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ORIGINAL ARTICLE – COLORECTAL CANCER

Learning by Example: An International Perspective on Reflex-Testing for Lynch Syndrome

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ABSTRACT

Background. Lynch syndrome (LS), an autosomal dominant cancer syndrome, is the most common cause of hereditary colon cancer. Currently, however, less than 5% of patients with LS have been identified. Reflex-testing programs (in which tumors of patients with colorectal cancer are routinely evaluated for LS) have been proposed for better identification of affected individuals, yet the uptake of these programs within health care systems is limited. This study explored the structure, implementation challenges, and future directions of existing international population-based reflex LS testing programs.

Methods. The study identified existing reflex-testing LS programs through the current literature and through a qualitative sampling approach. Key informants from each program were interviewed. Qualitative data were analyzed using a grounded theory analytic technique approach.

Results. The interviews were completed by 26 informants across seven identified programs. Three key themes were identified: (1) tension between a program imposed on stakeholders (a top-down approach) versus initiation of the program at the stakeholder level (bottom-up approach), (2) identification of pathologists as drivers of program success, and (3) strategies to optimize possible LS patients liaising with genetic counselors. Barriers to successful implementation included lack of stakeholder engagement and concerns regarding cost. Facilitators included strong administration to coordinate patient tracking and flexibility during the implementation process.

Conclusions. Existing reflex-testing LS programs have varying structures, standards, and protocols. Program design can have a direct effect on the uptake of genetic testing. These are important considerations in the large-scale planning of LS reflex-testing programs within health systems.

Lynch syndrome (LS) is the most common cause of hereditary colorectal cancer (CRC), accounting for 3–5% of all cases.[1] Inherited in an autosomal dominant manner, LS is caused by defects in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[2] Individuals with LS have a 70% lifetime risk of colon cancer development, a 40–60% chance of endometrial cancer development, and increased risk of other tumors.[3,4]

Fortunately, both surveillance programs and prophylactic surgery have been shown to improve cancer-related mortality among LS patients and their affected relatives.[5–7] Currently, however, it is estimated that less than 5% of individuals with LS have been identified.[8]

Traditional methods for identifying LS patients, including various family history criteria, miss up to 68% of patients. Therefore, national and international guidelines advocate reflex LS testing for patients with a CRC diagnosis.[9–13] Reflex-testing (also known as universal

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screening) refers to the process whereby the tumors from patients with CRC are systematically evaluated for LS using microsatellite instability (MSI) or immunohistochemistry (IHC) to identify which patients have tumors that are characteristic of LS. The at-risk patients then undergo germline testing to evaluate whether they have any of the LS-associated genetic mutations.

Although reflex-testing programs are endorsed by both national and international organizations, the uptake of population-based or programmatic reflex LS testing within health care systems is limited.[12,14, 15] A small number of studies have examined factors underlying the limited uptake of reflex testing for LS.[16–18] Issues identified include concerns relating to cost, lack of leadership, and consent. Other studies have evaluated the implementation of reflex testing at individual institutions and have found similar barriers.[19–21] However, given the numerous challenges to programmatic implementation, the literature is limited. To enhance generalizability, barriers and facilitators across jurisdictions need to be understood.

This study aimed to explore the program structure, implementation challenges, and future directions of existing reflex LS testing programs in various jurisdictions. To achieve this aim, we performed an environmental scan of existing reflex-testing LS programs and conducted qualitative interviews with key stakeholders from the identified programs.

METHODS

The protocol for this study was approved by the Research Ethics Board at St. Michael's Hospital in Toronto.

Existing Reflex LS Programs

The study identified existing programmatic reflex-testing LS programs through the literature (peer-reviewed and gray literature), as well as through qualitative sampling techniques. The latter included purposeful, convenience–based, and snowball sampling.[22] Our objective was to identify multi-institutional programs (programs that covered an entire population) or programs that covered all persons in a defined system. Any program that met either criterion was included in the study.

Recruitment and Participants

Key stakeholders involved in the development or management of these identified programs were recruited to participate in individual, semi-structured interviews. We chose participants deliberately to represent a range of disciplines including pathology, family medicine, genetic counselors, geneticists, medical oncology, researchers, and program directors. We used a purposeful role-based sampling technique.[22,23] Recruitment continued until data saturation was reached.[24,25]

Data Collection

A trained qualitative interviewer (N.A.B.) conducted all the interviews using a semi-structured interview guide. The guide was pilot-tested among study team members and modified accordingly ("Appendix" section). All interviews were audio-recorded, transcribed, and verified for accuracy. The interviews lasted on average 45 min. We used an iterative and inductive approach for both data collection and analysis, drawing on best practices in grounded theory methodology.[26–28]

Data Analysis

For analysis, we used a technique combining features of qualitative description with those of grounded theory, developing coding and themes based on the language and descriptions used by participants.[29] We used NVivo, a qualitative data management software program, for data organization and to facilitate the analysis. For the analysis, we read transcripts multiple times and labeled key data bytes with descriptive codes.[26–28] Through comparison and analysis of codes, themes were discerned and developed. Key features of each program were extracted and used to create a model of each program's overall structure and to understand how individual patients would flow through the program. We then used these program maps as a framework for further refinement of themes developed from analysis of the interviews. Specifically, the program maps were used as visual aides to facilitate further interpretation of the interview data.

RESULTS

Key Informants and Program Structure

We identified seven programs with existing reflex LS testing located in Manitoba, Canada (MB), New South Wales, Australia (NSW), Western Australia (WA), Southern California (SC), Ohio (OH), Utah (UT), and Pennsylvania (PA). Qualitative interviews were conducted with 26 participants associated with these programs and/or with known expertise in population-based LS program development or screening. The characteristics of the study participants are presented in Table 1. The characteristics of the identified programs are summarized in Table 2.

TABLE 1 Characteristics of the study participants

Type of representation	Region																								
	Existing population-based Lynch syndrome screening programs										Other expertise														
	Canada	Australia		United States							Canada	Australia			New Zealand	United States								United Kingdom	
	Manitoba	Western Australia	New South Wales	Pennsylvania	Southern California	Utah	Ohio				British Columbia	Melbourne	Victoria		New Zealand	Georgia	Tennessee	Florida	Washington DC					Oxford	
Family practitioner												1		1										1	
Genetic counselor	1	1			1		1	2							1	1	1								
Medical geneticist					1																				
Medical oncologist											1														
Pathologist	2					1																			
Program director	1			1		1					1														
Researcher		1	1	1														1	1						

Patient Flow Through the Reflex-Testing Pathway

Key features of each identified program were used to create maps of how each reflex-testing program functioned (Fig. 1). In six of seven programs, IHC for MMR proteins is the first-line somatic reflex test (Table 2). In most programs, the time from submission of the tumor for IHC testing to the generation of the final report ranges from 1 to 2 weeks. The exception is the WA program, which can have a 2- to 3-month delay from tumor sampling to a physician receiving the results.

The recipient of the somatic test results varies between programs. In several programs (OH, UT, SC, MB), genetic counselors directly receive the results of somatic testing. This occurs in different ways. For example, in OH, the results are provided to the surgeon and any other treating clinicians via an addendum to the pathology report. In addition, the genetic counselor receives an e-mail from pathology regarding any abnormal IHC tests, and all IHC results also are tracked in a pathology database. In other programs (NSW, WA), however, the surgeon is the recipient of the somatic test results and is charged with informing the patient.

Follow-up germline testing is organized using various strategies. In two programs (WA, NSW), the surgeon refers the patient for genetic counseling. In others (UT, OH), genetic counselors are present at the first postoperative appointment and reach out to patients directly to make an appointment (SC) or liaise with the surgeon directly to ensure that patients meet with them (MB). In all programs, the genetic counselor is responsible for informing the patient of his or her germline test results. Similarly, in all programs, the patient is charged with informing his or her relatives.

The differences in the structure of the identified programs may contribute to the wide range in the percentage of patients who are seen by genetic counselors and have the opportunity to receive germline testing. Indeed, our key informants relayed that in WA, where surgeons refer patients for genetic counseling, only approximately 50% of possible LS patients meet with a genetic counselor and consent to testing. In OH, however, where genetic counselors attend the postoperative surgical visit, approximately 85% of possible LS patients meet with a genetic counselor, and of those, nearly 100% get referred for germline testing.

Program Design, Implementation, and Sustainability

Three themes were identified that related to program design, implementation, and sustainability: (1) tension between a program developed by external mandate (top-down approach) versus a program developed from input by local stakeholders (bottom-up approach), (2) pathologists

TABLE 2 Characteristics of existing population-based Lynch syndrome screening programs

Program	Administration and funding	Screening age limit	Screening tests	Referral to GC	Referral of relatives for counseling and testing	Quality assurance
Manitoba	Population-based; government funded	< 70 years	IHC → BRAF; supplemental MSI	Surgeon refers patient; prompted by GC	By patient; GC provides a customized letter for relatives	Pathologist maintains a list of cases screened for LS
Western Australia	Population-based; government funded	< 60 years	IHC; supplemental MSI + BRAF	Surgeon or PCP refers patient; prompted by GC	By patient	GSWA tracks abnormal test results and maintains a voluntary LS carrier registry
New South Wales	Population-based; government funded	–	IHC → BRAF	Surgeon refers patient; support from Lynch Team	By patient	Patient registry is inactive
Pennsylvania	Operated by Geisinger	–	IHC → BRAF	Treating physician refers patient; prompted by GC	By patient; GC may provide a letter for relatives	GCs track abnormal test results
Southern California	Operated by Kaiser Permanente HMO	–	IHC → BRAF → MLH1 methylation	GC contacts patient directly and solicits support from PCP	By patient, given customized letter with referrals to GCs in relatives' geographic location	GC manager checks with pathology labs and genetic counselors to prevent missed cases
Utah	Hospital-based; funded by institution	–	IHC → BRAF → MLH1 methylation	GC contacts a patient directly or in conjunction with treating physician	By patient, GC provides electronic/hard-copy resources for relatives	GC tracks abnormal test results and maintains a voluntary LS carrier registry
Ohio	Hospital-based; funded by institution	–	IHC → MLH1 methylation	GC or trained genetics nurse contacts patient directly	By patient, GC provides referrals to GCs in relatives' geographic location in the patient letter and provides family member letter upon request	GC checks pathology database for new cases and maintains a LS carrier registry

GC, genetic counselor; IHC, immunohistochemistry; PCP, primary care practitioner; MSI, microsatellite instability; LS, Lynch syndrome; HMO, health maintenance organization

as essential contributors to the overall success of the program, and (3) important strategies to ensure that possible LS patients are liaised with genetic counselors.

Top-Down Versus Bottom-Up Approach

> "You may experience resistance from certain specialties (e.g., surgery) unless you directly communicate with them."— Program Director

Many participants spoke concerning the time efficiency of having a reflex-testing program come officially from the "top down," mandated either at a policy or an executive level. Interviewees described the top-down approach as facilitating the implementation process and creating an overall standard of care. However, participants acknowledged a tension as top-down implementation strategies often were seen as too authoritarian and therefore were commonly met with resistance. Other participants described a "bottom-up" approach, in which key stakeholders are involved from the start, as an important component of effective program design and sustainability. Ultimately, most participants stated that a balance needed to be achieved between the two approaches, and that determining the culture in which the reflex-testing program will be implemented is essential in deciding which approach might be the most successful.

Program Drivers

> "One approach is presenting to all of the chiefs. Once you present you may receive more understanding and support and even eagerness: they were very interested, and there were times that we would get calls from pathology chiefs at various centers saying: 'why haven't you started at our centers yet?'"—Genetic Counselor

Pathologists were identified by most participants as the key group driving the program. Participants also described possible resistance from pathologists because reflex-testing introduces a new step in a busy workload. This again speaks concerning the importance of stakeholder involvement and engagement, with the pathologists as one of the key stakeholders in this program. Genetic counselors also were seen as having a key role in program success, especially as critical advocates for the reflex-testing program.

Key Strategies for Following Patients

> "There's no point in identifying patients if you're not going to follow them properly"—Genetic Counselor

In a hypothetical, ideal program, participants described having electronic records or databases that flag every case in which further testing or genetic counseling is required. This was conceptualized as a built-in quality-assurance step. Some participants described dedicating specific time for the patient to meet the genetic counselor at the postoperative clinical appointment to be educated about the importance of genetic counseling.

Participants also mentioned the tension created by wanting family practice physicians to be more involved, but acknowledged that family doctors have many competing demands. Proposed strategies included educational resources for primary care physicians and ensuring standardization of pathology reporting to minimize confusion.

Barriers and Facilitators

> "Don't get bogged down by all the potential problems…; you need the best basic plan that you think is going to work up front, but you should be open to changing that over time as you learn what works and what doesn't work for you"—Program Director

Participants identified several barriers and facilitators to the overall success of reflex-testing programs (Fig. 2). The barriers included resistance or lack of interest from stakeholders, particularly from the pathologists if there is a perception that the program is adding to their workload. Another cited barrier involved concerns regarding funding, particularly given that this is a program focusing on cancer prevention, not cancer treatment. Still another barrier mentioned was a lack of clear guidelines for genetic counselors to facilitate their workflow. For example, participants mentioned that there are different issues with hereditary versus sporadic results and that guidelines should be implemented in these situations to give pathologists clarity regarding the management of these patients.

Facilitators included stakeholder engagement, particularly with pathologists due to the aforementioned increase in workload. In addition, a strong administration with a dedicated individual to coordinate patient tracking was mentioned as critical to program success. Finally, flexibility during the implementation process to tailor the program to the relevant clinical sites was thought to be an important driver of success. Participants mentioned the importance of taking notes during the implementation process to allow for future reflection on what parts of implementation went well and what parts went poorly. This

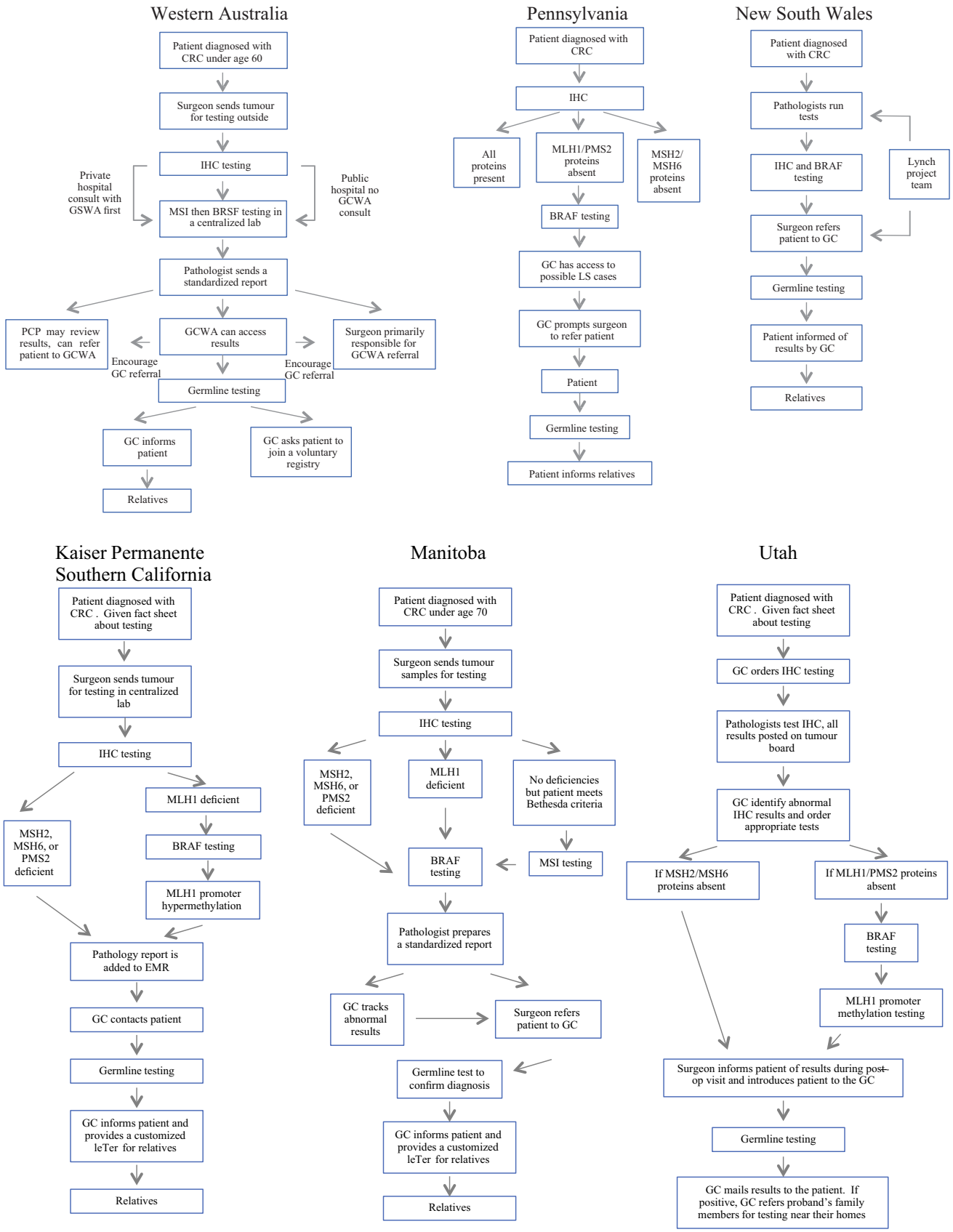

FIG. 1 A review of existing Lynch syndrome screening programs

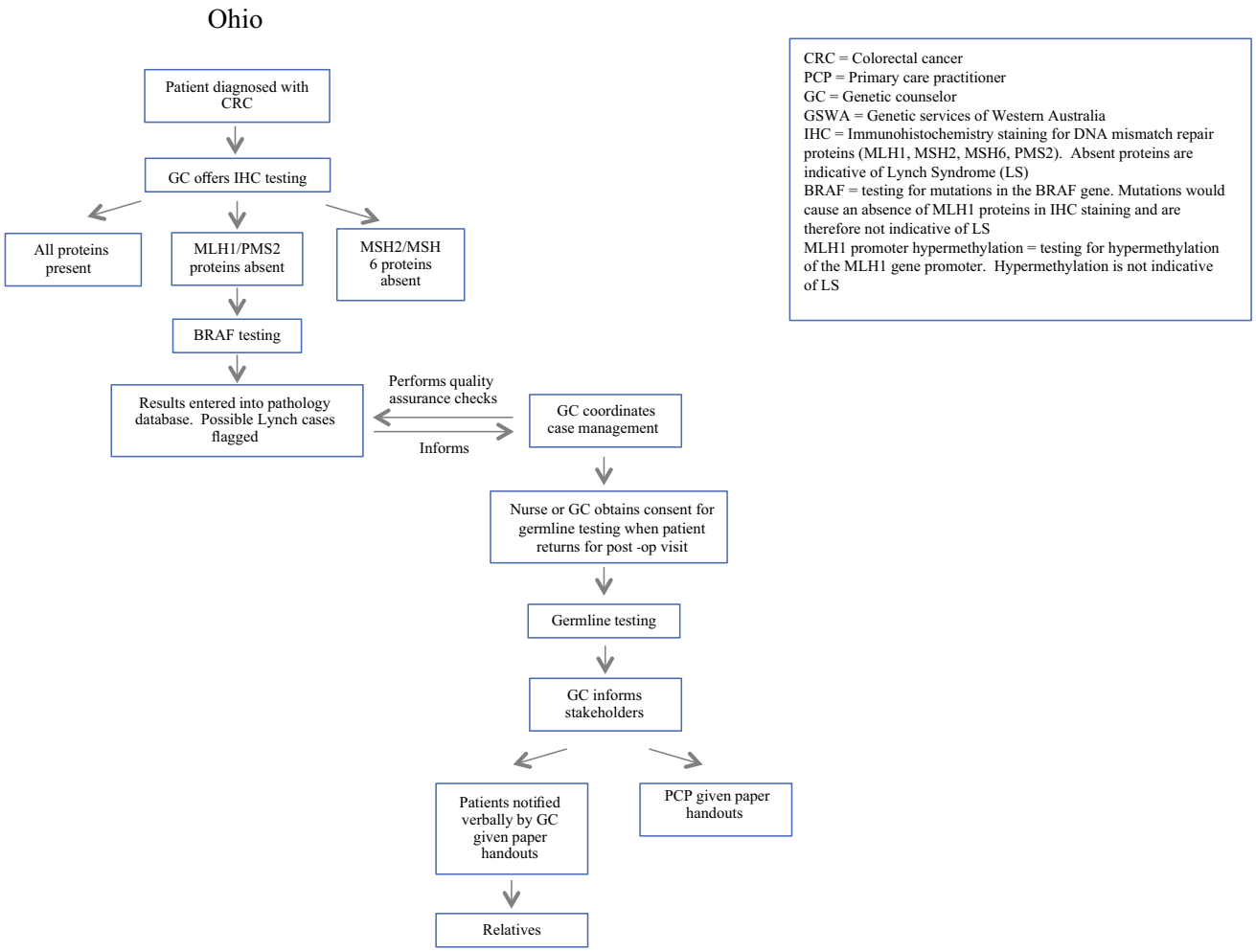

FIG. 1 continued

is especially relevant if there are multiple sites and a rolling implementation approach is used.

DISCUSSION

This study, which combined an environmental scan with stakeholder interviews, identified reflex LS testing programs in Canada, the United States, and Australia. These screening programs were diverse in terms of organizational framework, testing protocol, patient and family reach, and quality assurance practices. Our findings illustrate that program design can influence the ultimate effectiveness of the overall reflex-testing program at several critical points.

Our study found a tension between top-down and bottom-up approaches to program implementation. Specifically, participants felt that programs should be mandated by an overall standard-of-care philosophy, but that key stakeholders and local players should be involved in overall design and implementation. The importance of stakeholder buy-in as well as involvement in early program planning and decision making has been echoed in other studies.[17,19] The idea of the external environment as a barrier to success has been preliminarily explored by Schneider et al.,[19] who highlight that a lack of clarity regarding reflex-testing guidelines can act as an impediment to successful program implementation. Ultimately, this study demonstrates that some degree of top-down oversight, ideally supported by a national policy, is necessary for successful program implementation. Combined with this, specific stakeholder engagement strategies composed of educational interventions and engagement of local champions are necessary to ensure local engagement with the process.

Although our study and others highlight the importance of stakeholder involvement, our finding that the process and flow from pathology to genetic counselor is critical to program success has been largely undescribed.

Interviewees mentioned the value of a dedicated coordinator as well as a system to ensure that patients at risk for LS are automatically sent to the genetic counselor. The

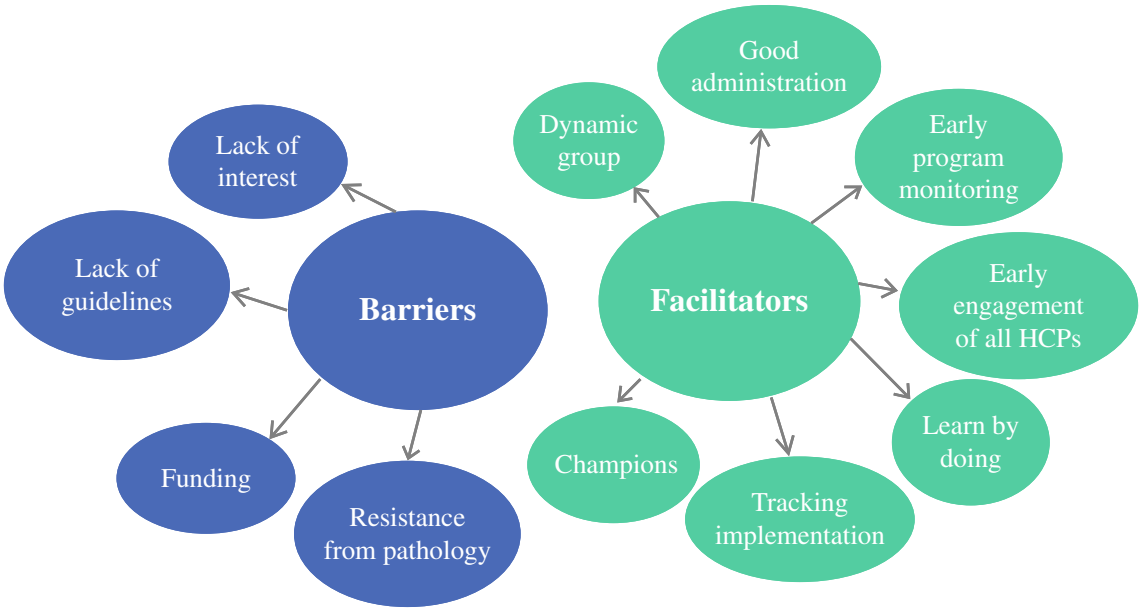

FIG. 2 Barriers and facilitators for effective program implementation. HCP, health care provider

importance of genetic counselor involvement is highlighted by our results, as well as by other work showing that programs dependent on surgeons referring the proband to genetic counseling have limited success, with less than 50% of patients receiving germline testing.[30] This contrasts with programs in which the genetic counselor meets every patient with abnormal screening results the patient's routine postoperative visit. Although these clearly are two extremes, they emphasize the importance of ensuring initial contact between a genetic counselor and a patient, and show that relying on surgeon referral is unlikely to result in program success.[31–33] This is supported by work that assessed the characteristics common to institutions that have a high percentage of patients that pursue germline testing after a screen-positive result.[21] These institutions do not rely on a physician referral to genetics counseling, but rather have a process in place to ensure that genetics automatically liaised with patients either at their postoperative appointment or via other nontraditional means.[21] These findings demonstrate that emphasis on some degree of program automatization or centralized oversight, eliminating the burden of referral on surgeons, may be critical to long-term success in the development of a large-scale reflex-testing program.

This study provided novel insights regarding not only factors facilitating success of a population-based reflex-testing program for LS, but also barriers to its implementation. Barriers highlighted by our key informants included difficulties with funding and a lack of local interest. Various studies have demonstrated that reflex-testing for LS is cost effective.[34–36] A recent study using decision-analysis modeling demonstrated that reflex-testing pathways for LS is cost effective compared with no testing and that the most cost-effective strategy is MMR testing, followed by BRAF testing, then germline mutational testing.[34] Specific stakeholder educational strategies related to the cost effectiveness of such programs could potentially help to mitigate these concerns.

The limitations of this study included the fact that although we deliberately interviewed a range of stakeholders with differing roles, we did not include the perspective of patients who had participated in these reflex-screening programs. Moreover, details and sub-themes specific to each program might not be completely generalizable to other programs. This study was unique, however, in that it drew on information from key informants representing a range of international programs, in different health systems, and at various stages of evolution. Another strength was the rigorous qualitative methodology we used, including qualitative descriptive techniques and a grounded theory approach.

This study provides a novel perspective on reflex-testing for LS by integrating the structure of the existing global population-based reflex-testing LS programs with insights from key informants in the programs themselves. Results from this study highlight important considerations when a reflex-testing LS program is developed and implemented. These include an overall policy and implementation plan balanced with local stakeholder engagement, a clear pathway for IHC-positive patients to access genetic counselors without relying on referrals from surgeons, and built-in quality assurance metrics to measure program outcomes and success.

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DISCLOSURE There are no conflicts of interest.

APPENDIX: INTERVIEW FRAMEWORK

Note: No key informant will be able to answer all of these questions. The questions posed will be based largely on the role of the individual. Technical questions may be answered by one individual per program (e.g., pathologist) and not everyone. The notes in the first column are related to the type of audience to which the questions are directed.

Interviewer: Thank you for taking the time to participate in this interview. The interview will last approximately 30–45 min. I will be asking you a series of questions about your Lynch syndrome screening program, its implementation, and how the program came to be in its current state. Your consent to participate in this study is implied by your answering of the questions that will follow. You may take a break at any time or feel free and decline to answer any question at any time.

I will begin the interview shortly, and responses will be recorded, but will remain confidential. At no time during the interview will I refer to you by name, but should it be stated, it will be deleted from the audio-recording. I ask that you please refrain from using your last name if possible. Some of your responses may be used as quotes when the study is complete. However, these quotes will not be linked to your name or any features that identify you.

Do you have any questions before we begin?

1. General questions (all)	1. Would you please describe the organization that you work for and your role?
	2. Does your organization currently have a reflex-testing program?
	If NO, see interview guide for programs without a successful program
	If YES, continue to program implementation section
2. Program implementation	1. Would you please describe the implementation of your reflex-testing program?
(best answered by program leads, managers, familial cancer registrars)	*Prompt:* Do you mind sharing why your reflex-testing program was implemented/what were the driving factors?
	Prompt: Would you mind sharing who the key people were in the startup?
	Prompt: When was your program implemented?
	2. Would you mind discussing your role in implementing the program?
	Prompt: Is this different from your current function now? Would you please describe the roles of the other key people involved in the implementation of the program?
	Prompt: Initiative leaders, stakeholders?
	3. Would you mind describing how these people worked together to implement the program?
	4. Would you please describe the barriers or major challenges faced during the implementation phase?
	Prompt: What was the most difficult barrier to overcome, and why was this?
	6. Would you please describe what steps were taken to overcome these barriers? Would you please describe things that made implementation easier?
	Prompt: How did these help implement the program?
3. Improvements	1. Taking into consideration what you know now, what would you do differently to improve implementation? What would you do the same?
(best answered by program leads, managers, familial cancer registrars)	2. In your opinion, what were the key lessons learned from the implementation of the program?
	3. Do you have any other recommendations or suggestions for successful implementation of a population-based LS reflex-testing program?
	4. Would you mind sharing how your program has changed since it was implemented?
	Prompt: What aspects of the program do you think have improved or gotten better?

	Prompt: What aspects of the program do you think have gotten worse?
	5. Would you please share the one single best thing about the program since the implementation?
	6. Would you mind sharing the one single thing that could be MOST improved upon since the program has been implemented?
	Prompt: What that would that look like?
4. Monitoring	1. Would you mind discussing how the program is monitored?
(best answered by program leads or program monitors, if applicable)	*Prompt:* If not monitored, then there are no further questions.
	Prompt: If monitored, who is responsible for monitoring?
	Prompt: What are the key deliverables or the aspects of the program being monitored?
	Prompt: Would you please describe how changes are implemented based on monitoring?
5. Financial	1. In your opinion, what are the financial considerations for a LS reflex-testing program?
(best answered by program leads, pathologists, or genetic counselors)	2. Would you mind describing how the costs of your program are covered?
	3. Are you aware of any different sources of funding for the reflex-testing?
	Prompt: What about sources of funding for genetic counseling?
6. Reflex-testing services	1. Would you please describe the sequence of reflex-testing?
(best answered by pathologists, genetic counselors, or managers)	*Prompt:* IHC, MMR, BRAF, methylation-testing
	2. How are specimens sent for reflex-testing?
	Prompt: To a hospital, central laboratory, etc.? If there is a central laboratory, how are the specimens sent to this facility?
	3. What is the time frame for completing reflex-testing services?
	4. Would you mind discussing how quality of testing is ensured?
	5. How are results reported to clinicians?
	Prompt: Which clinicians are informed of test results?
	6. Are there steps to ensure quality?
	Prompt: What if there were inconclusive results? Or a prolonged time frame for results?
7. Patient population	1. Would you mind sharing who receives reflex-testing as part of the program?
(best answered by managers and/or genetic counselors)	2. Would you please describe whether your program has a systematic procedure in place for identifying patients for reflex-testing?
	Prompt: If yes, please describe it
	3. Would you mind sharing how patients are informed about this program?
	4. Would you please walk me through an example of how patients are informed about the results of their tests?
	Prompt: Who usually informs the patient?
	Prompt: Are there any services immediately available for the patients once they are informed?
	Prompt: In your experience, how have patients generally responded to being informed in this manner?
	Prompt: Would you mind sharing whether there are any changes you might make to how patients are informed?
	5. Would you mind sharing how patients are referred for genetic counseling and/or testing?
	Prompt: When in their testing, are they referred?
	Prompt: Does your program have a preference of who patients are referred to?
	Prompt: While patient's are awaiting their referral, are any services offered available to patients?
	6. Would you mind sharing how relatives are referred for genetic-testing?
	Prompt: Would you mind sharing how relatives are notified by your program?
	Prompt: Would you mind providing an example of what the process looks like when relatives are referred?
	Prompt: Would you mind sharing how this information has been typically received by patients relatives?

	Prompt: Does your program have a preference of who relatives are referred to?
8. Program outcomes	1. Would you mind sharing how patients have responded to the reflex-testing program?
(best answered by managers and/or genetic counselors)	*Prompt:* Family members? Medical community? General public?
	2. Would you please describe what the benefits of this reflex-testing program have been?
	Prompt: With respect to patients, families, medical community?
	3. In your opinion, have there been any negative consequences associated with the introduction of the program?
	Prompt: Would you mind describing these consequences?
	Prompt: Would you mind sharing what approaches may have or might be taken to address these?
	4. Are there implications of this program on the availability and demand for molecular-testing and genetic counseling in the region?
9. Other programs (all)	We are very interested in trying to understand both what works well and what has not worked well with Lynch screening programs. Would you be able to share the names of other Lynch screening programs that have been successful or not successful at implementing reflex-testing?
	Prompt: Both current and previous program names would be helpful (if yes, ask for names and contact information)
	Do you have suggestions for other people we should speak to about your program?

Is there anything else you would like to share about your reflex-screening program that you feel we have not touched upon today?

Thank you very much for taking the time to speak with me today.

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