UNDERSTANDING PATIENT AND CLINICIAN PERSPECTIVES ON THE ROLE OF GENOMIC TESTING IN CANCER TREATMENT DECISIONS

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By
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CERTIFICATION OF APPROVAL

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ABSTRACT

The federal Precision Medicine Initiative was launched in 2015 with the goal of increasing targeted treatments for diseases. Currently there is not much known about patients undergoing large scale genomic testing with the goal of utilizing precision medicine, and their resulting treatment outcomes. The aim of this project is to learn about patient and clinician understanding of large scale genomic testing in oncology, the communication around germline findings, and the resulting "actionability" of these tests. A combination of ethnographic participant observations and in-depth interviews with clinicians ordering a 500 gene panel, which analyzes both tumor and germline DNA, and their patients were undertaken. The patients were interviewed at varying stages in the testing process, including before and/or after results disclosure. Participants included 6 patients, 3 family members, and 9 clinicians. A total of 15 interviews and 20 hours of observation were conducted. Analysis included coding and thematic development and was informed by a modified version of grounded theory. Results of this project show that the purpose of this testing may be viewed differently by different individuals and the challenges in communicating the difference between an analysis of the tumour tissue versus the germline tissue. Additional findings highlight the difficulty of finding "actionable" genetic information, as well as the diverse experiences patients have in disclosing germline findings to family members. This study's results will help to improve understandings of how clinicians are utilizing this technology with their patients. The findings will also serve to highlight

the perspective of patients undergoing large scale germline and tumour testing, and the impact that testing has had on their health and that of their families. These insights should aid in the development of physician and patient education materials to support the decision-making process around pursuing large scale genomic testing in oncology.

CHAPTER I

INTRODUCTION

Precision Medicine

The term precision medicine gathered popularity with President Obama's State of the union address in 2015. President Obama announced that he would allocate 215 million dollars towards tailoring treatment to a specific individual based on their genetic makeup or tumour profile (The White House, Office of the Press Secretary, 2015). The goal of precision medicine has been defined as to "quickly efficiently and accurately predict the most appropriate course of action for the patient" (Aronson & Rehm, 2015). This concept is the driving force behind integrating genomic testing into cancer care. Simultaneous sequencing of the tumour and germline DNA allows the assessment of multiple genes implicated in hereditary cancers, as well as genes associated with tumour progression. Identification of a specific gene mutation can point clinicians to specific treatment and identify inherited cancer predispositions. In fact, one of the main aims of this government initiative is creating "more and better treatments for cancer" (The White House, Office of the Press Secretary, 2015). This will hopefully lead to more effective treatments for patients than the current chemotherapy regimens. Precision medicine should help deliver safe and more successful treatments by reducing toxic side effects of less specific chemotherapy (Ciardiello et al., 2014)

While simultaneous tumour and germline sequencing has only been clinically available for a few years, genomic markers have been used to inform cancer diagnoses, prognoses and treatment decisions for a long time. Genomic sequencing provides another level of insight into the tumour functioning that goes beyond what can be seen when examining tumour tissue under the microscope. In the 1970's karyotypes were correlated with disease prognosis for the first time (Garraway, 2013). With today's precision medicine, genomic signatures can not only help us identify cancer type, but can also identify specific molecular pathways involved in cancer proliferation which we can target with certain treatments. Both somatic and germline genetic mutations are involved in tumour survival and progression (Garraway, 2013). Both types of mutation can help inform individualized treatment, and information about germline mutations in particular can be used to inform family members of their risk for developing cancer. There are some well-known examples of cancer types for which genomic sequencing has served to individualized treatment and better outcomes for patients.

Non-small cell lung carcinoma is one of the best-known examples of the utility of precision medicine. In the early 2000's, there were 4 standard chemotherapy regimens for this particular type of cancer, which together achieved a response rate of less than 20% with a median survival of around 8 months in advanced patients (Schiller et al., 2002). In an effort to identify which factors lead to a good response rate in these patients, genomic sequencing was used to further profile non-small cell lung carcinoma. Through genomic testing, about a quarter of patients with non-small

cell lung carcinoma were identified to have an EGFR mutation, ALK rearrangement, or BRAF V600E mutation and saw greater benefits when given a novel treatment regimen, targeting their specific driver mutations (de Langen & Smit, 2016; Lazarus & Ost, 2013). Overall, genomic sequencing has allowed a much more detailed and complex tumour profile to be established than was possible with earlier technologies (Garraway, 2013). Non-small cell lung carcinoma is just one of the examples of how it can alter treatment decision and outcomes for cancer patients.

Ethics and Concerns around Genomic Testing

Many concerns around the ethical, legal and social implications of paired tumour and germline testing have been raised and are applicable to precision oncology. Areas for concern for clinicians include informed consent, privacy, access to testing and targeted therapies, costs, disclosure of germline results, and interpretation of results (McGowan, Settersten, Juengst, & Fishman, 2014; Raymond et al., 2016). The importance of understanding germline findings in particular is highlighted for oncologists. The ability of oncologists to recognize inherited cancer syndromes and communicate germline findings obtained through genomic testing are encouraged by both ASCO and ACMG (Parsons, Roy, Plon, Roychowdhury, & Chinnaiyan, 2014; Robson et al., 2015). Both ACMG and ESMO also recommend support be provided for oncologists ordering this type of testing. This support can come in the form of a multidisciplinary team approach, where genetic counselors and medical geneticists are involved, or available, for patients receiving this type of

testing (Ciardiello et al., 2014; Parsons et al., 2014). Medical genetics professionals have a lot of expertise to offer in the context of interpreting germline testing results.

Another main concern is around the patient and their family members' ability to actually understand the implications of this testing and the possible results. Currently there aren't great tools to help patients absorb large amounts of complex information returned with genomic sequencing (Hunter, 2016). This type of testing can return findings which have an impact for a patient's current health, but also the health of their family, their future health, their life insurance policy, or even findings of uncertain significance. Despite the name of precision medicine implying that decision-making will be more precise, a great tolerance of uncertainty is often required for interpreting genomic results (Hunter, 2016).

Inherited germline findings are an area that many oncologists may not be familiar with. However, the ability to accurately analyze and disclose germline findings is a concern for clinicians who are ordering large scale genomic sequencing in their patients (Dancey et al., 2012; Raymond et al., 2016). In interviews conducted with various stakeholders in genomic testing, most patients reported that they would not have the genetic literacy to understand the difference between somatic and germline testing (McGowan et al., 2014). This is concerning, as a patient's family members may not then receive early screening or prevention for a cancer they are at risk for or may be subjected to unnecessary invasive procedures if germline findings are not explained in an understandable way. For this reason, it is recommended that support in both the forms of availability of genetics professionals, like genetic

counselors or medical geneticists, be available to ensure that patients truly understand the limitations, benefits and implications of receiving somatic and germline findings. (Garraway, 2013). Germline information increases the complexity of genomic sequencing in oncology and brings considerations other than the use for targeted treatments into the equation.

Barriers to Implementing Simultaneous Tumour and Germline Testing

One of the reasons why initiating paired tumour and germline sequencing in clinical practice is challenging is the technical aspect of the test itself. The ability to perform a biopsy to collect the tissue, and sometimes multiple biopsies, can be challenging based on a tumour's location and a patient's health status (Garraway, 2013). The current standard for preserving tumour tissue is not ideal for preserving the nucleic acids required for genomic testing (Dancey, Bedard, Onetto, & Hudson, 2012). These barriers can prevent the test from even being completed. Once the sample is obtained, genomic testing for somatic tissue required a much higher read depth, sometimes more than 100x coverage (Dancey et al., 2012). Typically, germline cancer genetic testing is looking for genetic changes present in 50% or 100% of the genetic information in a person's cells, but with a somatic tumour testing the mutations are in much lower frequencies. After testing has been completed, assembling enough patients for a clinical trial can be difficult. The number of patients needed for clinical trials is difficult to achieve due to the highly individualized nature of a genomic profile (Dancey et al., 2012). Achieving large scale genomic sequencing

in cancer patients and then being able to assess the utility of those findings with clinical trials is challenging on multiple levels.

As technology has improved, genetic and genomic testing has become more pervasive in medicine. Seventeen years ago, the majority of primary care physicians did not feel that genetics was relevant to their practice (Mountcastle-Shah & Holtzman, 2000), but the reality is that genetics is now pervasive in medicine. A more recent survey of internists found that 65% had counseled a patient on a genetic condition (Klitzman et al., 2013). In a survey of oncologists and surgeons, 43% anticipated testing most of their patients, or testing patients frequently (Gray, Hicks-Courant, Cronin, Rollins, & Weeks, 2014). Many physicians feel uncomfortable with their knowledge of genetics. By self-report 74% of internists in a recent study rated their knowledge of genetics as somewhat poor or poor, yet 44%, had ordered a genetic test (Klitzman et al., 2013). This situation is problematic because physicians are being placed into situations where a general knowledge of genetics is required, yet they have not necessarily been provided with the opportunities to learn about genetics.

One of the major difficulties with implementing new technology for public health purposes is making sure it is truly available to the entire population. New technologies are often more expensive, and therefore can seem exclusively available to those who have the means to pay for it. In a recent survey of physicians, cost was identified as the main barrier to precision medicine (Petersen, Prows, Martin, & Maglo, 2014). Both the cost of the testing and the cost of the potential therapies

identified by precision medicine have been identified as barriers (Mountcastle-Shah & Holtzman, 2000; Petersen et al., 2014). A survey of the general population found that few people would pay over $1000, or even $500 for large sequencing tests (Marshall et al., 2016). In fact, the cost of paired tumour and germline sequencing often far exceeds $1000. Addressing the physician comfort and knowledge with this technology, decreasing the cost, and increasing the data around the clinical utility of precision medicine will aid in the adoption of paired tumour and germline testing in the clinical setting.

Actionability of Test Results

If genomic findings are identified, are successful treatments always found for those patients? One way to measure this is by identifying actionable findings. Actionability has been defined as "variants that are considered to be clinically useful and can be acted on" (Marshall et al., 2016). This means that variants with uncertain clinical significance, or variants where there is no intervention possible, are not actionable. The goal of identifying actionable findings would be to make a significant change in a person's diagnosis or treatment.

Although the identification of an actionable finding may seem like a straightforward path from genomic test to treatment with a specific drug, there are many obstacles that may prevent treatment. The availability of targeted drugs themselves is also a major barrier to implementing precision medicine (Petersen et al., 2014). Creating a drug that is so targeted implies that it will only be effective for a small slice of the population, which can be both undesirable for companies to create

and difficult to test in large trials which are required to prove effectiveness. The targeted outcomes from tumour sequencing often indicates drugs that are off-label, in clinical trials or those still under development (Nelson, Keating, & Cambrosio, 2013). Due to those circumstances, not all patients are truly able to access the drugs that are recommended. Actionability must also be viewed within the context of the cancer. There are some mutations that have proven to be very treatable in one type of cancer like BRAF V600E mutations which are significant in melanoma, but do not lead to targeted treatment in colorectal cancer (Nelson et al., 2013). Sometimes actionability can be viewed in different ways too. If a hereditary germline finding is identified for a family, it may not have any actionable ramifications for the patient's treatment but there are often actions that their family members can take.

As this is a relatively new avenue for clinical treatment, there are few studies that have looked into the outcomes of using large scale genomic testing and treatment outcomes on a large scale. Currently, it seems as though when actionable results are identified, the targeted treatment leads to short lived responses (Nelson et al., 2013). There are many theoretical benefits to having targeted treatments in oncology, but very few studies have address this process in large cohorts.

There have been 2 recently published studies tracking the outcomes for cancer patients who have had simultaneous tumour and germline genomic sequencing. The first study involved 100 cases of treatment resistant cancer in British Columbia. They defined actionable findings as those with potential targets or risk factors which affected a patient's treatment plan, such as a somatic mutation with an available

targeted drug, or a BRCA germline mutation (Laskin et al., 2015). Out of the 78 patients that were able to obtain enough tumour tissue to analyze, 71% (n=55) had an actionable finding, 44% (n=34) obtained new systemic therapy and 18% (n=14) saw clinical/radiographic improvement (Laskin et al., 2015). Another study was done using the UCSF 500 test pediatric neuro-oncology patients who had diagnostic uncertainty or poor responses to prior therapies. There were 31 patients sequenced, and they measured results that impacted management including diagnosis, germline findings and targetable alterations (Kline et al., 2016). Out of the 31 patients, 81% (n=25) had results that impacted management, and of those 61% (n=19) had alterations where there were specific drugs identified to target them (Kline et al., 2016) . In both studies, 6% (n=5) and 19% (n=6) of patients were given a new diagnosis (Kline et al., 2016; Laskin et al., 2015). A new diagnosis can help guide treatment decisions without providing a targeted treatment. Additionally, in the pediatric population 35% (n=11) of the patients had germline findings (Kline et al., 2016). This is much higher than the approximately 2% of patients with hereditary findings which is seen when large scale genomic sequencing is done in the healthy adult population (Lindor, Thibodeau, & Burke, 2017). These findings seem to suggest that a large number of patients could obtain targeted treatments through large scale genomic testing, although not all of them will benefit from these treatments.

CHAPTER II

METHODS

The aim of this project is to learn about patient and clinician communication and understanding of paired tumour and germline testing in oncology, communication around germline findings, and the resulting "actionability" of these tests. In this pilot study, we solicited interviews with physicians ordering the UCSF500 test and their patients in order to better understand the experience with tumour and germline sequencing for oncology patients. The UCSF500 is a comprehensive gene panel, including over 500 genes that are associated with both hereditary forms of cancer and somatic tumor alterations. This test requires both tumour tissue and a blood sample from patients in order to assess for both tumour and germline changes. This test is performed at the CLIA approved UCSF Clinical Cancer Genomic Laboratory. The results of this test are sent to the ordering physician, and are also available to be discussed with oncologists, pathologists, and clinical trials coordinators at a weekly molecular tumour board meeting. This study received approval by the Institutional Review Boards of both the University of California, San Francisco and California State University, Stanislaus.

Inclusion criteria for physicians included having ordered the UCSF500 test at least once for their patients. Physicians who were active users of the tests were sought out as they would have the most experience, which gives them the richest insight into how this test is used in a clinical setting. Inclusion criteria for patients involved being

over 18 years of age and having had the UCSF500 ordered or the results returned. Eligible physicians were identified at the UCSF Molecular Tumour board and were recruited in-person and through e-mail. After interviewing each physician, a consent to be contacted form was given to them to pass on to the patients for whom they ordered the UCSF500 test. Patients who agreed to be contacted were phoned or e-mailed to schedule an interview. A total of 8 physicians were interviewed, 3 were from neuro oncology, 2 from clinical trials and the other 4 had specialties in gastro-intestinal oncology, genitourinary oncology, melanoma, and breast cancer respectively. A total of 6 patients were interviewed. Three patients elected to be interviewed with a family support persons to the interview, which brings the total of patients and family members together to 9. The diagnoses for the patient cohort included 4 patients with brain tumours and 2 patients with prostate cancer.

Semi-structured interviews lasting between 30 minutes and 1 hour were conducted with each participant, and their family member if applicable, in a comfortable location, including their homes, offices, or a private room near the hospital. Ethnographic observations of the weekly Molecular Tumour board meeting and two appointments at which the patient participant's physician disclosed the UCSF500 results were performed to give a more rounded understanding of the entire testing and communication process between the entire healthcare team and the patients.

Each interview was digitally recorded after obtaining written consent and transcribed verbatim by a professional transcriptionist. Once transcribed each

interview was listened to and edited if need be to ensure accuracy. The data was then uploaded into Dedoose, a qualitative data software program (SocioCultural Research Consultants, LLC, 2015). Analysis included coding and thematic development and was informed by a modified version of grounded theory (Corbin & Strauss, 2008). This analysis was guided with the constant comparative approach, so the data analysis began as it was collected and was used to inform subsequent data collection and analysis (Corbin & Strauss, 2008). Through multiples readings of interview transcripts, codes were developed and used to create themes.

CHAPTER III

RESULTS

Overall, there were 3 main themes identified; barriers to obtain results, the value or purpose of this test, and the communication around germline results. Subthemes included the distinct barriers to obtaining genomic testing and to obtaining actionable results from the test, as well as the value attributed to germline testing, the patient's understanding of germline testing, and patterns of communication when physicians disclose results to patients and when patients disclose germline results to family.

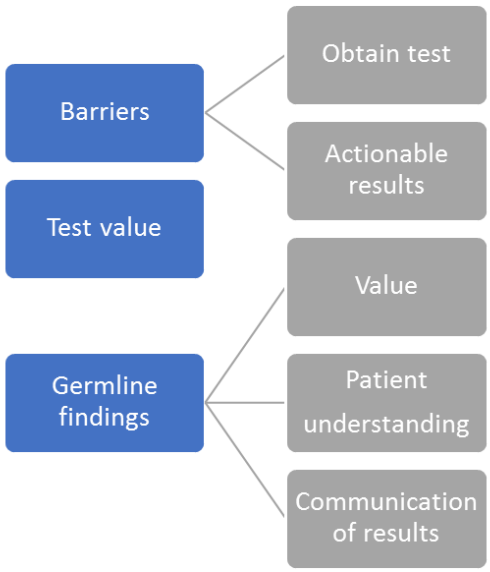

Figure 1- Themes Identified

Value of Simultaneous Tumour and Germline Testing

All patients expressed that a goal for this test was to identify a targeted treatment. Most patients seemed to have a fairly good understanding that the identification of a particular genomic profile could indicate that certain drugs would work better or worse for their individual case.

> P2, BRAIN TUMOUR: That is part of the goal of the study is to see is there any marker that might indicate an agent that we have not considered or thought of or some sort of study that might make sense.

Every single physician also mentioned identifying targeted treatment was a goal for this type of testing; however, this was not always the primary goal for utilizing this test. Notably, physicians from neuro-oncology felt that there was more value to using this test to diagnose the specific cancer type, as opposed to identifying individualized treatment.

> MD6, NEURO ONCOLOGY: One is that it is often something that we are thinking about on the diagnostic level rather than necessarily a treatment level, where there are tumors that look fairly indolent or relatively low grade but with the initial pathology sample and some of the specific gene tests that get done the pattern does not come back as the standard pattern that we would expect for a Grade 2 glioma, as an example, and the panel is an efficient way of testing multiple other things hoping that we come up with a mutation that is more characteristic of a Grade 1 tumor to distinguish between Grade 1 and Grade 2. The potential treatment implications between those two are fairly significant although not actually specifically genetically targeted the majority of the time.

Patient 4, with a brain tumour, reiterated that this same idea; she described the test as “helpful in determining what type of tumour it was” with the hope that “certain medications would better for this certain type of tumour”.

Another purpose was that arose was collection of data. Physicians explained how collecting more research data would help inform their understanding of the test results for future patients. This was highlighted by many physicians who feel that this test is straddling the boundaries of a clinical test versus a research protocol.

> MD2, NEURO ONCOLOGY: My understanding – and we are just getting involved in this study so I am still learning – my understanding of the reason to do this kind of gene panel is both clinical, of course, in terms of patient care, but also in terms of wanting to amass data like you are describing.

Patient's also felt that this test would be valuable in a research context. Some patients verbalized how the test could have something to offer others, even if it was unlikely to help themselves. Overall, the low likelihood of the results from this test impacting management was understood well by patients, but they seemed to retain a sense of hope that they could be the lucky ones, or at least help someone else in a similar situation one day.

> P6, BRAIN TUMOUR: Yes. I have understood this as research. This is not a personal attempt to identify my problems and solve them. I am someone who suffers from something that a number of other people suffer and they are trying to gather information from a lot of people at once, period.

The value of testing, even if no mutation was found was also underlined by one physician. He felt that patients would benefit from the knowledge that they had attempted to find a targeted treatment. This sentiment was expressed by both physicians and patients.

Barriers to Obtaining Genomic Testing

Physician Knowledge

One barrier to the consideration and utilization of large scale genomic testing, is the clinician's own comfort with ordering and interpreting this type of testing. Most physicians who were ordering this test expressed that they felt that they, or their colleagues, had a lack of knowledge about genomic testing.

> MD7, BREAST CANCER: It is a different language, different skill sets, different backgrounds. The people in the breast cancer tumour board are all clinicians. You talk about the genes and he pathways and stuff and they will pretend they know, and they do not. They do not really understand, they do not understand the relevance of it.

In addition to not being familiar with the material, oncologists highlighted the reluctance to admit that they do not know about certain topics in genomics. It can be hard to facilitate genomics education when displaying a lack of knowledge is not socially acceptable.

> MD4, CLINICAL TRIALS: If I just had a genetics background, I could probably communicate [with patients] more effectively… I think just a better understanding of what we are doing here. I think people are sort of embarrassed to admit they do not know things as they get higher up.

Many of the ordering physicians expressed that they had pursued genomics education, either through books, journal articles, or completing courses. Some departments have even begun to include genomic cases in their weekly tumour boards for education purposes, which a neuro oncologist described as "actually been really helpful to me". Continued educational support for clinicians, in a judgement-free

environment can help them feel more comfortable ordering and interpreting this type of testing.

Patient Finances

The biggest barrier physicians themselves noted for ordering the test for patients was their concern that patients' health insurance would not cover the cost of the test, which was unknown but estimated to be over $1000. If the physician had the sense that a patient could not afford to pay out of pocket, they often hesitated to recommend the test; almost all physicians noted that a patient's financial situation was likely to impact the patient's likelihood of obtaining the test. Some indicated that the barrier was brought up by the patients. A neuro oncologist, MD6, described patients who were already facing large medical bills feeling the need to stop and think about the necessity of test when cost was introduced to them. Patients themselves reported that they would have been hesitant to have the testing done if they thought it was not going to be covered by insurance. Many patients responded that they would have to think about having the test done if the out of pocket cost would be $1000.

> P1, PROSTATE CANCER: I would not do it [if the test cost $1000].
> P1 FAMILY SUPPORT PERSON: I would do it for $1000 if there was a reasonable chance that it would pay off.
> P1: If there is a reasonable chance for some enlightenment but I do not think the chance is reasonable so I would not pay that.

In some cases, patients could not recall a discussion about the cost of testing ever occurring. This was cause for concern, as some patients may be receiving a large and unexpected bill after obtaining this test. Mentioning the potential cost upfront could mitigate the possibility of distress from an unexpected large medical bill.

> P4, BRAIN TUMOUR: Actually, I should have thought about that [cost of the test] before. I did not at all. I was just like, "Okay."
> I: You would assume your insurance was going to pay for it, right?
> P4: Yes. Right.

Other physicians indicated that the patient's financial situation may influence their likelihood of even offering the test in the first place. Overall, physicians were divided, with about half reporting that a patient's financial situation may prevent them from discussing this test as an option, while the other half said it would not prevent them from doing so.

> MD5, NEURO ONCOLOGY: I have not come across an instance where the patients were just like, "I can't financially cover that." So, I do not know what that means? That just means that everyone is getting it covered or it is not really that much of a financial hardship or I am just not asking those patients whether or not to do the test, which is probably more likely. Yes, I think it is hard enough for patients to come here, to park in the parking lot, drive from Redding or Modesto or Fresno or Bakersfield. It is hard enough for them to do that and then to ask them to fork out $1500 for predominantly academic information is a tough pill to swallow I think.

This puts physicians in an interesting ethical position. Is it better to withhold the information that a test with a possibility, albeit a low likelihood, of impacting their treatment exists if the patient may not be able to afford testing? Is it better to present the option, even if the patient is already struggling to afford traditional and proven therapies?

Other Barriers

Other barriers to ordering large scale genomic testing focused around 3 situations: using tumour tissue, patient's health status, and clinician time. Tissue is a finite resource, and it is often required for entry in a clinical trial, so some physicians

were recommending saving the tumour tissue for specific clinical trials instead of genomic testing. Additionally, if tissue is limited or is difficult to access, such as from a brain tumour, it can impact the decision about pursuing this test.

> MD2, NEURO ONCOLOGY: At the beginning… the thought was still to do it [large panel sequencing] for patients just because we were uncertain of the value of the results. Since then the pendulum has swung the other way which is "Why don't you keep your tissue? Tissue is finite, you might need it later on."

Although, some others feel that large panel testing can help save more of the patient's remaining tissue for future trials. Genomic tests that simultaneously analyze both tumour and germline allow patients to have the benefit of having multiple tests run at once, as well as an assessment for hereditary cancers.

> MD5, NEURO ONCOLOGY: I have had one example off the top of my head and I think more and more the pathologists are recommending UCSF500 testing because that is limiting the number of tests that they have to run on the tissue and you can get most of the answers all once. That has been very helpful

A patient's health status can understandably be involved in making the decision to offer testing. If a patient is not well enough to undergo a biopsy to access tissue, this test may not be presented as an option. Prognosis can also impact the chance of obtaining this test; physicians are reluctant to order this test for patients who may have just a few weeks to live, as the long turnaround time for this test could mean that they would not receive results in time to make any changes in treatment.

The lack of time to coordinate the testing process was also mentioned as another barrier to ordering this test. This type of large scale genomic testing requires the time to educate patients on this type of testing, obtain informed consent, collect a

tumour sample, order a blood draw, interpret the test results, attend tumour board to discuss the results, identify treatment options or clinical trials, disclose both the somatic and germline results to the patients, and then finally discuss those options with the patient. This process falls entirely on the shoulders of the ordering provider, and is much more labour intensive than some other types of clinical tests. MD1 suggested having someone specially trained for this role could help eliminate the "time factor" as a barrier to ordering this test.

> MD1, GASTROINTESTINAL ONCOLOGY: [what we thought would help] was to have essentially a specialized nurse practitioner being the point of contact for the patient, who would be trained in this whole approach, who would help with consenting, who would help with test interpretation, who would help with finding clinical trials and so on; be an expert nurse practitioner on helping patients getting care based on genomic features. That would be great. Building this kind of specialty position that would take the burden from the doctor in having to explain all this.

Actionability of Test Results

Actionable findings in this context comprised of a change in treatment, that was specifically directed by the test results. These actionable treatments targeted a particular molecular change that was identified by the genomic sequencing. Through interviewing physicians, we found that there were multiple different points which influenced whether or not a patient has an actionable finding; identifying a molecular target and accessing the targeted treatment.

Identifying a Molecular Target

Physicians in several specialties told us that the initial likelihood of identifying a targetable finding is not very high. Although targeted treatments are

available for some types of cancer more than others, the physicians we interviewed emphasized that a targetable mutation will not be found in the majority of patients.

> MD1, GASTROINTESTINAL ONCOLOGY: “We make a therapeutic recommendation on about 35% of the cases

Despite the recent advances in precision medicine, there are still relatively few drugs that are useful in targeted cancer treatment. So, even if a targetable mutation is found, there is no guarantee that there is a drug that will be effective at targeting the specific tumour, in that part of the body.

> MD5, NEURO ONCOLOGY: The more information that we gather about these things, the more we try to understand the pathophysiology behind it. But so many of these drugs have not been tested for CNS penetration and things along those – Even though you might find something that clearly looks targetable, whether it is going to truly be effectively targeted with an agent that works in the lung cancer is not likely just because they’re, it’s just as much the microenvironment of the tumor as opposed to its fundamental genetics.

With the novelty of this type of testing, patients are understandably aware that there aren’t many treatment options yet. Those who have undergone this testing seem to have a clear understanding that the number of drugs available that target specific genetic alterations is low. Patient 1 described the situation as “pretty frustrating”, as he understood there were few targeted drugs likely to be recommended for prostate cancer, but wanted to participate in testing nonetheless. Clearly the communication around the low likelihood of identifying a targeted treatment is good. Patients have a realistic perspective on the chances that something actionable is found, however they still have the ability to retain some hope that they will be part of the minority who will have some success identifying a targeted treatment.

Accessing Targeted Treatment

The last hurdle for obtaining actionable results with this test, is the ability to access targeted treatments. Sometimes, even if a clinical trial was identified, a patient may not be eligible because of their cancer type, their health status (i.e. being on dialysis), or the distance is too great for the patient to travel. Sometimes physicians are able to obtain compassionate use for their patients who aren't able to access the research studies or clinical trials on the drugs that are indicated. Compassionate use is defined as "is the use outside of a clinical trial of an investigational medical product" by the Food and Drug Administration (FDA) and requires an application which is then evaluated by the FDA for each individual patient. However, this takes a lot of time and effort on the part of the physician, and there are no guarantees that it will work. Another barrier on this end is financial. Some insurance companies will not cover treatments that are approved for a different cancer type than the patient has, or require studies with large numbers, which doesn't happen in rare cancer types to approve the claim. This leaves the patients with the option of paying out of pocket or not receiving the drugs.

> MD4, PHASE 1 CLINICAL TRIALS: In terms of barriers to getting drugs for it, in Phase 1 it could be that this patient has a mutation and we have a drug for that mutation but the trial has no slots or the drug companies want to focus on a cohort within that mutation, a cohort within that cohort. Then, obviously, there is the issue of if someone has a HER2 amplification but they do not have breast cancer you can think about getting off-label Herceptin but you have to petition to the drug company for it because it will not be paid for, for people without breast cancer. There are indications for things and when you become disease agnostic then you have to worry about reimbursement. That is, again, why it is nice to have these things early because getting the drug is not a trivial thing, it takes a little while.

In addition to the issues inherent with accessing clinical trials and drugs in development, accessing FDA approved treatments was often challenging. Insurance companies frequently cited that the drug was not indicated to treat the specific cancer type, or cancer subtype, and therefore denied coverage, despite molecular evidence to the contrary. It takes time and effort to try to find another way to access the approved drugs when insurance coverage had been denied.

> MD3, GENITOURINARY ONCOLOGY: I just had a patient with kidney cancer, I was trying to get him this new drug that is actually FDA-approved for kidney cancer and the insurance company came back and said, "He does not have the subtype that was tested in the study, therefore we are not going to pay for it until you show me a Phase 3 study that – I was like, "That is bullshit. You are never going to have a Phase 3 study in this rare type of kidney cancer." They are just trying to pass the buck. I was ready to literally punch a wall with this. I usually do not get that upset but this freaking insurance company – I am like, "Look, this kid is dying of cancer. He needs to get –" he is a young guy "– he needs to get this drug." Finally, we got it through the company's compassionate use program but it took a while.

Physicians also seem to have a tempered, but hopeful view on the testing because they were all able to recall both scenarios in which it has not been helpful those where test had been helpful with guiding treatment..

> MD3, GENITOURINARY ONCOLOGY: [I had a patient] Whose husband we did this for and we gave him a drug based on that and he had a partial response. His tumor shrank for a few months and she paid for drug for the first month and then she went to the insurance company and said, "Here is the scan, it is working," and they reimbursed her. That was like the success. It did not work forever, it worked for a couple of months but it was a benefit. It was genomically guided. She has become very active in the bladder cancer world and in this idea of getting access to clinical trials more easily, trying to make that from the patient's end something that can happen.

This finding was truly actionable; as a mutation was identified, which had a targeted treatment, and the patient was able to access the indicated treatment, which

caused some clinical improvement. In other situations, molecular findings did not lead to clear treatment decisions. Other physicians underlined how challenging it was to access clinical trials and to access off label treatments. Most often, it is difficult to access the recommended treatment.

> MD8, MELANOMA: It depends on what it is. I have had people with RAS mutations where I am trying to get a MEK inhibitor and I'm sometimes able to identify a study, sometimes I am trying to get off-label, which is very difficult and most often gets refused.

Germline Findings

Value of Germline Findings

There are multiple different aspects which makes obtaining germline information simultaneous with the tumour sequencing desirable. Many physicians mentioned that it was useful in the interpretation of the testing itself. They also highlighted the benefits for risk assessment and surveillance of the patient and their families.

> MD3, GENITOURINARY ONCOLOGY: Interestingly, for the first patient they said, "Yes, this is the germline CHEK2 and maybe it explains why he developed cancer in the first place." He was younger too, which kind of made sense. They were really happy that they found it – the family. Not obviously happy to have it but that they found it because he had daughters and the daughters were going to get checked out and his sister, etc., etc. They will get screened earlier or whatever if they are positive for the mutation. That was I thought actually a useful test and it made me wonder how many of these patients where we see over the last – I have been doing this for almost ten years now, a little less, how many of these patients have gone by where I have just totally missed the germline mutation because we are not screening everybody's germline routinely. What have we missed that we are not getting. I think there is some value there. It is hard to say what that number is or are we really preventing his daughter from getting whatever cancer in ten years or twenty years but maybe. I think there is a lot to be said there.

Despite family testing being a benefit that physicians are aware of, not all patients seemed to grasp this concept. Some patients reported an inaccurate understanding of how genes were inherited. These ideas included thinking that a cancer predisposition can be passed down only through the paternal side if a father was affected with cancer, or vice versa. Others thought that because they did not have direct descendants that genetic information would not be relevant for others in their families, despite the fact that siblings share about 50% of their DNA, which is just as much parents and children do. These misunderstandings may have contributed to why the benefit to their families was not identified by some of the patients interviewed.

> P1, PROSTATE CANCER: I do not think about it [the possibility of the children inheriting a genetic mutation].
> P1, FAMILY SUPPORT PERSON: We have only had daughters. I do not know that it would affect the next generation.

In some instances, the germline findings brought limited information to the patients or to their families. Some of the mutations reported back are moderate risk alleles or even polymorphisms with mildly increased risks. The clinical implications of these findings are less clear than those with high risk, high penetrance alleles, and low risk findings may seem less pertinent in the face of a current cancer diagnosis.

> MD6, NEURO ONCOLOGY: The only one I can think of that I have had was some SNP that might very slightly affect the risk of colon cancer, by like a factor of 2 or something. I have not had some major finding. The person who had that finding, when I talked with them about it, it was pretty clear that they were already 60, they were already getting colonoscopies and they were like "this does not seem important, I'm going to pay attention to the brain tumour" I was like, "I think you are right".

Other aspects that physicians found valuable about the germline information was the ability to make a diagnosis or to affect treatment decisions. Even if it is not guided by genomic results, a diagnosis can lead to more specific treatment that isn't individualized on a molecular level. In certain types of hereditary cancer, treatments are contraindicated.

> MD1, GASTROINTESTINAL ONCOLOGY: We had a case of a child that had like a bi-allelic BRCA mutation where we recommended against the use of Parp inhibitors, because it might be very toxic. There are other mutations when we then stay away from radiation when we know, Li Fraumeni syndrome for example. Yes, there are these consequences sometimes.

Even with the varying value different patients see in germline findings, the vast majority desired to receive their germline findings. It was reported that overall, approximately 2% of patients opt-out of receiving germline finings for this particular test. Physicians described the patients as wanting to know everything. At this point, patients are already aware that they have limited options for treatments, and that the test has a low likelihood of influencing their treatment plan, so they want all the information they could possibly gather, in case it might help. Reasons for those who have wavered in their decision-making or who have opted-out entirely included a fear of learning about a new diagnosis or lack of family members it may impact.

> MD9, CLINICAL TRIALS: I think the most common is they do not see the immediate impact for themselves in terms of treatment. Maybe they have pretty advanced disease, maybe they do not have a lot of family or whatever. They just do not see the clear need to go down that route. I think that probably some of it is concern over opening up a can of worms, a little bit of a fear of unknown, and a little bit of not wanting to know.

When asking patients about their decisions to receive their germline findings or not most patients reiterated what the physicians had indicated. The desire to know everything was the most pervasive reason for opting in for germline findings. They also mentioned the benefits to their own health management, such as being forewarned about their future cancer risks.

> P4, BRAIN TUMOUR: I was pretty confident [opting in for germline findings]. I just – again, for me it seemed like a no-brainer. Like I said, I am making myself susceptible with chemo and stuff so it helps that they know what to look for. If I have symptoms of something else it would just alert people more as opposed to thinking I was crazy and just being like – You know, a lot of times with cancer stuff you have very vague symptoms sometimes and primary care physicians are – not that they are going to tell you to get out of there office but they are going to be like, "Oh, it's fine.".

Patient Understanding of Germline Testing

Many physicians commented on how it was difficult to explain the distinction between tumour DNA and germline DNA to patients. MD 7, who works with breast cancer described this concept as "a simple concept scientifically, but it is kinda difficult to understand". Interestingly, there was an almost even divide of physicians who felt that their patients understood the distinction and those that felt that their patients did not understand the distinction. Some described their patients' understanding as to variable to be generalize.

> INTERVIEWER: Do you have a sense that most of your patients understand the tumor/germline distinction in terms of the DNA level?
> MD6, NEURO ONCOLOGY: I think so. I'm not 100% sure.
>
> INTERVIEWER: What is your sense of how well patients understand the tumor/germline distinction? To what extent do you even get into that with them?

> MD2, NEURO ONCOLOGY: We always get into it with them. I do not think they understand it at all. I do not think they get the significance of it. That might change with time.

When asking patients about their understanding of the difference between the germline and tumour results we saw a range of levels of comprehension. Some understood this concept, but most seemed either unclear or even unaware of the difference. The majority of patients reported that the idea that a tumour would have a different genetic profile than the rest of their body was a new concept, introduced when discussing this test.

> P3, BRAIN TUMOUR: I have a somewhat foggy memory of some of this [tumour/germline distinction]. It is possible that analyzing my regular tissue could surface information about a disease that I could get in the future that others in my family might be – possible for them to get and then I would have to figure out what do I do with that information, do I tell them, etc… It did not surprise me to hear that but it was not something that I was familiar with either.

> P6, FAMILY SUPPORT PERSON, BRAIN, TUMOUR: When you just said the DNA that is floating around in your body could be different than the DNA that is in the tumor cell, that struck me as news … something that had not occurred to me.

Even after the discussion of the tumor/germline mutation distinction, there can still be pervasive misconceptions in patients' minds. It can be very challenging to correct common misconceptions in the short amount of appointment time, especially when there is a lot of new content to be covered.

> MD7, BREAST CANCER. Even the germline stuff, just understanding that no matter what you tell them, patients think that BRCA1 or 2 comes from your mother, it cannot come from your father. I cannot tell you how much of that there is out there.

Communicating Germline Results to Family Members

Despite all the patients having elected to receive germline findings, their opinions on how the information should be shared with their family members varied greatly. Some patients had informed their entire families that they were testing, while others kept it secret. Some gave their family members the choice of learning about any germline findings, others decided to only share what they felt was important for their families to know, and some decided to share nothing at all. This first patient did not elect to share because she did not want her family members to worry about their potential cancer risks at the moment.

> P4, BRAIN TUMOUR: I really just decided to like – I did not like internalize it and keep quiet about it but I just did not really say anything to them and actually did not say to any of them – My sister-in-law, my oldest brother's wife, is a psychologist and she works with patients – she is a clinician, she works in the hospital, and so she has a pretty – a good medical knowledge also. Again, it is not a secret but like I just did not share information with them. If they asked specifically like, "Did you get a genetic test?" I would say, "Of course, I did." But I am not going to come out and be like, "All you guys, you are susceptible to sarcoma and all your kids have higher probability of having it."

The following patient is describing how they would make the decision based on their assessment of the specific change. Having opportunities for screening or prevention would influence their likelihood to share this information.

> P3, BRAIN TUMOUR: I would want to know more information first like how actionable is it for them to have this information? Is there something positive they can do with it? What is the likelihood that this disease would happen and so on? My default tendency would be to share the information. It would seem very difficult not to, but I would certainly want to get more information.

This patient described having formed a plan for disclosing to all his close relatives. He had included family members in the discussions around how the results should be shared.

> INTERVIEWER: Which family members did you talk to?
> P2, BRAIN TUMOUR: My parents as well as my brother and my sister-in-law because they also have two kids. Anything that, also goes, you know. I told them I can tell my brother alone or – it was their mutual decision to whether they tell the kids. It was my brother's decision to find out whether he wanted to know so him and his wife can decide what they wanted for the kids when it comes down to it.

Communicating Germline Results to Patients

Physicians described some discomfort with discussing germline findings with their patients. Disclosing hereditary high risk germline findings was reported as difficult, especially if the oncologist was not very familiar with the condition. Other conditions that are not primary hereditary cancer syndromes, such as neurofibromatosis 1, were also identified as difficult to discuss with patients due to physician's unfamiliarity with the condition.

> MD5, NEURO ONCOLOGY: I was mainly prepared to send them to genetic counseling. That was what I was going to do. I did not feel like I had enough training or expertise to understand what risks they specifically needed to address and was not going to punt but realized I was out of my depth and say that, "You need to see a genetic counselor."

Many physicians identified genetic counseling as a resource for their patients. They saw genetic counselors as valuable in their ability to both explain the germline findings to the patients and in communicating the recommendations about any germline findings to the oncologists.

> MD3, GENITOURINARY ONCOLOGY: The best thing I get from [genetic counseling] is the guidance about what frequency to scan patients with and

> what other things I have to think about because that is, again, clinical. Thinking about it as a pure clinician, you just need recommendations.

Even though most physicians were aware of the presence of genetic counselors and the ability to make referrals to them, they were not all familiar with what happens during a genetic counseling session. Being more familiar with the genetic counselling scope of practice could help physicians explain the referral better to patients and help ensure that all patients who would be appropriate to be seen in genetic counseling would be referred.

> MD2, NEURO ONCOLOGY: Then I will say, "I wash my hands of it," in a way saying, "I'm going to send you to genetic counseling. I really do not have any idea of what they are going to tell you. I am interested in what they do. We will go from there."

CHAPTER IV

DISCUSSION

Value of Simultaneous Tumour and Germline Testing

Despite identifying actionable findings being the main goal of precision medicine and targeted tumour and germline sequencing, both patients and providers were able to identify a variety of other purposes for this test, including obtaining a more accurate diagnosis and gathering data for research. A new diagnosis can guide treatment, in a more general way than molecular targets can, by identifying which traditional therapy types might be best suited for this patient. This is different from the molecularly targeted treatment, which will act on a specific cellular pathway to impede the progression of the patient's cancer. Other oncologists who have used simultaneous tumour and germline testing have highlighted that a more accurate diagnosis falls is a purpose of the test, and that it can help guide treatment (Kline et al., 2016; Laskin et al., 2015). Gathering data for research will also help inform treatment for patients in the future, but it will not likely help the patients undergoing genomic sequencing today. As this type of testing is used more frequently, the value of the results will increase as we will have a better understanding of what they mean in the context of oncology.

Barriers and Actionability of Testing

Finances were one of the main barriers identified in trying to obtain simultaneous tumour germline testing. Currently, many physicians do take finances

into account when considering genomic sequencing, but not all discuss it in detail with their patients. In this study, multiple patents mentioned the price point of $1000, as being the line where they would debate going forward with testing. This is similar to what the general population has described, where 97% of people would not pay $1000 dollars out of pocket to receive genetic testing (Marshall et al., 2016).

Another major barrier was physician knowledge of genomics. Most oncologists in this study professed some uncertainty around their knowledge of genetics, but many had sought out education and resources independently. This echoes what has been seen in the medical education system, where most programs do not include adequate genetics content in the curriculum (Haspel & Saffitz, 2015). Institutions can also help facilitate accessible education in genetics for their oncologists. Unfortunately, the continuing education is often geared toward those who already have some background in the subject (McGowan et al., 2014). This challenge is compounded by the feelings of embarrassment and unwillingness to ask questions due to a lack of knowledge that was brought up in the interviews. The ability to provide a non-judgmental space for learning about this test are essential to encourage those who are less knowledge to participate.

Other barriers included poor health status, lack of time to preform this test and the limited amount of tumour tissue. Prioritization of the use of tumour tissue, and the implications of poor health status can be included in the initial discussion around testing with patients. The issue with the lack of time to devote to testing could be addressed by utilizing resources, such as a tumour board or a genetics professional to

help interpret or deliver results. This would alleviate some of the burden from oncologists and allow those with expertise in genetics to be involved in patient care.

The nuances of what makes a finding actionable were discussed with patients and physicians. As it stands, even if a targetable mutation is found, the drug may not be accessible. Oncologists pursuing simultaneous tumour and germline testing should be aware of the barriers to accessing drugs, including lack of insurance coverage, exclusion from clinical trials, or difficulty accessing drugs approved for certain types of cancer only. Avenues to facilitate access include appropriate clinical trials, compassionate use programs and negotiating with insurance companies directly. This often involves a significant amount of coordination on the part of the oncologist. Even with all the uncertainty around this type of testing, a realistic view of the likelihood to find a variant that has a targeted treatment is being communicated well to patients. They were all able to describe that the likelihood was low, but remained optimistic that this test could result in something that would impact their management, or help others in the future.

Germline Findings

Discussing the germline element of this test was identified to be the most challenging by many of the physicians. They were able to identify the value of having the germline information to assist in interpretation of the test, provide management options for the patient or assist in determining the risk of other family members to develop cancer. Not all patients understood these implications. It is

challenging to describe a new concept, but there are communication strategies that could make this easier for patients to understand.

When describing the tumour portion of the testing, metaphors or illustrative language has been successful. A study of patients found that the majority of patients appreciated when their oncologist used metaphors like “gas pedal” or “light switch” to describe complex ideas like driver mutations (Pinheiro et al., 2017). When describing germline testing, emphasizing that it looks for cancer predispositions, and could give more information about your risk, and your relatives risk to develop cancer in the future is the key message that should be conveyed. Emphasizing that siblings, parents, nieces and nephews, and aunts and uncles could all be impacted by this information and not just children is important, as some patients in this study seemed to feel germline findings were irrelevant if they did not have biological children. Another misconception is that a father who has cancer can only pass a genetic risk down to his sons, or a mother to her daughters. Describing that an inherited cancer predisposition can cause different cancers in different people, for example Lynch Syndrome, which can cause colon cancer in some family members and uterine cancer in others, can help address this misconception.

Patients described multiple different communication preferences when disclosing results of their test to their families. This ranged from not disclosing the results, to planning the discussion before the results were even returned. Those who wanted to withhold the results were afraid of worrying their family members with the fact that they could be at a higher risk to develop cancer in the future. Those who

disclosed fully wanted everyone to be informed, so that they could be proactive should an inherited cancer risk arise. There were also some patients who felt that they were not certain how much they would disclose, and that it would depend on the results they received. The knowledge of whether they carrier a high or moderate risk allele combined with the screening and prevention options could impact this decision. It is imperative that patients understand the limitations and benefits of any medical test they consent o have. Fully understanding the potential implications of germline testing and having the results interpreted could help in the decision-making process.

Oncologists also described a discomfort with discussing germline results to patients. This is in line with what has been described in other studies. A recent survey of oncologists asking about simultaneous tumour germline testing showed that 46% felt comfortable discussing the tumour results with patients, while 37% felt comfortable discussing germline results with patients (Johnson et al., 2017). Ways to mitigate this discomfort include more exposure to germline cancer results through education, more experience with the test, or involvement of a genetics professional in the results disclosure. In that same survey, 93% of oncologists would like to consult a genetic counselor before disclosing the results and 68% felt that it would be useful to have a genetic counselor present at the results disclosure session (Johnson et al., 2017). Establishing genetic counselors as an available resource to help physicians and patients navigate simultaneous tumour and germline sequencing could help alleviate some of this discomfort.

CHAPTER V

CONCLUSIONS

Through interviews with patients and their family members, and physicians a range of value for this type of testing was described. There is value in managing treatment, more accurate diagnosis, research data and informing family member of their risk. The low likelihood of identifying actionable results and the challenges of obtaining targeted treatments were understood by patients undergoing this test. However, patients did not express a good the different types of results, tumour and germline, from this test and the implications of each type of finding. Helping patients understand this distinction will allow them to make an informed decision about opting in or out of receiving these findings, and communication the results with their family members. Communicating in clear and simple language, and repeating new concepts can help patients grasp this information. Utilizing genetics professionals as resources, like genetic counselors, can help patients and physicians understand the germline testing results and their implications.

CHAPTER VI

IMPLICATIONS FOR PRACTICE

It is important for genetic counselors who are seeing patients who have had simultaneous tumour and germline testing to know that their pre-test counseling is variable. There are no standard ways these patients are being informed and consented for this test, and even if they have opted in to receive germline findings, they may have no idea what they are. They may have little explanation from their oncologist as to what their genetic counseling appointment is about, so patients may not know what to expect at their appointment. The detail in the discussion of germline findings with their oncologist also varies greatly.

This type of testing is largely treatment driven, and oncologists feel more comfortable discussing tumour results. Patients may not be aware of the other roles for germline testing. They may not give much focus to germline findings at the time, as these patients are all currently undergoing treatment, and many of them have cancer that is not responding, or is suspected not to respond well to traditional therapy.

Recommendations

Recommendations include:

- The cost of genetic testing should be discussed with the patient, especially if the out of pocket cost could be over $1000

- There are resources for physicians to learn more about this type of testing, and genetics professionals can be consulted to assist with interpretation or disclosure of results.
- Physicians and patients should be aware that even if they find a targeted treatment, there may be barriers to accessing it
- The difference between the genetic information in a tumour and germline is a new concept for most patients, and difficult to understand.
    - Explaining this concept in a basic way and more than once in a session can help
    - Until patients have a good understanding what germline testing is, they won't fully comprehend the limitations and benefits of this part of the test

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APPENDIX

APPENDIX: INTERVIEW GUIDES

Interview Guide for UCSF Physicians

First, I'll briefly describe the purpose of this interview. We're talking with physicians who have ordered the UCSF500 genomic sequencing test. We are particularly interested in how you explain the test to patients and how you use the information produced by the test to inform clinical decisions.

1. We'll start with some background questions. Can you tell me about your area of specialty in oncology?
2. Before the UCSF500 gene panel was launched, how much experience did you have with clinical genetics and genomics?

   Follow up: What other types of genetic tests do you routinely ordered for patients (tumor or germline)?

   Probe for comfort level with clinical genomics' concepts and terminology.
3. What is your understanding of the purpose of the UCSF500?
4. Can you describe for me the criteria you use when deciding whether to order the UCSF500 test for a patient?

   Probe for causes of uncertainty about appropriateness of genomic sequencing for individual patients; ask for specific examples.

   Probe for whether test is ordered for patients with poor prognosis.
5. How do you describe the purpose of the test to patients?

   Probe for: how/whether the following is communicated to patients/families: information about the anticipated benefits of genomic information; the likelihood of identifying a targeted treatment; the difference between tumor and germline DNA; the possible implications of germline findings for family members.
6. How well do you think most patients understand the test?
7. How do you explain the somatic/germline distinction to patients?
8. Who pays for the cost of the test?

9. How do you obtain the results of the UCSF500?
   Probe for: whether participant attends Molecular Tumor Board meetings to discuss findings and why/why not.
10. How are clinical recommendations based on USF500 results conveyed to you?
   Probe for whether/how discussion with molecular tumor board influences treatment decisions.
11. How do you communicate the results to patients and/or parents/guardians of patients?
   Probe for details about setting, who is present, what terms and tools are used to explain results to patients, whether patients are given a copy of the UCSF500 report.
12. If a new treatment is suggested by the UCSF500 results, how do you and your patient decide whether to try the treatment?
   Follow up:
   How does availability of a treatment influence your decision?
   How involved are patients and their family members in the decision?
   Probe for economic, regulatory and other factors that shape drug availability, e.g. cost, clinical trial accessibility or eligibility
13. Do you discuss variants of uncertain clinical significance (VUS) with patients? If so, how do you explain them?
14. Does a VUS ever prompt you to change a patient's course of treatment?
15. If a UCSF500 report contains information with inherited disease risk implications, how do you communicate this information to patients and their family members?
16. How do you decide whether to refer a patient for genetic counseling?
17. Do pathogenic germline variants eve influence your treatment recommendations?
18. What resources would help you and your colleagues as you make decisions about recommending genomic sequencing for your patients?
19. What would help you to more effectively communicate with patients about cancer genomics?

20. What other suggestions do you have for improving the use of genomic sequencing in cancer care?

Patient interviews

First I'll briefly describe the purpose of this interview. We're talking with patients at UCSF whose doctor has ordered a genetic test to help them make decisions about cancer treatment. We're interested in understanding more about what you and your doctor expect from this test.

1. We'll start with some background questions. First, how are you feeling today?

2. How long have you been a patient at UCSF?

3. Can you tell me when you were first diagnosed with cancer?

4. What treatments have you been through?

5. When you were first diagnosed, what were your thoughts about the causes of your illness?

6. Has anyone in your family had a similar illness?

Now I have a few questions about a test that your doctor recently ordered for you.

7. Are you aware that your doctor recommended and ordered a genetic test for you?

8. [If no, try to jog patient's memory. If still no recall, conclude the interview.]

9. [If yes], how did your doctor explain the test to you?

   Follow-up:
   a) How well did you understand the explanation?
   b) Is there anything about the test you don't understand?

   Probe for understanding of purpose of test.

10. What are your hopes for the test results?

11. Do you have any fears about the test?

12. What did your doctor tell you about the types of genetic information that the test will look for?

13. Do you recall the consent form that you signed in order to undergo the test?

    Probe for recall of information on consent form. If patient was given copy of consent form, did they look at it again afterwards?

14. If yes to 13, did you decide to receive information about genes that run in your family if they are found by the test?
    Why/why not?

    Probe for understanding of a) somatic/germline distinction and b) implications of germline info for family members' disease risk.

15. Is there anything about the genetic test that you wish your doctor had explained to you in more detail?

16. After your doctor ordered the test, did you seek out additional information about cancer genetics?

    Follow up: If so, from what sources? What did you learn?

17. Do you know whether the test will be paid for by your health insurance?

18. Have you ever had another genetic test before this one?

    Follow-up: Have any of your family members had genetic tests?

POST:

19. What did your doctor tell you about the test results?

    Follow-up: Did your doctor give you a copy of the test results?

20. Did you understand your doctor's explanation of the test results?

    Probe for specific terms/concepts that were difficult to understand.

21. Were the results what you expected?

22. Were there any results that were unclear to you or your doctor?

23. Did your doctor recommend that you try a new cancer treatment?

    Follow up: If yes, what is the new treatment?

24. [If yes to #7], did you decide to try the new treatment?
    Why/why not?

25. [If yes to #7], does the new treatment require you to participate in a clinical trial?

    Probe for understanding of clinical trial process.

    Follow up: If yes, do you have any concerns about participating in a clinical trial?

26. [If yes to #7], What are your hopes for the new treatment?

27. [If yes to #7], Do you have any concerns about the new treatment?

    Probe for concerns about cost/payment/availability of new treatment.

28. [If no to #7], Did your doctor recommend that you continue with the same treatment you were receiving before the genetic test?

    Probe for agreement/disagreement with decision.

29. How do you feel about the decision to [try to new treatment/continue with same treatment/discontinue treatment]?

30. Did your test results include any information about genes that run in your family?

31. [If yes to #7], how did your doctor explain this gene(s) to you?

32. [If yes to #7], did your doctor recommend that you or your family members see a genetic counselor?

    Follow up:
    a) *What was the reason they gave you for recommending that you see a genetic counselor?*

b) Do you think you will follow their advice and make an appointment with a genetic counselor? Why/why not?

33. Will you share the results of the test with other family members? Why/why not?

Follow up:
a) Do you have any concerns about sharing your genetic information with family members?
b) What effect do you think your test results will have on your family members?

34. Do the test results make you think any differently about the cause of your illness?