RESEARCH ARTICLE

Cascade Genetic Testing for Lynch Syndrome: Current Understanding, Challenges, and Emerging Opportunities

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Abstract

Cascade genetic testing, a highly effective method of identifying high penetrance cancer risk mutations in the family, is a promising method of prevention. Cascade testing is defined as directed genetic testing of at-risk relatives of individuals known to have actionable mutations However, it is tremendously underutilized in clinical practice, and the reasons are complex and diverse. We discuss these reasons and consider areas of research for key findings, strengths and weaknesses. We offer testable solutions for increasing interest and use of cascade testing opportunities in families and in clinical practice using colorectal cancer as an example. This area of clinical research has great potential to save lives by improving cancer prevention and early detection in families at high genetic risk, and should be actively pursued with resources and ideas.

Keywords: Cascade testing, population testing, cancer risk, genetic risk

1. INTRODUCTION

Cascade genetic testing, a highly effective method of identifying high penetrant cancer risk mutations in the family and is a promising method of cancer prevention. Its ability to enable precise application of cancer screening without over treating family members who are not at risk, and overall ability to maximize public health has allowed it to be designated as a Tier-1 genomic application for Lynch Syndrome by the Centers for Disease Control and Prevention. Lynch Syndrome (LS) is an autosomal dominant cancer susceptibility syndrome conferred by inherited mutations in one of four DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*). Lifetime risks of many cancers in patients with LS are dramatically elevated but vary by gene. In particular, lifetime risk of colorectal cancer (CRC) may be as high as 70-80% and endometrial cancer 50-60%[1,2]. Other increased cancer risks include pancreas, ovary, hepatobiliary, stomach, urinary tract, and brain.

Cancer prevention guidelines for individuals with a pathogenic variant known to cause LS include colonoscopies every one or two years starting in their twenties, consideration of risk-reducing hysterectomy and bilateral salpingo-oophorectomy, and consideration of screening for other extracolonic cancers[1]. Early initiation of regular colonoscopies has been shown to reduce the incidence of colorectal cancer as well as reduce mortality in individuals with LS[3]. This clinical benefit provides the rationale for large-scale efforts to identify individuals at risk for LS including screening all colorectal and endometrial cancers for LS-associated molecular alterations. Once LS is suspected based on a cancer diagnosis or pattern of cancers in the family, genetic testing provides the opportunity to define the causative mutation. Knowing the specific mutation provides information to the tested individual about specific risks and allows definition of which relatives are and are not at risk.

1.1 The need to test within families that have known mutations (cascade testing)

Cascade testing is defined as directed genetic testing of at-risk relatives of individuals known to have actionable mutations.[4,5] Siblings, parents, and children (1st degree relatives) have a 50% chance of sharing the pathogenic variant; 2nd degree relatives (grandparents, aunts, uncles, etc.) have a 25% chance, and 3rd degree relatives have a 12.5% chance of sharing the same variant. Cascade testing has been shown to save lives in a cost effective way through multiple modeling studies.[6–8] The 2016 National Comprehensive Cancer Network indicated that for all families with a known mutation in the testing of relatives is recommended[9] and cascade testing is endorsed by the World Gastroenterology Association[9], CDC, as well as a national review of LS testing recommendations.[10]

Although clearly recommended, cascade screening for LS and other dominant genetic syndromes, such as hereditary breast and ovarian cancer has poor clinical uptake in the United States. Estimates of cascade testing success rates among relatives are highly variable, with estimates ranging from 10-30% of at-risk relatives tested.[11–18] Variables in project design may account for some of these ranges, including the proportion of living relatives deemed eligible or contactable for testing, the intervention strategies attempting to contact and or inform relatives, the properties of genetic testing including unrealistic out-of-pocket cost to relatives, underrepresentation of males and non-Europeans as study subjects, and the methods of calculating the proportion of relatives tested.[19] Usual care for cascade testing involves providing probands with a recommendation to inform relatives of the need for genetic testing. Two recently

published systematic reviews of the cascade testing intervention literature have been published, with reported effects ranging from 20-50%[20,21]. Most studies had small convenience samples and did not use denominator-driven outcome calculation (i.e., reporting number of relatives tested or informed without a corresponding denominator of number of possible relatives to be tested or informed). A recent national meeting explored multiple issues surrounding the low rates of cascade testing for Lynch Syndrome, estimating the proportion of relatives who currently receive testing in the United States as between 10- 20% of eligible family members.[22] Multiple research projects primarily outside the U.S. (Australia, Europe) have attempted to improve cascade testing rates with targeted interventions, with cascade testing success rates between 20 and 40%, but study samples have been small, and most have not used control groups in which usual care was delivered.[19] Taken together, the best methods of increasing cascade testing for LS in the US are not known and have not been systematically evaluated or directly compared.

1.2 Current barriers limit the potential of cascade testing efforts to save lives

Perceived legal barriers to communication: Informing relatives about LS risk is not a simple task. Under current privacy law, "providers are neither required nor permitted to warn at-risk relatives without the consent of their patients"; however, with consent of the patient, family members can legally be approached and invited to receive testing[23,24] There has been extensive debate about the need to respect privacy of individuals who undergo genetic testing, the right (or lack of a right) of relatives to be notified about genetic information that might change the relative's risk, and the extent that physicians or genetic counselors are responsible for notifying at-risk relatives. Those discussions reflect real and perceived legal worries about the collection, use and release of genetic information and have prompted concerns about the appropriate role of physicians in cascade testing.[25] As just one example, there is misunderstanding about whether it would be legally permissible in the practice setting for a provider of a proband who has tested positive to be involved in notifying at-risk relatives even when the patient has consented to such contact.[23,26] Well known legal scholar Mark Rothstein has stated that "[t]he duty to warn genetically at-risk relatives of patients is one of the most misunderstood legal and ethical issues affecting clinical genetics."[26,27] However, current misunderstandings about HIPAA law, combined with concerns about documenting patient preferences seem to be a barrier to active provider involvement in communication with at-risk relatives. There is a need for comprehensive legal research and analysis to identify legal risks to support decision-making about future strategies and policies to mitigate concerns that prevent effective family-centered care. It is also important to consider legal barriers to the implementation of cascade testing by conducting doctrinal legal research to provide important legal context for frontline actors in the clinical setting and to otherwise incorporate relevant legal guidance and insights into new cascade testing efforts.

Barriers in healthcare delivery: Availability and genetic literacy of providers, and the health care systems that support them, are another barrier to full implementation of cascade testing for LS.[22] Genetic counselors are not distributed in every health care setting where testing could occur, and are not usually reimbursed for contacting relatives as about risk.[28] Primary care providers have a relatively low comfort level with discussing genetics with their patients, and this lack of engagement with genetics leads to under-referral and underutilization of genetic testing in clinical settings.[29] Although frequently

posited as the frontline actors in implementation scenarios, primary care providers are unlikely to effectively carry out cascade testing in at risk relatives[22] and frequently report insufficient knowledge about genetics and insufficient time as barriers to integrating genetics within primary care settings[30].

Family communication barriers: Another set of barriers to cascade testing comes from the family itself. Communication between an informed, tested member of a family with LS and other relatives is the critical link in getting relatives to undergo genetic counseling and testing and, when appropriate, to initiate recommended cancer screening at appropriate ages.[31,32] Only about 30% of CRC survivors were aware of their relatives' elevated cancer risk associated with their own diagnosis. Communication with 1st degree relatives (FDRs) does occur in between 10% and 40% of eligible relatives, although not all FDRs are told.[33,34] Communication to 2nd degree relatives is considerably less complete.[32] Reasons offered for not communicating with adult relatives include perception of the recipient as lacking sufficient maturity,[35] estrangement and family disruption,[31,36] and hesitancy in conveying potentially painful information, i.e., to keep others from ''feeling the same sorrow''.[33,37] Also mentioned were difficulties with understanding complex genetic and medical information about LS; indeed misconceptions about hereditability are common among tested individuals.[31] If a first attempt at family communication does not work, communication becomes much less likely without assistance.[36]

1.3 Family support for cascade testing is an intervention option

One option to improve cascade testing might lie within the family itself. Families comprise social ties and structures that deliver social contact, form normative beliefs, and shape individual members' reactions to disease and disease risk.[38–40] A system for reaching, informing, and engaging families as they make new choices and health behavioral decisions around genetic information is becoming critically important. If we can increase family communication about testing and risk, we could increase the proportion of relatives tested. In addition to the proband, we and others have found that identifying a family communicator, a person in a family system who has taken responsibility for communication, is key to the success of family communication about cancer risk. The proband will not have complete responsibility for making all connections with other family members.

Existing research to improve communication[41,42] focuses on convergence (i.e., shared agreement and accuracy among participating family members) regarding the meaning of information exchanged. This is important for inducing family support, mutual understanding, and influence to foster positive health behaviors. We applied these concepts to our previous study with melanoma families, finding significant improvements in family agreement on melanoma-related topics after use of a web-based intervention.[43] This same principle can potentially improve cascade testing by increasing the agreement and understanding in the risk beliefs among family members about the need for, and methods of, testing.

1.4 Professional support for cascade testing is another option

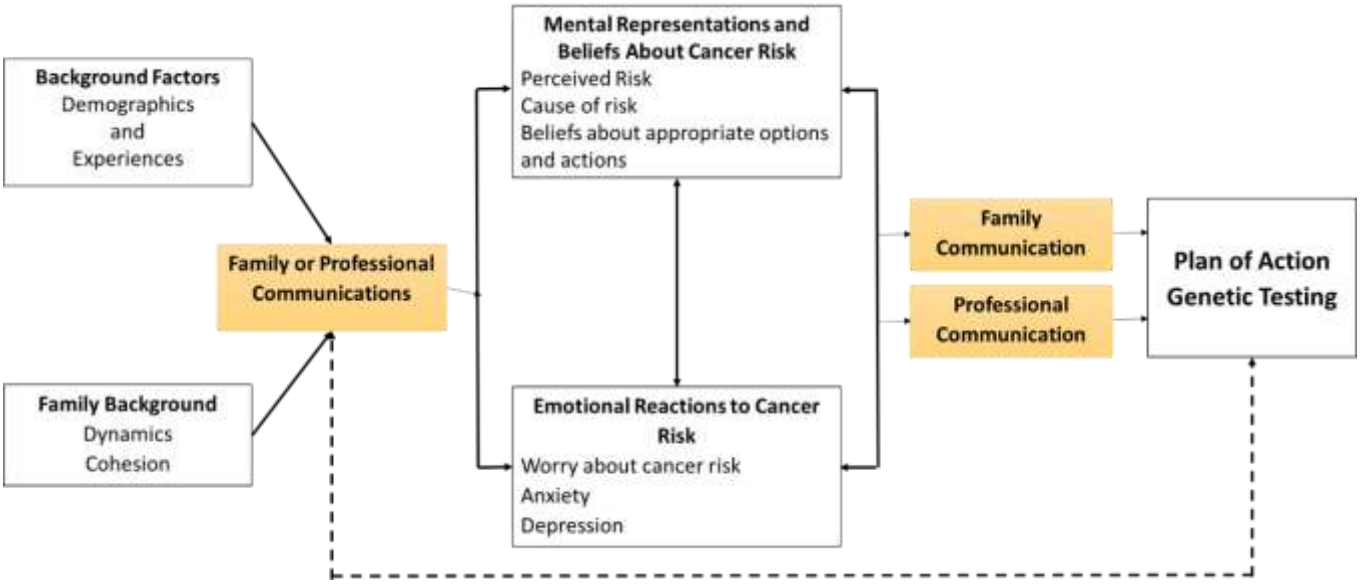
Another model for potentially improving the rates of cascade testing comes from current research in genetic epidemiology, where entire multigenerational families are recruited and tested to perform linkage calculations, to avoid sampling bias, and to develop exposure estimates. In these settings, the professionally trained genetic counselor or clinical geneticist coordinates the

initial contact and encourages family members to obtain testing. This method of contact has been successful in the research setting[12,44–46] and in other countries,[47,48] but has not been evaluated as a potential clinical model in the US. Professional support can overcome several of the barriers to obtaining cascade genetic testing. At-risk family members can be provided with counseling over telephone, given directions for sample collection and testing, eliminating the need for multiple provider visits. The work of communicating can be done by professionally trained counselors; while probands may be actively involved, they need not be solely responsible for communicating complex genetic information to numerous first- and second-degree relatives. Staff can be trained and supported in the basics of coaching families to communicate more effectively. For families that are not very cohesive or who have difficult or nonexistent communication, the offer of professional support can be a helpful addition, saving family members from feeling compelled to communicate with difficult or estranged family members. Finally, the emotionally charged work of communicating about life threatening illness or risk is removed from family members, perhaps making communication easier.

We believe that effective implementation of education for family support or professional support will enable dramatic improvements in uptake of cascade testing, which is likely to reduce cancer mortality and morbidity. Both approaches have potential to allow improved cancer prevention that is effective in low resource, low population density areas.

We have devised an integrated model to represent the process of cascade testing in LS families using an adaption of the Common-Sense Model[49,50] to understand the relationship between communication about risk and testing behaviors in families (Figure 1). According to this integrated model, potential intervention begins at the communication process by engaging family members in information exchanges about LS, the positive test received in the proband, and the need for testing in 1st and 2nd degree relatives.

Figure 1. Mechanisms of cascade testing using adapted self-regulation model of health behavior.



This communication source may be different depending on the methods selected (either the professional or family support). The proband as well as each individual within the family will then begin coping with risk for LS when they learn about risk for the disease. All individuals have complex emotional reactions and beliefs, or mental representations of what elevated risk means. Emotional variables include the person's specific emotional reactions to the risk information, as well as emotions about their family's risk. Areas of beliefs include identity (disease label and associated characteristics or symptoms indicative of vulnerability), cause (factors responsible for disease development, such as genetic mutations or behaviors), timeline (including anticipated onset of the disease in life), consequences (likely outcomes such as death or disability), and control (methods for prevention, control, or cure).[51] Potential interventions therefore will need to include preparations for providing samples and testing, as well as consideration of preventive approaches including arrangement for physician's visits for screening/ surveillance, other personal behaviors (such as dietary changes), and/or avoiding thinking about risk. These are represented in this model as a series of variables related to family functioning and communication, e.g., content and frequency of genetic risk communication, LS-related communication, influences individuals' thoughts and feelings about cancer risk and ultimately, their testing behaviors. This influence may be positive (i.e., supporting the process of testing) or negative (e.g., interfering with testing). Integrated models such as these are also necessary to guide assessment of secondary outcomes and mechanisms of intervention effectiveness that will be key for real world implementation of effective interventions.

Prior cost-effectiveness analyses have shown that genetic testing for LS in newly diagnosed CRC patients and cascade testing of relatives of the proband are generally cost-effective strategies in the US healthcare system.[52,53] Existing studies also highlighted that extent or magnitude of cost-effectiveness could be sensitive to the number of FDRs tested per proband, frequency of colonoscopies performed, cost of genetic testing and colonoscopy, and the inclusion of other surveillance and prevention options.[53] One study especially called for critical re-analysis of epidemiologic assumptions underlying cost effectiveness analysis models and objective assessment of model input assumptions.[54] We anticipate that between the options described above, cost of the family-driven method might be lower than for professionally driven testing. Cost should be a part of all cascade testing projects as it presents a significant challenege in implementing successful cascade genetic risk evaluation in the real world.

2. Lessons learned from FamilyTalk

The electronic medical records and genomics phase 3 (eMERGE 3) study evaluated the clinical benefit of genomic screening for hereditary CRC. FamilyTalk is an intervention from eMERGE3 which uses naturally existing familial structures to improve cancer screening through notification of first-degree relatives of patients who receive pathogenic genetic test results.[55] This involved development of a booklet with information on CRC and screening, followed by introduction of a website that included screening reports, family communication materials, provider communication materials, and additional resources for patients with CRC, patients with colon polyps, and their relatives.

As a part of eMERGE3, a randomized control trial assigned patients diagnosed with either CRC or more than one colon polyp to either receive support through FamilyTalk or usual clinical care[56]. The outcomes of interest were the frequency in familial communication

and cancer family impact. Although there were no differences in the communication frequency between intervention and control arms, there were significant differences in several communication variables between CRC patients and patients with colon polyps; for example, CRC patients reported higher communication impact than polyp patients. Additionally, more patients from the intervention arm increased their communication frequency from baseline to a six-month follow up compared to patients in the control arm ($p = 0.03$).

Although there was no significant difference in FamilyTalk's primary outcome of interest for all patients enrolled in the randomized trial, further analysis revealed complex communication problems where future intervention is needed. Analysis showed that the most frequently selected reason for sharing results with relatives was to provide them with necessary risk information. The most frequently encountered problem for patients who want to discuss genetic test results with their relatives was lack of knowledge about what to discuss and how to interpret the genetic information. Overall, the RCT revealed strong and consistent effects in subgroups (probands with pathogenic genetic test results and probands with low baseline communication frequency) that might need additional assistance to understand or cope with their results, such as intervention. Patients in these subgroups might benefit from more communication assistance with relatives to start the handoff of genetic test results and begin cascade testing.

3. Future research

Future studies could aim to build from what we learned in eMERGE3 and other studies of this type, to provide additional intervention methodologies to improve how family members, especially those who may be particularly susceptible to behavior change messaging, communicate about genetic testing and inherited cancer risk. We believe that providing additional support in both familial and professional communication will improve the uptake of cascade testing for family members of individuals with known LS genetic variants. Families need to talk more about CRC risk and the benefits of testing within relative groups and should discuss the methods of obtaining testing that are right for them and for family members. Similar information could be provided to relevant family members to alert them to this possibility and to help them find methods of achieving tested status.

Increasing medical team contact with patients regarding cascade testing might also be beneficial in raising awareness of the need for cascade testing. Genetic counselors now act as testing promoters for probands and similar actions could be taken with relatives who are eligible for cascade testing. Given the relative shortage of genetic counselors, non-counselor professionals with good social skills (e.g., genetic counseling assistants) can be trained to contact relatives to encourage testing, and offer options for genetic testing. We currently employ such nongenetic counselor team members in research projects and similar training and protocols could be used in clinical settings.

Of course, having both familial and professional methods of contact might allow us to make comparisons about the most effective (both in terms of cost and in terms of reducing the burden of cancer) way to communicate to families about their risk of developing Lynch syndrome and their options for genetic testing/counseling. Some individuals need multiple exposures and ways of considering testing before they agree to a behavioral change activity. Similar to obtaining a laboratory test of completing a survey on symptoms, genetic testing and cascade testing could become part of a standard of care that prioritizes prevention as highly as treatment efforts.

4. Conclusions

We can conclude a few things from this brief discussion of cascade testing. First, the process of cascade testing is complex, multilevel, and multistepped. Viewing it as not a single act, but a process of communications, referrals, and actions might help us to improve current rate in the US. And, considering all relevant levels might be a fruitful avenue to explore and use clinically to improve rates. Focusing on proband communication while ignoring family dynamics has not worked well for the field.

Second, because of the complexity of the problem, we have multiple intervention modalities and levels to consider, evaluate, and promote. Improvements in family communication might not be enough to change rates if there is still a gap between what the provider or guidelines request and what the proband's understanding of the issues and solutions. Taking a systems approach to cascade testing might be helpful here, for researchers and clinicians seeking to improve rates of cascade testing. The design of multilevel research projects in recent years has improved, allowing us to better understand and ultimately change, activities at all relevant levels as part of an intervention to improve testing rates.

Finally, the findings from our eMERGE3 trial and others might be identifying a vulnerable subgroup of probands and families that might benefit from these interventions. This vulnerable subgroup can be defined, addressed, and ultimately supported through the process to improve rates. Efforts to improve population screening might result from a combination of basic support for all probands, combined with more targeted support for these vulnerable families

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