5-2018

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Capstone Manuscript

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Submitted in partial completion of the Master of Science Degree at Sarah Lawrence College, May 2018

Abstract

Polygenic tests such as genome-wide small nucleotide polymorphism (SNP) risk testing, exome or genome sequencing are currently on the horizon for genetic testing for inherited cancer risk. We are unsure of how patients would accept this future genetic testing and the best way to fully understand the experience of undergoing a polygenic test for breast cancer risk is to explore the experience of women who have already undergone the process. In Ontario, these individuals are those who have already had gene panel testing (GPT). This group's opinions and experiences will be directly related to the refinement and modification of the existing GPT process and will provide guidance for polygenic testing offered in the future. **Methods:** Fourteen women who have undergone GPT in the past year were interviewed in a semi-structured manner regarding their GPT experience. Interviews were recorded and transcribed, then qualitatively coded to identify key words, phrases, and expressed concepts surrounding GPT. **Results:** Participants had an overall favourable opinion regarding their GPT experience, with minor changes to be considered in future provision of GPT. In general, GPT appears to be well-tolerated within the context of a traditional genetics assessment and participants that did not receive a clinically significant result through GPT felt that they would be open to pursuing other forms of genetic testing in the future such as polygenic testing, despite the possibility of receiving an uncertain result.

Key Words: Genetic counselling, inherited breast cancer risk, gene panel testing, future genetic testing

Introduction

Gene panel testing refers to the concurrent sequencing of a predetermined set of genes via a next-generation sequencing technology. In recent years, several commercial genetic testing labs and academic institutions have introduced gene panel tests. Cancer risk panels usually include cancer-predisposition genes that have a high and/or moderate penetrance. High penetrance genes confer a lifetime cancer risk of anywhere from seventy to one hundred percent (i.e. *BRCA1, BRCA2, TP53*, etc.), while moderate penetrance genes confer a lifetime cancer risk of anywhere from thirty to sixty percent (i.e. *CHEK2, ATM, PALB2*, etc.).

There are many advantages to gene panel testing when compared to sequential single-gene testing, a practice which was only recently made obsolete by the introduction of gene panel testing. Firstly, panel tests are typically found to lower the cost of sequencing per gene. In other words, customers are receiving more for their money. With panel testing, there is also the potential to identify patients who have mutations co-occurring in different genes, potentially impacting their healthcare management. In regards to clinical efficiency, there is a quicker turnaround time for panel testing versus sequential genetic testing, which may also impact the patient's healthcare management or decision-making process. There is also less hassle for the patient and provider since informed consent can be performed all at once instead of each consecutive time a new test is ordered. With gene panel testing there may be improved detection of mutations in patients with abnormal cancer phenotypes, absent family history data, a family history that does not meet testing criteria, or when the family history meets criteria for several inherited cancer predisposition syndromes. Lastly, many genetic testing companies have

flexibility in what they offer on their panels, such that clinicians may add or subtract certain genes from the panel according to their preferences and the patient's needs (Hall et al., 2014).

Conversely, there are some drawbacks to panel testing. First, incidental findings may often arise when administering a panel test, either in addition to or instead of a mutation that explains the patient's phenotype. Particularly in the field of cancer genetics, incidental findings can cause challenges when mutations are found in genes where there is limited or no data regarding medical management. This is specifically relevant for moderate penetrance genes in which expression may be also be influenced by external factors such as the environment (Hall et. al., 2014). Patients receiving uncertain information regarding genetic risk information and clinical management may find this information difficult to accept (Hiraki et al., 2014). Additionally, with the increased number of genes now available on panel tests comes an increased prevalence of variants of unknown significance (VUSes). These VUSes can often be misinterpreted by the provider and/or patient as a true pathogenic mutation that is causing the patient's or their family's phenotype. This can lead to erroneous risk management recommendations by the provider. This is particularly troubling when we acknowledge that over time, the majority of VUSes are classified as a benign variation in the patient's genetic code (Hall et al., 2010). A small fraction of VUSes will be reclassified to pathogenic, and relaying this data to the patients often requires time and manpower.

Equivalent rates of *BRCA1/2* mutations and *BRCA1/2* VUSes are found in patients that have solely BRCA1/2 testing versus those that have gene panel testing. Gene

panel testing increases diagnostic yield and increases the rate of VUS findings (Kapoor et al., 2015; Buys et al., 2017). Approximately half of individuals who test positive for a non-BRCA mutation receive cancer screening and prevention recommendations that are altered from management that was previously determine solely from their family history (Desmond et al., 2015).

Collectively, these findings highlight not only the efficacy of gene panels at identifying BRCA mutations, but also the impact that identification of non-BRCA mutations has on diagnostic yield and patient care.

Breast Cancer Genetic Testing: The Decision to Test

One of the biggest initial questions after the introduction of *BRCA1/2* genetic testing was regarding patients' motivations for testing. Women who undergo BRCA1/2 testing are at a higher risk of being carriers for a *BRCA1* mutation, are more likely to be Ashkenazi Jewish, are more likely to have a known family mutation, are more likely to want ovarian cancer risk information for themselves, and are more likely to want breast and ovarian cancer risk information for family members. They are also less likely to be worried about insurance or job discrimination (Armstrong et al., 2000).

Research by Augestad et al. (2016) on women who were newly diagnosed with breast or ovarian cancer and who had been offered and accepted genetic testing found that patients are overwhelmed with the amount of information regarding all things breast cancer-related. Patients indicated that they need support and counselling from a healthcare professional in order to assist their decision-making process. Researchers believe that the ability to obtain such services might enable women to improve their

ability to sort through emotions and comprehend the overwhelming details of their breast cancer and genetic testing experience.

Psychosocial Implications of Cancer Panel Gene Testing

Unaffected individuals with a family history of hereditary breast and ovarian cancer who receive positive genetic testing results are most considerably affected by intrusive thoughts and feelings of avoidance and distress. Additionally, genetic testing-specific stress is generally increased in patients that are of a lower age, of African-American race, of lower education level, of lower genetic knowledge, or of Hispanic origin (Lumish et al., 2017).

Cancer Genetic Testing in Ontario

In Canada, women who have personal or family histories consistent with a hereditary breast or ovarian cancer syndrome may be referred for genetic counselling and genetic testing, which are available through the socialized health care system. The Ministry of Health and Long Term Care has published a set of guidelines for individuals in the province of Ontario who should be offered genetic counseling and who are eligible for genetic testing. These guidelines base recommendations on the individual's personal and/or familial cancer history (Genetic counseling eligibility, UHN). Genetic testing for *BRCA1/2* was introduced to Ontarians in 2001 and since then over 30,000 individuals have been tested (Finch et al., 2015). However, only in the past two to three years have Ontario genetics clinics begun utilizing gene panel testing (GPT).

Understanding GPT and Possible Future Testing Options

Currently, additional testing methods are being developed to provide a more thorough look at inherited cancer risk by using polygenic tests such as genome-wide

small nucleotide polymorphism (SNP) risk testing, or exome and genome sequencing. The best way to fully understand the process and experience of undergoing a polygenic test for breast cancer risk is to explore the experience of women who have already undergone the process. In Ontario, these individuals are those who have already had GPT. This group's knowledge, opinions and experiences will be directly related to the refinement and modification of the existing GPT process. Additionally, it will provide guidance for future polygenic testing that may be offered in the future.

As previously mentioned, GPT has been introduced to many high risk cancer genetics clinics in Ontario within the past couple of years. As we know, many of the genes included on GPT panels can lead to results of uncertain significance or positive results in moderate-risk genes and thus may have uncertain clinical management implications. We are unsure of how patients would accept future genetic testing or how they would utilize the information resulting from it. Given the complexity of themes surrounding the GPT process, qualitative analysis would be ideal for exploring patient's opinions and preferences surrounding the introduction of this future genetic testing method in Ontario. In addition, these explorations will also inform the provision of possible future polygenic tests for breast cancer susceptibility. Furthermore, concepts and themes discovered during this process could guide future quantitative research on the topic.

Methods

This study aims to explore the opinions, preferences, understanding, and psychological/health behavior impacts of gene panel testing for individuals that received genetic counseling and genetic testing for breast cancer risk. Additionally, this study aims

to explore opinions regarding the provision of a future hypothetical polygenic breast cancer risk test. The protocol for this study was developed by Gord Glendon, MSc of the Lunenfeld-Tanenbaum Research Institute and Mount Sinai Hospital, Mount Sinai Health System (MSH).

Participants

A chart review of all female patients who had undergone breast cancer gene panel testing (GPT) at the Marvelle Koffler Breast Center at MSH was performed to identify eligible participants. Eligible participants were considered to be those who had their results session within a year of the study invitation date and who were fluent in the English language. Ineligible participants included women who were actively undergoing cancer treatment or who were not fluent in the English language. Eligible participants were mailed an invitation letter, a study consent form, and a stamped return envelope. Individuals who returned completed consent forms were contacted via phone to set up a time for a taped qualitative telephone interview. Individuals who did not return a consent form were re-contacted by telephone within an approximate three-week period to determine if the invitation arrived and to address any questions the invitee might have. Purposive sampling was attempted to ensure that the study included participants that were both affected and unaffected by breast cancer and had received both clinically informative and uninformative results. There was a total of fourteen participants. The demographics of the study participants are shown in Appendix 1.

Interview

The study team previously created a list of pertinent issues to be discussed in a semi-structured interview. These issues were developed and refined into interview

questions. The interview guide comprised of questions that aimed to understand the participants' GPT experience, impacts of GPT, opinions and preferences regarding the provision of GPT, as well as participants' opinion regarding the provision of a future polygenic test. The following is an example of an interview question and related prompts: 'Do you feel that the GPT helped to explain your personal or family history of breast cancer? Do you feel the GPT added any information beyond what you may have learned from your BRCA1/2 test? Do you feel that this test added anything to your understanding of your cancer / your family's cancer / your breast cancer risk?' Participants were encouraged to bring up additional topics related to GPT that they wanted to discuss. No additional topics came up during the course of the interviews that would have considerably altered the interview guides. Each interview was conducted by Gord Glendon, Angelina Tryon, or both. Interview questions may be found in the Appendix.

Data Analysis

The interviews were transcribed verbatim and the transcripts were read closely by the interviewing team to facilitate the coding process. Transcription quality was ensured by comparing the interview audio with the transcribed text for 4 randomly selected interviews. The development of codes took place in joint reviews after each interview by the interviewing team, which facilitated the complete set of themes and sub-themes that made up the majority of the study findings. The codes and themes were elucidated in this fashion. Coding was able to identify key words, phrases, and expressed concepts surrounding GPT. Interviews continued until thematic saturation was complete.

Genetic Testing

All genetic testing was performed at MSH. All participants received the same gene panel test, comprised of the following genes which confer for increased lifetime risks of breast and/or ovarian cancer: *BRCA1, BRCA2, CDH1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, STK11, TP53, ATM, BRIP1, CHEK2, RAD51C, RAD51D, BARD1, FANCC, NBN.* Each panel included both Next-Generation Sequencing and deletion/duplication analysis.

IRB Approval

This study was approved by the Mount Sinai Hospital Research Ethics Board on June 14, 2017 and was approved for expedited review by the Sarah Lawrence College Institutional Review Board.

Results

Understanding the Participants' GPT Experience: Timeline and Testing

When asked about motivations behind pursuing GPT, participants indicated a variety of reasons. The majority of participants indicated that they wished to pursue GPT because it had been recommended by their physician and because pursuing GPT would satisfy their information-seeking behaviours. One participant noted, 'Dr X was in the Mount Sinai clinic the day I had the appointment. And he went over things with me, recommended that under the circumstances genetic screening would be useful and brought in [GC X] while I was still there…Now I'm single and adopted, I have no genetic information. So this was extra useful. Not that I have any kids to warn but just for my own peace of mind'. Other participants indicated that the reason for pursuing testing was

for the sake of their children or other family members. One participant stated, ‘And I know that was one of the decisions – or one of the factors that impacted on my decision to do the gene testing, was whether it could have any relevance for other family members who might, depending on my results, then need to go through gene testing themselves, if they so wished’. Additional reasons for pursuing GPT included that it would allow the participants to make decisions regarding treatment of their breast cancer or decisions regarding cancer screening.

Participants displayed an overall good understanding of the GPT test. The majority of participants explicitly acknowledged that they knew GPT was different than a BRCA1/2 genetic test in that it looked at more than two genes. Some participants even correctly recalled that the GPT looked at 20 genes specifically. One participant stated, ‘… it's a screening for 20 particular genes that they know cause -where they know mutations can cause an increased risk of cancer. And from what I know it can tell you you have an increased risk of cancer, it doesn’t tell you you'll definitely get it or if you don’t test positively for the genes that you won't get it. It's just people who do test positive for genes like BRCA 1 or 2 tend to have a much, much higher incident of breast cancer and therefore there's also special preventative measure that they can take if they find that they have the gene, so, yeah and so it's just, as far as I understand, just looking whether you fit into your particularly high risk group or not’. At least half of participants expressed that they knew that GPT results can have impacts on cancer recurrence risk and risk of future cancers. More than half of participants also explicitly understood that different genes on the panel can have different impacts in regards to types of cancers that

a person may be at risk for. Two participants even acknowledged that this test may have implications for obtaining insurance in the future.

All participants had their GPT results delivered over the phone, by a genetic counsellor. Most participants who tested negative did not come for an in-person follow-up appointment in additional to the initial results phone call. Some participants indicated that they preferred phone results, given that the process is quicker than coming for a results appointment. One participant was glad that her results were delivered over the phone, but did emphasize that results might be best delivered based on patient preference. She noted, '…it was quicker, it was, you know, done quickly, you had an opportunity to process it in your own way …What I might suggest and I don't know, but I might suggest giving the person an option, you know, "Would you prefer that we - that the result is shared with you over the phone or would you prefer to come down and have an appointment?" [Interviewer: Mm-hmm, yeah it might help accommodate those people who-] Yes, who need a face-to-face, they need more explanation, they - you know that kind of thing. Now obviously if that had come back positive, you know she had indicated to me she would like to have a follow-up appointment'.

Some participants recalled the entire process from genetics consultation up until results disclosure to be around two months, while other participants recalled this process taking as long as five months. Several participants indicated that they wished the process had taken less time, with a minority even specifying that they had some anxiety during the waiting period for results. One woman stated, 'You know, I was a bit anxious during that time period. I wouldn't say it super negatively affected my quality of life particularly because I'm just anxious in general. And so it's not that much of a difference. But yeah,

the long waiting period was a bit nerve wracking in some ways. In other ways though it was, like okay really I have to wait to make this decision and I'd rather have the information sooner rather than later when it comes down to that'. On the other hand, a couple of participants did not think much about the test or possible results during the waiting period. One woman noted, 'Yeah, whatever it was I had no investment, I obviously wanted it to be a negative but, I mean, I…forgot about it and… then I got the results'.

Impacts of GPT for Participants

Overall, participants affected by breast cancer displayed an accurate understanding of what their GPT results meant in regards to their personal history of breast cancer. One participant who tested negative and when speaking about her previous cancer diagnosis stated, 'So, it's not genetic it looks like. So, it's just the luck of the draw and I will just keep an eye on things because there is the possibility that as genetic testing improves and they find more related genes, there will be more information forthcoming'. However, one participant affected by breast cancer and who tested positive for a *CHEK2* gene mutation displayed incorrect understanding regarding her test results and what that meant in regards to her breast cancer diagnosis. She stated, '…the cancer I've got isn't genetic…Breast cancer is not, you know, a genetic … disorder or I don't have a genetic predisposition for it or anything like that. It's just one of those things'. Generally, participants affected and unaffected by breast cancer understood the meaning of their GPT results in relation to their family history and their future risk of breast cancer. One unaffected participant who tested negative noted, 'I didn't have any of the mutations and so now it's just I'm part of the high risk screening program because of my family history'.

A minority (2) of participants displayed uncertainty or incorrect knowledge in regards to the meaning of negative test results. One participant, when asked what the results mean in regards to her risk for breast cancer stated, 'I don't have a risk, or my genes say I don't have a risk at all actually', and when asked about whether she thought her risk for cancer was either at or above population risk, she stated, 'I don't know maybe population risk, I don't know'. Furthermore, several participants had a general understanding as to whether their results would or would not have implications for family members. One participant affected with breast cancer, who tested negative with one VUS in *ATM* stated, '…the results are relevant to, like I said before, family members who now, you know, don't necessarily need to undergo genetic testing, because it doesn't look like I can carry a family-based gene. So that suggested others don't necessarily need to undergo testing immediately, or at any point necessarily, although they will be eligible for advanced screening methods as in my own diagnosis'.

A majority of participants who tested negative or received a VUS result did not feel as though the GPT explained their personal or family history of breast cancer. One affected participant noted, 'So for me, it did not, because I don't have a family history of breast cancer. I am very young. You know, statistically speaking, I should not have breast cancer. And so this couldn't clear things up for us, it just made it more of a mystery'. Another affected participant explained, '…it still leaves the unanswered question right because I mean I'm a very fit person, I breastfed each of my kids for two years, I never took the pill, all of those things that medically are supposed to put a woman at higher risk were not the case for me, so that kind of leaves the big question mark 'well why'…'. A third affected participant, though her results were negative, indicated that these results

may have inspired her to pursue reconnecting with her biological family since she was adopted at birth, '…it eliminated some possibilities, the hereditary possibilities. I always wondered but I've never followed up on looking for my biological family…And this might have triggered that search'. A majority of participants who tested negative felt that their GPT results gave the peace of mind. One woman stated, '…certain genes, if they come back positive, it also increases your breast – or suggests that you're at higher risk for getting ovarian cancer. You know, I certainly don't want any other kinds of cancer. So in that sense, knowing that I don't have any genes, means that I'm not, as far as we know, predisposed to getting ovarian cancer, so that was a huge relief for me'. Another woman noted, 'Well - no I feel much, much better and I feel that, you know, it's an answer to a fear that I had and the thing is that I did decide to have a child even though with this big thing weighing on my mind that this child - that I may pass on this illness or disease to him and his future family, and so knowing that he's not a carrier has just - it has lifted a huge worry off my shoulder…' Additionally, participants that tested positive for a gene mutation as a result worried more about their breast cancer risk or risk for other cancers. One participant affected by breast cancer who tested positive for an *ATM* mutation stated, 'I'm just a little worried about a couple of the other cancers I can get because there's nothing they can do about them. You can't test for them'.

Participants with VUS results were asked whether they felt any feelings of uncertainty in regards to these types of ambiguous results. One individual stated that she felt her VUS results gave her some anxiety. She stated, 'It gives me a little bit of anxiety and for sure, I have it in mind, what does that mean. I know I cannot do anything, and this might take years before we understand what exactly that is. And maybe in the future

you'll find something that might help us understand that'. On the other hand, another participant stated that the VUS result didn't make her feel anxious. She noted, 'How do I feel, not too...not too badly. I mean I'm not really that concerned about this. I mean I said … I wanted to have the genetic testing and I said, "As far I'm concerned the more information the better", and so yeah I don't - it doesn't make me anxious or anything … I'm not ignoring it … you know it's unclear whether this possible variant changes anything, I don't think so as far as I'm concerned moving forward'. A third participant related the uncertainty of GPT results to inherent uncertainty in life. She said, 'I have discovered that life is uncertain, really. Yeah at this point in my life I'm much better at taking it as it comes. [Interviewer: Right. So you were willing to undertake a little bit of uncertainty in your sort of quest to understand better what was going on. Is that kind of a good summary?] Yes. That pretty well sums it up, yes'. One woman also made a point to say that she thought clinics should take responsibility for recontacting patients regarding VUSes. She stated, 'Yeah it's probably not the greatest system just to sort of leave it up to me to contact her but, you know, it is what it is.

…I think it might be better system to have the clinic contact the person but I'm prepared to diarize it'.

All participants who were asked about whether they shared their test results with family and friends admitted that they were open about their testing process and results with either select friends and family or all friends and family. One participant was particularly open about her testing process and results, 'Oh yeah, yes I - my whole family knows about it and...yes and I have a sister too so she's well aware of what's happened and the results of it and everything. Yeah and I've told my friends as well, you know,

because it's good news right [laughs] that I don't have any of the genes, so yes I shared it with everyone in my life actually'. Another participant who tested positive for a *BRCA2* mutation was a bit more reserved with telling anyone outside of her aunts and husband. She noted, 'Yeah, I don't know. I just wasn't comfortable telling them yet. I don't know why. It's one of those weird things I'm not quite sure. I think because I want to figure out what I'm going to do about it first before people ask me what my plan is'.

The majority of participants explicitly expressed their knowledge of what actions and/or medical screening were recommended by their medical team based on their GPT results. One affected participant who received a VUS result stated, '… if it had come back positive…I would probably have said, okay, I'm going to --- double mastectomy, and I'm certain that would have been the recommendation of my doctors as well… So that certainly has impacted on that decision, and again, my doctors as well, because now their recommendation is only to do a single, whereas if the results had been different, they would have said do a double. So it certainly impacted on me in that sense'. An unaffected participant who tested negative also stated, '… I got a phone call from my genetic counsellor and … she was going to refer me because of my family history to the high risk screening program but that there wouldn't be any other steps that we needed to take'. On the other hand, an affected participant who tested positive for a *CHEK2* mutation recalled being told that she would need to make an appointment for a colonoscopy, but when asked whether she would need more frequent colonoscopies than other people her age, she stated, 'I have no idea'.

Participants were also asked about health behaviour changes post-GPT return of results. Two participants expressed that they would change their health behaviour such as

diet and/or exercise based on their GPT results. A participant affected by breast cancer who tested negative stated, ‘Well the thing is that the test results I feel like they are backing-up, you know, my diagnosis of breast cancer, so once I was diagnosed with breast cancer it's like I'm forced to change everything about my diet, you know my activity level, everything, even my mental wellbeing right, emotional and everything…I think that the genetic test results are like complimentary to it where it says to you, "You know what, you don't have this gene, you don’t have any of these genes", so look at the environment factors, look at your diet, look at all these other things’. One participant was unsure about whether the results would change her health behaviours, while several participants indicated that they would not change health behaviours based on their results. One unaffected participant, when asked whether the result would change her health behaviour replied, ‘No, no. I mean it's always good to stay positive and proactive about your health regardless’. Another participant, affected with breast cancer who tested positive for a *CHEK2* mutation stated that ‘…Most of the changes have been made simply because of the triple negative [breast cancer]’. Some participants indicated that they would change their cancer screening based on GPT results, with one participant who tested positive for a *CHEK2* mutation indicating, ‘… in terms of impact that's about the only thing - for me it was to say, okay, we'll make an appointment to have a colonoscopy’. A participant who tested positive for a *BRCA2* mutation also indicated, ‘… in a week I had MRI and a mammogram booked. Already. Like done. She had those booked for me within a week for my breasts. And so I went down there. So that whole week was very - like stressful because all of a sudden I'm going for these test, one right after the other. And then I have two appointments coming up in February’. Other

participants indicated they would not be changing their cancer screening habits either due to personal preference or due to doctor's recommendation. One unaffected participant who tested negative stated, 'No, I'll just have my routine screenings like I usually do and that's it. It'll stay the same just to be on the safe side even though it says no but it's always good to keep checking'.

Opinions and Preferences on the Provision of GPT

Participants were retrospectively asked about their understanding of what their possible GPT results could have been (ie. positive, negative, and/or VUS). Several participants felt they understood what the possible test results could be, with some participants even identifying possible results as being either positive, negative, or VUS. One woman explained, '… there's the positive and there's the negative, and then there's the ones where they're unsure, or something like that. Yeah, that was a little like "Okay, well what do you do with that information" that I guess sounded like . . . I don't know. I think the way it sounded was that they would continue to have developments in research and somehow – I don't know, someday that would make sense. I don't know, I can't recall, I just know that there was one that was like the one answer to the testing that was like inconclusive kind of'. Conversely, one participant did not feel as though she understood much about possible test results, She stated, '…at the time I thought I told her [the genetic counsellor] that I had a science background so I kind of understood a little bit but… I realize that I don't really understand very much about this'. Most participants recalled that at the time of the genetics appointment, they felt they had a good understanding of what kind of clinical recommendation could be gleaned from test results, with one woman affected with breast cancer stating, 'Yes she was very clear

about that, she talked about if the test negative, you know, obviously I didn't - wouldn't have had the X gene, if the test was positive she said she'd like me to come back and talk about the possibility of a hysterectomy and I said well that's kind of down the road, I have not made that decision yet but I really appreciated her kind of saying that, you know, rather than just, "Here's your result, see you later, good luck", you know, that she said she would like to see me again for a follow-up appointment for sure and, you know; so that was - she kind of gave the scenario for one and two, option one and two'. On the other hand, one unaffected woman who tested positive for a *BRCA2* mutation noted, '…I knew that if it comes back positive that they're going to tell me you have a risk for this or a risk for that… what I didn't expect was, like, the discussion of, like, so fast that you have to - you should do this now and you should do this, and be thinking about this, this, and this type of thing. About different surgeries. Like I just felt like wow, that was - just a lot to think about. I knew - I expected different - like I expected if she said you're positive with this gene that you're going to get this - this is what you're at risk for. Yes. I did. [Interviewer: Do you feel like you had a good understanding of what possible clinical recommendations could be made based on the results] No, that's what I would say no'.

Most participants indicated they would not change anything in regards to their preparation or pre-test counselling for the GPT. One participant stated, 'Yeah, so I mean, for the most part the experience, you know, was really well-managed and, almost – to use your previous word – positive. You know, it's a very complicated thing to explain to people who have no knowledge whatsoever of genetics, and so we were given some really useful resources and things that were pretty – you know, some very informative

information that was pretty clearly spelled-out'. Another participant wished she had been given information in advance of what a genetic test was, 'The information of what is a genetic test, maybe to give you some information before you go to the test itself, and what are they. Maybe provide some more information. …It could be printed, it could be online, some additional information or reference to some websites that you link to, maybe. Or just a quick handout, you know, a handout with simple information, but put everything plain and simple…' Alternatively, another participant wished she had been given a handout after the appointment, 'I think I would have liked to have gotten a little bit more information on paper about the tests themselves just because it would have saved me some excessive Googling after the appointment'. One woman indicated that the information went over her head, 'So yeah, so she had explained about, you know, how the genes fit into the DNA sequence, but I didn't really understand that….And it wasn't really practical in terms of assisting me in my decision-making process, but she did explain how things kind of all fit in, etcetera'.

Several participants indicated that they would not change how results were returned or anything about the patient letter. However, some participants took issue with the complexity of information presented in the patient letter. One woman noted, '… I received the results, and I received the papers and there's so much information that it's … I cannot understand it. It's just the experts will decipher that thing, because it's like a code, you know what I mean? It doesn't make any difference to me to have all these pages printed with its code and information I cannot understand. So just put it plain and simple, and keep the rest for yourself. I mean, the technicians need that information, that's fine for them, I don't need it'. Another participant agreed and would have preferred

a patient letter in layman's terms, 'The only thing I would say is that the results were not as clearly spelled-out as the initial information. So you know, they have, like, really – you know, some good diagrams and explanations and stuff done to explain why would you undergo genetic testing. And then we did get full results after the fact, which was great – I'm really happy to have them, because those full results are definitely more technical in their write-up, there's not really the layman's version of them'. A couple of participants also had thoughts on receiving results that have no clear implications for risk or management. One woman explained, '…if it's not clear it just freaks people out', while another stated, '… I don't know if that would just make you more crazy. I don't know, I can't answer that because I think that depends on the person'.

Participants had an overall favourable opinion regarding their GPT experience, with many going as far as to recommend this test to others in a similar situation. One participant noted, 'You know overall I was impressed by the process. I hadn't had too much experience with this kind of program in the health system in Ontario particularly. I'm a relatively young, healthy woman so I didn't have too much reason to. And overall it was a positive experience. I think it was helpful. And certainly all the staff I worked with and everyone I talked to has been really professional and explaining things at a level that's not, you know requiring an MD which I always appreciate. So it's been a good experience'. One participant affected with breast cancer stated, '…it was a good experience, it wasn't a traumatising experience or anything like that, it was really a very simple process. And when you have cancer, you're already going through so … it's like the easiest part of it. So why not, really?' Another participant noted, '…I'm from Mexico. So this is something that in, in Mexico, the women that have had breast cancer in my

family, and I had a choice to receive this type of genetic test. I mean, I believe that we have a privilege here in Canada to have this option, and for sure, I would recommend it to my friends'. However, many participants indicated that the decision to pursue GPT may depend on the individual and their particular situation. A participant commented, '… I love the idea that knowledge is power but I also understand that if you're not in the right state of mind to deal with this it could actually force you to put your head in the sand and not want to deal with it…if you're in a negative state of mind, if you're depressed or whatever, this is not the right time for you to get the results right; but if you're in a position where you're like fight or flight type of mode where you're like, "My health is in jeopardy I need to do something about it"; so I think that that will empower you to move forward in the steps of deciding, you know, what's best for you…'

Future Polygenic Testing

Participants who tested negative or received VUS results via GPT were asked their opinion on whether they would be interested in pursing future polygenic testing that would look at SNPs or thousands of genes across the genome. This testing would help participants try and understand how cancer runs in families. Participants indicated that they would be motivated to pursue this future polygenic testing. Several of these participants indicated that they would be motivated to pursue this testing in order to find answers that GPT did not give them. When asked why she would be motivated to pursue future testing, one unaffected participant who had negative GPT results noted, 'I would say just because for me I - and particularly going through this process I just realized it was much more comforting to me to think about having the information even if it wasn't the results I wanted or it wasn't - or if it was something that was serious about my health.

To me that's better than finding out five years after I could have been diagnosed that I suddenly have cancer, you know. And I've seen that happen to a lot of women over my life and that's not - you know, as much as I can avoid that kind of medical surprise I would prefer to'.

Participants were also asked about their willingness to pursue this future testing, given the possibility of receiving uncertain results as with GPT. Participants seemed fairly alright with this possibility, with some willing to risk the possibility of receiving uncertain results if it meant there was a chance they could get an answer. One affected participant who tested negative stated, 'I mean, really, like, you already have uncertainty, right. From my perspective, you don't know what's in your genes, but whatever is there, is already there, there's nothing you can do about it. So getting any more uncertainty, like, doesn't change anything, right, you're already in that position where you don't know, so … And if you get results that are meaningful, then it gives you something that you can take action on'. Again, another participant commented that this uncertainty may not be for everyone, 'I will tell you, I think it will cause more anxiety and not everybody might handle that type of information very well, but in my case, I would like to know it and start preparing'.

Participants were asked whether they would pursue this future testing if it could also provide information regarding risks for other diseases aside from cancer, even diseases that do not have treatment or medical screening available. Many individuals were also interested in pursuing this testing, however many acknowledged the psychological difficulties that may come with learning this information. One participant noted, 'No, no, I would like to know about any other disease that I could have in the

future. Whereas I know it's important, what are the worst things that I could deal in the future…but just the fact that you know it, might change some decisions that I take now or in the future. It's something that will probably cause me anxiety, yes, but I still want to know'. Another participant said, 'Yeah, you know, I think I would probably ultimately decide that I wanted to know. But I think finding out something about a disease that has not really been in my consciousness or in my family history would really, would be a bit more of a psychological difficulty to take I guess. Like I would find that bit more of like oh, I'm worried about breast cancer but actually I'm going to get Alzheimer's…' One participant also highlighted that medical screening may not be the only way to 'prevent' disease. She said, '…it depends on how you define what you can do about it. There's spiritual ways and… there are physical and medical ways and social ways…I think that there are all these things that can be done, depends on how you define that'. One participant was not interested in learning about risks for other diseases at this point in time, 'When it comes to testing, you know, my probabilities for every disease under the sun, I think, you know, there's certainly an aspect that appeals to me. Like I said, having that information you can ---, you can take action. But I mean, at the moment I'm certainly not in a position where I would want to do that, because I have enough to deal with, right. Like, I don't need to know that I'm also at risk of getting Alzheimer's and whatever else they would test…'.

In regards to the provision of this future polygenic test, participants had varied opinions. A few participants brought up the point of having this test provided with the context of a hospital system or specialty breast clinic. One participant admitted, 'I also feel strongly that you deal with one hospital system and stick with it and everything you

do – as I joke I say I go to X for all my cancers. But, you know, it's not such a joke, I think that it really is, I like to go to the hospital, I like to go to the same hospital each time so they have everything from whatever I'm dealing with…They're able to coordinate everything all in one…'. Another participant stated, '… I think the best one ideally would be to a breast, like clinic, because they have people who are experienced working in it versus – like I like my GP but I mean some people don't have a GP so they'd go through like a walk-in clinic. I don't know. So, ideally it would be better to be in an environment where they work with breast cancer on a regular basis'. A third participant emphasized the necessity of a genetic counsellor or trained genetics expert to be involved in this testing process, 'I think a genetic counsellor is somebody who really does know genetics. I think more specific knowledge, I think, is very important. Because genetics is very confusing…'. Conversely, many individuals thought that this test could potentially be provided by their family doctor. One participant stated, 'So I think the obvious place would be the family physician right, like I mentioned …a person has that trust factor hopefully with their doctor and, you know, in terms of around getting that test out to people….' Another participant noted, '….should be a discussion that you should have with your family doctor, and all family doctors should be prepared on how to deal with this type of testing, with the questions from the patients, with the results'. Many participants thought that this future polygenic might be beneficial if publicly available, however certain concerns such as public education, cultural concerns, personalized service, and possible online accessibility would need to be addressed. One participant noted, '…public education a no-brainer, like I - you know if you'd have forums in different parts of the province where people could come and just, you know, have a Q&A

and a bit of a presentation or people could go online and log in. I think I might do a few different venues, I think I might have like kind of a town hall thing where the professionals come and they explain what would go on and that sort of thing. For those people who couldn't get out to a town hall or something they could go online and maybe participate in a webcast or something; God with technology now there's so many options right'. Another participant emphasized education for family doctors, '…I do think the education component would be important, you know, making sure the doctors, even if they're not genetic counsellors have a sheet or some information or a website to refer people to that explains in basic terms what the testing is'. One participant emphasized, 'I think a personal interaction is better because, you know, sometime we can read things on the net that we shouldn't interpret them differently. I think it's better to have one face to face so that you can ask questions if you have them'. Lastly, one participant emphasized cultural needs, '…Medical information is something that is personal but it's also a tool for having a long and healthy life. I think some ethnic groups have more trouble with trusting doctors …And how to get it across in multiple languages in Ontario…getting it across to a language group as well to older women who have not worked outside the home and never got comfortable with English'.

Miscellaneous Themes

One participant brought up the point of the utility of other parts of the genetics assessment (ie. risk models) as having influenced her medical treatment for breast cancer. She stated, '… the results also came back with a calculation of my risk of developing a new primary breast cancer, so the breast that is currently not affected. So that is definitely – you know, the probability of that, of a new primary cancer, certainly is impacting my

decision in terms of moving forward with a mastectomy – a double mastectomy or not, so it is very relevant'.

Many participants talked about how they delivered the news of their GPT results to family members and their family members' reactions to the news. An affected individual who tested negative stated, '…it went well, and I think they also were worried about the results. I think the whole family was concerned about this, and knowing the genetic results was very important for all of us. And we knew that there was a bit of risk on both sides of the family, so for us in particular, it was very important to know the results'. An unaffected individual who tested positive for a *BRCA2* mutation stated, 'Well they were both upset which then made me more upset. But my husband's very like, typical. Typical man I'd say. Okay, well this is the problem, we're going to fix it this way, what do you have to do kind of thing'.

A few participants highlighted the importance of having a genetic counsellor apart of their GPT experience. One individual stated, 'I think having the genetics counsellor in the clinic itself, is fantastic. I don't know if that's standard process across most hospitals or not, or if your study is even going to have any kind of influence on that sort of thing, but absolutely, I mean, the fact that the genetic counsellor is in my breast clinic, is available on a daily basis, is able to be flexible enough to come and talk to me, you know, while I'm getting chemotherapy, explain the results, that sort of thing, I mean, that makes all the difference. Because if it wasn't that easy, I probably would have, you know, maybe delayed it more, or not taken it as seriously…' Another individual explained, '… I do want to mention that I had a great time and a positive experience talking with my counsellor. I think she did a great job of explaining to me more or less

everything, asking the right questions and trying to understand my situation, my family history, and trying to understand more about myself and how I developed this cancer. She was very empathic – I think empathy was an important thing to me, the fact that you are not just seen as a number, but a patient with an issue, and this is something extra that is helping you. That, I think, was great – we had a good time with her'.

Some patients indicated that they had done their own research either before or after the GPT consultation. One unaffected participant stated, 'I had done some research on this before and even though my mom hadn't had breast cancer the fact that I got it so young I think that's one of the markers for a genetic mutation... '

Based on their GPT results, some affected participants who tested negative now believe that their cancer may have been due to alternative causes. One woman stated, '…I have my own faith, and so to me, this was really kind of an indication that, you know, this was an act of God and this has to do with the path I am to walk in my life, and to some extent, that is comforting to me, to know that this is for a reason, and it's not just science gone amuck…And for me, I justify it as saying, okay, this is something purposeful and there must be something I'm to learn from it, so … whereas other people might take comfort knowing, okay, this is just genes, genetics and there's nothing I could do and ya-da-ya-da…' Another participant explained, 'Yeah, the family history is important, it's a part of the whole story. In my case, the use of patches and birth control pills for over twenty years… So yeah, it's been a long time using steroids, you know, so birth control, weight control. That, I think is a huge risk…the fact that I smoke for over fifteen years or so, that also had an impact…The lifestyle, the food – I take a lot of red meat, sausages, packaged ---. So a few things. I'm not doing as much exercise as I should

do, so there are so many factors that I think that have been involved. But for sure, one of those was – yeah, the steroids and the hormones'. In another case, a woman who tested positive for a *CHEK2* mutation originally thought her family history of cancer had alternate causes but her GPT results changed that, '…through the chemicals my mom used when she did roses for 20 years, before they stopped the poisons and stuff. [Interviewer: So you felt maybe the cancer might have been a result of that.] Yeah…'

A couple of participants expressed anxiety in regards to waiting to receive their GPT results. One woman indicated, '… every day was just like you're trying to - I don't think I've done so much yoga in my life but anyways, yeah it was definitely stressful because as I said I thought because of my age and, you know, maternal breast cancer I thought that the dice could, you know, not be in my favour here; and then I would be upset that I had waited so long and had, you know, done that earlier for my daughter'.

Some participants who did not receive VUS results were asked their opinions on how they would have felt had they received an uncertain result from their GPT. One participant indicated, 'I didn't receive any inconclusive results but the thing is just I do think there's value in it…it's better to be proactive about it than not being proactive about it…So I think that if something had come back inconclusive it would have just indicated that I'm not safe. It could be … maybe a recommendation to test again in a few years, but it actually - I think that from the way I think about things I think that, you know, it's a cautious approach to things …and then you could start looking at well is there anything I can do, you know. It could reinforce how I handle my diet, exercise or whatever it is. But

I think there is value in knowing what an inconclusive results means to a person because prior to that I thought that inconclusive would mean…'

Two participants who did not receive VUS results still felt as though there was some uncertainty. One participant who tested positive for a *CHEK2* mutation stated, '… it wasn't definitive. It's not saying I'm definitely going to get colon cancer in six months. It's just there is a predisposition to colon cancer in my genetic background. There you go. So it's still an if, and, or maybe. Not a definitive'. Another participant who was affected by breast cancer but tested negative felt there was still uncertainty as to what caused her cancer, '…Like I said there's always there million dollar question why did this happen to a healthy 34 year old female right'.

Some participants used the phrase 'the more the better' or similar. There was also an underlying theme of knowledge is power; that they participants felt empowered by the information that they received as a result of this test. For example, one participant who was affected by breast cancer but tested negative stated, '…being diagnosed with breast cancer I find that I think if it come back positive it would have - I would have been prepared for what's to come … it's information right and information is power so I think that having an answer even if it's not a favourable answer, you know, forces you to move forward in one direction…' Most participants who were asked explicitly whether they prefer to have more information rather than less in life situations replied that this was true for them.

Discussion

Over the past 20 years, genetic testing for breast cancer susceptibility has centred around BRCA1/2 analysis. The discovery of additional genes involved in breast cancer

susceptibility coupled with cheaper and faster analyses has lead to the production of gene panel tests. This has led to increased rate of not only mutation detection, but also an increase in VUS results. Currently, most risk assessment centres in the province of Ontario are using or contemplating using GPTs as the routine genetic analysis in individuals who meeting criteria for what was once only BRCA1/2 analysis. Most of this change to GPT has been carried out within the same established protocols of genetic counselling in high risk clinics as it has been with BRCA1/2. For example, patients who test negative or receive a VUS result from GPT are still assessed for future breast cancer risk using risk-modeling software. It is within this context that we asked participants of their experiences with the provision of GPT.

Presently, more and more individuals are seeing GPT and cancer risk assessment as the 'next step' in either their cancer care process or in their quest to find out why they have a personal or family history of cancer. Many individuals are keen on being prepared for potential future health risks and want information on how to prepare for and/or mitigate these risks.

Our research suggests that issues surrounding GPT closely resemble issues encountered during traditional single-gene genetic testing. One of the main issues in GPT is pre and post-test counselling for VUS and negative test results. Patients should be advised that a negative GPT result does not return them back to population risk for future cancers, nor does it preclude them from having a mutation in a gene that was not included in the panel or has not yet been discovered. Other issues surrounding GPT include testing positive for a mutation that confers risks for additional types of cancers (some of which may not be screenable) and implications for family members if a mutation is found.

Participants were generally pleased with the provision of this test and the pre and post-test counselling that they received. However, some of the opinions collected during this research suggest that while patients are interested in having a lot of information regarding their GPT pre and post-test, perhaps this information should be better tailored to the patient's preference and/or education level. Additionally, some participants wished that there was a shorter turnaround time for results.

Participants that received VUS results generally indicated that they had a good understanding of these results and the subsequent clinical implications (i.e. screening and management are to based on personal/family history of cancer). Furthermore, most participants indicated that these results did not cause much stress or strong emotional reactions. These individuals did not seem to be very concerned or anxious regarding their result, however some acknowledged that uncertainty is not handled the same by everyone and that this should be taken into consideration when carrying out GPT. Some participants took comfort in that one day uncertain results (ie. VUS results) might be elucidated, as more data is gathered. Given these findings, one might infer that patients are generally capable of understanding an uncertain result and would fare similarly if uncertain results were to arise in future genetic tests.

Overall, GPT appears to be well-tolerated within the context of a traditional genetics assessment. Participants generally had positive feelings in regards to their experience receiving GPT and felt that they would recommend the process to others in a similar situation.

From the inception of breast cancer genetic testing with BRCA1/2 analysis, to the introduction of GPT within the context of a cancer risk assessment, we are now faced

with the advent of polygenic genetic testing via whole exome, whole genome, or SNP platforms (Li et al., 2017). SNPs, or single nucleotide polymorphisms, can be relatively common in the general population and individually may not mean much, but when combined may carry an additional risk for breast cancer. Recently, many of these SNP tests have been validated however there has yet to be a widespread implementation of this testing within the framework of a routine cancer risk assessment.

Responses from the participants in this study suggest that they would be willing to take the next step into receiving genetic testing via these new technologies and are not too concerned by the uncertainty that it might provide. There was a general consensus among participants that did not receive a clinically significant result through GPT that they would be open to pursuing future polygenic testing that looked at more genetic elements than GPT, despite the possibility of again receiving an uncertain result. Motivating factors for pursuing these tests resembled motivating factors for pursuing GPT. Participants also seemed open to finding out information regarding diseases other than cancer, however some individuals had reservations about learning about diseases for which there is no cure or screening available.

In the future, there is the potential that all females may be offered this polygenic test to determine proper levels of screening for individuals in the population regardless of their familial cancer risk. In other words a more personally stratified assessment of breast cancer risk regardless of any existing family cancer history. Participants found value in this proposition but also had mixed responses as to whether this future polygenic testing should be provided through their hospital, a specialty breast clinic, genetic services or their family doctor. Many acknowledged the possible burden to these communities and

agreed that widespread uptake of polygenic testing could take place as part of a Provincial program that is used for population screening such as the Ontario Breast Screening Program. If the provision of this test was to fall under the typical scenarios that single gene and GPT currently are, issues such as education of providers and the general public, cultural considerations, and the availability of a genetic counsellor or specialist to personally answer questions or concerns would need to be addressed.

Study Limitations

Study participants were recruited based on their history of receiving genetic testing at the Marvelle Koffler Breast Centre at Mount Sinai Hospital. As a result, the opinions are reflective of the genetic counselling process at this specific hospital. While one might hope that these opinions would be representative of patients' experiences at genetic testing clinics across the province of Ontario, this may not truly be the case. Furthermore, study participants were only those who proactively returned the study consent form to indicate their interest in study participation, or individuals who agreed to participate after being contacted by phone. It is possible that certain opinions were missed based on who was recruited for the study, such as participants who received secondary findings as a result of the test or participants who had negative opinions regarding GPT and thus were uninterested in participating in the study. Also, although we interviewed to beyond thematic saturation, we have only interviewed a small number of clinic participants. It is also possible that people self-selected for those who had a good experience in the testing process.

Practice Implications

Data obtained during the course of this research study may have implications on future genetic testing and genetic counselling practices in Canada. Understanding the underlying motivations and experiences of individuals who underwent GPT is critical to providing support during the cancer genetic counselling session.

Additionally, this research will inform future polygenic testing. Given the positive reception that GPT received during the course of this study, genetics clinics may be more open to offering more complex, polygenic testing to patients in the near future.

Conclusions & Future Directions

The data suggests that GPT is well-tolerated within the context of a traditional genetics assessment and that individuals would be open to pursuing future polygenic testing within this framework to help answer the question as to why they developed cancer or have a family history of cancer. Further quantitative research would provide robust data on whether a larger population of individuals would be open to this more expansive genetic testing and how individuals would prefer that it be provided.

Conflict of Interest

Angelina Tryon and Gord Glendon declare that they have no conflict of interest.

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Acknowledgments

We would like to thank the MSH Breast Clinic Genetic Counselling Team for their assistance and working space over the course of this project. We would also like to thank the participants for sharing their stories with us in the hopes of improving the provision of cancer genetic testing and counselling in the future.

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Appendix - 1:

Interviewee demographic characteristics

Characteristic	N = 14
Mean age in years (range)	47.6 (32 – 68)
Race/Ethnicity	
Non-Hispanic White	5
Ashkenazi Jewish	2
Hispanic	3
Aboriginal	1
Mixed Ethinicity – Indian/Pakistani/Irish/Scottish/Welsh	1
Mixed Ethnicity – Aboriginal/Polish/Macedonian	1
Unknown	1
Marital Status	
Married	8
Never married	5
Divorced/Separated/Widowed	1
Gene panel test result	
Positive	3 [*ATM, CHEK2 & BRCA2*]
VUS	4 [*ATM, PALB2, MLH1 & MLH1*]
Negative	7
Cancer status	
Affected	9
Unaffected	5

Appendix – 2: Interview Questions

Developed by Gord Glendon, MSc.

Introduction

- Hello, may I please speak to X.
- This is X calling from the, ***Understanding Gene Panel Testing study*** for our scheduled interview. Thank you for taking my call.
- As a reminder, we will be audio taping this interview and then transcribing it into a word document. This is so we can later explore the details of what we have discussed today. Is that alright with you? Your transcript will be identified only by a number and will not contain any directly identifying information such as your name, address or date of birth.
- If there is any topic or question you don't want to talk about for any reason, just say 'skip' and we will move onto another question.
- Please feel free to discuss anything you would like to with respect to your genetic counselling and testing experiences. This interview is the forum for you to speak your mind and there are no right or wrong answers.
- Please keep in mind that we cannot give you any medical advice or answer any questions about your results.
- A typical interview of this type could last up to 30 to 45 minutes.
- Are you ready to go ahead with the interview now?

Understanding the participants GPT experience: Defining the timeline and type of testing

We understand that you have been seen in the Familial Breast Cancer Clinic at the Marvelle Koffler Centre for a risk assessment within the last year. We also understand that you had a genetic test or tests there. We would like to talk to you about how that process took place.

- Can you walk us through your risk assessment process? Did you receive genetic counselling and then testing? Did you have 2 separate tests (one for BRCA1/2 and one called a gene panel test)?

- Do you know what the test you had is called (prompt for GPT)?

- Can you explain to me what the GPT is? Is it a blood test? What does it look for? Is it different from the first blood test you had (BRCA1/2)? Does it look at more than one gene at a time or only one?

- Did you receive the results from the genetic testing you had? If you did would you mind sharing them with us to help us better understand the impact the testing may have had on you?

- How were the results communicated to you? Were results delivered by the genetic counsellor or the physician or both? Was it over the phone or in person? Did you bring someone with you or were you alone for the results session? Did you have a follow up session with the genetics team after the results session?

- How long was the process from the time of giving blood to getting the results?

Impact of GPT for participant

We know that having genetic testing can sometimes lead to results that have a direct effect on our health, especially when the results are positive. Even the experience of having a negative genetic test, without getting a clinically significant result can have an effect for some. Now, we would like to hear what impact, if any, did undergoing the GPT have for you and possibly your family? We are interested in both how it may have impacted your thinking and feelings as well as any impact it may have had on your health behaviours such as screening, surgeries. Also did your results have any effect on other family members if any (siblings, children, parents)

- What were you told your result means in terms of your risk for breast cancer? What were you told the results mean with respect to the cause of your cancer? What were you told the results means with respect to your family's history of cancer?

- Do you feel that the GPT helped to explain your personal or family history of breast cancer? Do you feel the GPT added any information beyond what you may have learned from your BRCA1/2 test? Do you feel that this test added anything to your understanding of your cancer / your family's cancer / your breast cancer risk?

- Do you feel there was uncertainty in the results you received from your test? In other words, did you receive a result that may or may not explain your / your family's cancer history? If so, how do you feel about that uncertainty? Does receiving this uncertainty make you feel worse, better or no different than before the test / after the BRCA1/2 test?

- In general, what are your feelings about your GPT results? Do the results give you peace of mind / cause you to worry more about breast cancer risk / not change how you feel about breast cancer?

- Have you told anyone about having the GPT? Results? Why or why not?

- Did you receive a specific course of action or screening recommendations after getting your GPT results? Did this course of action / screening

recommendation change from what you had been recommended previously?

- Do you think that you will change any of your health behaviours or cancer screening based on the information you received in this test? Is there any health behaviour you have wanted to change that the test result will help motivate you to carry out? Do you feel that possibly changing aspects of your lifestyle like diet, exercise or screening could affect your chance for developing cancer?

Opinions and Preferences on the Provision of GPT

Now that you have gone through the process of GPT, we would like to hear about your opinions and preferences for how the test should be delivered. This test is new in Ontario and any feedback you have can be extremely valuable.

- Now that you have received your results, do you think, in retrospect, that you had a good understanding of the possible results you could get from the test (no increase in cancer risk to moderate increase to high increase)? Do you feel that you had a good understanding of the complexity of the test before you received your results? Do you feel you had a good understanding of the wide range of clinical recommendations you could get from the results of this test (from no change in screening to slightly modified screening to frequent screening with a discussion of prophylactic measures)?

- What would you change, if anything, about your preparation for the test? Would you prefer more, less or the same amount of pre-test information? Are there specific things that, in retrospect, you would have liked to know more about? Did you feel that there was too much information presented to you before the test, not enough or just the right amount?

- What would you change, if anything, about the process of receiving results from this kind of test? Would you have liked more or less detailed information about the results? What was your opinion on the patient letter that was sent to you after the test? Do you feel like it helped reinforce your results, or were you left with a greater sense of confusion?

- Do you feel there's any benefit to receive test results that have no clear implication for cancer risk or clinical management? Do you have an opinion about the usefulness of receiving results with uncertain significance?

- If you received results of unknown significance, you were likely told that these results are typically re-classified over time and you were asked to keep in touch with your genetics clinic every few years to see if your

results have been re-classified. Would you prefer to be responsible for contacting your clinic regarding any changes in classification, or you would you prefer to have the clinic automatically contact patients instead?

- Would you recommend this test to others? Would you recommend this test to others in your family?

- In general, what is your opinion of GPT? Are there aspects of the test that you would not advocate for?

- Is there anything else you would like to discuss with respect to your opinions or preferences for the delivery of this test? Is GPT something that genetics clinics should continue to offer?

Future Polygenic Test

Understanding the genetic causes of familial breast cancer is constantly evolving. You have gone through the first 2 generations of genetic testing. The first test looked at BRCA1/2 genes. The second is GPT which examines another 20 or so genes associated with familial breast cancer. Just over the horizon is another group of tests that will look at a much larger part of the human genome to try and understand how cancer runs in families. The techniques will vary but the underlying idea is that we will be able to look at thousands of genes at the same time and something called SNPs. Individually, these elements may not mean much, but together they will give us a much more complete picture of breast cancer risk. You may have heard of whole genome sequencing which is an example of this. The promise of these tests is that they may be able identify someone's cancer risk from very low to very high allowing better screening and treatment, but also your risk to develop other diseases. We would like to get your reaction to such a possible test.

- If this test was available as I described it, would you be motivated to have it? Why or why not? Was there anything in your experience with GPT that would make it more or less likely to be interested in this type of more comprehensive test?

- If this test had a possibility of giving a result of uncertain clinical usefulness, would that make you more or less likely to pursue it? Why or why not?

- It is possible that such a test could also reveal risks for diseases other than cancer. If this was the case, would you like to know about those other risks as well? Why or why not? Do you think that if you have a test for cancer risk, the results should be strictly related to cancer or include risks for other diseases? Would you want to know about results that show that you are at risk for something but there was nothing you could do to reduce that risk?

- If a company provided this test directly to the public, outside of the medical system, and was reasonably priced, would you consider having it? Why or why not? Do you feel that these types of tests should be provided only by a doctor in an established medical setting to patients who meet criteria for testing, or be available to anyone who wants to have it and is willing to pay out of pocket for the information?

Conclusion

Thank you very much for talking with us today. Your thoughts and suggestions are very valuable in helping health professionals to provide the best possible service going forward.

- Do you have anything else you would like to discuss with respect to GPT? Feel free to comment on anything we discussed earlier or anything we didn't cover that you may feel is important.

- Thanks again for your contribution.