CANCER GENETICS

Cascade Genetic Testing for Hereditary Cancer Risk: An Underutilized Tool for Cancer Prevention

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INTRODUCTION

Approximately 5%-10% of all cancer is due to hereditary causes. Over the last 2 decades, the ability to detect genes responsible for hereditary cancers has dramatically improved, and now, more than 400 cancer predisposition genes have been described.[1,2] Hereditary cancer syndromes (HCS) are conditions in which a germline pathogenic variant (PV) in a single gene leads to an increased risk of cancer. Most HCS have an autosomal dominant inheritance pattern in which the offspring of a PV carrier has a 50% risk of inheriting the familial gene defect. HCS can also, less commonly, result from recessively inherited genes in which case an affected individual must inherit two copies of a hereditary cancer risk gene. Offspring of parents who both carry a recessively inherited cancer risk gene has a 25% chance of inheriting a PV from each parent to manifest increased cancer risk caused by biallelic PVs.

Genetic testing (GT) of at-risk relatives (ARR) to identify additional carriers of a previously identified familial PV presents an opportunity to leverage GT to target cancer screening and implement potentially lifesaving cancer prevention interventions in high-risk populations. GT is most efficiently performed first in a family member with cancer or a family member in closest proximity to an individual affected with cancer. The first person identified with a heritable genetic risk in a family is referred to as the proband. Once a PV is identified in a proband through germline GT, the potential for cancer risk stratification and cancer prevention may extend, through communication about genetic risk and a process called cascade testing (CT), from this first individual to blood relatives within the family. An additional emerging pathway to identification of hereditary risk PV in a proband is tumor testing, which may identify a PV likely or definitively found in the germline (the latter if a normal DNA sample is sequenced alongside the tumor sample) that may then serve as the nidus of CT in family members.

CT refers to the conduct of genetic counseling and testing in blood relatives of individuals who have been identified to carry a PV in a sequential manner, with testing starting in relatives closest to the proband and moving out to more distant relatives as carriers are distinguished from noncarriers.[3,4] Although CT is the desired outcome of the efficient transmission of risk information within a family, barriers at the provider, patient, and system level delay this process (Fig 1). An example of CT within a family with a familial *BRCA2* PV is shown in Figure 2. Importantly, CT allows for a systematic process that appropriately identifies first-degree relatives (FDRs) who carry a PV and allows the implementation of targeted interventions for cancer surveillance and risk reduction, while also identifying FDRs who do not carry the PV who can forego unnecessary interventions. The children of tested FDRs also immediately benefit from CT results, as only offsprings of FDRs who carry the familial PV will themselves be at risk for inheriting the familial risk and need to pursue their own GT.

CT is a critical element of cancer prevention in families at high hereditary cancer risk, and the value of interventions to increase the uptake of CT in families can be measured in the cancers prevented, cancers discovered at earlier vs later stages, health care costs reduced in preventing versus treating cancer, and the lives saved from reduced cancer mortality. Because of CT research previously focused in families with hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS), the social and economic benefits of CT in these populations are well-described. The successful conduct of CT in families where a PV has been identified has the potential to accelerate the determination of cancer risk in our population on a large scale. Recently, a model-based analysis of a targeted CT approach to the ARR of cancer patients with PVs in cancer predisposition genes estimated that all US carriers with PVs in 18 clinically relevant cancer susceptibility genes could be identified within 9.9 years if there was a 70% CT uptake among first-, second-, and third-degree relatives, compared with 59.5 years with no CT.[5]

Importantly, CT and implementation of appropriate cancer risk reduction strategies in asymptomatic ARR have been shown to increase life expectancy[6] and to support decreased health care costs.[7,8] The cost-effectiveness of CT has been shown to increase as more ARR are tested for a familial risk, primarily because of the costs saved from less expensive single-site

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CONTEXT

Key Objective

Cascade testing (CT) for hereditary cancer is grossly underutilized, and it is critical that clinicians understand the importance of CT for early detection and cancer prevention. This manuscript uniquely provides an in-depth narrative review, rather than a systematic review of previous challenges related to CT, but more importantly, ongoing research efforts are centered around improved uptake of CT.

Knowledge Generated

There is increasing interest among researchers to develop interventions that will improve rates of CT. There remains a need for CT research among racially diverse populations and men.

Relevance

Significant improvements in the uptake of CT are needed to realize the promise of cancer prevention that arises from early identification of a cancer-predisposing pathogenic variant in family members before a cancer diagnosis. Efforts to improve CT uptake should be a high priority given its important benefits.

CT and from improved survival by preventing cancer and early diagnosis.[9] The CDC have designated CT as a tier 1 genomic application for LS and HBOC.[8,10,11]

Despite its importance to at-risk patients and inherent value to the health care system, rates of CT are low and significant barriers prevent its widespread use. Consequently, these barriers serve as direct deterrents to uptake of cancer prevention and screening in high-risk populations.[12] With the growing relevance of germline GT in clinical oncology for treatment planning (POLO,[13] SOLO,[14]PROfound,[15] EMBRACA,[16] and OlympiAD[17]), it is critical to implement effective CT strategies for ARR of patients with cancer identified to have new PVs. The growing emphasis on CT for optimal risk management for ARR is demonstrated through the number of recently completed and ongoing CT studies (Table 1).

This manuscript will review CT uptake and existing barriers to successful utilization. Additionally, it will highlight previously investigated innovative approaches to CT and their impact on CT uptake.

HOW SHOULD CT BE PERFORMED

Once a PV has been identified in the proband, several important issues arise related to how best to approach CT.

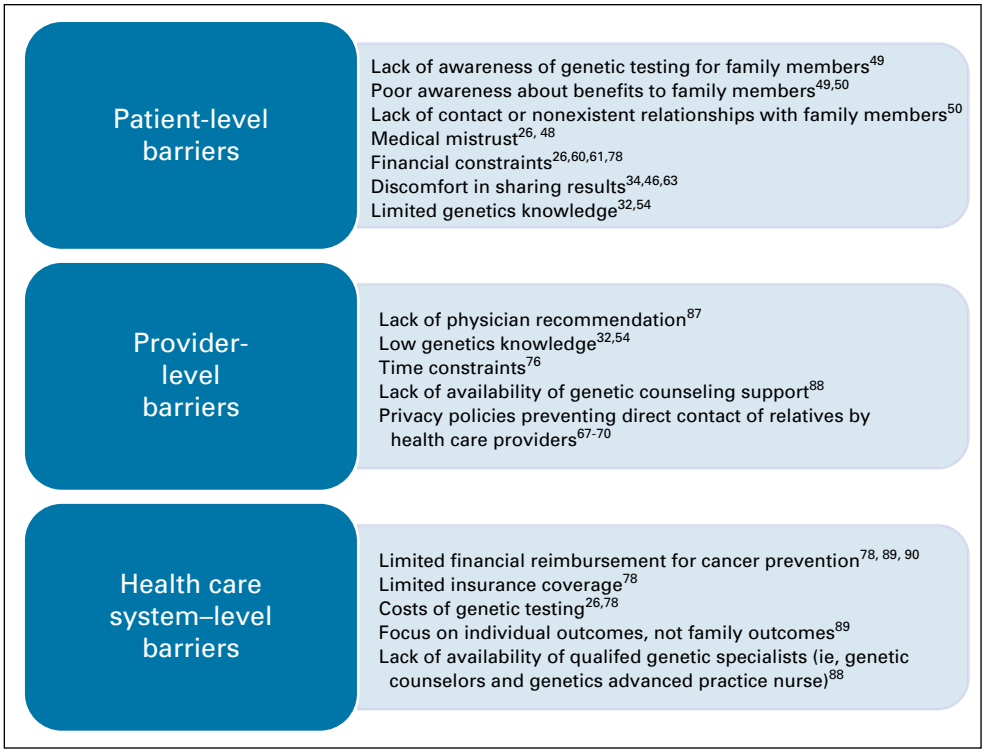

FIG 1. Barriers to cascade testing.

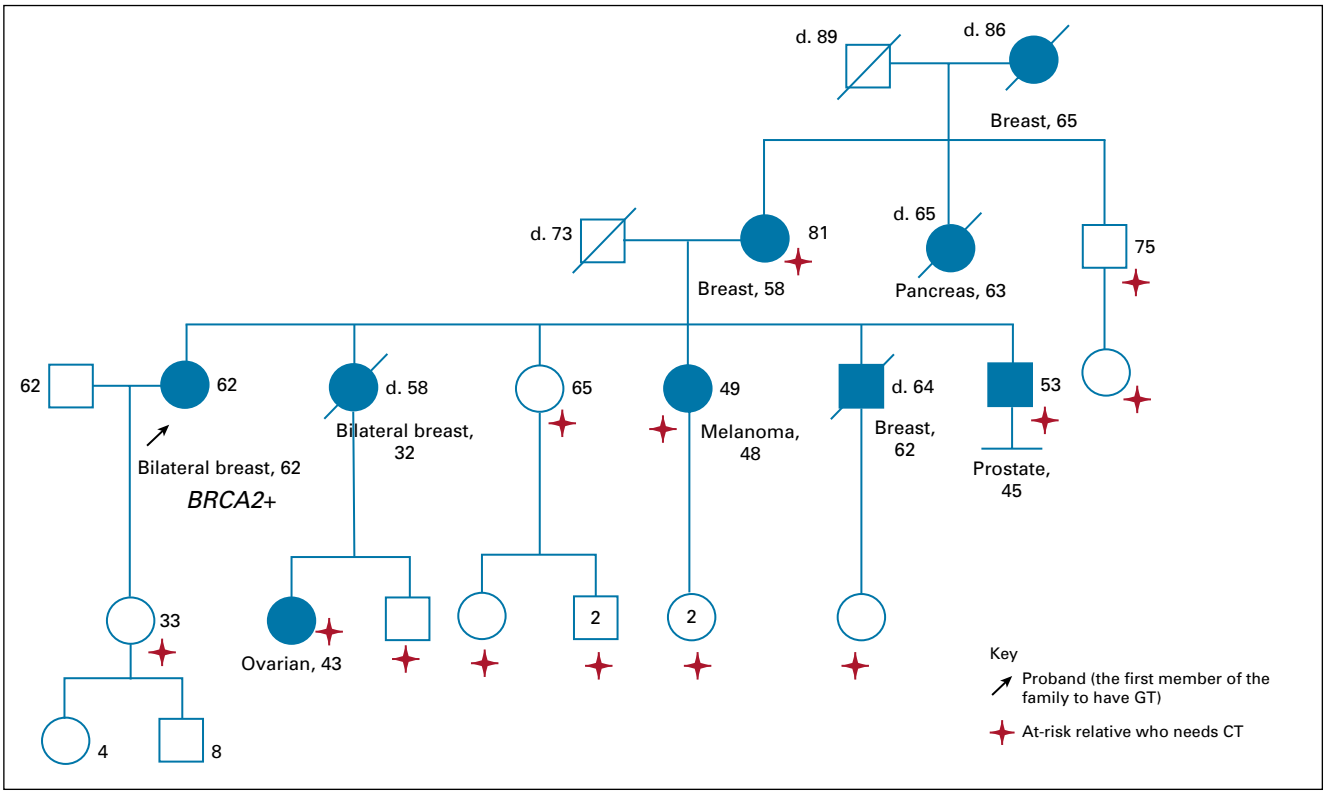

FIG 2. Example of CT within a family with BRCA2 pathogenic variant. CT, cascade testing; GT, genetic testing; PV, pathogenic variant.

Historically, CT has equated to the conduct of single-gene or single-site testing in a proband's relatives, with cost advantage to this approach. However, with the growing use and decreased costs of multigene panel testing in the assessment of high-risk patients, it remains unclear whether single-site or single-gene should continue to be the standard offering to ARR undergoing CT. Although data are limited, one study has demonstrated that up to 9.5% of individuals carry clinically significant PVs in two different genes.[18] Other research has shown that up to 5% of FDRs undergoing CT might have an unexpected PV that the proband did not share.[19] Among the challenges of replacing single-site or single-gene CT with panel testing is the potential to identify low- to moderate-penetrance PVs known to be commonly found in the population (eg, the *MUTYH* Y165C and G398C founders in the White population). On the other hand, it would seem irresponsible to perform single-site or single-gene testing in an Ashkenazi Jewish woman concerned about her risk of cancer because of the identification of an *ATM* PV in her sister when she has a substantial risk of carrying the *ATM* PV (50%), the Ashkenazi *BRCA1/2* founder PV (2%), or the *APC* I1307K founder (approximately 10%). In this case, identification of a PV in either the *BRCA* or *ATM* gene has important implications for cancer screening. Therefore, in patients with significant family history of cancer that may not be fully explained by the familial PV, or from a known high-risk population, it may be appropriate to consider multigene panel testing in ARR. However, it should be noted that this approach may be limited by insurance restrictions, which may only cover single-gene testing for ARR.

Beyond uncertainty about what type of genetic test is best to use for CT, there is also a lack of consensus about what specific genes should prompt CT. Given studies that have examined the utility of CT in Lynch and HBOC families and found testing of unaffected ARR to be cost-effective on the basis of quality-adjusted life-years gained and syndrome-related cancer events avoided,[8,20-23] there is agreement for CT for individuals at risk of these syndromes. However, because of a lack of conclusive evidence on the impact of newly discovered cancer predisposition genes and a lack of evidence-based guidelines for the management of individuals who carry PVs in these genes, the relevance of CT for these genes remains uncertain. The role of CT in moderate- and low-penetrance genes that lack management guidelines remains an essential question, but one that is additionally confounded by overall uncertainty about the interpretation of risk in many moderate-penetrance genes (*MUTYH* and CRC, *CHEK2* I157T). Uncertainty about the optimal clinical management of PVs in moderate- and low-penetrance genes highlights the need for targeted genetic counseling education to guide risk management in these individuals.

UPTAKE OF CT

A growing number of studies have examined the uptake of CT for hereditary cancer and factors associated with

TABLE 1. Ongoing CT Studies for Hereditary Cancer

Study Title	Study Population	Intervention	Location
GIA in CT	Age ≥ 18 years Undergoing GT at UVA for a personal or family history of breast or gynecologic cancer	GIA chatbot tool to facilitate dissemination of genetic results to family members	University of Virginia
CT in families with newly diagnosed HBOC syndrome	Age ≥ 18 years First- or second-degree family member with any of the following mutations: *BRCA*, *BRIP1*, *MSH2*, *MLH1*, *MSH6*, *EPCAM*, *PMS2*, *RAD51C*, and *RAD51D*	Direct contact of relatives of probands by genetic counselors	New York Langone Medical Center
Factors influencing CT among women with hereditary gynecologic cancers and their relatives	Age ≥ 18 years First-degree relative of proband meeting following criteria: Confirmed or suspected PV in a hereditary gynecologic or breast cancer predisposition gene Diagnosis of female breast, ovarian, or endometrial cancer	Semistructured interviews and survey questionnaires conducted in probands and their FDRs about GT	MD Anderson Cancer Center
Implementation of the FACTT of HBOC and LS	Age ≥ 18 years Documented HBOC- or Lynch-associated pathogenic or likely PV Diagnosis of one or more invasive cancers: epithelial ovarian, fallopian tube, primary peritoneal, breast, colorectal, and endometrial	FACTT with tools to support CT given to both the proband and the family member	Washington University School of Medicine
ECHO	Age ≥ 18 years Proband must carry high-risk cancer predisposition gene Relative of proband must be deemed at risk for familial genetic mutation and eligible for GT	Disclosure toolkit for probands to facilitate communication of results	Abramson Cancer Center
The DIALOGUE Study: Swiss-Korean Bilateral Collaboration (DIALOGUE)	Age ≥ 19 years PV in gene associated with HBOC or has ≥ 1 first- or second-degree relative or first cousin with HBOC	Adapted Family Gene Toolkit with five web-based modules to facilitate communication of results Comparison website with targeted HBOC info and ability to share test results	
Cascade GT for hereditary breast or ovarian cancer and LS in Switzerland (CASCADE)	Age ≥ 18 years Carrier of mutation associated with HBOC or LS with at least one living blood relative	Surveys administered to probands and their first- and second-degree relative about screening behaviors and CT uptake	Switzerland (multiple sites)
FaCT trial	Age ≥ 18 years *BRCA1/2* mutation carrier	Facilitated CT (educational video, mailed saliva kit for GT, and telephone counseling for first-degree relatives)	Weill Medical College of Cornell University

Abbreviations: CT, cascade testing; ECHO, Evaluating Cascade Communication Methods; FaCT, facilitated CT; FACTT, families accelerating CT toolkit; FDRs, first-degree relatives; GIA, Genetic Information Assistant; GT, genetic testing; HBOC, hereditary breast and ovarian cancer; LS, Lynch syndrome; PV, pathogenic variant; UVA, ultraviolet A.

increased or decreased CT uptake among at-risk patients and their families (Table 2). These studies have primarily examined CT in non-Hispanic White female cohorts and FDRs of probands with HBOC or LS.[24-26] Rates of CT have been variably reported in the literature, but generally are low with fewer than 30% of eligible FDRs undergoing testing.[27-37] Low completion rates of GT by ARR hold true even when 86% of at-risk FDRs are aware that a PV has been identified in the family.[25] Studies have shown that probands are less likely to share information about HBOC PVs to male relatives compared with female relatives.[38,39] Female ARR are more likely to pursue GT; studies have demonstrated that sisters and mothers of the proband have greater uptake of CT.[11,32,33,40,41] Male ARR have been shown not only to be less likely to pursue CT[34] but also to have less awareness of the familial PV. The rates of CT uptake among male ARR do not appear to vary significantly regardless of whether they are at risk of HBOC or LS. First- and second-degree relatives tend to have higher CT uptake than more distantly related relatives.[29,36,40-42] Other predictors of CT uptake are shown in Table 2.[26,31,34,36] A recent study by Griffin et al[25] did not find personal history of cancer in the proband, neither stage nor cancer site, to be predictive of CT in relatives, whereas Samadder et al,[43] despite a striking 13% positive rate for a hereditary cancer PV among unselected patients with cancer, reported only 17% of eligible relatives pursued CT when offered free panel testing.

TABLE 2. Predictors of Successful Uptake of Cascade Testing in at-Risk Relatives

Proband-level predictors	Family-level predictors
High education level[41]	Female gender[25,40]
Closeness with relatives[68]	Degree of relatedness (first degree relatives > distant relatives)[28,32,36,40,42]
Effective communication skills[62]	Higher level of education[33] parenthood[41]
Higher comfort level with disclosure of results[25]	Relative of a proband with higher educational level[41]
Single relationship status[25]	Previous diagnosis of cancer[41]
Higher socioeconomic status[46]	White race[47]

Substantial research has described barriers to genetic risk assessment in racial minorities; however, our understanding of the communication of genetic risk and its impact on CT in these populations remains limited. Few studies have demonstrated that race affects rates of disclosure of GT results and subsequent CT uptake. Recent studies have demonstrated that African American (AA) and Asian individuals undergoing GT were less likely to disclose the results to family members than non-Hispanic Whites.[44,45] Even when probands disclosed the results, AA and Asian family members were less likely to undergo CT.[44] Additionally, a racially diverse survey study of probands with *BRCA1/2* PVs reported that only 29% of blood relatives completed CT and also suggested that relatives of non-White patients were less likely to undergo CT.[46] Another study demonstrated that AA breast cancer patients with *BRCA* PVs were less likely to disclose their results to their daughters compared with women with negative or variant of uncertain significance result.[47] Although the drivers of the disparate communication of GT results and CT uptake within racial minorities have not been explored, unique attitudes and concerns related to the utilization of GT have been identified, such as medical mistrust and fear of discrimination, and may dictate whether AAs who have undergone GT share their results with family members and whether those family members chose to pursue testing once they are aware of the familial PV.[48-51]

BARRIERS TO CT

A multitude of barriers to successful transmission of familial risk information within families and subsequent CT uptake have been identified in our own research and in that of others.[19,52,53] These barriers can be grouped by whether they originate at the provider, patient, or system level and whether they affect risk communication or more specifically uptake and completion of GT in relatives (Fig 1).

The Health Insurance Portability and Accountability Act privacy legislation has introduced complexities surrounding sharing of GT results to ARR and consequently introduced a provider-level barrier. Although health care providers are generally prohibited from contacting a proband's ARR to inform them of the PV in the family or to recommend them to undergo GT, providers can contact ARR if given permission by the proband.[54,55] However, most commonly, providers encourage the proband to inform ARR of their potential risk. Challenges arise if the proband refuses to notify ARR and is unwilling to allow the provider to directly contact ARR. These scenarios raise the question of whether providers have a legal duty to warn relatives directly that a PV has been identified in the family as this may directly affect their risk. Although the issue of legal duty to warn remains a topic of active discussion in the United States, there is wide consensus that providers do not have a legal duty to warn relatives.[56] Although it is generally agreed that providers do not have a *legal* duty to warn, many providers report a *sense* of duty to warn ARR. Several studies found that medical geneticists and genetic counselors reported an obligation to inform ARR.[57,58] This predominant sentiment of obligation to inform despite not legally being bound to further complicates this issue.

Provider-level barriers also emerge as a result of knowledge limitations, time, or lack of support resources. In the past, community providers were hampered by limited genetics knowledge although genetics knowledge has improved over time. Some providers may also lack practical know-how in supporting risk communication between patients and ARR. Furthermore, genetic counseling support is not always immediately available to community providers who order testing, which can have a negative impact on the quality and content of discussions of results with patients. Additionally, if the health care provider extends counseling to address the risks of the proband's family, this requires additional time, which the provider may not have.

Patients experience barriers in the form of strained or nonexistent relationships with some family members, poor awareness, and understanding of risks to family members, a limited skill set to disclose complex, often negative, and highly charged information, literacy and numeracy inadequacies, and race-specific barriers. Poor knowledge of the process and potential risks and benefits of CT is the most frequently cited reason for nondisclosure of genetic information to family members by probands. Interestingly, even in situations where probands appropriately share genetic information with their ARR, poor understanding about the individual benefits of GT for ARR who are generally unaffected by cancer serves as a barrier to CT uptake.[33,59-61] Additional factors that limit disclosure of genetic information include concerns about genetic discrimination, lack of contact,[62] discomfort with sharing results,[34,36,46,63] adoption, sperm donation, and nonpaternity.

Successful implementation of CT relies on the proband sharing his or her GT results with their ARR. Typically, the proband is asked to disseminate genetic results to ARR with the aid of a family letter that describes the PV, associated cancer risks, and steps for ARR to complete GT. However,

family letters have demonstrated limited efficacy for facilitating communication of results.[64,65] A study of patients with LS found individuals share information including results letter or counseling note with 53% of relatives and educational materials, such as a family letter with 33% of relatives.[66] The infrequent utilization of these materials may hamper accurate flow of risk information in families.

Disclosure of genetic information has been described as a process rather than a simple act and may take place over weeks to months, leading to delays in CT completion. When deciding to disclose genetic information to ARR, probands often go through a period of deliberation where they decide what information to disclose, the effects of the disclosure, and the timing of the disclosure.[67,68] Probands struggle with disclosing results because of their desire to protect family members against potential harms while also providing them with information that may be important for their health.[69,70] Preceding this deliberation period, some individuals will first take time to make sense of their personal risk before deciding who to share this information with their families.[71,72] The complexities of this process result in the proband incompletely sharing genetic information[36,38-40,73]; in some cases, probands express that they do not want to share information with family at all. The inconsistent sharing of results to ARR creates a barrier in the first step necessary to successfully implement CT. Although some studies have reported that up to 90% of relatives are aware of the familial PV in HBOC or LS families,[33,68,69] others have reported that 20%-40% of ARR are unaware of the familial PV.[68,74-77]

Finally, system-level barriers related to access to genetic services have been identified. GT cost and limited insurance coverage are common barriers to testing.[78] Additionally, limited access to genetic counselors, because of either geographic barriers or long wait times, introduces barriers.[79] Insurance may also be an important factor in CT uptake—many lower-budget insurers may capitate to less-experienced laboratories for GT, which could increase barriers to CT. Furthermore, the introduction of a mandate by some insurers that GT is accompanied by counseling by a genetic counselor further intensified the barrier of accessing appropriate GT.[80]

Alternative Care Delivery Models for Improved Uptake of CT for Hereditary Cancer

As previously described, current practices result in suboptimal CT uptake. Consequently, studies have investigated strategies to improve CT uptake. The interventions used in these studies aimed to remove the proband's burden of disclosure of results and to eliminate challenges related to accessing genetic services. Previous research has identified the supportive role of the health care provider as a key factor that aids in family communication about hereditary cancer.[74] In a study by Suthers et al,[75] the number of ARR who underwent GT nearly doubled when ARR were sent a letter by a member of the health care team stating that GT was available rather than relying on the standard proband-dependent approach. Interestingly, this finding differs from studies that have shown that family letters shared with ARR do not consistently improve CT uptake.[64,65] Forrest et al[76] demonstrated that additional telephone counseling support for probands after disclosure of results increased rates of CT from 36% to 61%. By contrast, Hodgson et al[77] reported that telephone counseling support did not increase CT uptake.

Sermijn et al examined an interventional counseling model, which consisted of two phases, among 20 families with *BRCA1/2* PVs seen in a Familial Clinic. During phase I, the proband informed ARR about their positive *BRCA1/2* test results. Six months after the proband received GT results, during phase II, ARR received a letter and a phone call if they had not responded to the letter within 6 months. Twenty-seven percent of relatives completed genetic counseling, and 98% of those underwent GT during phase I. An additional 24% presented for genetic counseling, and 98% ARR completed GT during phase II.[81] Similarly, Frey et al[82] examined a facilitated CT approach in which the genetics team identified and contacted ARR of 30 probands with newly diagnosed cancer-associated PVs and offered them telephone genetic counseling and mailed saliva testing. Fifty-eight percent of ARR completed GT. Taken together, these studies demonstrate that an intervention that involves direct contact of ARR by health care providers improves rates of CT, yet this approach is limited to research settings, countries outside of the United States, or isolated situations when the proband explicitly provides permission for this because of current privacy laws.

In another study, the ARR of 24 probands who were Trinidadian women with breast cancer were invited by letter to attend a family counseling session where the positive test results, gene-associated cancer risks, risks for cancer recurrence, and options for screening and risk reduction were reviewed. ARR were offered free CT.[83] Using this approach, 62% of ARR attended the counseling session and 99% of those ARR who attended the session pursued CT. Other studies have also examined the impact of reducing the cost barrier, while incorporating innovative approaches for the delivery of genetics services. Caswell-Jin et al[19] sent e-mails to FDR identified by probands participating in the family testing program and invited them to undergo GT costing $50 US dollars. During the first year of the study, 2,280 FDRs were invited and 47.5% of invited FDRs underwent testing.[19] Similarly, another study demonstrated that free CT was significantly associated with uptake.[84] These findings demonstrate that direct contact of ARR and the provision of free or low-cost GT for ARR may result in higher rates of CT.

Enhanced Patient Support to Improve CT Uptake

Although direct contact of ARR by health care providers might be an effective future strategy to improve CT uptake, strategies to support communication of GT results to ARR

might be an effective strategy for now. Previous studies have demonstrated that patients have an interest in and desire to have access to support tools to facilitate communication of GT results to family members. A previous study found that patients undergoing *BRCA1/2* testing were highly interested in multiple resources to aid in familial communication.[85] 52% of participants had interests in an educational website, and 50% had interest in an educational booklet. Interestingly, only 38% of participants expressed interest in a personalized letter, which is the most used support tool currently. Another study demonstrated that probands preferred that testing facilities provide a summary of results and implications of results as well as make additional resources available to them to prepare them for challenging discussions with ARR.[86] These findings suggest that support tools focused on education and especially those that use more novel and modern technology, such as online websites, may be the most well-received tool. More tools,[91] a secure website used to share GT results, are in the early stages of exploration, and whether they effectively improve CT rates is unknown. Until such interventions to facilitate improved communication are more widely available, oncology providers should encourage familial diffusion of GT results in their cancer patients with cancer-predisposing PVs by helping their patients understand the genetic information and its significance to their ARR.

In conclusion, CT rates are only about 30% and have essentially remained unchanged for many years. The suboptimal rates of CT clearly demonstrate a critical need for targeted efforts to improve the CT uptake. Now that we have identified the patient-level, provider-level, and health system–level barriers to CT in primarily non-Hispanic White populations, it is important that efforts are focused on designing interventions that address these barriers. It is equally important that we must expand our understanding of barriers to CT and perceived support needs to facilitate this process in diverse patient populations, including racial minorities, men, and patients with cancer predisposition associated with more modest increases in cancer risk (low- and moderate-penetrance genes).

Although CT remains a relatively understudied area despite its large impact on cancer prevention, there are important ongoing research efforts. These efforts are focused on facilitated CT, the process of health care directing contact of ARR[33] and enhancing support tools for effective communication within families (Table 1). Many of these studies include not only participants who carry high-penetrance cancer-causing genes like *BRCA*1/2 or the genes responsible for LS but also carriers of moderate-penetrance genes like *CHEK2* and *ATM* and will provide valuable information about the efficacy of different interventions, as well as differences in the process of CT between individuals who carry moderate-penetrance versus high-penetrance PVs.

Notably missing from ongoing research efforts are studies examining the process of CT in racial minorities. As research related to CT in racial minorities is in its infancy, it will be important for future studies to begin with understanding communication practices and examining barriers and facilitators to CT to inform the development of effective interventions in these populations. Because patterns of family communication are developed within a cultural context, it is very likely that familial communication patterns differ among different racial groups. It is critical that future studies examining CT include diverse populations as only then can interventions to improve CT uptake and familial communication be tailored to ensure that they are effective in all patient populations. Additionally, research studies examining the patterns of dissemination within families are necessary to determine if CT efforts should be focused within FDRs only or also more distantly related relatives.

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