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Gene Expression Profiling Tests for Breast Cancer: A Rapid Qualitative Review

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Abbreviations

ER+	estrogen receptor-positive
GEP	gene expression profiling

Context and Policy Issues

Gene expression profiling (GEP) tests are increasingly used in clinical practice to identify which patients with early-stage estrogen receptor-positive (ER+) lymph node negative breast cancer are likely to have a higher risk of recurrence.[1] These tests provide personalized information based on analysis of the expression of multiple genes in a patient's tumour.[1] Test results are presented with a recurrence score, which is typically a numeric score that is then placed into a risk category. All tests have a low and a high risk category, with some tests (e.g., Oncotype DX and Prosigna) also having an intermediate risk category. Both low and high scores are used to support treatment decision making. Specifically, those patients who are identified as having a low risk of cancer recurrence may benefit little from adjuvant chemotherapy, while those identified as having a high risk are more likely to experience benefit.[1] Test results allow those patients identified as low risk to avoid possible unnecessary treatment and the short and long-term side effects associated with chemotherapy.[1]

Several commercially available GEP tests are available, including Oncotype DX, Prosigna (PAM 50), EndoPredict, and MammaPrint. Oncotype DX is the most commonly used test and is intended for ER+ and lymph node negative tumours.[1] The test is performed by the manufacturer, Genomic Health Inc., in California. All four have demonstrated prognostic ability (ability to determine the risk of distant recurrence), while Oncotype DX has also demonstrated predictive ability (ability to determine benefit of chemotherapy).[1] The tests are typically performed after surgery once hormone and lymph node status are known, in conjunction with gathering other information such as tumour size and grade.

Some oncologists have reported valuing GEP tests as a treatment decision support tool that can enhance their confidence in, and uncertainty around, treatment decision making.[2] At the same time, oncologists have raised concerns about the test's cost, overuse, inappropriate use, and an overreliance on the test results within the medical community.[2] To inform decisions about appropriate use and reimbursement, it is important to have a more fulsome understanding of the role of GEP testing in treatment decision making through the perspectives of patients and their health care providers. The purpose of this report is to identify and describe patients' and clinicians' experiences and perspectives on using GEP to support making treatment decisions.

Research Questions

1. What are patients' and clinicians' expectations of gene expression profiling tests for breast cancer?
2. How do patients and clinicians understand, communicate, and make decisions to undergo gene expression profiling testing for breast cancer?
3. How do patients and clinicians understand, communicate and make decisions based on the results?

4. How does the option, or not, of gene expression profile testing help to shape patients', and clinicians' experiences and perceptions of breast cancer and its treatment?

Key Findings

- Gene expression profiling testing is seen by patients and oncologists as a valuable aid in making decisions about whether or not to undergo chemotherapy. Many patients and oncologists rely heavily on the results (i.e., recurrence risk score) for treatment decision making.
- Patients expect tests to provide valid, personalized, individualized and authoritative results that determine the most appropriate course of treatment. While low and high risk results may meet these expectations, intermediate results defy them. Instead, people identified with intermediate risk face further confusion and anxiety in what is an already emotionally-laden decision.
- Oncologists use gene expression profiling testing for a range of purposes from communicating to patients, to reducing uncertainty and helping them feel more confident in their decisions for clinically indicated disease and beyond. Some oncologists expressed concern around overreliance on the results of gene expression profiling testing in treatment decision making, with inadequate consideration of other relevant clinical and pathological characteristics.
- Patients' preferences for chemotherapy were viewed as critical to determining whether or not to proceed with gene expression profiling testing, as the value of testing is seen as contingent on its ability to be used in treatment decision making. While understanding patients' preferences for and willingness to undergo chemotherapy were identified as critical to guide testing decisions, patients' preferences were not used consistently by oncologists in deciding whether to order testing.
- Some patients did not understand the nature of testing and the possibility of it being fallible. Instead its certainty and validity was assumed through notions of testing being of a personalized and individual nature.
- Because of the need to communicate complex information about the nature and purpose of the test, elicit patients' preferences for treatment, and make decisions based on the results, implementation of gene expression profiling testing would likely require additional time in terms of length and number of consultations with oncologists.
- Ordering the test at the appropriate time in care is important so as to avoid delays in testing and subsequent delays in treatment or by initiating unnecessary treatment.

Methods

Literature Search Methods

The main search concepts were breast cancer, gene expression profiling, and precision medicine. A limited literature search, with main concepts appearing in title, abstract, or major subject heading, was conducted on key resources including Ovid MEDLINE, CINAHL, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. A methodological filter was applied to limit retrieval to qualitative

studies. The search was limited to English language documents published between January 1, 2002 and March 18, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and the full-text of potentially relevant articles were retrieved and assessed for inclusion by the same reviewer. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Inclusion Criteria

Population	• Adults with breast cancer of any age, and with any stage, receptor status, or lymph node status, with any number of lymph nodes involved • Health care providers who order, interpret, and consult patients on the use of gene expression profiling tests for breast cancer
Intervention	Gene expression profiling tests for breast cancer, including four commercially available tests (Oncotype DX, Prosigna (PAM 50), EndoPredict, MammaPrint)
Comparator	None
Outcomes	Issues emerging from the literature including but not limited to the perspectives and experiences of patients and their health care providers regarding: • Expectations of testing, the perceived value of results, trust and confidence in test results. • Experiences and perspectives on decision making to undertake testing. • Experiences and perspectives on communicating and understanding the purpose of testing and of test results, including information needs and pathway of care. • Experiences and perspectives of using test results, including making treatment decisions.
Study Designs	Primary qualitative studies; qualitative evidence syntheses

Exclusion Criteria

Articles were excluded if they did not meet the inclusion criteria outlined in Table 1, they were duplicate publications, or were published prior to 2002.

Critical Appraisal of Individual Studies

One reviewer assessed the quality of the included publications. The ten items from the CASP Qualitative Tool[3] were used as prompts for reflection, and the appraisal was guided by three primary questions intended to assess if and how a study demonstrated that it collected rich data, conducted a rigorous analysis, and incorporated reflexive practices leading to robust results that were useful for the objectives of this review: Is it credible? Is it trustworthy? Are the results transferable?[4,5] Results of the critical appraisal were not used to exclude studies from this review, rather they were used to understand the methodological and conceptual limitations of the included publications in specific relation to this review. Particularly, the critical appraisal contributed to the analysis by identifying the limits of transferability of the results of included publications.

Data Analysis

A framework analysis was used to organize and analyze results of the included studies.[6] The a priori framework consisted of orienting concepts identified through project scoping. These included types of perspectives and experiences relating to the process of undertaking GEP testing (e.g., deciding to order the test, ordering the test, and waiting for

test results) and perspectives and experiences of receiving, interpreting, and using test results in treatment decision making.

One reviewer conducted the analysis. Included primary studies were read and re-read to identify key findings and concepts that mapped on the framework, which was modified as new concepts emerged. During the reading and re-reading of studies, memos were made, noting details and observations about the study's methodology, findings, and interpretations, and connections to other studies and concepts in the framework. Diagraming was used to explore how emerging concepts mapped across study findings and across concepts. Using these techniques, concepts were re-ordered and organized into thematic categories. Re-reading, memoing and diagramming continued until themes were appropriately described and supported by data from the included publications. During the analysis, issues with transferability and the results of the critical appraisal were reflected on to aid with interpretation. The objective of the analysis was to identify and describe categories that reflect how patients and their health care providers experience and understand GEP testing for breast cancer.

Summary of Evidence

Quantity of Research Available

A total of 181 citations were identified in the literature search. Following screening of titles and abstracts, 153 citations were excluded and 28 reports were retrieved for full-text review. Of these potentially relevant articles, 16 were excluded because they were not about GEP and one publication was excluded for not being a qualitative study. Eleven publications met the inclusion criteria and were included in this report. One study contributed to three publications,[2,7,8] and another study contributed to two publications.[9,10] In both studies, the associated publications used the same data but reported on different findings and are hence included. Appendix 1 presents the PRISMA[11] flowchart of the study selection.

Summary of Study Characteristics

Details regarding the characteristics of included publications are available in Appendix 2 and about patient and health care provider participants in Appendix 3 and Appendix 4.

Study Design and Data Collection

Of the eleven publications, authors of eight of the publications did not specify the type of study design used.[2,7-10,12-14] One publication was described as qualitative description,[15] one as Framework Approach,[16] and one as grounded theory.[17]

Seven publications used semi-structured interviews as the method of data collection,[2,9,10,13,15-17] two publications used semi-structured interviews and focus groups,[7,8] and one publication used focus groups.[14] One publication used posts from publically accessible online forms.[12]

Country of Origin

Four publications representing two studies were conducted in Canada,[2,7,8,15] five publications representing four studies in the United States,[9,10,13,14,16] and one study each was conducted in the United Kingdom,[10,12] and France.[17]

Patient and Clinician Characteristics

Four publications included patient participants,[7,12,14,17] five publications included clinician participants,[2,9,10,13,15] and two publications included both patients and clinicians.[8,16]

Patient participants in three of the six of publications that included patients were diagnosed with early-stage breast cancer and had undergone GEP testing.[7,8,17] One publication included patients with breast and colorectal cancer, some of whom had had GEP testing.[14] Another included patient advocates, some of whom had had breast cancer,[16] and one included online posts from a breast cancer forum from patients who had breast cancer and some of whom had GEP testing.[12]

Of the six publications that included patients, one reported the sex of participants.[14] Authors of another publication consistently referred to the participants as "women".[12] The remaining publications (n=4) did not specify the sex of patient participants.[7,8,16,17]

Clinician participants in included publications were primarily medical oncologists[2,8,9,13,15] and surgical oncologists[10,13] who had knowledge of or experience with GEP tests for breast cancer. One publication reported including clinician participants who were described as social workers, psychologists, nurses and physicians who had knowledge of GEP tests.[16]

Interventions

Five publications reported on a specific commercial GEP test – Oncotype DX.[9,10,12,13,16] Five publications focused on patients' and/or clinicians' experiences with commercially available tests otherwise not named,[2,7,8,14,15] and one publication reported on the use of an unnamed GEP test in a clinical trial.[17]

Summary of Critical Appraisal

The included publications ranged in quality from low to high. Taken together, the studies were of moderate-high quality. Details of the critical appraisal, capturing key points on credibility, trustworthiness, and transferability can be found in Appendix 5.

The criterion of credibility assessed whether and how researchers were true to their participants' voices, by demonstrating credibility through clear descriptions of data collection methodology, supporting descriptive analyses with raw data, and reflexively engaging with the processes leading to their findings. Six publications were assessed as credible,[2,7,8,10,12,15] four as partially credible,[9,13,16,17] and one assessed as not credible.[14] The credibility of included publications rested largely how researchers engaged with the data and analysis and created space for emergent findings. Conversely, the primary issue that affected the assessment of credible a study related to the use of data collection and analysis methods that were highly deductive and influenced by a priori assumptions. This raised the concern that the data collected confirmed investigators initial assumptions and expectations and prohibited the emergence of new or contradictory findings.

The criterion of trustworthiness involves the concepts of dependability and confirmability, and assessed whether there was analytical consistency in the findings and whether the authors demonstrated reflexive engagement with assumptions. Six publications were assessed as trustworthy,[2,7-10,12,15] four assessed as partially trustworthy,[9,13,16,17] and one assessed as not trustworthy.[14] Those publications assessed as trustworthy supported their findings with data and analyzed findings across data types and sources. Publications that were assessed as partially trustworthy[9,13,16,17] reported a superficial analysis where data

collection and analysis methods likely confirmed researchers' assumptions. The data for the study that was assessed as not credible was trustworthy, but the analysis was not well developed.[14]

The criterion of transferability assessed whether and how the study was relevant to the current review. The assessment was made by exploring reporting of characteristics of individual study participants, situations and analyses. Eight publications were assessed as transferable,[2,7-10,12,13,15] with three publications assessed as partially transferable.[14,16,17] The primary issue of transferability was the jurisdiction in which the study was conducted, specifically whether the jurisdiction had public reimbursement for GEP tests. One study was conducted in the context of a clinical trial for breast cancer treatment and was assessed as being of limited transferability.[17]

Summary of Findings

Oncologists value GEP tests for reducing uncertainty in treatment decision making but worry about overreliance and inappropriate use

Oncologists consistently expressed that GEP was beneficial because of its ability to identify those patients who would likely experience little benefit from chemotherapy and who could safely avoid it.[2,8,10,13,15,16] For some, they felt testing addressed their concerns about overtreatment or unnecessary treatment by being able to avoid therapy for conditions with limited incremental benefit.[10,15]

> Quite honestly, [they] used to be frustrating discussions for all of us, because we knew that there was a significant portion of the ER+ node negative disease that we were giving chemotherapy where we probably were not benefitting patients at all.(p. 359)[10]

Oncologists described several ways in which they used information on a patient's recurrence risk as identified through GEP in making treatment decisions. One study found medical oncologists used GEP testing when they questioned the accuracy of a patient's pathology report due to practice variation in pathology testing and reporting.[2] Other ways included reducing their uncertainty around the best course of action,[2,9,13,15] increasing their confidence in decision making,[2,15] and supporting patients in decision making.[2] No studies probed what led oncologists to feel uncertain in deciding the best course of care for their patients with breast cancer in the absence of GEP, aside from worries about unnecessary treatment because of the possibility of chemotherapy offering little benefit for ER+ node negative disease.

> The biggest thing is that it's given some additional confidence to the pathology and to trying to identify these women who have relatively low-risk disease who can really avoid treatment…and I think it also gives patients some confidence as well in terms of allaying their anxieties that really they're not going to be forgoing a small potential benefit by avoiding chemotherapy if they're really, truly low risk.(p. 353)[2]

Oncologists reported a range of views on how GEP tests impacted their practice. Some expressed that it augmented decision making but did not radically alter their practice,[2,13] while others saw its impact on practice as profound:[13]

> It has really represented a paradigm shift…in the approach to chemotherapy decisions. It's trained us to pay attention to (cancer biology)…if we could have only one piece of information about the woman's cancer, most people would pick the Oncotype DX over any of those other parameters. So I think it has a massive impact.[13](p. 2112)

This points to a concern around the overreliance on the results of GEP testing in decision making. Raised by oncologists in several studies, several expressed worries about others placing too much weight on test results, and inadequate consideration of other relevant clinical and pathological characteristics.[2,13,15] As one oncologist described it:

> The only misgiving I would have is for people who tend to rely on it too much… I think we forget that it's still a test, it's still not infallible and it really is only one factor in the big decision that we're making.[2] (p. 354)

Of note, oncologists' descriptions of the perceived value of the test focused on the ability to act on recurrence scores in the low or high risk categories. Intermediate test results were consistently described as challenging to encounter, as these were not perceived as reducing uncertainty or increasing their confidence in treatment decision making.[10,13,15,17] In these cases, oncologists placed lower emphasis on test results, and instead clinical parameters and patient values assumed a greater role in decision making.[10]

Oncologists in several studies also raised concerns about the proprietary nature the tests and the marketing surrounding the tests:[2,10,15] "I think part of the appeal of Oncotype is their tremendous marketing campaign… I'm always so uncomfortable with something that's hyped so directly to patients."(p. 354)[2] Some described how manufacturer representatives had played a role in how they had learned about GEP testing and that they found this uncomfortable.[15] Others raised questions about the technical proficiency of manufacturers' pathologists due to its proprietary nature:

> We don't really know how good they [company's pathologists] are, we don't know which part of the tumour they selected, so if the initial pathology suggests high-risk disease and the Oncotype says low-risk, I would be very concerned by that. (p. 354)[2]

While concerns about the role of manufacturers and the proprietary nature of the tests were raised, they were not described as deterring use of GEP tests, diminishing their perceived value in clinical care, or impacting confidence in test results or resultant clinical treatment decisions. Indeed, oncologists reported that they were confident the tests were reliable and valid.[9]

Patients value GEP testing to support personalized and individualized treatment decision making, yet some are skeptical and invoke broader sociocultural views of the unpredictable nature of cancer

Patients similarly viewed GEP tests as facilitating their treatment decisions, specifically that it offers the potential to avoid chemotherapy and its toxicities.[7,8,12,16] Tests were viewed as providing clarity during a challenging time of decision making for patients.[7]

In their reflections, patients emphasized the personalized and individualized nature of the test that used their own tumour to generate results.[7,12] This personalized nature led them to trust the results of GEP tests more so than other algorithms used in clinical practice, which were in contrast not seen as personalized or individualized:[7,12]

> It would actually take something concrete from my body and it would use a finer scientific way of actually deciding… what treatment would best benefit me. It would not be based on other peoples' statistics, mortality rates… It would define my risk factors. (p. e206)[7]

Overall patients tended to trust the validity of GEP testing, taking the truth value of results for granted.[7,14] In one Canadian jurisdiction where a decision to publicly reimburse GEP

tests was recently made, the public funding of testing was described as a confirmation of the validity of the test.[7] In this context, prior to reimbursement, patients' understanding of the value and importance of GEP testing was influenced by challenges in access to testing due to reimbursement issues.[7] In the same jurisdiction, prior media coverage drew attention to the lack of public reimbursement of GEP testing, "framing the issue as one of inequitable access to a highly effective game-changing technology."[8] Patients described feeling as though something beneficial to their care was being withheld, and heightened their desires for testing.[8]

Though many patients expressed positive acceptance of GEP and how it helped inform treatment decisions, there were divergent accounts of its value. Some expressed skepticism of the tests' ability to 'predict the future'.[12] Accounts of decision making around testing and treatment evoked sociocultural views of cancer,[7,12] including notions of cancer as able to escape and hide without detection. The very nature of cancer was seen as introducing irresolvable uncertainty about their future prognosis.[12] The impact of GEP testing was felt by patients beyond the act of decision making, and their experience of testing was shaped by their experiences and outcomes of their treatment.[17]

Both the skepticism of testing and the desire for it point to the ways in which patients' perceptions and experiences are at once personal and individual and are shaped by the sociocultural context in which they are situated. This suggests that broader social framings of breast cancer and access to testing and treatments may be relevant when considering patients' preferences for GEP testing.

Knowing patients' eligibility and preferences for chemotherapy is important before testing, as the perceived value of testing is contingent on its ability to be used in treatment decision making

Oncologists consistently stated that they thought ordering GEP tests was appropriate when it would impact treatment decision making.[2,8,15] Similarly, they described how they would not offer GEP testing to those who were not eligible for chemotherapy due to advanced age, extensive comorbidities or life expectancy of less than 10 years,[10] or if a patient was certain about a decision to not undergo chemotherapy.[13]

For many oncologists, their perceptions of a patient's preference for chemotherapy influenced their decision to order the test.[2,9,10,13,15,16] However, some described ordering testing even when patients had already articulated a strong preference. Here, oncologists described using test results as an opportunity for risk communication to further demonstrate the potential value of an alternate treatment decision.[2,9]

In some cases, the high cost of testing was cited as a reason for ensuring that a patient's preference for chemotherapy was explored prior to ordering the test:[2,15] "I'm very clear with them that if we're going to spend $4,000 on a test and if the test comes back and it says you need chemotherapy, that they need to take chemotherapy."(p.353)[2] Several oncologists described how younger women tended to want to proceed with chemotherapy despite being identified low risk.[10] Similarly, several oncologists described that they assumed "patients are anxious to start chemotherapy, and they may not offer Oncotype DX or may recommend proceeding with chemotherapy before receiving results."[16](p. e27) In the same study, patient advocates, on the other hand, described patients as wanting to consider all relevant tests in their treatment decision making.[16]

Beyond core agreement on the perceived value of testing being contingent on its ability to be used in treatment decision making, oncologists varied in their perceptions of when GEP

testing was medically appropriate.[8,15,16] In several studies, oncologists described it as being used inappropriately by others, primarily in tumour grades or types for which the test had not been validated.[2,13] One oncologist described their decision on using GEP testing outside of the typical indication of early-stage ER+ node negative disease:

> If it's a grade 3 tumour, I'll use it because I would appreciate a low result on that for not having chemo, and all the grade 2's I think I send regardless… Maybe there's some reason why I'm really sitting on the fence about chemotherapy with them… they may have co-morbid illness or something else that I would like a reason not to give them chemotherapy."(p. 353)[2]

Oncologists' descriptions of why they decide to order GEP tests draws attention to varying ways they are seen to support deciding on treatment options for patients. As a consequence, it may be important to account for variations in the interpretation and application of appropriate use beyond the indication of early-stage ER+ node negative disease.

Patients see ordering GEP testing as opening up options and conversations

For patients, their ability to decide on testing is dependent on being offered the test. In some cases, patients described learning about the test late in their care, or that their oncologists were not always forthcoming about the test.[8] Some patients felt like their oncologists did not offer the test because they had already decided on administering chemotherapy. One such patient described their discomfort with this:

> My sense was "We don't really want to talk about it because, looking at your case, we don't think it would be worth it" because it's a $4000 test… As it turns out I got the Onco results then, and the oncologist said, "I can't believe it, but your score indicates that you don't need to do chemo."… I was surprised… that they never mentioned it to me as a possibility of a test… Why wait? (p.e429)[8]

In this sense, testing was seen by patients as an opportunity to gather more information to guide care, and to understand the options for treatment that were available for them.

The ability to have testing done without their active participation was described by some patients as making them comfortable with testing:

> I had a tumor analyzed as everybody does, and well, my doctor just said, 'I think we should get an Oncotype DX done'. Well, it is now out of your body, and it is in their laboratory so right or wrong they didn't ask any questions at all because it wasn't touching me. It doesn't really affect you.[14](p. 404)

For most, testing was key to creating space for conversations about decision making with their clinicians and empowered patients to actively engage in their care, particularly if they had a poor rapport with their clinician.[7] Underlying how patients experience GEP tests as engaged or passive participants is the context in which they are making decisions – that is, after receiving a recent diagnosis of breast cancer and through a relationship with their clinician that may be perceived or experienced as either good, or poor. This context is important as patients' descriptions of receiving results were often inflected with the emotional weight of the diagnosis and the decision at hand.[7,12]

Communicating test results requires longer and/or multiple visits, with intermediate results presenting particular challenges for oncologists

While oncologists described primarily using the risk recurrence score and the categories of low and high in decision making,[10,13] they used a range of approaches to communicate the results of GEP testing to patients.[2,9,13] Some focused on the predictive interpretation of test results (the potential value of chemotherapy), and others emphasized prognostic interpretations (the likelihood of a recurrence).[2,9] For those who were using Oncotype DX, several reported using the Oncotype DX report as a communication tool with patients.[9,13] "I show them the graph and the recurrences and where they fall. I think the visual picture is easier to portray that way…"(p. 2113)[13] This draws attention to the ways that oncologists worked to find ways to communicate the complicated information provided from test results to their patients.

Oncologists described that patients often appeared to experience "information overload" when they explained the recurrence risk the potential for risk reduction through adjuvant chemotherapy.[10,13] Patients' misconceptions were noted frequently, with some oncologists stressing that GEP testing needs to be discussed over multiple visits.[2] Typically, an additional consultation was required to review and discuss test results.[15] And, additional consultations were described by oncologists as especially difficult for patients who have to travel long distance for their care or who live in rural areas.[10]

Intermediate test results were consistently described as challenging to communicate[9,10,13,15,17] because they did not result in reducing uncertainty in decision making or increase confidence in a treatment decision:

> My other concern is that the intermediate score is very difficult to explain to a patient. It's very difficult for the oncologists to help them make decisions and I've had lots of patients tell me they're so torn because now they have this extra piece of information that tells them maybe or maybe not they need it. Now I don't know what to do with that. (p. 2113)[13]

Because of the lack of data to support treatment decisions in these cases, clinical parameters and patient values assumed a greater role in decision making after intermediate risk test results.[10] Some oncologists prepared patients for the possibility of intermediate scores and described that it would require making decisions "the same way we used to 10 years ago as if this didn't exist."(p. 209)[9]

Patients experience receiving GEP results as determining their treatment decisions – unless they are identified as of intermediate risk

Patients described the ways in which test scores influenced and informed their decision making. In many descriptions, high and low risk test results in particular held a power and influence over patients' decision making, and were seen by patients as determining their treatment decisions: "I have [an] Oncotype DX score of 17 so no chemo".(p.78)[12] In this way, test results were imbued with agency and viewed as authoritative.[7,12] As one patient put it: "I know if my score is high then I cannot refuse [chemotherapy]".(p. 78)[12]

Alongside this deterministic understanding of test results was patients' misunderstanding about testing, and confusion and struggle in interpreting the numbers, charts and graphs that were presented to them.[7] Thus while patients described how testing offers clarity and direction, they often experienced it as a fragmented and confused process.

Patients' treatment decision making based on test results invoked their experiences and memories of cancer and their prior treatments, their emotional sense of being vulnerable to cancer, and their personal histories and connections.[7,12] This embodied decision making means that an individual's decision is highly situated. Patients found themselves negotiating their desire to avoid chemotherapy that would be of limited benefit and the imperative of avoiding future cancer recurrence.[12]

Patients accounts of making treatment decisions following receiving an intermediate score were described as complex, and fragmented, with patients feeling left in a "grey zone".[12,17] Here the test was not authoritative, it was not deterministic, and instead patients were required to enter into complex decision making about their treatment. Patients with intermediate test results found themselves thrust into stress, worry and anxiety around whether to have further treatment.[7,12] "In many of these cases, the score became a powerful and direct representation of their current and possible future experiences of cancer…"(p. 78)[12]

Recipients of an intermediate score described manipulating and re-interpreting their scores to aid in their decision making, such as reconstructing risk categories or their own category of risk.[12] For example, one patient described how "[t]he other factor influencing my decision was the knowledge that studies have been conducted where the intermediate groups was redefined as 11-26 which firmly puts me in the high category."(p. 78-79)[12] This suggests the ways in which patients rely heavily, or even exclusively, on the results to determine treatment decisions, and illustrates some of the expected ways that testing will aid with decision making are not borne out in experience.

The timing of ordering GEP testing is important to ensure the information is available for decision making

The timing of ordering GEP testing in clinical care arose as a theme in several studies.[2,10,15,16] Specifically, the process of ordering the test, sending the specimen to the lab, receiving results and communicating results was described as a lengthy and complex process.[16] In order for test results to be used for treatment decisions, testing had to be ordered with enough lead time to enable the results to be available for decision making.[16] Both oncologists and patients offered accounts of almost commencing treatment before results were returned.[7,16]

In some cases, a failure to order testing with adequate lead time was reported to lead to treatment delays.[2,10,13,15] Some oncologists developed work arounds, including prepping patients for test results, and having them sign consent forms before hormone status results were available.[15] In one study, some surgical oncologists routinely ordered GEP testing to allow for enough lead time and to avoid delays.[13] In this same study, medical oncologists, who received patients and their test results, often expressed frustration at testing being ordered before patients' preferences for treatment (or not) were established.[13] Silos were identified as a barrier for the seamless use of GEP testing, and multidisciplinary teams were seen as increasing communication and coordination between surgical and medical oncologists.[10] This points to the logistical considerations that shape oncologists' testing decisions.

Limitations

The included publications focused on oncologists' and patients' perceptions and experiences of the acts of making GEP testing decisions, ordering GEP testing, communicating test results and subsequent decision making for treatment. These publications did not however, for the most part, analyze or present findings by levels or categories of test results (i.e. low, intermediate, high). While patients' and oncologists' experiences of low and intermediate risk were available through publications' supporting data, a more nuanced analysis of perceptions and experiences by category of risk may reveal additional considerations, particularly for communicating findings and using test results in treatment decision making.

One study examined patients' views of testing after they had received treatment directed by their test results, but was of limited transferability because of the type of GEP test used and that participants' treatment was in the context of a clinical trial.[17] As the impact of GEP tests on patients extends beyond the act of testing and making treatment decisions to the experiences of treatment and its outcomes,[12] it becomes important to consider patients' views after testing and making treatment decisions.

The lack of reporting of the sex and gender of participants within the included publications is suggestive of an assumption that the majority of patient participants were cis-women. The implications are that the experiences of cis-men and non-gender conforming persons were not captured or explored in the included publications but may be important to consider as the meaning and experiences of breasts, breast cancer and its treatment are likely to be different.

For those studies that included patient participants, there was no analysis of differences in experiences by different populations, for example as defined by socio-economic status, geographic location, or ethnicity as factors that may be expected to influence or shape patients' experiences. Such differences may be important to explore as vulnerable or marginalized patients may require specific considerations not addressed or identified in the included publications or this analysis.

Of the six publications that reported on the views of oncologists, three were conducted within one Canadian jurisdiction (Ontario). Differences in the organization of cancer care across and within jurisdictions may influence how oncologists understand and use GEP testing, although it was not possible to explore through the included publications.

Conclusions and Implications for Decision or Policy Making

This review used a framework analysis to synthesize results of eleven included publications and describes key features of how patients and clinicians understand, use, interpret and communicate around GEP testing for breast cancer.

As an example of personalized medicine for patients with breast cancer,[1] GEP testing is seen by patients and oncologists as a valuable aid in making decisions about whether or not to undergo subsequent chemotherapy. However, this review also found that GEP testing can introduce additional complexity into care. In the particular case of intermediate results, testing was seen to introduce challenges and may not consistently meet patients' and oncologists' expectations.

Oncologists use testing for a range of purposes including communicating risk to patients, reducing uncertainty, and helping them feel more confident in their treatment recommendations. While some oncologists report feeling uncomfortable seeing their colleagues do so, some oncologists appear to be using tests beyond the indication for which they are validated. When considering the increased use of GEP testing, practice variation points to the importance of specifying the boundaries of the indication for appropriate use and reimbursement.

The tendency of some patients and oncologists to rely heavily, even exclusively, on recurrence risk as indicated by GEP testing for treatment decision making highlights the perceptions and expectations of the validity of GEP testing. In some cases, patients did not understand the nature of testing and the possibility of it being fallible, instead its certainty and validity was reinforced by notions of testing being of a personalized and individual nature. Conversations about the nature of testing and its measurement properties may have a role in conversations around the decision to order testing, or to act on the results.

While understanding patients' preferences for and willingness to undergo chemotherapy were identified as key to the usefulness of testing by oncologists, it is not clear that patients' preferences are assessed and used consistently in deciding to order testing. Part of the issue relates to the timing of testing (allowing for lead time for the receipt of results), but the findings of this review also point to the possibility that in some cases oncologists' assumptions about patients' preferences guide their decisions on ordering testing. Patient-centred approaches to decision making require understanding patients' preferences for treatment, and these are likely to vary, as they are embodied experiences. Specifically, it is important to recognize that some patients will prefer to undergo or forgo chemotherapy regardless of their identified risk of recurrence.

Patients expect tests to provide valid, personalized, individualized and authoritative results that determine the most appropriate course of treatment; however, intermediate results defy these expectations instead adding confusion and stress into what is an already emotionally laden decision. The likelihood of an intermediate result and its implications for decision making may be important to consider and discuss when gaining patient consent for testing.

Because of the need to communicate complex information about the nature and purpose of the test, patients' preferences for treatment, and making decisions based on the results, implementation of GEP testing is likely to require additional time in terms of length and number of consultations with oncologists. As a result, increased use of GEP testing would likely impact health care systems in terms of oncologists' workloads and resource use.

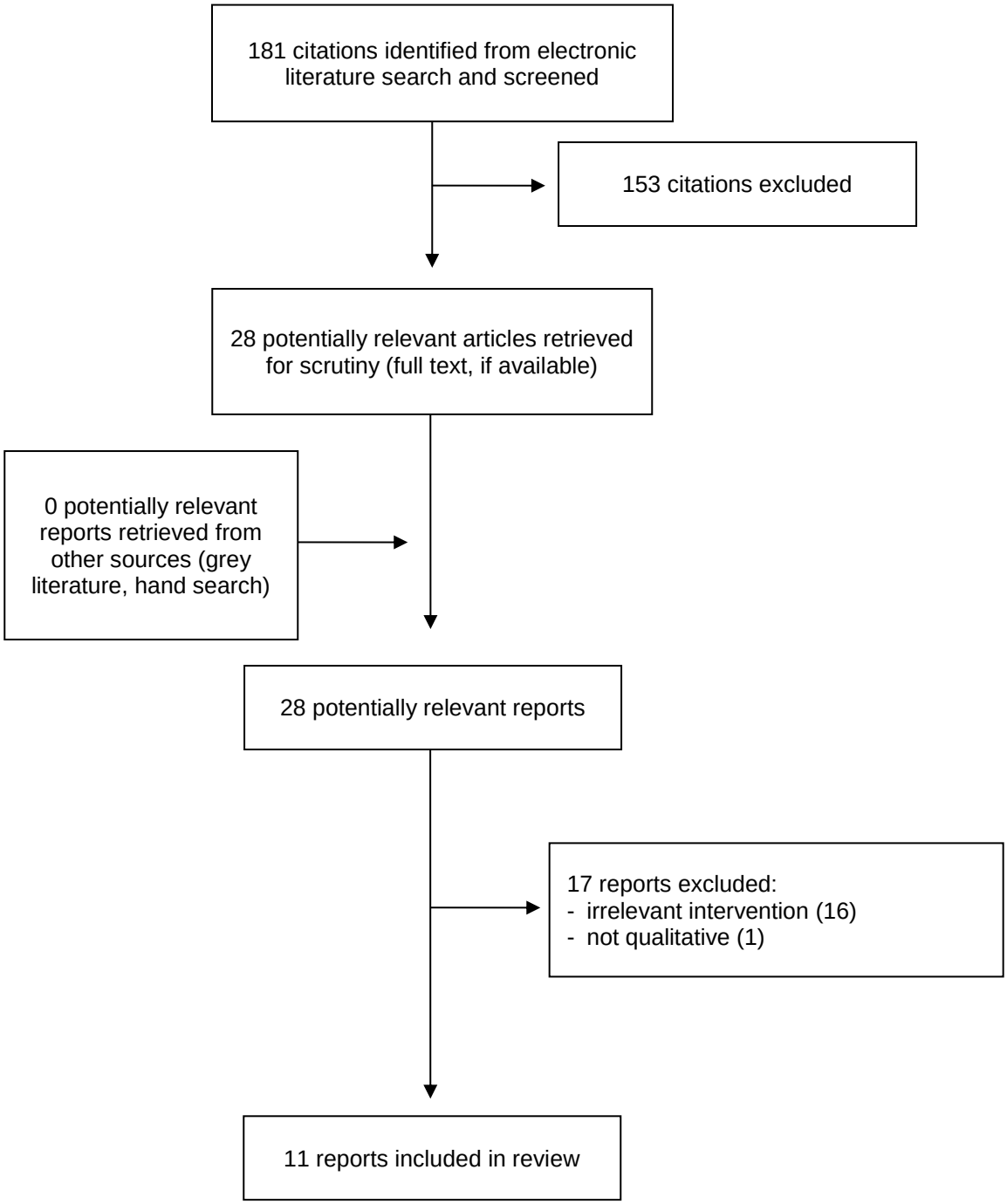
This review found that challenges with the timing of and process for ordering GEP tests can create delays in treatment or may conversely mean initiating unnecessary treatment. It suggests that coordinating the process for, and timing of, ordering tests can ensure test results are available for treatment decision making.

GEP testing offers a new tool to use in shared decision making about treatment that may help to reduce unnecessary treatment for patients with breast cancer. Further explorations of patients' perceptions and understandings of GEP post treatment, by level of recurrence risk, and attention to patient populations who may be marginalized or vulnerable in their experiences with breast cancer, testing, and treatment would add to this area.

References

1. Gene expression tests for women with early stage breast cancer: a review of clinical utility and cost-effectiveness. Ottawa (ON): CADTH; 2017 Oct: https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0934%20Mlc%20Tests%20for%20Breast%20Cancer%20Final.pdf. Accessed 2019 Apr 17.
2. Bombard Y, Rozmovits L, Trudeau M, Leighl NB, Deal K, Marshall DA. The value of personalizing medicine: medical oncologists' views on gene expression profiling in breast cancer treatment. *Oncologist.* 2015;20(4):351-356.
3. Critical appraisal skills programme checklist. Oxford (UK): CASP; 2018: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf. Accessed 2019 Mar 26.
4. Krefting L. Rigor in qualitative research: the assessment of trustworthiness. *Am J Occup Ther.* 1991;45(3):214-222.
5. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet.* 2001;358(9280):483-488.
6. Booth A, Noyes J, Flemming K, et al. Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions. Bremen (DE): Integrate-HTA; 2016: https://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-on-choosing-qualitative-evidence-synthesis-methods-for-use-in-HTA-of-complex-interventions.pdf. Accessed 2019 Mar 26.
7. Bombard Y, Rozmovits L, Trudeau ME, Leighl NB, Deal K, Marshall DA. Patients' perceptions of gene expression profiling in breast cancer treatment decisions. *Curr Oncol.* 2014;21(2):e203-211.
8. Bombard Y, Rozmovits L, Trudeau M, Leighl NB, Deal K, Marshall DA. Access to personalized medicine: factors influencing the use and value of gene expression profiling in breast cancer treatment. *Curr Oncol.* 2014;21(3):e426-433.
9. Roberts MC, Bryson A, Weinberger M, et al. Patient-centered communication for discussing Oncotype DX testing. *Cancer Invest.* 2016;34(5):205-212.
10. Roberts MC, Bryson A, Weinberger M, et al. Oncologists' barriers and facilitators for Oncotype Dx use: qualitative study. *Int J Technol Assess Health Care.* 2016;32(5):355-361.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
12. Ross E, Swallow J, Kerr A, Cunningham-Burley S. Online accounts of gene expression profiling in early-stage breast cancer: Interpreting genomic testing for chemotherapy decision making. *Health Expect.* 2019;22(1):74-82.
13. Spellman E, Sulayman N, Eggly S, et al. Conveying genomic recurrence risk estimates to patients with early-stage breast cancer: oncologist perspectives. *Psychooncology.* 2013;22(9):2110-2116.
14. Issa AM, Hutchinson JF, Tufail W, Fletcher E, Ajike R, Tenorio J. Provision of personalized genomic diagnostic technologies for breast and colorectal cancer: an analysis of patient needs, expectations and priorities. *Per Med.* 2011;8(4):401-411.
15. O'Brien MA, Dhesy-Thind S, Charles C, Hammond Mobilio M, Leighl NB, Grunfeld E. Uptake of a 21-gene expression assay in breast cancer practice: views of academic and community-based oncologists. *Curr Oncol.* 2017;24(2):e138-e145.
16. Weldon CB, Trosman JR, Gradishar WJ, Benson AB 3rd, Schink JC. Barriers to the use of personalized medicine in breast cancer. *J Oncol Pract.* 2012;8(4):e24-31.
17. Pellegrini I, Rapti M, Extra JM, et al. Tailored chemotherapy based on tumour gene expression analysis: breast cancer patients' misinterpretations and positive attitudes. *Eur J Cancer Care (Engl).* 2012;21(2):242-250.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design (Data Analysis)	Study Objectives	Sample Size	Inclusion Criteria	Data Collection
Ross, 2018, UK[12]	NS (Thematic analysis)	To explore women's interpretations of and decision making around GEP through online accounts	132 discussion threads from 7 forums	Posts including the term "oncotype" on publically accessible online forms by two UK cancer charities	Electronic search of online forums
O'Brien, 2017, Canada[15]	Qualitative descriptive (Constant comparative method)	To describe medical oncologists' experiences and perception of GEP	21 medical oncologists	Medical oncologists who provided care for women with breast cancer	Semi-structured face-to-face interviews
Roberts, 2016, USA[10]	NS (Template analysis)	To describe barriers and facilitators for oncologists' use of Oncotype DX	5 surgical oncologists 10 medical oncologists	Medical or surgical oncologists who were seeing >five breast cancer patients a week	Semi-structured telephone interview
Roberts, 2016, USA[9]	NS (Template analysis)	To identify aspects of patient-centred communication that are and are not being used by clinicians	5 surgical oncologists 10 medical oncologists	Medical or surgical oncologists who were seeing >five breast cancer patients a week	Semi-structured telephone interview
Bombard, 2015, Canada[2]	NS (Constant comparative method)	To explore medical oncologists' views of GEP tests and factors impacting their use in clinical practice	14 medical oncologists	Medical oncologists working at two academic oncology clinics	Semi-structured telephone interviews
Bombard, 2014, Canada[8]	NS (Content analysis)	To explore how oncologists perceived the clinical utility of GEP tests	14 oncologists 28 patients	Early-stage breast cancer patients who were offered GEP and medical oncologists	Semi-structured telephone interviews with oncologists; focus groups with patients (n=24); semi-structured telephone interviews with patients (n=4)
Bombard, 2014, Canada[7]	NS (Content analysis)	To explore patients' perceptions of GEP and its impact on chemotherapy decisions	28 patients	Early-stage breast cancer patients who were offered GEP	Focus groups (n=24) and semi-structured telephone interviews with patients (n=4)

First Author, Publication Year, Country	Study Design (Data Analysis)	Study Objectives	Sample Size	Inclusion Criteria	Data Collection
Spellman, 2013, USA[13]	NS (Phenomenological approach)	To describe oncologists' perception of the use and integration of Oncotype DX in clinical practice	10 medical oncologists 10 surgical oncologists	Board certified medical or surgical oncologists primarily treating patients with breast cancer	Semi-structured telephone interviews
Weldon, 2012, USA[16]	Framework Approach (Thematic Analysis)	To explore barriers to the use of personalized medicine for patients with breast cancer	25 clinicians (including nurses, psychologists, and physicians) 20 senior executives of health plans 6 representatives of patient advocacy groups	Clinicians, patient advocates and payers involved in a collaboration integrating BRAC*Analysis* and Oncotype DX in breast cancer care	Semi-structured telephone interviews
Issa, 2011, USA[14]	Qualitative component of mixed method study NS (NS)	To examine patients' preferences and perceptions of the value and use of genomic diagnostics for breast and colorectal cancer	44 patients	Patients with breast or colorectal cancer	Focus groups
Pellegrini, 2011, France[17]	Grounded theory (Grounded theory)	To investigate patients' perceptions and attitudes of choosing chemotherapy after GEP	37 patients	Patients recruited from three cancer centres who were part a clinical trial and who underwent GEP and subsequent treatment	Semi-structured face-to-face interviews

NS = not specified; GEP = gene expression profiling; UK = United Kingdom; USA = United States of America;

Appendix 3: Characteristics of Patient Participants

Table 3: Characteristics of Patient Participants

First Author, Publication Year, Country	Sample Size (Patients)	Sex (% male)	Age range in years	Test result; treatment decision
Ross, 2019, UK[12]	132 discussion threads	NA	NA	NA
Bombard, 2014, Canada[8]	28	NS	21% >50 years of age	All received GEP testing; 68% did not undergo chemotherapy
Bombard, 2014, Canada[7]	28	NS	30-79	All received GEP testing; 68% did not undergo chemotherapy
Weldon, 2012, USA[16]	6	NS	NS	NS; NS
Issa, 2011, USA[14]	44 (breast and colorectal)	0%	60% between 45-64 years	13% of breast cancer patients underwent genomic testing; NS
Pellegrini, 2011, France[17]	37	NS	35-69	All received GEP testing; NS

NA = not applicable; NS = not specified; GEP = gene expression profiling; UK = United Kingdom; USA = United States of America

Appendix 4: Characteristics of Health Care Provider Participants

Table 4: Characteristics of Health Care Provider Participants

First Author, Publication Year, Country	Sample Size	Sex (% male)	Age range in years	Experience with GEP tests
O'Brien, 2017, Canada[15]	21	43%	35-77	Practicing in a region with recent public reimbursement of GEP tests
Roberts, 2016, USA[10]	15	53%	Mean of 50	Ordered an average of 4.4 Oncotype DX tests per month
Roberts, 2016, USA[9]	15	53%	Mean of 50	Ordered an average of 4 Oncotype DX tests per month
Bombard, 2015, Canada[2]	14	NS	64% <40 years of age	Practicing in a region with recent public reimbursement of GEP tests
Bombard, 2014, Canada[8]	14	NS	64% <40 years of age	Practicing in a region with recent public reimbursement of GEP tests
Spellman, 2013, USA[13]	20	30%	NS	Medical and surgical oncologists with experience ordering and interpreting Oncotype DX
Weldon, 2012, USA[16]	25	NS	NS	Clinicians (including nurses, genetic counsellors, psychologists and physicians) with self-reported knowledge and experience in ordering and interpreting Oncotype DX

NR = not reported; NS = not specified; UK = United Kingdom; USA = United States of America

Appendix 5: Critical Appraisal of Included Publications

Table 5: Critical Appraisal of Included Publications

First Author, Publication Year, Country	Is the study credible?	Is the study trustworthy? (dependable, confirmable)	Is the study transferable?
Ross, 2018, UK[12]	Yes. Data collection methods lead to a set of rich data which are analyzed using thematic analysis. The findings are well described and their dimensions are drawn out (including going beyond the superficial descriptions of patients' accounts of testing).	Yes. Data are presented that support the findings and their dimensions. Contradictions in patients' accounts are presented and analyzed. Authors are clear about the limits of their analysis because of the type of data used.	Yes. The research question and findings are highly relevant to this review and take place in a comparable single payer system.
O'Brien, 2017, Canada[15]	Yes. Methods described are consistent with qualitative descriptive study. Authors describe how interview guide was modified based on emerging findings and their process for determining saturation. Findings are higher order concepts, and well described.	Yes. Data are presented to support the findings, and their dimensions. Authors describe techniques for addressing transparency including audit trail and analytic decisions.	Yes. The research question and findings are highly relevant to this review and take place within a Canadian jurisdiction.
Roberts, 2016, USA[10]	Yes. The study describes methods of data collection and analysis that were largely deductive but allowed for emergent findings. Multiple authors were involved in the analysis. The findings are well described and explore providers' perspectives in depth and how they relate to organization factors.	Yes. Findings are described in detail and data are presented that support them. Differences in responses between types of providers are explored and analyzed.	Yes. The research question and findings are relevant to this review. While some differences between health systems of US and Canada because multiple payers, many of the findings are transferable.
Roberts, 2016, USA[9]	Partially. The study uses semi-structured interviews to evaluate how oncologists' consultations are consistent with patient-centred communication. Main concern arises in data source and how what a respondent says they talk about something is not necessarily how they do so. (i.e., conflating what one says with what one does). The objective would have been better served by using consultations as the data source.	Partially. The findings are supported by the data. No analysis by type of respondent (surgical versus medical oncologists) and wonder if consultations would differ given the differences in why and when GEP is ordered by medical versus surgical oncologists.	Yes. The research question and findings are relevant to this review.
Bombard, 2015, Canada[2]	Yes. The study authors describe using constant comparative method during data analysis to identify emergent and discordant findings. The themes, though topical, are well-described and	Yes. Findings are supported by the data. Discrepancies in data are analyzed and described in detail.	Yes. The research question and findings are highly relevant to this review and take place within a Canadian jurisdiction.

First Author, Publication Year, Country	Is the study credible?	Is the study trustworthy? (dependable, confirmable)	Is the study transferable?
	analytically consistent. Authors do not describe how they decided to stop collecting data, which matters as it does appear that some of the inconsistencies in oncologists' views could have been further explored.		
Bombard, 2014, Canada[8]	Yes. The study authors describe using constant comparative method during data analysis to identify emergent and discordant findings. The themes, though topical, are well-described and analytically consistent.	Yes. Findings are supported by the data. Discrepancies in data are analyzed and described in detail.	Yes. The research question and findings are highly relevant to this review and take place within a Canadian jurisdiction.
Bombard, 2014, Canada[7]	Yes. The study authors describe using constant comparative method during data analysis to identify emergent and discordant findings. The themes, though topical, are well-described and analytically consistent.	Yes. Findings are supported by the data. Discrepancies in data are analyzed and described in detail.	Yes. The research question and findings are highly relevant to this review and take place within a Canadian jurisdiction.
Spellman, 203, USA[13]	Partially. Described as using a phenomenological approach, methods of data collection and analysis do not seem to focus on the lived experience of participants. Rather, a focused interview guide directed data collection towards four pre-identified themes, and thus the analysis is very deductive with limited space for emergent findings. An emphasis on the proportion of respondents who held a particular view, suggestive of a crude aggregation of superficial themes.	Partially. Data are presented to support the findings. While the findings are trustworthy in that they make sense and are consistent with other studies in this area, they are a highly superficial description and likely to be very influenced by the line of questioning in the interviewing (see credibility).	Yes. The research question and findings are relevant to this review.
Weldon, 2012, USA[16]	Partially. The primary concern around credibility of the study is that the interview questions focused on the process and timing of ordering tests and the process of reimbursement. Thus it is no surprise that the results are challenges with ordering, timing of testing and process of reimbursement. Interview left little space to identify other factors (other than directly questioning about barriers). Implications are that there was limited to no space	Partially. No data are presented that support the findings. The findings are trustworthy in that they make sense and are consistent with other studies in this area. However, they are a highly superficial description and likely to be very influenced by the line of questioning in the interviewing (see credibility).	Yes. The research question and findings are relevant to this review. While some differences between health systems of US and Canada influence differences in types of respondents (i.e., Canada does not have multiple private payers in this treatment area), many of the findings are transferable.

First Author, Publication Year, Country	Is the study credible?	Is the study trustworthy? (dependable, confirmable)	Is the study transferable?
	for emergent findings. Focus is on health care delivery, system issues, and less so on how the test is used, interpreted, and how that might be a barrier to adoption itself. Also, limited analysis of differences in findings across types of participants; differences are described (and analyzed statistically) but not explained.		
Issa, 2011, USA[14]	No. This mixed method study does not describe the qualitative methods used in any detail. Findings are poorly reported and very thin, and are heavily reliant on data, suggestive that data analysis was limited and consisted of grouping like with like. The categories or themes are topics, not concepts.	No. Issues with credibility mean that the data appear 'trustworthy' but the analysis is not dependable.	Partially. The research question and findings are only partially relevant to this review as it included patient with colorectal and breast cancer, without separate reporting by condition. Also conducted in the US, and focuses on willingness to pay and insurance costs, which are only limitedly relevant to a single payer system such as Canada.
Pellegrini, 2011, France[17]	Partially. Primary concern about credibility is that patients' experiences of GEP testing is intertwined with their eligibility and subsequent recruitment (or not) in a clinical trial. Thus their reported perceptions and understandings are contingent on a non-routine use of the test (e.g., as part of eligibility criteria for their treatment), and the data presented consistently refers to the trial. This affects credibility because the objective is to explore patients' perspectives of testing – very unclear if this is what they actually were able to explore based on their inclusion criteria and study context. Data analysis is consistent with grounded theory.	Partially. Issues with credibility affect the dependability of findings. Data are presented which support the findings. Authors describe using methods that increase the dependability of findings including triangulation and team discussion.	Partially. The GEP test used is not a commercial one and was not part of routine clinical use (trial context).

GEP = gene expression profiling; UK = United Kingdom; USA = United States of America