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Effectively communicating comprehensive tumor genomic profiling results: Mitigating uncertainty for advanced cancer patients

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Effectively communicating comprehensive tumor genomic profiling results: Mitigating uncertainty for advanced cancer patients

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ABSTRACT

Objective: To understand advanced cancer patients' experience of uncertainty when receiving comprehensive tumor genomic profiling (CTGP) results, and their perceptions of how healthcare provider (HCP) communication impacts uncertainty.
Methods: Thirty-seven semi-structured interviews with advanced cancer patients were conducted within two weeks of patients receiving CTGP results. Transcripts were thematically analyzed, using an inductive approach.
Results: We identified three themes that illustrate patient experience of uncertainties when receiving CTGP results: 1. Type and degree of uncertainty fluctuates along with changing illness circumstances and the nature of the CTGP results; 2. HCPs' co-ordination of care and communication shapes uncertainty, with immediate, clearer and simpler information promoting certainty; and 3. Patients felt that communicating results to reduce relatives' uncertainty is important, with patients choosing the time and process for achieving this and desiring HCPs support.
Conclusion: Oncology patients are confronted with an array of uncertainties. Clear, simple communication from HCPs about results and their implications, and support to manage uncertainty, will be of benefit.
Practice implications: If CTGP is to become routine clinical practice, clear communication will be crucial in reducing uncertainty. Awareness of potential uncertainties experienced by patients when receiving results, will assist HCPs to address uncertainties, reduce uncertainty where possible, and offer targeted support to patients struggling with uncertainty.

1. Introduction

Illness uncertainty has been defined as 'the inability to determine the meaning of illness-related events' [1]. It occurs within the context of many illnesses when there is: a) ambiguity about the state of the illness, b) complexity regarding treatment and the system of care, c) lack of information about the diagnosis and seriousness of the illness, and/or d) unpredictability of the course of the disease and prognosis. Illness uncertainty can change over the course of an illness, such as cancer [1,2]. Uncertainties about diagnosis and prognosis are major factors that influence patients' cancer experience [3]. Uncertainty is typically highest at diagnosis when the patient lacks an understanding of their illness. Yet it can also increase when patients are making treatment decisions [4], or when disease progresses. In lung cancer patients, cancer related illness uncertainty has been associated with higher stress, more psychological and depressive symptoms, and poorer emotional well-being [5].

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Cancer-related uncertainties can be somewhat reduced for patients by using genetics as a clinical tool [6,7]. Single gene cancer testing is a part of routine clinical practice. For example, gene testing is used to identify molecular subtypes of common cancers which are more receptive to specific therapeutic approaches, and thus lead to more targeted treatment [8]. More recently, somatic genomic testing has been used, which involves broader investigation than single gene testing by simultaneously testing for multiple gene variants [9] with the hope of increasing the likelihood of identifying a gene variant that might guide prognostication and treatment. Thus, patients and clinicians may look to genomics to reduce uncertainties about disease prognosis [10], how to manage a hereditary cancer syndrome [11], and about the family's risk [12].

While somatic genomics testing provides hope for improvement in cancer morbidity and mortality by helping to identify specific pathogenic variants to guide therapeutic approaches [9,13], the complexity of genomics has the potential to introduce novel scientific, practical and personal uncertainties for patients [14]. Genomic testing, via comprehensive tumor genomic profiling (CTGP) (somatic testing with possible follow-up for results that may have a germline origin), can reveal variants that are: 1) clinically actionable versus non–clinically actionable (no proven treatments); 2) of uncertain clinical significance (VUS); and 3) germline genetic variants (with implications for relatives) [15]. Additionally, therapeutic approaches targeting actionable genomic results are often experimental, which has the potential to introduce further therapeutic uncertainties.

Newson et al. [16] define five types of uncertainty specific to the genomic context, including: 1) inherent uncertainty, related to the inability of a genomic test to provide black and white answers (e.g. a number of genes and environmental conditions may contribute to risk, making precise risk estimates difficult, while VUS are not readily interpretable); 2) Informational uncertainty, arising from the sheer complexity and volume of information arising from genomic testing, as well as how well that information is conveyed; 3) Views on uncertainty, impacted by the recipients' views on the likelihood of a certain test outcome; 4) Structuring of information, arising from how recipients structure or integrate genomic results with existing beliefs, attitudes and values; and 5) Personal views about knowledge, arising from attitudes to uncertainty as being positive or negative. In combination, these different types of uncertainty can impact how an individual defines, responds to, and copes with genomic uncertainty. This framework also suggests that how key people within the patient's support network, such as health care professionals (HCPs) and family members, communicate about genomics and uncertainty, may influence how a patient views and responds to uncertainty.

To date, the literature on patient uncertainties in cancer genomics has focused mainly on genomic testing to identify risk of hereditary cancer syndromes, with only a few studies investigating genomic testing to guide treatment decisions for breast cancer patients [7]. Furthermore, literature on how HCPs, patients and relatives communicate about uncertainties in this setting is sparse, with most literature focusing how results are delivered, rather than how uncertainty is discussed [17–19]. The purpose of this study, therefore, was to increase our understanding of advanced cancer patients' experience of uncertainties when receiving CTGP results, and their experiences and preferences regarding communication of these uncertainties with HCPs and their relatives.

2. Methods

2.1. Participants

The Molecular Screening and Therapeutics (MoST) Program is an Australia-wide program recruiting adult (≥18 years) cancer patients with pathologically confirmed advanced or metastatic solid cancers, with a focus on rare cancers. To be eligible, patients need sufficient accessible tissue for CTGP, and to be receiving their last line of standard treatment (or have received and failed/be ineligible for all standard treatment) [20].

MoST participants potentially receive one of three results from their CTGP: 1) actionable, with a clinical trial available through MoST (actionable – MoST sub-study); 2) actionable, no clinical trial available through MoST (actionable – other treatment); or 3) no actionable variant (NAV). These results are usually conveyed to patients by their oncologists, but some patients may be directly contacted by the researchers if their oncologist is unavailable. If there are actionable findings with a therapeutic trial available through the MoST program, participants are offered enrollment in the trial, where appropriate. (Some patients may have still been considering this decision at the time of data collection for this paper). VUS results are not returned in this study [20].

The Psychosocial issues in Genomic Oncology (PiGeOn) Project, is a psychosocial sub-study of the MoST Program [21]. Participants give written consent to participate in the PiGeOn Project while consenting to the MoST Program. The PiGeOn project aims to investigate the psychosocial, ethical, and behavioral implications for patients when undertaking CTGP.

2.2. Data collection

The PiGeOn project collects questionnaire data from all participants and conducts semi-structured telephone interviews (with a subset) at: baseline; within two weeks of participants receiving their results; and 2 months following receipt of results. The focus of this paper is the second timepoint, following receipt of results. Interview participants were purposively sampled [22] to ensure diversity and maximize the likelihood of eliciting all relevant viewpoints. Patients were selected who had received different CTGP results, had diverse cancer diagnoses, varied in age, and represented both genders. Demographic and disease characteristics were extracted from the study database.

Interviews were conducted by two trained qualitative interviewers (NB, AF) from November 2017 to May 2019, continuing until data saturation (no new information after three consecutive interviews) [23]. Interview guides were developed by a multi-disciplinary research team, including stakeholders, and informed by the literature. Interview questions covered topics such as reaction to results, communication of results, and included specific questions on perceptions of uncertainty. Interview questions were iteratively modified over the course of the study guided by prior interview responses.

2.3. Data analysis

Interviews were audio-recorded, transcribed verbatim, anonymized and thematically analyzed, using an inductive approach [24,25]. Individual coding of an initial six transcripts was completed by three researchers (NB, MB, and PB) to determine a preliminary coding framework, which was refined after reading a further five transcripts. The remaining 16 transcripts were coded by one researcher (NB) using the final coding framework. Relevant quotes to illustrate the identified themes were extracted. Differences in researcher interpretation of the data were resolved through discussion, with the multidisciplinary nature of the research team (psychology, bioethics, medicine) minimizing researcher bias regarding the meaning of results [26].

3. Results

Of participants invited to an interview, 95% agreed. Interviewees were on average 61.9 years old, and 49% were female (Table 1).

Table 1
Demographic and disease characteristics of PiGeOn interviewees.

Variable	PiGeOn interviewees (N = 37) N (%)
Sex	18 (48.6)
Female	19 (51.4)
Male	
Married	58 (75.7)
Parent	29 (78.4)
Education	15 (40.5)
Secondary school	6 (16.2)
Vocational training	16 (43.2)
University	
Accessibility/Remoteness Index of	22 (59.5)
Australia[a]	8 (21.6
Major city	7 (18.9)
Inner regional	
Outer regional	
Cancer incidence	28 (75.7)
Rare (<6 cases/100,00)[b]	4 (10.8)
Less common (6–12 cases/100,00)[c]	5 (13.5)
Common (>12 cases/100,000)[d]	
Comprehensive tumor profiling result	10 (27.1)
Actionable – MoST sub-study	15 (40.5)
Actionable – other treatment	12 (32.4)
No actionable variant (NAV)	
Multiple primary diagnosis	5 (13.5)
Visited a family cancer clinic prior to the study	5 (13.5)
Previous genetic testing	6 (16.7)
Eastern Cooperative Oncology Group	21 (56.8%)
Performance Status	14 (37.8%)
0	2 (5.4%)
1	
2	
Age at consent (years)	61.9 (7.7)
Mean (SD)	63.0 (12.0)
Median (IQR)	45.0–75.0
Range	
Time since diagnosis (years)	2.6 (1.6)
Mean (SD)	0.1–12.4
Range	
Length of interview	23:42
Mean (mm:ss)	10:07–36:40
Range (mm:ss)	

[a]Derived from self-reported postcode and the Australian Bureau of Statistics Accessibility/Remoteness Index of Australia.
[b]Includes cancers of the biliary tract, bladder, brain, lung, oesophagus, ovary, peritoneum, sarcoma, thyroid and unknown primary.
[c]Includes cancers of the stomach and pancreas.
[d]Includes cancers of the breast and prostate.

Three themes emerged from the analysis: 1. Uncertainty is diverse and fluctuating, with changing illness circumstances, CTGP results and diverse coping strategies associated with perturbations; 2. HCPs' co-ordination of care and communication can shape uncertainty, with immediate, clearer, and simpler information promoting more certainty; and 3. Patients felt communicating results to reduce relatives' uncertainty is important and requires confidence and care, with many patients choosing the optimal time and process to optimize relatives' outcomes.

3.1. Uncertainty is diverse and fluctuating

3.1.1. Illness uncertainties are dominant

Interviewees discussed the intense experience of uncertainties inherent to cancer. The desire to reduce uncertainties was part of their motivation to undertake CTGP. Interviewees hoped that their result would help explain their rare or unknown primary diagnosis, provide insight into their prognosis, or inform treatment. When asked what type of uncertainties related to the CTGP they were experiencing, most interviewees instead discussed their illness-related uncertainties, suggesting that their existential uncertainty outweighed CTGP-related uncertainties.

> *"The uncertainty is that it's a terminal disease but there's no end point. No one can say, you've got three months or you've got six months, because they really don't know. The whole actual cancer is uncertain." Female, 58 years, endometrial cancer (rare), actionable - MoST sub-study*

3.1.2. Waves of uncertainty

Interviewees discussed being unsure about how effective their current treatments were and the waves of uncertainty that occur throughout the treatment process. In particular, prior to key scans or new treatments, participants described feeling greater uncertainty and associated anxiety.

> *"I've been taking targeted therapy tablets, and we don't know if they've done anything yet. … I'm a bit anxious about that, you're always a bit anxious when you have a scan. But I'm probably more anxious this time because it's either make or break, so either these tablets have worked or they haven't." Female, 58 years, endometrial cancer (rare), actionable - MoST sub-study.*

3.1.3. CTGP reduces illness and treatment uncertainties

Regardless of the result (no actionable or actionable variants), results relieved future treatment uncertainty to some degree. Those who had exhausted traditional lines of treatment and received actionable results were reassured that they now had a treatment option with which to move forward, and where interviewees were currently on a treatment which appeared to be effective, an actionable result provided them with a back-up plan, relieving their uncertainty about the future.

> *"[Oncologist] said "We're doing so well on the stuff at the moment that we should stay with that for a bit, and then if we get to a point where that starts to break down, then we've got this as a fall-back position. It provides that back up, which is really nice to have." Male, 60 years, pancreatic cancer & sarcoma (less common), actionable - other treatment*

A no actionable variant result increased uncertainty about future options for interviewees, as there were no immediate treatment recommendations. However, it also resolved some uncertainty. Interviewees who received this type of result still felt it provided useful information for treatment decision-making around which drugs not to pursue. Without a gene variant identified, interviewees also had peace of mind that traditional lines of treatment, such as chemotherapy, had been their best treatment option.

> *"Because I'm not a PARP, I'm not going to respond probably well to a PARP inhibitor and it costs a nominal amount of money, so obviously that's guided me already to say I'm not even going to pursue that line." Female, 60 years, ovarian cancer (rare), NAV*

> *"I now know that there's nothing out there that I should be trying." Female, 62 years, lung cancer (less common), NAV*

The absence of germline results alleviated uncertainty related to whether the interviewee's cancers were hereditary, and therefore helped to reduce participants' uncertainty about their family's risk.

> *"Happy that it's not genetic. It's good to know that my children won't have it, or my sisters. Except for the normal chance of getting it." Female, 58 years, endometrial cancer (rare), actionable - MoST sub-study*

For some, actionable variants also provided an explanation as to why they had responded surprisingly well to treatment or survived longer than expected.

"there were two genetic markers, one that proved why the Enzalutamide worked longer. that's why that worked so well for 40 months. it's nice to know why it worked, because most people were only getting 4–6 months out if it." Male, 62 years, prostate cancer (common), actionable – other treatment

3.1.4. CTGP-related uncertainties

Despite seeing CTGP as a tool to reduce treatment uncertainty, interviewees did experience some uncertainties about treatment recommendations based on their result. Interviewees discussed the uncertainty of being recommended a trial treatment with limited efficacy data. They also wondered how such treatment would fit with conventional treatments, such as chemotherapy, or if they would need to stop their current treatments. Further, interviewees discussed feeling unsure about how they would cope with more treatment and the potential side-effects.

"I mean there's obviously no guarantee that any trial will work, but at least if you know the markers, surely you have a better percentage of working." Female, 53 years, neuroblastoma (rare), actionable - other treatment

"that's the absolute last treatment I can have. what I can gather, they've been getting reasonable results from it but it's hard to find out any information. just to see how that trial has been going." Male, 62 years, prostate cancer (common), actionable - other treatment

"just what side effects. Am I going to be crook, similar to when I went through chemo?" Male, 63 years, bladder cancer (rare), actionable - other treatment

Interviewees discussed deficits in their own knowledge around genomics and the research processes. These uncertainties included potential costs and travel associated with treatment, limited knowledge about genomics, how secure study data (and therefore their genetic information) was, and unknowns about the research process.

"I can't drive down there, so I had to put a lot of thought into do I need to do this, or do I stay on the treatment I'm on at the moment? Financially how much is it going to cost?" Female, 68 years, pancreatic cancer (less common), actionable - MoST sub-study

"It's the security of the data. The Program does what it can to keep data secure. It's who's on the other end trying to get in that's the issue, and you can't control that." Female, 65 years, sarcoma & squamous cell carcinoma (rare), actionable - other treatment

"I didn't really know how the program continued from there on in, was I to be called in, is it once a month, once a week, once a fortnight, once a year?. I don't know what the situation is, do I still have the opportunity to go into that program or am I already in that program?' Male, 68 years, pancreatic cancer (less common), actionable – other treatment

Interviewees did, however, demonstrate an understanding that genomics is an evolving field, and that there are limitations to what is currently known. Interviewees discussed how research studies such as the MoST program help to reduce this scientific uncertainty, by adding to scientific knowledge. Interviewees acknowledged that receiving a variant of uncertain significance (although not returned as part of the MoST study) would be disappointing, but that it was still information and could potentially be helpful for themselves or others in the future.

"The way I was looking at it when they couldn't find the genetic marker. It's just that the science isn't there yet. If it goes into a bank that provides someone with an answer further down the track, well done." Female, 65 years, sarcoma & squamous cell carcinoma (rare), actionable – other treatment

3.1.5. Coping with uncertainties

Interviewees engaged in a variety of coping strategies to deal with their uncertainties. Interviewees discussed strategies which actively aimed to reduce their perceptions of uncertainty, such as information seeking and making changes to their lifestyle, and those used to manage the emotions generated by uncertainty, such as: prescription drugs, seeking support, relying on their faith, maintaining a positive outlook, and preparing for the worst outcome. Finally, some interviewees used hobbies to distract themselves from their uncertainty, compartmentalized their uncertainty, or just accepted uncertainty.

"The more I can keep informed the more I feel as if I'm in control of what I'm doing. I've got little notes that I take with me to the doctor and ask questions as I go." Female, 67 years, pancreatic cancer (less common), actionable - MoST sub-study

"I pray a lot. I just put it onto Him." Male, 52 years, liver cancer (rare), NAV

"I prepared myself to receive results that there was no benefit for me. And that way when the results came through, there was no disappointment, no stress. I didn't spend time worrying about it because I knew there was an extremely high likelihood that nothing would come of it, so that's what I prepared myself for." Female, 56 years, sarcoma (rare), non-actionable variant

"Uncertainty is there. the uncertainty is always there, every day. I just accept it." Male, 49 years, angiosarcoma (rare), NAV

3.2. HCPs communication shapes perceptions of uncertainty

3.2.1. A trusted source

Many interviewees who reported a positive relationship with their HCP (i.e., oncologist, surgeon, neurologist) described trusting their HCP's advice and the information provided and seemed to convey less perceived uncertainties about results and treatment recommendations. Interviewees valued expertise; some saw the researchers as holding the greatest knowledge, others felt their HCP understood their illness the best.

"We've been speaking to each other now for the best part of five or six years, so, he knows everything that's going on with me, and I know how he deals with things. I definitely think he's the right person to be doing it for sure." Male, 60 years, pancreatic cancer & sarcoma (less common), actionable – other treatment

"I have confidence in my oncology professor. I would listen to his advice and recommendations." Female, 63 years, cancer unknown primary (rare), actionable – other treatment

"It was a registrar [who returned results], and I don't think he really knew very much about what it was. So, because I'm on a clinical trial I actually asked a doctor at the [cancer centre] to go through it with me. I was much more able to understand what the results meant." Female, 61 years, breast cancer (common), actionable – other treatment

3.2.2. HP Co-ordination of care and communication

HCP co-ordination of care and communication style also impacted uncertainty perceptions for interviewees. When HCPs had provided insufficient or quick information or used complex language to communicate results, some interviewees reported experiencing uncertainties about the results and treatment options. Some interviewees also reported prolonged uncertainty when there were

delays in communicating their results with them. Such delays could occur due to a breakdown in co-ordination of care, with results not being communicated effectively between institutions, or because the Oncologist delayed conveying received results to the patient.

> *"I didn't receive any verbal, face-to-face discussion at all. I received a message to say that the results had been sent to [Oncologist] and when I didn't hear anything from [Oncologist] I sent a message to his secretary, and said I'm assuming the fact that I didn't hear anything means that nothing was found to help me. And she said she would forward me the results, and it was a single sheet that said nothing had been found. So, nothing was explained to me or discussed with me." Female, 56 years, sarcoma (rare), NAV*

> *"[Oncologist] was using all these big words and I thought, I really don't understand what you mean by that." Female, 67 years, pancreatic cancer (less common), actionable – MoST sub-study*

> *"I had to chase the [hospital] up, and the [hospital] said they hadn't received them. And I said, "Well, I've spoken to the MoST study and they said they definitely sent them." I was quite anxious about knowing the outcome of those results. I had to really pressure both sides, and then they got resent. then I've had to ring around and get hold of the oncologist and have a chat. there was nothing really electrifying in the results other than that drug that he'd already canvased as an option to commence treatment on would work to kill the tumours." Male, 55 years, sarcoma (rare), actionable - MoST sub-study*

Receiving conflicting information from different HCPs heightened one interviewees' perception of uncertainties about their results and treatment options.

> *"[Oncologist] said that there was a couple of pathways. one was a stronger one. and there was a weaker one. And she said that they weren't going to continue on even though the markers in this trial covered that, because it was near my brain. But my neurosurgeon said it wouldn't need to go through the blood-brain barrier, it's not in your brain, just near it. I expected because they had the markers, they would continue the study, but they haven't. I think the oncologist should have spoken to my neurosurgeon because she is a brain specialist. I think working collaboratively with her would have been a more informed decision." Female, 53 years, neuroblastoma (rare), actionable – other treatment*

Conversely, where HCPs were described as providing clear information about results and implications for future treatment or facilitated appointments with the research or clinical trial team, interviewees reported perceiving greater certainty about their results and treatment options.

> *"[Oncologist] is a fantastic doctor and she goes to great lengths to make sure you fully understand everything. she always stops and says, "Now do you understand that?" She's very thorough, I always walk out of there feeling like I fully understand everything." Female, 63 years, ovarian cancer (rare), actionable – other treatment*

Interviewees also highlighted the importance of a two-way communication pathway with their HCP in reducing their uncertainty, giving them the opportunity to ask questions to resolve some of their uncertainties. This practice was also appreciated for the opportunity to communicate their understanding of the uncertainties inherent in cancer and genomics to their HCP.

> *"you know we just discussed them together and I asked her what certain things were." Female, 62 years, lung cancer (less common), NAV*

3.3. Communicating results to reduce relatives' uncertainty is important and requires confidence and care

Interviewees highlighted the importance of understanding their results before communicating them with their relatives.

> *"I've just told them that my bloods were good and my CT has no changes and I'm not eligible [for] any trials. But I haven't in depth, I'm just about to visit everyone, so I'll read this and talk [to the family] more about it." Female, 60 years, ovarian cancer (rare), NAV*

Interviewees believed results could reduce their relatives' uncertainties both about their own future risk of cancer, as well as the interviewee's disease and prognosis. Knowing they had reduced their relatives' uncertainty in turn provided the interviewees peace of mind and promoted their wellbeing.

> *"I have a brother and a sister, and I spoke to both of them and I gave them a copy of the report… I said to them, "Look, I'm going to do this," and they said, "Yes, we think you should do this too." They were quite positive about the whole thing… I think they were grateful because they've got children and grandchildren so I think they were jolly grateful that I made that decision." Female, 67 years, cancer of unknown primary & renal cancer (rare), actionable - MoST sub-study*

> *"Being able to go back to [three daughters] and know that there was nothing there that they need to concern themselves with. They've been under the pressure of what I've been under and to see them being effectively cleared of any ongoing issues based on what I've had. To be able to relieve them from that was very good." Male, 60 years, pancreatic cancer & sarcoma (less common), actionable – other treatment*

> *"It's relieved some of the pressure on [wife]. To me that's massive. In her dealing with things better, it's eased the pressure on me. Trying to manage how other people are going as well as managing your own illness can be extremely difficult. I think her having a more in-depth understanding of, well this is not going to kill us tomorrow, has been a tremendous leap forward for her, and that helps me tremendously as well." Male, 60 years, pancreatic cancer & sarcoma (less common), actionable – other treatment*

4. Discussion and conclusion

4.1. Discussion

This qualitative study investigated uncertainties experienced by advanced cancer patients when receiving CTGP results. Similar to previous research on patient uncertainty in cancer genomics [6,7], we found that reducing illness and treatment uncertainties is a motivating factor for advanced cancer patients accessing CTGP. Notably, both actionable and non-actionable results were reported to reduce uncertainty by our patients. Non-actionable results, for example, could relieve patients' uncertainty regarding whether they were missing out on potentially effective treatment for their cancer. Awareness of this response may allow HCPs to give "bad" news regarding non-actionable results in a manner that supports patients to feel confident in moving forward with traditional treatments.

Consistent with published evidence, we also found that CTGP raised some uncertainties for these patients [27]. Our results suggest

it is important to convey to patients the ability of CTGP to both increase and decrease uncertainty to ensure realistic expectations.

Our results provide further support for Han and colleagues taxonomy of medical uncertainties in clinical genome sequencing [14], providing evidence from the perspective of the advanced cancer patient. Uncertainties experienced in this study overlap on a number of uncertainties noted in the taxonomy. Uncertainty was experienced across the scientific, personal, and practical categories identified in the taxonomy. For example, therapeutic uncertainties such as effectiveness of recommended treatments; economic uncertainties, such as cost of recommended treatments; and procedural uncertainties about the research process.

Our results also support the framework developed by Newson et al., by highlighting the importance of HCP communication in alleviating uncertainties when receiving results. Patients whose HCP explained results comprehensively and were perceived as trusted experts, described experiencing less uncertainty. Dean and Davidson [28] also found that HCPs who were perceived as knowledgeable, provided information and resources, answered questions, and checked understanding, were perceived as relieving uncertainty by patients receiving hereditary breast and ovarian cancer predisposition results. Such communication strategies are regularly used by genetic HCPs, such as genetic counselors [18]. As genomics becomes part of routine clinical practice, non-genetic HCPs will also need to implement these strategies when returning results. Medendorp and colleagues [29] suggest that communication skills training could be beneficial for improving non-genetic HCPs communication in delivering results. However, we know little about which communication skills are critical and how effective communication skills training in this context is. Further research on optimal strategies to improve non-genetic HCP communication in genomics is required to provide an evidence-based approach. The results from this study do suggest that elements such as avoiding complicated language and encouraging patient questions are beneficial from the patient's perspective.

It is not possible or necessary to avoid or eradicate all uncertainty in genomics, and not all uncertainties are considered a negative experience [2,16]. Our results also provide information on the variety of coping strategies engaged in by advanced cancer patients to deal with their unresolved uncertainties. Understanding patient coping strategies will allow HCPs to more effectively support patients to manage different uncertainties. For example, lowering expectations about the likelihood of receiving results that will be of benefit, may result in less hope of cure being invested in the results, and greater tolerance of uncertainty. Newson et al. [16] have also emphasized the importance of viewing uncertainty as requiring appraisal and management, rather than elimination. Future research could examine the effectiveness of different coping strategies, given that their success depends on the match between the source of uncertainty leading to stress and the approach taken to manage that stress [30].

Notably, patients in our study acknowledged that not only they, but their relatives experience uncertainty, and that CTGP results can provide information of importance in reducing relatives' uncertainties as well as their own. Patients reported experiencing significant relief when they were able to reduce relatives' uncertainty and associated suffering. Indeed, uncertainty can ripple throughout the family as families consider the genetic risks of each generation [12]. Patients in the current study clearly felt a responsibility to convey information clearly to relatives, so as not to unintentionally increase uncertainty. Other studies [31] have noted that patients carefully navigate communication of genetic information to relatives and may require support to do this.

4.2. Limitations

While we purposively sampled across gender, age, cancer and result types in an attempt to obtain good representation of experience, qualitative findings are not intended to be generalizable. However, we believe that findings reported here are likely transferrable to the experiences of patients not represented in our sample (such as those from different countries and healthcare settings, or with different cancers) [32]. Furthermore, work is required to establish similarities and differences between groups in their experience of uncertainty after CTGP.

While this study provides an in-depth exploration of advanced cancer patients' uncertainty when receiving CTGP results, it does not provide information on whether this uncertainty is ongoing or resolves itself with time as patients are able to add new information to their experience. Longitudinal data collection is required. Our follow-up (of two weeks post-test receipt) was short, and it would be interesting to explore uncertainty within a longer time-frame.

4.3. Conclusion

Advanced cancer patients are confronted with a considerable array of uncertainties. Managing uncertainty during CTGP by improving communication with HCPs and facilitating engagement of effective coping strategies by which patients can live with ongoing uncertainty, and reduce uncertainty where possible through receipt of clear information, will benefit these patients.

4.4. Practice implications

If CTGP is to become routine clinical practice, HCP communication will be crucial in supporting patients to manage uncertainty. Awareness among HCPs of the potential uncertainties that patients may experience when receiving genomic results and identification of areas where uncertainty may be perceived as a threat, may guide providers regarding when to initiate discussions about uncertainties and how to manage them. Further, HCPs may be able to address some uncertainties directly by providing additional information. Other uncertainties may not be resolvable and thus providers may choose to support patients to manage the stress of the uncertainties through the use of coping strategies that are consistent with the stressor. For example, existential uncertainties are best addressed by emotion-focused (rather than problem-focused) coping [30].

Our results emphasize that uncertainties may arise periodically for patients in response to changes to their illness and the type of test results received. Our findings suggest that patient perceptions of uncertainties should remain on the clinicians' agenda throughout the CTGP journey.

Our participants described the importance of receiving genomic information in a timely manner, a goal that was sometimes thwarted by poor care co-ordination. As genomic testing becomes mainstreamed, it will be increasingly important that results are moved rapidly between HCPs and that all HCPs, including oncologists, are upskilled to communicate results clearly and supportively to patients.

Our results support Barlow-Stewart's [33] recommendation to foster resilience, welfare, autonomy and solidarity when offering genomic testing. This approach is underpinned by pre-test counseling that addresses the likelihood of uncertainties as part of the informed consent process. It is reinforced by a care relationship at result delivery that fosters trust, encouraging patients to remain engaged with and feel free to re-contact services to resolve any

remaining questions. Frameworks for HCP communication training developed for the simpler genetic context, such as that by Shilling et al. [34] may be translatable in part to the more complex genomic setting and provide an avenue for training HPs in these important skills.

Our results also emphasize the importance of helping patients to assist relatives with their own uncertainties, through provision of information and support. Wiens et al. [35,35] developed a useful framework to assist genetic services to develop tools to support patients in communicating genetic risk information to family members, which may be adopted for CTGP. Overall, uncertainties are key issues for HCPs to address for patients and their family members during clinical encounters.

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CRediT authorship contribution statement

Nicci Bartley: Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Megan C. Best:** Conceptualization, Supervision, Formal analysis, Methodology, Writing - review & editing. **Barbara B. Biesecker:** Conceptualization, Methodology, Writing - review & editing. **Alana Fisher:** Data curation, Writing - review & editing. **David Goldstein:** Conceptualization, Methodology, Writing - review & editing. **Bettina Meiser:** Conceptualization, Methodology, Writing - review & editing. **David M. Thomas:** Conceptualization, Methodology, Writing - review & editing. **Mandy L. Ballinger:** Conceptualization, Methodology, Writing - review & editing. **Phyllis Butow:** Conceptualization, Supervision, Formal analysis, Methodology, Writing - review & editing.

Declaration of Competing Interest

BM has a remunerated consultant role with the company Astrazeneca with respect to an unrelated project. The other authors declare no conflicts of interest.

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