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Original Article

"Game Changer": Health Professionals' Views on the Clinical Utility of Circulating Tumor DNA Testing in Hereditary Cancer Syndrome Management

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Abstract

Background: We explored health professionals' views on the utility of circulating tumor DNA (ctDNA) testing in hereditary cancer syndrome (HCS) management.

Materials and Methods: A qualitative interpretive description study was conducted, using semi-structured interviews with professionals across Canada. Thematic analysis employing constant comparison was used for analysis. 2 investigators coded each transcript. Differences were reconciled through discussion and the codebook was modified as new codes and themes emerged from the data.

Results: Thirty-five professionals participated and included genetic counselors (n = 12), geneticists (n = 9), oncologists (n = 4), family doctors (n = 3), lab directors and scientists (n = 3), a health-system decision maker, a surgeon, a pathologist, and a nurse. Professionals described ctDNA as "transformative" and a "game-changer". However, they were divided on its use in HCS management, with some being optimistic (optimists) while others were hesitant (pessimists). Differences were driven by views on 3 factors: (1) clinical utility, (2) ctDNA's role in cancer screening, and (3) ctDNA's invasiveness. Optimists anticipated ctDNA testing would have clinical utility for HCS patients, its role would be akin to a diagnostic test and would be less invasive than standard screening (eg imaging). Pessimistic participants felt ctDNA testing would add limited utility; it would effectively be another screening test in the pathway, likely triggering additional investigations downstream, thereby increasing invasiveness.

Conclusions: Providers anticipated ctDNA testing will transform early cancer detection for HCS families. However, the contrasting positions on ctDNA's role in the care pathway raise potential practice variations, highlighting a need to develop evidence to support clinical implementation and guidelines to standardize adoption.

Key words: circulating tumor DNA; cancer detection; genomics; hereditary cancer syndromes; clinical utility.

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Implications for Practice

Circulating tumor DNA (ctDNA) is emerging as a powerful biomarker for use in cancer treatment. However, the "holy grail" is the potential for its application in early cancer detection in asymptomatic patients, especially those with a higher lifetime risk (hereditary cancer syndrome patients; HCS). Here we explored views of health professionals on the utility of ctDNA in early cancer detection for HCS. While professionals anticipated that ctDNA testing will transform early cancer detection, they had contrasting opinions on its role in the cancer care pathway. This suggests a need for evidence to support clinical implementation and guidelines to standardize adoption.

Introduction

Circulating tumor DNA (ctDNA) analysis is emerging as a powerful biomarker in oncology with promising clinical applications in cancer treatment.[1, 2] Using plasma from a routine blood draw, fragmented DNA derived from a tumor cell can be analyzed to gain insight into the tumor genome.[3,4] Preliminary evidence suggests that ctDNA levels can be used to monitor treatment response and identify development of therapeutic resistance months before standard radiological tests can detect disease progression, creating a window of opportunity for adjusting therapies and improving treatment response and survival.[5-7] In comparison to standard monitoring approaches in oncology, ctDNA analysis is advantageous in that it does not require radiation, as well as being minimally invasive and providing real-time DNA profiles of a growing tumor.[8] However, ctDNA has potential limitations, including discordance with tissue biopsy results, rigid sample processing requirements, and low levels of viable ctDNA on which to conduct analysis. [3, 8, 9]

The "holy grail" [3] of ctDNA is the potential for its application in early cancer detection in otherwise asymptomatic patients.[10] In particular, early detection using ctDNA may revolutionize management of families with hereditary cancer syndromes (HCS). These individuals, who represent approximately 1 in 10 patients with cancer,[11,12] undergo costly annual screening with physical exams and frequent imaging. Despite these efforts, many at-risk organs (eg ovaries and pancreas) associated with HCS have substandard or invasive screening options while others have no established screening modalities.[13,14] For example, patients with *BRCA1* or *BRCA2* mutations are typically eligible for high-risk breast screening encompassing breast MRIs and mammograms, which have a high sensitivity for breast cancer detection. However, there is no equivalent screening to address the ovarian cancer risk in these patients. The lack of established screening has contributed to late-stage diagnoses and increased morbidity, mortality, and costs to the healthcare system.[13-19] CtDNA screening could be used to fill this gap in early cancer detection for this high-risk population, providing opportunities for early diagnosis, reduced treatment-associated morbidity and improved curability and survival.[3, 20]

While the evidence for ctDNA assay development and sensitivity is rapidly growing,[2, 21] there is limited research evaluating views on the clinical utility of ctDNA in this population. The small number of studies conducted have been limited to addressing the utility of ctDNA within treatment settings or in the context of professional guidelines.[8, 9] To our knowledge, there is no primary research exploring the clinical utility of ctDNA testing in early cancer detection within the HCS population.[22-24] Our study aimed to fill this critical gap by exploring perspectives of health professionals on the use of ctDNA testing in early cancer detection; understanding the views of professionals who will be involved in the delivery of the test will help inform its clinical implementation and potential challenges.

Materials and Methods

Design and Setting

We conducted a qualitative study using semi-structured interviews to explore health professionals' views on the clinical utility of ctDNA testing in the HCS context. We elected to use qualitative methods as they would provide us rich data on professionals' experiences, appropriate for understanding perceptions of clinical utility of ctDNA testing in the clinical setting.[25] The Research Ethics Board at St. Michael's Hospital (Toronto, Ontario) approved the study (REB#18-315). All participants provided informed verbal or written consent. The standards for reporting qualitative research recommendations were followed (Supplementary Appendix 1).[26]

Population and Recruitment

Eligible participants were health professionals including clinicians within the circle of care for HCS and professionals who were directly or indirectly involved in policy and research relevant to HCS. This included genetic counselors, medical geneticists, oncologists, family doctors, laboratory directors, nurse navigators and coordinators, scientists and decision makers from academic and community hospitals working in a Canadian centre. We initially aimed to interview 20 participants across these professional groups, sufficient to reach thematic saturation and consistent with similar work and populations in this field. [27]

We used a purposeful variation sampling approach to obtain a broad range of views and experiences of professionals across Canada.[28] Initial sampling was based on practitioner type (eg genetic counselors, medical geneticists, and oncologists). After preliminary analysis, we identified a divergence of opinions on the utility of ctDNA for ovarian and pancreatic cancer, and a gap in views from providers practicing in the community setting and from providers located outside of Ontario. Therefore, we subsequently used theoretical sampling to maximize variation in views of utility from clinicians in pancreatic/ovarian cancer settings, community practices, and non-Ontario regions.[25,28]

Investigators from the CHARM (ctDNA in Hereditary And High-Risk Malignancies) consortium (Y.B., R.H.K. A.K., and T.J.P.) identified individuals within their professional network working in HCS care and invited them to participate. CHARM is a pan-Canadian consortium of clinicians, scientists and decision makers, led by Y.B., R.H.K., A.P., and T.J.P., with the goal to evaluate the use of ctDNA in early cancer detection in HCS patients (www.charmconsortium.ca). Eligible participants were emailed a detailed study information letter from CHARM investigators (Y.B., A.K., R.H.K., or T.J.P.). Interested participants were forwarded to a study coordinator

(M.C., L.E.O., or S.S.) for follow-up and scheduling of interviews. This method was supplemented with snowball sampling and continued until thematic saturation was reached and no new codes or themes were identified in the data.[25]

Data Collection

Interviews were conducted between March 2019 and November 2020 over the phone or in-person and were approximately 30-40 minutes in length. M.C., L.E.O., or S.S. conducted all interviews and used an interview guide (Supplementary Appendix 2) developed following a literature review and clinical consultation. The interviews explored professionals' experiences with current cancer screening in the context of HCS and perspectives on the anticipated clinical utility of ctDNA for HCS patients.

Analysis

Interviews were audio-recorded, transcribed verbatim, and deidentified. Thematic analysis,[29] employing constant comparison,[25] was used to analyze transcripts. An interpretive description approach[30] guided the study procedures and was chosen because this method is commonly used to understand practical and relevant applications in clinical settings, consistent with our aim to evaluate the clinical utility of ctDNA testing in HCS care.

A codebook was developed initially based on the interview guide, literature review, the mock interviews, and interpretations of health professionals' views on the utility of ctDNA drawn from the first round of interviews. The mock interviews were conducted to serve as a quality check, to ensure appropriate content and flow of interviews, and did not influence the analysis. Consistent with the constant comparison technique, data collection, and analysis were concurrent and ongoing throughout the entire study period; this allowed for adaption of the interview guide and the sampling strategy as themes emerged. As analysis progressed, the codebook and interview guide were modified as new codes and themes emerged and interpreted from the data. The team compared emergent and existing findings, modified the guide and coding framework, analysis and refined the sampling strategy based on these findings. This process was completed through peer debriefing and team discussions that provided interpretive insights. To ensure consistency in coding, multiple coders (M.C., C.M., L.E.O., S.S., and A.S.) coded the first 12 interviews and differences were reconciled through discussion. Once consensus was reached, the transcript was recoded where necessary and analytic decisions documented. Throughout the analysis and writing, the investigators undertook a practice of reflexivity, reflecting upon and documenting beliefs and assumptions related to the research topic that may influence approach and interpretation. This included taking reflexive field notes after each interview, which were then discussed during analysis meetings, and informed the framing of interview questions and the data analysis. During the analysis meetings, team members (including experienced qualitative researchers, clinicians, and non-clinicians) reviewed field notes and discussed how assumptions and past clinical experiences may have influenced the interviews or data analysis. Our analysis of the data also considered the role of self-identified gender and profession type in influencing participants' views on the utility of ctDNA broadly, and more specifically, within sex-specific cancers (eg ovarian cancer, prostate cancer). The collaborative nature of the analysis process and the simultaneous comparing and contrasting of participants' views on the utility of ctDNA moved the analysis to a higher level of conceptualizing the data on the utility of ctDNA. Overall, this facilitated an interpretive analysis of the themes that emerged based on health professionals views on the clinical utility of ctDNA.

Results

Participant Characteristics

Thirty-five (28/35 female) of the 53 professionals invited to the study participated in the interviews, and included genetic counselors (n = 12), medical geneticists (n = 9), oncologists (n = 4), family doctors (n = 3), lab directors and scientists (n = 3), a health-system decision maker, a surgeon, a pathologist, and a nurse (Table 1). Given that our study's recruitment period overlapped with the first year of the COVID pandemic and that most of our target sample were front-line healthcare providers, we anticipated that many of them were unable to participate because of the increased workload. Indeed 4 professionals who provided a response for declining attributed their inability to participate to the pandemic and workload.

Twenty-eight participants practiced or worked in urban academic centers, 5 in rural centers and 2 practiced in both. Of the clinicians practicing in HCS settings, there was representation from pediatric HCS, adult HCS and specialty clinics (eg Lynch syndrome). The study included participants from Western Canada (2), Prairie provinces (8), Central Canada (22), and the Atlantic provinces (3). All participants were provided with the option to receive an explanation of ctDNA to familiarize them with the topic prior to the interview questions. Almost all of the healthcare professionals did not feel they needed assistance with understanding ctDNA with the exception of some primary care providers.

Health Professionals' Views on ctDNA in Management of HCS Patients

Our qualitative analysis revealed that there was generally broad enthusiasm for ctDNA: providers described the test as "transformative" and a "game-changer". However, professionals were divided on its use in HCS management, with some providers being optimistic while others were

Table 1. Characteristics of participating professionals (N = 35).

Characteristic		No.
Sex	Female	28
Role	Genetic counselor	12
	Geneticist	9
	Oncologist [gynecology (2) breast (1), general (1)]	4
	Family physician	3
	Scientist/laboratory director	3
	Health-system decision maker	1
	Surgeon	1
	Nurse	1
	Pathologist	1
Region	Central	22
	Prairie provinces	8
	Atlantic	3
	Western	2

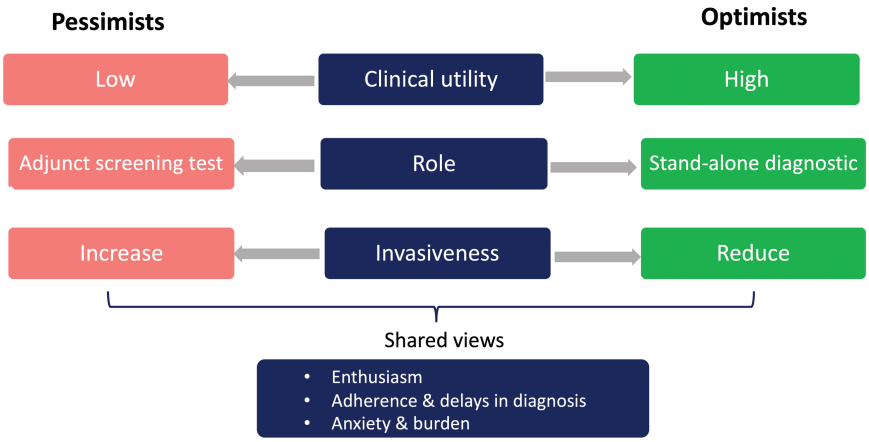

Figure 1. Health professionals' contrasting views on ctDNA's utility in HCS management. Summary of health professionals views on ctDNA testing in HCS patients and the contrasting perspectives on 3 themes between optimists and pessimists.

pessimistic. Differences were driven by views on 3 factors: (1) clinical utility, (2) the role of ctDNA in cancer screening, and (3) the invasiveness of ctDNA itself and downstream investigations (Fig. 1, Table 2). Optimists anticipated ctDNA testing would have clinical utility for HCS patients, that its role would be akin to a diagnostic test and that it would be less invasive than standard screening (eg, imaging). Pessimistic participants felt that ctDNA testing would add limited utility; it would effectively be another screening test in the pathway, likely triggering additional investigations downstream, thereby increasing invasiveness. However, both groups of professionals were concerned about patient burden, reduced adherence to scheduled screening, and delayed diagnosis.

Clinical Utility of ctDNA Testing

Optimistic professionals had the opinion that ctDNA testing would have high clinical utility among some HCS-associated cancers, particularly for cancers without effective screening, such as pancreatic and ovarian cancers (Table 2). As one provider (ctDNA06) explained, "everyone would jump on board because we have no prevention and we have no screening" for these cancers. Some optimistic professionals anticipated that ctDNA testing could also provide premenopausal women with *BRCA1/2* mutations the option to delay prophylactic oophorectomies and offset the risks and side effects of surgical menopause.[31]

Conversely, pessimistic professionals expressed hesitation about the utility of ctDNA testing for cancers with effective risk-reducing surgeries, such as ovarian cancer. They questioned whether patients would be willing to take a risk and choose a novel screening test over an established intervention. One provider (ctDNA20) reflected on his patient population:

> "But, when we look at ovarian cancer risk. I mean we have a fairly successful intervention model. It's not ideal. It's not what anybody wants to do. But, people really believe 'if I do this, this is going to save my life.' So, if I'm looking at doing this blood test in order to avoid that [oophorectomy], am I putting myself at risk?"

Given this hesitation, some clinicians expressed doubts about using ctDNA results to inform subsequent treatment strategies, such as delaying prophylactic surgery.

Pessimistic clinicians also expressed uncertainty about the utility of ctDNA in detecting early, nascent tumors. They emphasized that "not all cancers have a detectable, pre-clinical phase" (ctDNA12) and highlighted the lack of knowledge around the natural history of certain cancers and evidence of improved survival from early detection and treatment.

Although self-identified gender did not influence views on utility, clinician type, and speciality did. First, genetics providers (genetic counselors and geneticists) expressed more optimistic views on the clinical utility of ctDNA testing for HCS management, while cancer clinicians expressed more uncertainty about whether ctDNA testing would add much utility to current management. Furthermore, among cancer clinicians, speciality appeared to determine views on pancreatic and ovarian cancer such that those caring for patients with pancreatic cancer and ovarian cancer (a sex-specific cancer) were more likely to hold pessimistic views about the utility of ctDNA for these cancers compared to clinicians specializing in other cancer types.

The Role of ctDNA Testing in HCS Management

Optimistic professionals expressed confidence that ctDNA testing could serve as a stand-alone test and that results could be used to inform treatment. However, optimists also acknowledged that there would likely be a period of time where ctDNA testing was performed in conjunction with standard screening until it was established to be "at least as effective, if not more effective than [standard] screening" (ctDNA08).

Pessimistic providers expressed more skepticism about the role of ctDNA testing in detecting cancer. They reiterated that ctDNA testing would always serve a supplementary role to other cancer screening modalities, stressing that "there's always going to be a need for diagnostic imaging" (ctDNA07). Moreover, pessimistic providers highlighted that certain screening procedures (eg, colonoscopies) also served a therapeutic role and, therefore, could never be replaced. Overall, views on the clinical role of ctDNA testing in HCS did not vary considerably between cancer and genetics professionals.

Invasiveness of ctDNA Testing

Generally, most clinicians agreed that HCS patients are burdened by frequent and invasive screening for multiple cancers over their lifetime. However, optimistic and pessimistic providers differed in their views on how ctDNA testing

Table 2. Key themes and illustrative quotes.

Theme	Optimistic	Pessimistic
Clinical utility	When it comes to like screening for pancreatic cancer, I think everyone would jump on board because we have no prevention and we have no screening. —ctDNA06	So, not all cancers have a detectable, per-clinical phase, which is the thing you're always trying to find with that. At least with the tests that we have. So, the question is 'would ctDNA, you know, for pancreas cancer would there be a detectable, pre-clinical phase where you could actually intervene and cure the cancer?' —ctDNA12
	Where catching them early is quite hard, ovarian cancer, pancreatic cancer. I think those are the priority ones. —ctDNA02	But, when we look at ovarian cancer risk...I mean we have a fairly successful intervention model. It's not ideal. It's not what anybody wants to do. But, people really believe 'if I do this, this is going to save my life.' So, if I'm looking at doing this blood test in order to afford that, am I putting myself at risk? —ctDNA20
	Ovarian and I'm thinking pancreatic and I think there would be huge buy-in in that population. —ctDNA30	I think it's probably potentially useful for certain cancers that we know we have reasonable treatment for. I would be very worried about ovarian and pancreas and those sort of, you know, those bad ones. Well, you know, I mean you'd be picking at a stage, I mean I assume you'd be picking it up at a little bit earlier stage than the patient presents with this, and then they'll undergo all those treatments, but they're still going to die fairly soon. —ctDNA03
Role in screening pathway	I think it's going to take a lot of time to get there which means I think that will probably be an interim period of probably many years where maybe it does serve as a supplement to you getting your mammogram, your MRI and your circulating tumor DNA... Or, if it's just, you know, showing that there's something on the circulating tumor DNA maybe that's the point where someone would say "ready to [go] for preventative surgery".—ctDNA06	Is there ever a point where you would feel comfortable not using confirmatory tests like mammography? I think I would always because that's just like a hint of where or what's happening. You don't actually know what's going on. You would still need to image them—ctDNA04
	And so, I think at the very least if we had cell-free tumor DNA monitoring that for a period of time it would have to be done in conjunction with screening in order for us to satisfy ourselves that it was at least as effective, if not more effective than the screening. So, I would envision them being done together for enough time, with a large enough cohort of patients that we could be satisfied that there was efficacy there. –ctDNA08	I don't see a world yet where it would be stand-alone and people not avail of all the other recommended screening preventions. –ctDNA25
	The golden ticket and we can scrap all course of screening and now just do this blood test. Of course it's not going to work like that. But then, maybe with further time, if it is that adjuvant test and it is running parallel and then you've got good results with it, then maybe you'll be able to make those alterations. —ctDNA10	I think that you know, one day there may be a utility for certain cancers. But, I can't see it necessarily being superior or used in isolation of the current screening which we know is really good. –ctDNA15
Invasiveness	Because it would be a simple blood test that could be done a little more often. It could be done quarterly or semi-annually.—ctDNA02	Well, I imagine that it would be very stressful for the patient because they would be worried that they have cancer we can't find; and just waiting for the other shoe to drop type of thing. I would imagine that for, as a clinician, that it would potentially force us to go on a big, you know, hunt. And, maybe require fairly extensive and who knows maybe unnecessary investigations. —ctDNA16
	I think it would be really welcomed and really exciting to be able to offer them something that's less invasive and hopefully better or earlier detection. —ctDNA06	It would, obviously add to the burden for the system because you might be doing additional investigations and finding nothing. —ctDNA08
	And so that gives the patient, you know, an opportunity to make some choices. If they were diagnosed at later stages then, you know, you still have a choice but you still…most people end up doing this chemotherapy. And, the chemotherapy is not easy; it's not. You know? If we can avoid that at any, you know at any way, shape or form that would be great. —ctDNA20	And then…like from the blood draw. And then, you're also going to want to make sure that you're not delaying the diagnosis beyond what your other strategies would, if you're looking for it as a replacement. —ctDNA04
Enthusiasm	And so, if you can skip your imaging and blood work for a single blood test that would clearly be superior for patients.—ctDNA01	
	I mean I think circulating DNA has the potential to be a game-changer. You know, obviously detecting cancers early would be amazing.—ctDNA32	
	I think most patients would be all over it. You know, if you're told you have a higher than average risk of getting a cancer and that there might be a blood test that helped detect that cancer early and there are really no…I mean, aside from minor inconvenience and bruising there's no down side to having a blood test… I think you'd want anything and everything that might find a cancer earlier.—ctDNA08	

Table 2. Continued

Theme	Optimistic	Pessimistic
Universal concerns		Often it's sort of a screening fatigue that happens after a few years of normal screening. —ctDNA01
		Unless you do your blood test first and then, you know, I don't know. I don't know. I mean if you have nothing that you can do beyond what you're already doing you're just going to have an anxious patient. —ctDNA03
		I'm generally not like a fishing expedition kind…you know what I mean? I'm like, if you have a question; target the question to get a target, you know to get your answer. But, I mean, all of that and then they consent to well, okay, well this is a general screening test for everybody and then what is [the] positive rate and then what is the subsequent work? And again, if it is very broad, then does that mean that, you know, whole body MRI's for basically everybody? —ctDNA10
		I mean, I think you're probably going to want to make sure that it's you know something you can get back within a few weeks, at most, like a month probably or so; ideally a few weeks. And then…like from the blood draw. And then, you're also going to want to make sure that you're not delaying the diagnosis beyond what your other strategies would, if you're looking for it as a replacement—ctDNA02
		A false-negative is a problem because somebody that might have had prophylactic surgery, is going to delay. And then, she's going to sit on that cancer.—ctDNA11
		You know, you can have p53 mutated and the cell dies and, you know. Right? And, there isn't a cancer anywhere. So, you could be chasing all sorts of stuff or left feeling like, you know, having the person feel like they're sitting on a time bomb when not really. So, you know, that's going to be a huge thing. And then, as you say false-negatives. So, you...it would have to be a pretty good test to say 'well, we're not going to do colonoscopies anymore. We're just going to do a blood test.' Isn't that great? It would do it but, yeah. So, I think there's potential for big false-negative and false-positive issues with this. So, we'll have to see how the science is for sure. —ctDNA12

would affect invasiveness at 2 junctures: (1) at the point-of-testing and (2) follow-up after a positive screen. Optimistic professionals suggested that ctDNA testing could reduce invasiveness at the point-of-testing. They emphasized that it would be "less invasive" (ctDNA06) and "a simple blood test" (ctDNA02). Optimistic providers also discussed the potential for ctDNA testing to reduce the need for invasive diagnostic investigations and treatment, which would otherwise be necessary if the patient underwent standard screening, and the cancer was detected at a more advanced stage. For example, early detection of cancer using ctDNA testing may reduce the need for multiple, invasive tissue biopsies that may be required in a metastatic stage.

Clinicians who were more pessimistic expressed concerns that the ctDNA test itself could increase invasiveness at the point-of-testing. They indicated that "patients don't like needle pokes" (ctDNA01) and may even be deterred by frequent blood draws. Furthermore, pessimistic providers also raised concerns about ctDNA results triggering additional unnecessary investigations downstream, thereby increasing invasiveness:

> "*As a clinician, it [ctDNA result] would potentially force us to go on a big, you know, hunt. And, maybe require fairly extensive and who knows, maybe unnecessary investigations*." -ctDNA16

Pessimistic providers also worried about over diagnosis and noted that the additional investigations triggered by ctDNA testing could delay diagnosis for patients beyond the standard diagnostic pathway and incur significant burden and costs to the healthcare system, over and above the cost of ctDNA testing itself.

Genetics providers were overall more optimistic about ctDNA's potential to reduce invasiveness, while non-genetics professionals emphasized the invasiveness ctDNA testing would add to current management strategies.

Universal Concerns Around ctDNA Testing

Both optimistic and pessimistic providers raised similar concerns about ctDNA testing in HCS management. Clinicians emphasized that HCS patients are already burdened by "screening fatigue" (ctDNA01) and worried ctDNA results would trigger extensive follow-up testing, further increasing fatigue for patients. They also feared positive results from ctDNA testing would prompt clinicians to go on a "fishing expedition" (ctDNA10) to identify the tumor site of origin, a process which may be further hindered by a lack of available diagnostic tools to establish the primary site.

Many participants also worried that false-negative results would reduce adherence to regular cancer screening. They raised concerns that patients may be falsely reassured by negative results, leading them to delay or even forego scheduled screening, potentially delaying diagnosis and treatment. This delay to treatment could contribute to poorer prognosis and further increase patient anxiety.

Discussion

There is a growing interest in using ctDNA testing for early cancer detection; our study is the first to report on the perceived utility of ctDNA in early cancer detection amongst HCS patients. Providers in our study described ctDNA as "transformative" and a "game-changer". However, participants were divided on use of ctDNA testing in HCS management with some participants being optimistic (optimists) while others were hesitant about the use of ctDNA testing in HCS management (pessimistic). Differences were driven by views on (1) clinical utility (2) ctDNA's role in cancer screening, and (3) ctDNA's invasiveness. While some professionals were optimistic that ctDNA would have clinical utility as a non-invasive diagnostic test for organs without existing screening modalities, others were pessimistic about its utility for aggressive cancers with unknown tumor etiology, arguing it would likely increase invasiveness. The contrasting

positions among professionals on the clinical role of ctDNA testing in the care pathway for HCS patients raise the potential for practice variations; this highlights a need to develop evidence to support clinical implementation and guidelines to standardize adoption.

A small number of studies have addressed the clinical utility of ctDNA testing, generally focusing on treatment. Our results are consistent with findings from a study exploring oncologists' views on the use of ctDNA in colon cancer treatment, where participants were generally enthusiastic about the clinical utility of ctDNA testing.[9] However, this study was limited to treatment within a metastatic colorectal cancer setting. Our study has broader application beyond colorectal cancer treatment, as we explored the clinical role of ctDNA testing across the entire management pathway of HCS patients which encompassed screening, detection, and diagnosis for all cancer types. Furthermore, the concerns highlighted by our providers are consistent with those discussed in a review by the American Society of Clinical Oncologists and the College of American Pathologists (ASCO/CAP).[8] Authors of the review raised concerns about the sensitivity of ctDNA and potential for over diagnosis when used for early cancer detection.[8] Together with the recommendations of the ASCO/CAP review, our findings highlight a need for further research on the clinical role of ctDNA testing in early cancer detection among HCS patients.

We found that providers anticipated using ctDNA testing in different ways in managing HCS patients. Of note, providers were split on the clinical utility of ctDNA testing in ovarian and pancreatic cancers, aggressive cancers that do not have effective screening, but are associated with late-stage diagnoses and high mortality rates. Pessimistic providers were doubtful that ovarian and pancreatic cancer could be routinely detected at an early stage, and skeptical about improvements in health outcomes from early detection, a view supported by recent findings.[32] These providers, typically oncologists, focused much of their pessimism on the lack of understanding of the pathobiology of these cancers. In contrast, optimists, typically genetics providers, felt that ctDNA could detect these cancers at early stages, and reduce morbidity and mortality in these populations. This equipoise emphasizes the need for research on the clinical utility of the test in comparison to other cancer screening and diagnostic modalities.

Our findings also suggest a need for research on patient-reported outcomes. Professionals' views that patient anxiety may be exacerbated by introducing ctDNA or that patients may be falsely reassured by negative results indicate a need to evaluate the psychological and behavioral consequences of introducing ctDNA testing into the care pathway. Overall, this evidence could inform development of mitigation strategies to ensure early diagnosis and reduce harms such as patient education and use of decision aids.

Our study has a few limitations. Participants' responses were based on hypothetical expectations of ctDNA testing; real-world experience with the test may differ. Of note, some of our participants did have direct experience with ctDNA in treatment settings and thus some of our results were informed by real-world experience with the technology. Furthermore, our analysis did not reveal a difference of views on ctDNA and its utility between the professionals who requested the ctDNA explanation and those with prior experience with ctDNA. Nevertheless, hypothetical studies provide an opportunity to explore the full spectrum of clinical utility across settings and contexts. Therefore, they can inform comprehensive measurement and reporting in future real-world studies, in particular in CHARM's upcoming non-hypothetical clinical trial (NCT04261972). Furthermore, many participants were genetics providers from tertiary academic centers in Central Canada with fewer participants practicing in community settings. This may limit transferability of our results to community settings or non-genetics specialists. However, many participants from academic settings care for patients in the community setting and provided views on the use of ctDNA for these patients. Nevertheless, qualitative research is not intended to generalize or represent views of the population. The goal of qualitative research is to describe and understand perspectives of individuals and their experiences, consistent with our goal to explore professionals' perspectives on the utility of ctDNA in HCS management. [33]

Conclusions

Despite these limitations, health professionals anticipate that ctDNA testing will transform early cancer detection and management for HCS. However, the contrasting positions on ctDNA's role in HCS management raise potential practice variations and highlight a need to develop evidence to support clinical implementation and guidelines to standardize adoption. Future large-scale prospective trials are needed to evaluate the clinical utility of ctDNA testing in the HCS population and provide the evidence to inform practice and reimbursement decisions.

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Conflict of Interest

William Foulkes: AstraZeneca (RF); **Sophie Sun:** Novartis, Bristol-Myers Squibb, Pfizer, Purdue, Takeda, AstraZeneca

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Author Contributions

Conception/design: Y.B., S.S., L.E.O., M.C. Provision of study material/patients: N.N.B., L.D., L.S.P., W.F., M.B., So.S., K.A.S., D.A.R,. A.K., A.P., T.J.P., R.H.K., Y.B. Collection and/or assembly of data: S.S., L.E.O., M.C., A.C. Data analysis and interpretation: S.S., L.E.O., M.C., C.M., A.S., A.C. Manuscript writing: S.S., Y.B. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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