-$50,000/year	0	

Figure 1. FamilyCONNECT process flow for Index patient and relatives



Legend: FH – family history; GC – genetic counselor; EHR – electronic health record; IP – index patient.