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Multigene expression profile testing in breast cancer: is there a role for family physicians?

M.A. O'Brien PhD,* J.C. Carroll MD,* D.P. Manca MD,† B. Miedema PhD,‡ P.A. Groome PhD,* T. Makuwaza MA,* J. Easley MA,‡ N. Sopcak PhD,† L. Jiang MSc,* K. Decker PhD,§ M.L. McBride MSc,‖ R. Moineddin PhD,* J.A. Permaul MA,* R. Heisey MD,* E.A. Eisenhauer MD,* M.K. Krzyzanowska MD,* S. Pruthi MD,# C. Sawka MD,* N. Schneider MA,** J. Sussman MD,* R. Urquhart PhD,†† C. Versaevel,** and E. Grunfeld MD DPhil* for the Canadian Team to Improve Community-Based Cancer Care Along the Continuum

ABSTRACT

Background Family physicians (FPs) play a role in aspects of personalized medicine in cancer, including assessment of increased risk because of family history. Little is known about the potential role of FPs in supporting cancer patients who undergo tumour gene expression profile (GEP) testing.

Methods We conducted a mixed-methods study with qualitative and quantitative components. Qualitative data from focus groups and interviews with FPs and cancer specialists about the role of FPs in breast cancer GEP testing were obtained during studies conducted within the pan-Canadian CanIMPACT research program. We determined the number of visits by breast cancer patients to a FP between the first medical oncology visit and the start of chemotherapy, a period when patients might be considering results of GEP testing.

Results The FPs and cancer specialists felt that ordering GEP tests and explaining the results was the role of the oncologist. A new FP role was identified relating to the FP–patient relationship: supporting patients in making adjuvant therapy decisions informed by GEP tests by considering the patient's comorbid conditions, social situation, and preferences. Lack of FP knowledge and resources, and challenges in FP–oncologist communication were seen as significant barriers to that role. Between 28% and 38% of patients visited a FP between the first oncology visit and the start of chemotherapy.

Conclusions Our findings suggest an emerging role for FPs in supporting patients who are making adjuvant treatment decisions after receiving the results of GEP testing. For success in this new role, education and point-of-care tools, together with more effective communication strategies between FPs and oncologists, are needed.

Key Words Personalized medicine, gene expression profile testing, breast cancer

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BACKGROUND

Advances in genomic medicine offer the potential to transform approaches to cancer risk assessment, screening, and therapy, adding new tools to existing personalized medicine approaches. Personalized medicine (or "precision medicine") refers to "diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements"[1]. Molecular prognostic evaluation of tumour tissue might be able to identify patients with low-risk disease from those with high-risk forms and to aid in decision-making about adjuvant therapy[2].

In early-stage breast cancer, molecular prognostic indicator tests—that is, gene expression profile (GEP) tests (such as the 21-gene expression array[3])—have been introduced to provide additional predictive and prognostic information beyond that provided by histopathologic variables, so that chemotherapy might be avoided without increasing the risk of recurrent disease[4]. In several Canadian provinces, a 21-gene expression array is funded for a subset of breast cancer patients. Although the clinical utility of the test has been questioned by some[5,6], medical oncologists are using test results to guide decision-making about the need for adjuvant chemotherapy[7–9]. Patients

Correspondence to: Mary Ann O'Brien, Department of Family and Community Medicine, University of Toronto, 500 University Avenue, Fifth Floor, Toronto, Ontario M5G 1V7. E-mail: maryann.obrien@utoronto.ca ■ **DOI:** https://doi.org/10.3747/co.24.3457

often perceive information from this type of testing as valuable[10], although some evidence of poor comprehension has been published[11]. Little is known about whether there is a role for family physicians (FPs) in supporting patients who have received information from GEP testing and whether patients would like their FP to have any role in this part of the cancer journey.

The purpose of the present work is to describe the role that FPs might play in supporting patients with early-stage breast cancer who have received the results of GEP testing and are considering adjuvant chemotherapy treatment options. We report the results of a mixed-methods study that describes the views of FPs and cancer specialists about this potential new role, describes challenges for FPs in assuming such a role, and examines the frequency of visits by patients to their FP after the first medical oncology consultation, when FPs could potentially discuss GEP test results. We used the 21-gene recurrence score as an example of GEP testing[3].

METHODS

We conducted a convergent parallel mixed-methods study[12] using datasets from the CanIMPACT (Canadian Team to Improve Community-Based Cancer Care Along the Continuum) research program (Canadian Institutes of Health Research grant no. 128272; Grunfeld E, principal investigator). The goals of this interdisciplinary and multi-jurisdictional Canadian program of research and knowledge translation are described in an accompanying paper in this issue of *Current Oncology*[13].

These datasets were used for the present study:

- A – Views and attitudes of 51 primary care providers, including FPs, about personalized medicine as already defined here, participating in five focus groups in Ontario and Alberta[14]
- B – Views and attitudes of 58 health care providers, including 21 FPs and 37 cancer specialists (surgeons, medical and radiation oncologists, general practitioners in oncology) from across Canada who participated in interviews about challenges in the coordination of cancer care between FPs and oncology care providers[15]
- C – Views and attitudes of 12 medical oncologists, practising in academic and community settings in Ontario, about the role of FPs in supporting patients who receive 21-gene recurrence scores (these data were part of an earlier study[16] and informed subsequent data collection for the CanIMPACT personalized medicine study[14])
- D – Population-based administrative health data from three provinces (British Columbia[17–19], Manitoba, and Ontario) reporting the number of FP visits by patients with stages I–III breast cancer during the interval between the first postsurgical medical oncologist visit and the start date of chemotherapy (if chosen). Women receiving neoadjuvant chemotherapy were excluded from the analyses. Data were collected for the periods 2007–2011 (British Columbia, Ontario) and 2007–2012 (Manitoba). To also include patients who saw a medical oncologist and who might have been eligible for adjuvant chemotherapy but who did not receive it, FP visits by those patients were calculated by defining the time interval for data collection as the average of the intervals from the date of the first postsurgical medical oncologist visit to the first chemotherapy visit for all patients who received chemotherapy in each province.

Research ethics approval was obtained from all relevant research ethics boards.

Qualitative Component: Recruitment, Sampling, and Data Collection

Detailed descriptions of procedures for participant recruitment, sampling, and data collection have previously been published[14,15]. Briefly, purposive sampling strategies were used to identify eligible participants, with suggestions from primary care provincial cancer leads and the research team (dataset A) and from online directories of provincial colleges of physicians and surgeons (datasets B and C). Inclusion criteria included, but were not limited to, medical specialty, geographic location, and setting. Invitation letters were sent to FP practices, individual FPs, and cancer specialists. Focus groups (dataset A) and interviews with medical oncologists (dataset C) were conducted in person. For dataset B, interviews were conducted by telephone. All focus group and interview recordings were transcribed verbatim and anonymized.

Quantitative Component: Data Collection

Detailed descriptions of the population-based quantitative component have previously been published[20]. Briefly, a breast cancer cohort derived from the population-based cancer registry was created for each province. Primary care utilization data were collected from each province's administrative claims data. Physician claims within the defined observation window for all patients in each provincial cohort were identified. Claims with location codes for the emergency department, an inpatient admission, or an unknown service were excluded. For each unique patient, all claims for the same physician on the same day were counted as one encounter. Subsequently, physician claims were linked to data about physician main specialty. Visits for physicians with the main specialties of general practitioner, FP, or FP (emergency medicine) were included.

Analysis

Qualitative Component

Initially, focus group and interview data were coded within each dataset using previously described coding procedures[14,15]. Analytic techniques were informed by a constructivist grounded-theory approach, including coding, interpretations of patterns in the data, and the constant comparative method[21–23]. Similar coding procedures, in which team members read the same transcripts and developed a coding guide, were used. The remaining transcripts were subsequently coded line-by-line by a research assistant (JE or TM) using the constant comparative method. Team members periodically met to review and refine codes; any discrepancies were resolved through discussion.

For the analysis, data pertaining to GEP testing stored in the NVivo 10 software (QSR International, Doncaster, Australia) from each qualitative source were exported to Microsoft Word (Microsoft, Redmond, WA, U.S.A.) for further analysis. Two members of the team (JCC, MAO) reviewed the coded data and corresponding interview segments. A third member (TM) checked the coded data for accuracy. Next, higher-order themes were derived by reviewing the coded data pertaining to GEP testing and validated by other team members.

Quantitative Component

Numbers of FP visits were analyzed descriptively using counts and percentages by province. Provincial data were not aggregated; analyses were conducted separately at designated research centres in each province using the SAS software application (version 9.4: SAS Institute, Cary, NC, U.S.A.). A negative binomial regression was used to compare, for the three provinces, rates per time interval (defined in dataset D) of FP visits by all patients, by patients who received adjuvant chemotherapy alone, and by patients who did not receive adjuvant chemotherapy.

Study Rigour

In the qualitative component, multiple team members participated in coding and analytic procedures. Confirming and disconfirming views were sought within and across datasets. Major analytic decisions were documented using memos. Multiple datasets were included, and triangulation was used to identify similarities and differences within and between datasets.

In the quantitative component, members from each participating province had face-to-face meetings and regular teleconferences to develop standardized algorithms and variable definitions. Similarly structured administrative databases and a common analytical plan were used in each province.

RESULTS

Qualitative Component

Detailed demographic data for the FPs and specialists who participated in the focus groups and interviews have previously been reported[14,15]. Each dataset is briefly described in the subsection that follows; Table I summarizes the data.

Datasets

Dataset A: Primary care providers ($n = 51$) were an average of 45 years of age (range: 23–65 years); 76% were women. Approximately 60% were FPs, 21% were registered nurses, and the remaining participants included nurse practitioners, a physician assistant, and residents or medical students. Three focus groups took place in Ontario, and two in Alberta.

Dataset B: Of the health care providers ($n = 58$, FPs and specialists), 52% were women. They represented all provinces and territories, with 28% coming from Western Canada (British Columbia, Alberta, Saskatchewan, Manitoba), 28% from central Canada (Ontario, Quebec), 40% from Eastern Canada (New Brunswick, Prince Edward Island, Nova Scotia, Newfoundland and Labrador), and 10% from the territories (Northwest Territories, Nunavut, Yukon Territory).

Dataset C: The medical oncologists ($n = 12$) had practices in 5 Ontario cities within academic and community cancer centres. Average age in this group was 47 years; 75% were women.

Views of FPs and Specialists

Major themes arising from the qualitative data analysis are presented together with supporting quotations. Views of FPs are presented first, followed by those of specialists.

Views of FPs: *FPs Perceived That Discussions About GEP Testing Are the Responsibility of the Oncologist* The FPs indicated that GEP testing and interpretation is a specialized area that lies within the scope of oncology practice. They perceived that oncologists have the expertise to discuss indications for testing, test results, and treatment implications with patients.

> I feel like that's the role for the oncologist, personally.
> — FP, Ontario

> We have no role in that. No, I don't think any role in that.... I think that's an oncology decision 100%.
> — FP, Ontario

FPs Do Not See Themselves As Having the Knowledge and Skills to Counsel Patients About GEP Testing Closely related to the first theme, FPs did not believe that they had sufficient knowledge about GEP testing. Most FPs in the focus groups and interviews had not heard of GEP testing. However, several FPs commented that they were interested in taking advantage of continuing education opportunities to learn more about the indications for and relevance of testing. They expected that patients would seek their advice about testing and treatment options in future.

> So I think that falls within the domain of the oncologist at this point; I don't feel I have the skills and the history and the background to be able to counsel them with respect to that. So maybe in the future, maybe with some wisdom, but I rely on the oncologist's expertise to guide them down that path.
> — FP, Ontario

> I wouldn't even be able to comment on that [21-gene array], on the utility of that one, like where it is indicated and where it isn't, so if we are going to implement things with confidence, you need to have the education.... I know, as everything else, things are changing. We always make sure we go to our refreshers and updates, and this would be a topic I would definitely want to see on those.... We can just inform our patients about what is appropriate for them and what is not. Because people, they will come in and ask, and we will be the one that they ask.
> — FP, Nova Scotia

TABLE I Summary of demographic characteristics of health care providers (qualitative study component)

Characteristic	Primary care providers (*n*=51)		Health care providers (*n*=58)		Medical oncologists (*n*=12)	
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Provider type						
Family physician	30	59	21	36		
Registered nurse	11	21				
Nurse practitioner	2	4				
Physician assistant	1	2				
Family medicine resident	4	8				
Medical student	1	2				
Surgeon (general, surgical oncologist)			15	26		
Medical oncologist			12	21	12	100
Radiation oncologist			6	10		
General practitioner in oncology			4	7		
Other	2	4				
Sex	(*n*=45)		(*n*=58)		(*n*=12)	
Women	34	76	30	52	9	75
Men	11	24	28	48	3	25
Setting						
Urban	44	86	45	78		
Rural	7	14	13	22		
Academic hospital					3	25
Community hospital					9	75
Geographic location						
Western Canada (AB)	20	39				
Central Canada (ON)	31	61			12	100
Western Canada (BC, AB, SK, MB)			16	28		
Central Canada (ON, QC)			13	22		
Eastern Canada (NB, PEI, NS, NL)			23	40		
Territories (NT, NU, YT)			6	10		

Some FPs See a Potential Role in Discussions with Patients Some FPs described having a trusting relationship with patients such that patients might want to discuss GEP testing results, treatment options, and decision-making with the FP. The FPs were clear that ordering GEP testing and interpreting the results requires oncologist expertise. However, it was not unusual for patients to discuss adjuvant treatment options with their FP as part of an ongoing and trusting relationship. Those circumstances presented a conundrum for FPs, because they did not believe that they were qualified to give advice, but understood that patients wanted their input.

> Although I think it's [the oncologist's role to explain GEP testing results], because our relationship is often quite strong with the patients, I can see the patients at least wanting to come and discuss it. Whether they even want an opinion from us, they may or may not.... But I have a feeling that, even though the oncologist probably will counsel them, they still may end up on our doorstep asking what we think or just wanting to kind of talk through it. And I feel like I'd be happy to do that, kind of help them talk through it and think through it, but probably not give them any particular opinion.... I don't think that I'm qualified to actually give them an opinion on what to do.
> — FP, Ontario

> I mean I obviously haven't heard of it and I haven't heard a patient ask me about it, but I do think that ... they have a medical oncologist and whoever to counsel them but to [another focus group member's] point, they often come back to us because they have a trusting relationship, ... for us to be able to reiterate that important information that they likely got from the medical oncologist—it might be helpful, especially for patients who might be not sure what to pursue.
> — FP, Ontario

Views of Specialists: The views of specialists largely echoed the comments from FPs. They commented that GEP

testing was an evolving area of oncology and one for which the evidence base was still being developed.

GEP Testing Is Complex and Ordering and Interpreting It Is the Role of Oncologists Because They Have the Necessary Expertise Specialists expressed concerns about patients potentially being given incorrect information by FPs.

> I think it's the role of a medical oncologist, and I think it is very specialized.... The oncologists, they are going to go over that, show them their risks, show them the reasons why chemo is very recommended, not recommended, or that they are in this grey zone.... I think you need somebody who is a specialist ... to share that kind of information with a patient to guide them properly. You want to make sure that you are telling them the right information, the correct information.
> — General practitioner in oncology, Ontario

> I think it should be the medical oncologist who [uses GEP testing] 'cause that's who's gonna be using it to make decisions.... But [name of test], that's a very tricky, complicated and expensive test.
> — General surgeon, Newfoundland and Labrador

Several Oncologists Perceived That FPs Might Play an Important Role in Providing Support to Breast Cancer Patients Undergoing Adjuvant Treatment The views of oncologists about specific aspects of the FP role varied and included discussion of the implications of GEP test results with patients within a trusting relationship. Several oncologists welcomed a greater role for FPs in reinforcing the implications of testing with respect to adjuvant chemotherapy and supporting the conversations that oncologists have with women. For example,

> It is usually after the [name of GEP test] results are back, so that they can bring that to their FP. I think it would be most useful ... with people who have a longstanding relationship with their family doctor and have that trust in them.
> — Medical oncologist, Ontario

> There are patients who live alone. Can that patient handle the toxicity of treatment and should they be alone ... right? So family doctors will be able to say, "You are going to be able to cope with this." But I don't think interpreting the [GEP] test results, I don't think it is fair.
> — Medical oncologist, Ontario

Other oncologists described experience of a more limited FP role, one in which FPs simply support decisions already made by patients and oncologists. Those oncologists thought that FPs could play more of a reassuring role rather than a role of decision-making.

> I find that [FPs] will just go and they will support whatever decision the patient is going to make with their oncologist, basically. Patients are looking for reassurance ... so it could be a reassuring role.... I am not sure they have the tools ... the knowledge to be able to have an extensive debate ... or discussion with the patient.
> — Medical oncologist, Ontario

There Is a Need for FP Education and Ongoing Communication Between Medical Oncologists and FPs For FPs to have a role in supporting patients who receive the results of GEP testing, medical oncologists identified a need for ongoing FP education about testing and its implications. Furthermore, they emphasized a need for clear lines of communication between oncologists and FPs. Oncologists suggested that their letters to the FP would be an appropriate source of information, but that FPs should be able to call the oncologist when they had questions.

> I think there is a lot of education and back and forth communication that has to happen between the FPs and the oncologists if we want to actively involve [FPs] in these decision-making processes.
> — Medical oncologist, Ontario

> I always copy family docs in the note; but ideally, if the patient is going to the family doctor, the family doctor should call. And I have a couple [of FPs] that call me and that is the best way so that I can explain if it is not clear. I try and make it clear in my note what factors are swaying me ... but if it is not clear, then I would very much welcome the family doctor call.
> — Medical oncologist, Ontario

Quantitative Component

FP Utilization by Patients with Breast Cancer

The British Columbia, Manitoba, and Ontario cohorts respectively included 10,828, 3465, and 29,633 stages I–III breast cancer patients. For the patients in those cohorts, the median time interval from the first postsurgical medical oncology visit to the start of adjuvant chemotherapy was, respectively, 23, 25, and 22 days; and 28.4%, 30.7%, and 37.6% of all patients had 1 or more visits to a FP during those intervals. Of patients who received chemotherapy alone, 28.2%, 41.7%, and 42.1% had 1 or more visits to an FP during those time intervals. Figure 1 shows, by province, the percentages of all patients with 0, 1, 2, 3, and 4 or more FP visits. Figure 2 shows similar data for patients who received chemotherapy alone.

For all patients, the rates for total FP visits per time interval were statistically different by province: 0.35 in British Columbia, 0.48 in Manitoba, and 0.63 in Ontario ($p < 0.0001$). For patients who received adjuvant chemotherapy alone, the rates for FP visits per time interval were 0.38, 0.70, and 0.81. The rates for British Columbia and Manitoba and for British Columbia and Ontario were statistically different ($p < 0.0001$), as were the rates for Manitoba and Ontario ($p = 0.0086$). For patients who did not receive adjuvant chemotherapy, the rates for FP visits per time interval were 0.33, 0.32, and 0.49. The rates for British Columbia and Manitoba were similar ($p = 0.7102$); the rates for British Columbia and

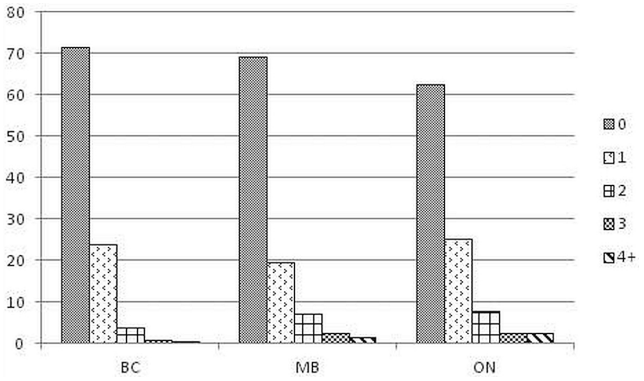

FIGURE 1 Percentage of patients with stages I–III breast cancer by number of family physician visits between the first postsurgical medical oncology visit and the start of adjuvant chemotherapy in British Columbia (BC), 2007–2011; Manitoba (MB), 2007–2012; and Ontario (ON), 2007–2011.

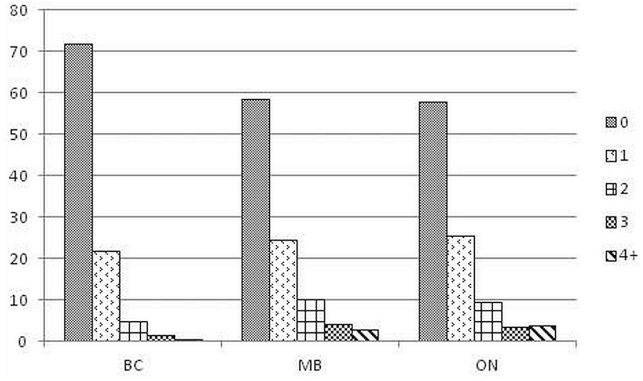

FIGURE 2 Percentage of patients with stages I–III breast cancer receiving adjuvant chemotherapy alone by number of family physician visits between the first postsurgical medical oncology visit and the start of adjuvant chemotherapy in British Columbia (BC), 2007–2011; Manitoba (MB), 2007–2012; and Ontario (ON), 2007–2011.

Ontario, and for Manitoba and Ontario, were statistically different ($p < 0.0001$).

DISCUSSION

The advent of personalized medicine into an already complex cancer system serves as an impetus to examine current and anticipated future roles of FPs so as to identify facilitators of and challenges to personalized medicine in cancer, and to understand its implications for communication and coordination between health care providers. For patients diagnosed with early-stage breast cancer, GEP testing is currently funded in several Canadian provinces. Oncologists and FPs both view the oncologist as having the role of providing information about testing and appropriate treatment options, but a patient might also seek information and desire decision-making support from their FP, who often knows that patient well. In addition to oncologists, FPs can use shared decision-making principles (for example, giving information, discussing patient preferences, and supporting decisions) to help patients navigate their treatment decisions[24–29], recognizing that treatment decision-making in breast cancer is often an iterative process for patients[25] and that the final adjuvant treatment choice will likely rest with the patient and the patient's oncologist.

Data from the present study suggest that, when faced with a patient seeking advice about adjuvant treatment options, FPs will defer to the oncologist's recommendation. Such deferral is understandable considering the views of FPs with respect to their lack of knowledge in personalized medicine in general and in GEP testing specifically. Yet, deferring to specialists could also limit patient access to advice and support from a trusted person who would support shared decision-making principles[30], particularly for patients with inconclusive GEP test results, significant comorbid conditions, or challenging social circumstances that could affect adjuvant treatment choice.

Results from administrative health databases in three provinces demonstrated that for patients with stages I–III breast cancer who received adjuvant chemotherapy, approximately 40% in Manitoba and Ontario and 30% in British Columbia had at least 1 visit to their FP during a period critical for adjuvant therapy decision-making. Although administrative health data cannot provide direct and specific information about the types of discussions that occurred during those visits, those data—together with our qualitative results—suggest that an opportunity might be available for patients to discuss with their FP adjuvant treatment options and possibly GEP test results (for patients who reside in provinces in which such tests are funded). Caution with respect to that interpretation is warranted, given that patients with stages I–III breast cancer were included in provincial cohorts, but that GEP testing is offered only to those with stage I node-negative disease.

Our quantitative analyses demonstrated higher rates of FP visits in Ontario and Manitoba than in British Columbia. The reasons for those interprovincial differences are not known, but the numbers might reflect provincial variation in the type of provider (specialist or primary care) who cares for cancer patients during the treatment phase of their disease.

Our results identified a need for close communication between FPs and oncologists about decision-making for adjuvant treatment. As part of the CANIMPACT program of research, Easley and colleagues[15] described important challenges with respect to communication between FPs and oncology specialists throughout the patient's cancer journey. One such problem described by FPs was the significant delay in receiving oncologist letters. Such communication difficulties will have to be overcome for FPs to have a meaningful role in supporting patients during the treatment phase of their cancer.

Although FPs are already involved in other areas of personalized medicine by assessing cancer risk in healthy patients and by providing advice about genetic testing and preventive strategies, further education is needed[14]. Previous work by a member of our team has found that patients want their FP to be involved in risk stratification[31–33]. Although our results suggest that FPs might have a role in supporting patients who have received the results of GEP

testing, additional training will be crucial, and point-of-care tools both for GEP testing and for shared decision-making will have to be created for FPs who wish to assume that role. Several personalized medicine tools are available for FPs [Genetics Education Canada (http://www.geneticseducation.ca), Genetics/Genomics Competency Center (http://genomicseducation.net/)], but currently, none address GEP testing. An ongoing study is evaluating FP use of personalized medicine tools, including information on GEP testing (Carroll JC. Personal communication). Additional GEP tests are expected to become available for breast cancer[34], and GEP testing is expected for other cancers in the future, and so it is important for family medicine to consider its role in this area and to facilitate related education for future physicians.

Study Limitations

In the qualitative component, all focus group and interview participants were volunteers. We do not know if their views would be similar to those of individuals who did not volunteer. During the time that the focus groups and interviews occurred, funding for a 21-gene array was available in several provinces, including Quebec and Ontario, but not in others such as Manitoba and New Brunswick. The experiences with testing of FPs and specialists working in provinces that did not have funding or in which funding had recently been approved (such as British Columbia) would have been limited, and those participants would have had less to contribute to discussions. Although the analysis of FP visit utilization suggested an opportunity for some patients to discuss GEP testing results and treatment options, we do not know if such discussions took place. Moreover, we do not know whether, compared with each cohort overall, the women who received the 21-gene array results had more, fewer, or the same number of FP visits.

CONCLUSIONS

This mixed-methods study has identified a potential role for FPs in helping patients with early-stage breast cancer understand the implications of GEP test results and treatment decision-making. However, training for FPs and ongoing communication between FPs and oncologists will be crucial. We suggest that oncologists and FPs can play complementary roles in supporting patients who are making adjuvant treatment decisions, and that the proffered support might, in turn, contribute to improved communication and coordination of cancer care.

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Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, views, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI.

The BC Cancer Agency and the B.C. Ministry of Health approved access to and use of their data for this study, facilitated by Population Data BC. All inferences, opinions, and conclusions drawn in this paper are those of the authors and do not reflect the opinions or policies of the B.C. Data Stewards.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Ontario: Department of Family and Community Medicine, University of Toronto, Toronto (Carroll, Grunfeld, Heisey, Makuwaza, Moineddin, O'Brien); Ray D. Wolfe Department of Family Medicine, Sinai Health System, Toronto (Carroll, Makuwaza, Permaul); Division of Cancer Care and Epidemiology, Cancer Research Institute at Queen's University, Kingston (Groome, Jiang); Department of Family and Community Medicine, Women's College Hospital, Toronto (Heisey); Department of Oncology, Kingston General Hospital, Kingston (Eisenhauer); Department of Oncology, Queen's University, Kingston (Eisenhauer); Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto (Krzyzanowska); Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto (Krzyzanowska, Sawka); Cancer Care Ontario, Toronto (Krzyzanowska); Department of Oncology, McMaster University, Hamilton (Sussman); Ontario Institute for Cancer Research, Toronto (Grunfeld); †Alberta: Department of Family Medicine, University of Alberta, Edmonton (Manca, Sopcak); ‡New Brunswick: Department of Family Medicine, Dalhousie University, Fredericton (Miedema, Easley); §Manitoba: CancerCare Manitoba, Winnipeg (Decker); Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg (Decker); ‖British Columbia: BC Cancer Agency, Vancouver (McBride); #United States: General Internal Medicine, Mayo Clinic, Rochester, MN (Pruthi); **Independent (Schneider, Versaevel); ††Nova Scotia: Beatrice Hunter Cancer Research Institute, Halifax (Urquhart); Department of Surgery, Dalhousie University, Halifax (Urquhart).

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