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Personalized Oncology Through High-throughput Sequencing: MI-ONCOSEQ (Michigan Oncology Sequencing Center) (HUM00046018)

(formerly known as "Personalized Medicine Based on Molecular Profiling of Patients with Cancer")

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Protocol Summary

Cancer is caused by multiple molecular alterations to normal host cells, which act in concert to drive unchecked cell self-renewal, growth, and invasion, leading to malignant transformation and cancer. There are few cancers that appear genetically homogeneous and may be characterized by singular, disease-defining molecular alterations such as the translocation and fusion of Bcr and Abl genes in chronic myeloid leukemia. The Bcr-Abl gene fusion discovery led to the development of tyrosine kinase inhibitors such as imatinib (Gleevec) that successfully target the Abl kinase in chronic myeloid leukemia. However, studies on the genomic landscape of human tumors show that homogeneity in cancer is likely the exception, and heterogeneity is the rule. This is clearly evident in the clinical management of cancer where a “one size fits all” approach is not effective. Thus, the personalization of therapy for cancer will require molecular characterization of unique and shared genetic alterations. Today, the promise of personalized medicine in cancer is rapidly moving forward and is supported by advances in fields of genomics, proteomics, and metabolomics where cost efficient technologies allow high-throughput capacity molecular testing. **We hypothesize that sequencing of individual cancers in real time will facilitate development and application of genetic biomarkers and improved therapeutic outcomes.** To address this, we propose to develop a platform for high-throughput sequencing of tumors from cancer patients to search for genetic alterations that may guide the future development of clinical trials based on biomarkers and/or lead to discovery of novel gene targets in cancer. This protocol merges the clinical and basic science expertise existing at University of Michigan to realize this platform and lead the way for personalizing clinical oncology research through the application of genome sequencing. This protocol implements a mechanism for patients who have advanced or refractory cancer to undergo tumor sequencing, sequence analysis, and return of clinically significant sequence results to patients and their clinicians.

Amendment 1, December 2011

Summary:

1) **Study Accrual Extension**

2) **Updated Eligibility**

3) **Administrative Changes**

1) Study Accrual Extension

Description: Extend the number of patients beyond the pilot phase, and begin open enrollment for all eligible patients seen at University of Michigan.

Justification: In the original protocol, the IRB provided feedback on our study suggesting a pilot phase due to concerns about feasibility. Therefore, we set a target enrollment of 20 patients, and defined some endpoints to measure feasibility. We believe we have met these goals (Study Update), and would like to expand the study for additional patients with indefinite enrollment. We plan to scale the study to be able to evaluate all patients with advanced cancer considering clinical trials. We anticipate this to be around 100-150 patients in 2012, and with increments of 50-100 patients/year. Because we anticipate an open-ended, expanding enrollment as the study moves forward, we have indicated "1000" for subject enrollment in eResearch.

2) Updated Eligibility

Description: We would like to amend the eligibility to allow patients with only **formalin-fixed paraffin-embedded tissues** (FFPE) available, despite not having a fresh biopsy.

Justification: Currently, eligibility requirements include tumor that is accessible for research biopsy. These biopsies have been successful in yielding adequate high quality tissue for analysis of DNA and RNA. Evaluating the site of the metastasis is biologically and clinically important, since the metastasis often has considerable genetic changes relative to the primary. In some instances, we have been referred patients who do **not** have disease that is accessible to biopsy. However, these patients may have specimens available from prior procedures, usually **formalin-fixed, paraffin embedded tissues**. We have recently developed protocols to utilize FFPE tissue, however these are **suboptimal** compared to genetic analysis of fresh-frozen tissues. Nonetheless, we would like to amend the eligibility to allow patients with some FFPE tissues to be enrolled, despite not having a fresh biopsy. These patients would remain eligible for a research biopsy at a later date (with their signed consent) if this became possible.

3) Administrative changes: Addition of Investigators, Study title change

Description: We have made some changes in the nomenclature of our multi-disciplinary team and study name, to better reflect the study's purpose. We have also supplemented our multi-disciplinary team with additional investigators.

Justification:

1) The **study name** has similarly been changed to "Personalized oncology strategies through the Michigan Oncology Sequencing Center (MI-ONCOSEQ)."

2) We have added study investigators, including Priya Kunju, MD (Pathology), Elena Stoffel, MD (Clinical Genetics), Felix Feng, MD (Radiation Oncology), and a clinical study coordinator (To be named).

Amendment 2, February 2012

Summary:

1) **Administrative Changes**

1) Administrative changes: Replacement of Genetic Counselor; addition of Study Coordinator
Description: We have added Shanna Gustafson, genetic counselor, and removed Jessica Long, genetic counselor. We have also added Lynda Hodges as clinical study coordinator.

Amendment 3, June 2012

Summary:
1) Administrative Changes

1) Administrative changes: Addition of team members; deletion of one team member
Description: We have added Ajjai Alva, Maha Hussain, Kathleen Cooney, Nancy Egerer, Mark Zalupski, Scott Schuetze, Frank Worden, Dan Hayes and Bruce Redman to the study team as co-investigators. We have removed Harry Erba from the study team as co-investigator since he is leaving U of M.

Amendment 4, September 2012

Summary:
1) Administrative Changes
2) Change to buccal swab collection count

1) Administrative changes: Addition of two team members; deletion of one team member
Description: We have added Nithya Ramnath to the study team as co-investigator and Jyoti Athanikar as a research staff member. We have removed Sameek Roychowdhury as PI since he left the university.

2) Change to buccal swab collection count (from 3 to 4) on p. 21.

Amendment 5, March 2013

Summary:
1) Administrative Changes

1) Administrative changes: Addition of team members; deletion of one team member
Description: We have added Rashmi Chugh, Greg Kalemkerian, Todd Morgan, Jeffrey Innis, Nalla Palanisamy, Scott Tomlins, Rohit Mehra, and Chandan Kumar as co-investigators and Erica Williams as a clinical coordinator. We have removed Ken Pienta as co-investigator since he left the university.

Amendment 6, May 2013

Summary:

1) Administrative Changes

1) Administrative changes: Addition of team members; deletion of one team member
Description: We have added Dan Robinson, Yi-Mi Wu, Dan Miller, Terry Barrette, Pankaj Vats, Shanker Kalyana-Sundaram, Christine Brennan, Xuhong Cao and Daniel Hertz as research staff members. We have removed Nancy Egerer as co-investigator since she left the department.

Amendment 7, October 2013

Summary:

1) **Administrative Changes**
2) **Clarified requirement of research physical**
3) **Added language regarding sharing results with family members after death of participant**

1) Administrative changes: Addition of two study team members, deletion of two study team members

Description: We have added Laurence Baker and Alexander Pearson as co-investigators, and have removed Shanna Gustafson and Scott Kim as co-investigators since they left the university.

2) Clarified requirement of research physical

Description: We clarified that physical exam need not be repeated during consent visit if performed by a co-investigator within 2 weeks of the scheduled research biopsy.

3) Added language regarding sharing results with family members after death of participant

Description: We added that in the event of death of the participant, either the oncologist or the genetic counselor can share clinically significant results with the family of the patient, upon request of the family.

Amendment 8, March 2014

Summary:

1) **Revision of billing calendar**
2) **Administrative changes**
3) **Addition of sub-study**

1) Added missing item to billing calendar.

2) Administrative change: Addition of study team members:

Description: We have added Anne Schott, Monika Burness, Norah Henry, Jeffrey Smerage, Max Wicha, Jennifer Griggs, Catherine Van Poznak, Sofia Merajver, Raymond De Vries, Scott Kim, and Brian Zikmund-Fisher to the study team as co-investigators. Additionally, Costanza Paoletti, Natalie Bartnik, Janet Childerhose, Nicole Exe, Michele Gornick, Lan Le, Kerry Ryan, and Erica Sutton have been added as research staff.

3) Sub-study: Addition of patient survey and telephone interviews and physician survey

Description: We would like to amend the objective of the study to include a secondary objective focused on examining the ethical and psychosocial impact of genome sequencing. Through a series of baseline and follow-up surveys and interviews, we will examine how MI-ONCOSEQ patients and clinicians respond to the tumor sequence results. Our aims are to 1) Develop and evaluate techniques for optimal communication of sequencing information to patients and 2) Assess cancer patients' psychological and behavioral responses to genomic sequencing results.

All newly consented MI-ONCOSEQ patients will be offered the opportunity to complete two self-reported surveys at two time points 1) After their clinic visit and 2) after tumor sequencing. These surveys will be given to the patients in clinic or mailed home to them to complete at their own pace. The survey questions are non-sensitive and aim to examine domains including 1) reasons for joining the study, 2) expectations about what information they will receive, 3)

knowledge of both the study informed consent form and gene sequencing in general. We will also interview a small subset of MI-ONCOSEQ patients (10-20 newly consented patients) by telephone at the same two time points. These qualitative interviews will focus on patients' expectations, motivation, and understanding of their results. Patients who have previously consented to the study will not be asked to take part in the phone interviews and surveys.
In addition, we will also survey referring oncologists to access their preferences for the return of results and their plans for use of the test results in the care of their patient. After MI-ONCOSEQ reports become available, referring oncologists will be invited to complete one brief survey for each of the patient that they referred to the study.

Amendment 9, June 2014

Summary:

1)Administrative Changes

1)Administrative changes: Addition of team members; deletion of one team member
Description: We have added Fengyun Su, Yu Ning, Rui Wang, and Pallavi Mohapatra as research staff members. We have removed Shanker Kalyana-Sundaram since he left the university.

Amendment 10, October 2014

Summary:

1) Administrative Changes
2) Revision of Billing Calendar

1)Administrative changes: Addition of team member; deletion of team member; name change
Description: We have added Ming Li as research staff, and have removed Dan Miller since he is no longer at the university. We changed Erica Williams to Erica Rabban (married name).

2) Added missing item to billing calendar

Amendment 11, April 2015

Summary:

1) **Revision of billing calendar**
2) **Administrative changes**
3) **FAQ, Results Notification Letter, and Thank-You Letter documents**
4) **Revision of section 9.1 of consent and section 8.3 of protocol to reflect current study database**

1) Administrative changes: Addition of four study team members, deletion of one study team members

Description: We added Vaibhav Sahai as co-investigator, and added Archana Bharadwaj, Xiaoxuan Dang, Marcin Cieslik, and Fuzon Chung to study team as research staff. We removed Victoria Raymond as co-investigator (she left the university).

2) Billing calendar revisions

Description: We added some missing items and deleted items that weren't needed.

3) FAQ, Results Notification Letter, and Thank-you Letter documents

Description: Per recommendation from the ethics group, we added several support documents to the study: a Frequently Asked Questions doc, a Vignette doc, a Results Notification Letter (one for patient, one for physician), and a Thank-you letter

4) Revision of section 9.1 of consent form and section 8.3 of protocol to reflect current study database

Description: We clarified that the clinical database includes patient identifiers.

Amendment 12, June 2015

Summary:

1) **Administrative changes**
2) **Addition of ONCO1500 targeted gene panel added to the protocol**
3) **Change in STB name and process in the protocol**
4) **Addition of data storage and processing information to the protocol**

1) Administrative changes: Addition of five research staff members

Description: We added genetic counselors Kristen Hanson and Michelle Jacobs as research staff and to the consent form, and have added Muneesh Tewari and Qing Kang as research staff. We have added Erin Cobain as co-investigator.

2) ONCO1500 targeted panel added to the protocol

Description: We added the ONCO1500 targeted gene panel test. The ONCO1500 is a CLIA-certified laboratory developed test (LDT) designed to efficiently identify non-synonymous somatic mutations in a panel of 1500 genes with suggestive links to cancer. ONCO1500 exome sequencing identifies non-synonymous somatic mutations by comparing tumor versus matched normal tissue. If the ONCO1500 panel will be utilized for sequencing, a test requisition will be sent to the referring physician to fill out and return (requirement to maintain CLIA validation).

3) STB (Sequencing Tumor Board) name changed to PMTB (Precision Medicine Tumor Board) and process change made in the protocol

Description: STB (Sequencing Tumor Board) name was changed to PMTB (Precision Medicine Tumor Board). As our volume has increased over time, primarily cases with clinically actionable findings will be presented at PMTB. These changes were made to the protocol.

4) Addition of data storage and processing information to protocol and consent form

Description: In section 9.3 of the protocol that we have indicated that we plan to start processing data in the cloud and have described the arrangements for the storage, management, and security of the data . We have added information to section 9.1 of the consent form that indicates that data from sequencing will be stored electronically in a secure manner.

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PROTOCOL SUMMARY

Title	**Personalized Oncology Through High-throughput Sequencing: MI-ONCOSEQ (Michigan Oncology Sequencing Center)**
Primary Objectives	Mechanism to profile the tumors of patients with cancer and create a clinical database for following outcomes to facilitate basic, clinical, and translational research. ***This is a not a therapeutic study and is focused on tissue collection and tumor sequencing.*** 1) To offer tumor sequencing to **patients with advanced or refractory cancer**. Patients undergo routine procedure or tissue biopsy for sequencing in real time. Clinically significant results will be disclosed to patients and their clinicians. 2) To facilitate **basic and translational research** that includes the correlation of biospecimens with corresponding clinical data, in order to develop and apply biomarkers for personalized medicine.
Secondary Objectives	Examine how patients and clinicians respond to tumor sequence results. 1) Develop and evaluate techniques for optimal communication of sequencing information to patients. 2) Assess cancer patients' psychological and behavioral responses to genomic sequencing results.
Study Population	Patients with advanced or refractory cancer who are considered eligible for clinical trials based on best medical practices in oncology
Eligibility: Patients with Advanced or Refractory Cancer	**Inclusion Criteria:** 1) A histologically or cytologically confirmed diagnosis of cancer 2) Patients with any malignancy. 3) Patients are undergoing standard of care surgeries or procedures where specimens will be first used for routine pathologic assessment and only then will leftover tissue be used for research purposes. **OR** 4) Patients must have tumor suitable for biopsy (as assessed by trained specialists in interventional radiology) Patients are medically fit to undergo a tissue biopsy or surgical procedure to get tumor tissue OR If Patients do not have a tumor suitable for biopsy but have another tissue available for molecular evaluation. 5) Procedure-specific signed informed consent prior to initiation of any study-related procedures. 6) Women and minorities are included in this protocol. 7) Patients with multiple malignancies remain eligible. 8) Patients with an inherited cancer syndrome or a medical history suggestive of an inherited cancer syndrome remain eligible. **Exclusion Criteria:** 1) It is the enrolling study physician's discretion to decide if a patient is not fit enough to undergo tissue biopsy. 2) Patients who are incarcerated are not eligible to participate.
Screening:	Screening includes the following: ☐ Complete History and Physical Exam to determine if fit for research biopsy (only if a research biopsy is being performed). Note: physical exam need not be repeated during consent visit if performed by a co-

	investigator within 2 weeks of the scheduled research biopsy. ☐ Review of medical records including pathology and molecular reports. ☐ **Either**, the participant is undergoing a routine standard of care procedure or surgery where specimens are first used for routine clinical pathologic assessment and leftover tissue is to be used for research purposes **OR** the participant has had a review of radiological scans to determine if tumor is accessible for biopsy AND patient is considered medically fit to undergo a biopsy. ☐ Labs including: PT, INR, PTT, and Platelets (only if a research biopsy is being performed).
Timeline	<u>Genetic counseling:</u> ▪ Eligible participants receive genetic counseling as part of their informed consent. ▪ Informed consent includes description of risk of genomic sequencing results, and includes patient preferences for disclosure. <u>Specimens</u>: ▪ Blood, serum, buccal smears, saliva, and urine will be collected and frozen. ▪ Eligible patients will undergo standard of care surgeries or procedures where specimens will be first used for routine pathologic assessment and only then will leftover tissue be used for research purposes **OR** patient will undergo tumor biopsy of an accessible lesion **OR** patient does not have tumor amenable to biopsy, but does have an existing specimen available for molecular evaluation (albeit suboptimal). ▪ For patients with blood cell cancers such as leukemia, generally collection of peripheral blood and bone marrow samples will be sufficient. ▪ Tumor specimens will be processed and frozen. Tumor specimens or blocks from a prior biopsy or surgery, if available, will be retrieved. Surveys and interviews ▪ Patients will be provided a copy of the baseline survey to take home. ▪ A research assistant will contact the patient 1-2 day after the clinic visit for a phone interview. ▪ Patients will be contacted to complete a follow-up survey and interview after the patient's tumor content have been analyzed. <u>Research Analysis</u>: ▪ Biopsies will be assessed for tumor content. ▪ DNA and RNA from tumors will be sequenced. ▪ After data is analyzed, a report with informative genes will be generated for review by the multi-disciplinary Precision MedicineTumor Board. ▪ Clinically significant results related to patient's cancer will be disclosed. If required for a study, results will be validated in a CLIA-certified lab or sent to a CLIA-certified lab if pertinent testing exists. ▪ Patients who elect to receive sequencing results regarding incidental findings and/or germ-line mutations will be offered a follow-up to meet with a cancer geneticist and genetic counselor to discuss implications of these findings for their personal and family's health. ▪ The protocol does not directly mandate or guide treatment decisions. CLIA-validated results may be used by referring clinicians and patients as they see fit. ▪ In the event of death of the participant, either the oncologist or the genetic counselor can share clinically significant results with the family of the patient,

	upon request of the family. ▪ Clinical outcomes are collected annual indefinitely.
Study size	▪ We have enrolled 20 patients in the pilot phase, and have been the objectives. In this amendment, we expand the study accrual to be an open-ended study, anticipating 100-150 patients in 2012, with annual increments of 50-100 patients per year.
Study follow up	▪ In order to update the clinical database for disease recurrence and overall survival, all enrolled patients will be contacted at 4 months, 8 months, 12 months, 18 months, and then annually until time of death. This includes review of medical records and phone contact if necessary.

1.0 Introduction

Physicians have long known that medicine is a personalized practice from the inherent heterogeneity of their patients and diseases. In 1892, Sir William Osler, a Canadian physician considered the Father of Internal Medicine, wrote:

"If it were not for the great variability among individuals, medicine might as well be a science, not an art."

This is clearly evident in the clinical management of cancer where a “one size fits all” approach is not effective. Today, the promise of personalized medicine in cancer is rapidly moving forward and is supported by advances in genomics, proteomics, and metabolomics where cost efficient technologies to analyze DNA, RNA and other cellular components with high-throughput capacity enable thousands of molecular tests per experiment or per patient[1, 2]. **This protocol seeks to implement a mechanism for patients who have advanced or refractory cancer to undergo tumor sequencing, sequence analysis, and return of clinically significant sequence results to patients and their clinicans**. We believe tumor sequencing can one day help guide clinicians toward a personalized approach for cancer patients through the advantage of molecular classification of tumors.

Our initial approach for tumor sequencing was ~~currently~~ not CLIA-approved. Clinical Laboratory Improvement Amendments (CLIA) provides for the standardization of clinical tests. If CLIA-testing is required for a treatment decision or clinical trial, validation will be completed by CLIA-certified labs at the Michigan Center for Translational Pathology, Michigan Medical Genetics Laboratory, or other clinical lab. Ideally, sequence results could be used by patients and clinical investigators in the context of gene targeted-based clinical trials. After a pilot phase, we anticipated obtaining CLIA certification for next generation sequencing of tumors, so that results could be directly utilized. Since study introduction, we have added the ONCO1500 CLIA-certified laboratory developed test (LDT) designed to identify non-synonymous somatic mutations.

2.0 Study Overview

This protocol is designed to facilitate tumor sequencing of individual patients with cancer and provide a platform for multi-disciplinary translational research.

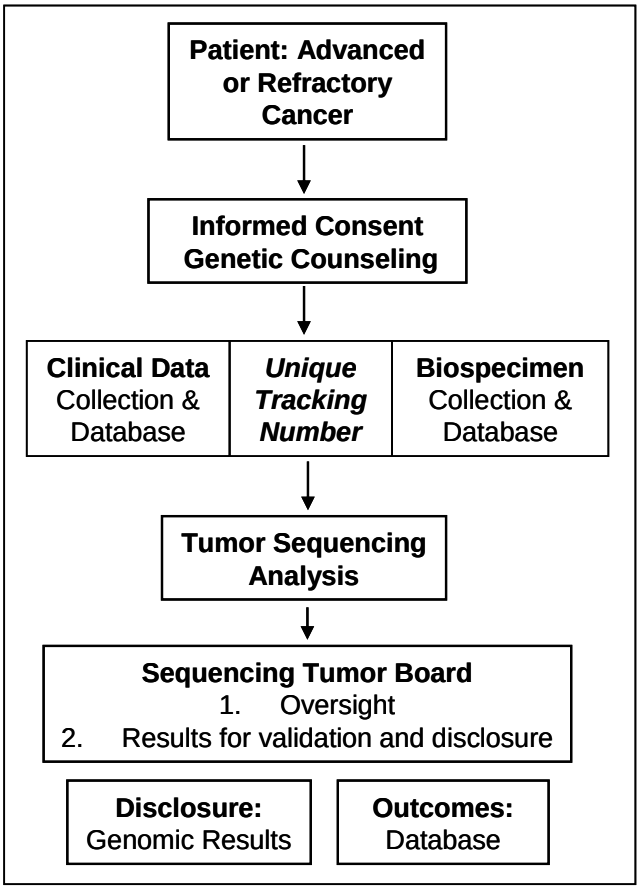


Figure 1: Study Schema

- **Subject identification, eligibility, genetic counseling, informed consent, and enrollment.** Individuals with advanced or refractory cancer must be identified by study personnel, deemed eligible for this study, and voluntarily agree to be enrolled in this protocol through an informed consent, **see section 5.0 and 6.0**. Informed consent includes genetic counseling about risks and benefits of genomic sequence results.
- **Biospecimen collection.** Patients with advanced or refractory cancer will donate tissue from an upcoming standard of care procedure or surgery OR undergo tumor biopsy for research purposes. If patients have a previously collected tumor block, this may be donated to the study. All patients will provide blood, buccal smear, serum, and urine samples. Further, patients may elect to contribute previously collected samples collected under another protocol, provided investigators from another existing IRB-approved study agree to collaborate in this regard. For detailed biospecimen collection procedures, **see section 7.0.**
- **Clinical data collection.** Data will consist of routine clinical data and outcomes such as disease recurrence, response to therapy, and survival. These data will be utilized to facilitate clinical and translational research. **See section 8.0.**
- Qualitative and quantitative data collection. Data collection will consist of two structured phone interviews and two self-reported surveys. **See section 8.5**
- **Tumor sequencing.** Tumors will be evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. To permit translational research efforts, each biospecimen will be labeled with a unique identification number that permits linkage to both clinical and biospecimen databases. **See section 10.0.**
- **Sequencing results.** We will employ a multi-disciplinary ~~**Sequencing Tumor Board (STB)**~~ **Precision Medicine Tumor Board (PMTB)** with expertise in clinical oncology, clinical genetics, pathology, genomics, bioinformatics, genetic counseling, psychology, and bioethics to deliberate on sequencing results and provide oversight for the study. **See section 11.0**.
- **Basic science research using specimens and/or data.** Data will be used for discovery and characterization of novel genetic aberrations in cancer. These data can be linked to clinical data for development of novel biomarkers. **See section 11.0**.

- Following genetic counseling, informed consent and the acquisition of biospecimens, patients will not undergo any further study procedures. However, laboratory research activities (such as those described in **section 10.0**), qualitative and quantitative research, and accrual of clinical data, such as relapse, subsequent treatment and survival, will be collected unless the patient decides to be removed from this study.
- In some instances, for patients who have progression of their cancer, they may be **re-consented** in this same protocol to undergo repeat biopsies.
- We implemented this protocol in a **Pilot phase**, targeting enrollment of 20 patients. We have since completed enrollment of 20 patients and met the preset goals for feasibility, and would now plan to continue and expand enrollment.

3.0 Background

Cancer is the second leading cause of death in the United States after heart disease[3]. The most common cancers in the United States are lung, skin, breast, prostate, and colon cancer[3]. The most prevalent cancers are heterogeneous and can be characterized by multiple molecular aberrations (e.g. breast or prostate cancer) rather than a single molecular event (e.g. chronic myeloid leukemia and the Bcr-Abl gene fusion). It is therefore evident that the management of cancer is not a "one size fits all" approach. Discriminating molecular subsets of cancer based on genetic **biomarkers** is essential to the development and application of personalized cancer medicine.

3.1 Cancer Biomarkers

What are cancer biomarkers? Generally, biomarkers can be used to answer three important clinical questions[4]: 1) Who needs treatment? 2) Which drug? 3) What dose of drug?

1) Who needs treatment? (Prognosis)

First, biomarkers that provide prognostic information could help discriminate which patients need additional therapy, and thereby avoid "overtreatment" for patients with low risk cancer. An example of a such a biomarker clinical trial is The Trial Assigning IndividuaLized Options for Treatment (Rx) or TAILORx, which is examining whether genes that are frequently associated with risk of recurrence for women with early stage breast cancer can be used to assign patients to the most appropriate and effective treatment[5]. TAILORx seeks to incorporate a gene expression profiling test (a technique that examines many genes simultaneously) into clinical decision making, and thus spare women from unnecessary treatment if chemotherapy is not likely to be of substantial benefit.

2) Which drug? (Predicting drug response)

Second, choosing the "right drug" for the "right patient" could lead to improved efficacy of targeted therapies, and avoid putting patients through ineffective therapies that waste time and resources. Further, there is an additional economic benefit for society by avoiding the use expensive but ineffective therapies. An example of such a predictive biomarker is the presence of Bcr-Abl gene fusions in leukemias. Imatinib, a tyrosine kinase inhibitor, is effective for Bcr-Abl positive leukemias[6, 7], but is generally not effective for other leukemia subsets. In another example, a subset of patients with breast and gastric cancer that express the ErbB-2 growth factor receptor will preferentially respond to therapy with trastuzumab (Herceptin), a monoclonal antibody against ErbB-2[8, 9].

3) What dose of drug? (Pharmacodynamics and pharmacogenomics)

Third, understanding the pharmacology of a drug is essential to delivering efficacious treatment[10]. For tamoxifen, part of hormonal treatment for estrogen receptor positive breast cancer, we have learned that the liver enzyme P450 CYP2D6 is essential for formation of

tamoxifen's main active metabolite[11]. Further, there are commonly prescribed drugs that influence CYP2D6 activity and could therefore negatively impact tamoxifen efficacy[12-14]. Thus, understanding these pharmacologic interactions is essential for delivering an effective therapy for an individual.

3.2 Biomarkers in Clinical Trials

The majority of novel agents in clinical trials are molecularly targeted therapies directed at protein kinases, receptors, or cell surface molecules. However, the majority of clinical trials in cancer do not select patients based on the presence of these targets or relevant biomarkers[15]. For example, in a large Phase 3 clinical trial of 1217 patients with lung cancer, 609 patients were randomized to receive gefitinib, an inhibitor of the epidermal growth factor receptor (EGFR). However, there was no *a priori* stratification based on mutations of EGFR, and only 261 patients had activating mutations in EGFR. Those patients who had mutations in EGFR displayed significantly better outcomes after treatment with gefitinib[16].

Similarly, in a recent Phase 1 clinical trial, an orally available B-Raf kinase inhibitor (PLX4032) was offered to patients with solid tumors that were refractory to standard therapy or for which standard or curative therapy did not exist[17]. In the initial phase, a total of 55 patients were treated, and only those patients who had the specific V600E B-Raf mutation (less than half the initial cohort) had complete or partial responses to therapy[17]. Subsequently, when an additional 32 patients with metastatic melanoma were enrolled on the basis of B-Raf mutations and treated in the extension phase, 80% of the patients had a response to therapy. This study illustrates the importance of molecular stratification of patients as a component of clinical trial design. Simply, we should be utilizing "targeted therapies" only for patients who have the right drug target.

Further, it's become evident that "druggable" gene targets that are prevalent in common cancers, may recur at lower frequencies in other cancer subtypes. A recent Phase 1 clinical trial reported on the use of an inhibitor for Anaplastic lymphoma kinase (ALK) which is rearranged in 5-7% of non-small cell lung cancers[18]. The trial screened 1500 patients to identify and treat 82 patients with ALK-rearranged cancer[19]. Interestingly, ALK may also be relevant in other cancers subtypes such as breast cancer and colorectal cancer (rearrangement)[20], and neuroblastoma (mutation) where it occurs at a lower frequency[21]. Importantly, the same ALK inhibitor had clinical efficacy for patients with a rare inflammatory myofibroblastic tumor found to have the same ALK rearrangement[22]. This illustrates the importance of an individualized approach to cancer based on common or rare molecular aberrations rather than tissue of origin alone.

Therefore, we believe that genomic approaches to catalog known genetic aberrations in an individual's cancer could provide useful data for retrospective studies or in the design of future prospective trials with targeted therapies. Through a "personalized" molecular profile, even low frequency genetic aberrations could be clinically meaningful to an individual patient.

3.3 Tumor Sequencing of Cancer Patients

Leadership. Delivering personalized cancer medicine based on molecular biomarkers depends on collaboration between clinical and basic science researchers who have an active program in clinical trials and cutting edge laboratory research respectively. This protocol merges the clinical and basic science expertise existing at University of Michigan to realize the promise of personalized medicine in clinical oncology research.

1) **Clinical Research:** Moshe Talpaz, MD is the Director of the **Translational Research Center** at University of Michigan and has over 40 years of experience in clinical trials in oncology. Further, the **Comprehensive Cancer Center** has 11 clinical research

programs and 6 basic science research programs which support 239 active clinical studies in cancer.

2) **Basic Science Research:** Arul Chinnaiyan, MD, PhD is a Howard Hughes Medical Investigator, American Cancer Society Clinical Research Professor, and a member of the Institute of Medicine. He is the Director of the **Michigan Center of Translational Pathology**, which is a focused initiative to bring research discoveries from molecular medicine to practical, clinical applications for the identification of biomarkers and therapeutic targets for cancers.
3) **Clinical Cancer Genetics:** Elena Stoffel, MD, is a clinical geneticist with expertise in colorectal cancers, and provide clinical cancer genetics expertise. Stephen Gruber, MD, PhD, MPH, has moved to University of Southern California as the Director of the Comprehensive Cancer Center, but continues to provide his expertise telephonically and electronically. is an expert in clinical cancer genetics and epidemiology and is the Director of the **Clinical Cancer Genetics Clinic and Program.** He is also Associate Director of **Cancer Prevention and Control** at the **Comprehensive Cancer Center**.
4) **Bioethics:** J. Scott Roberts, PhD, is trained as a clinical psychologist and is an Assistant Professor of Health Behavior & Health Education in the University of Michigan's School of Public Health, where he also serves as teaching faculty in the School's **Public Health Genomics Program** and **Center for Bioethics and Social Sciences in Medicine (CBSSM)**. His research expertise lies in assessing the process and impact of genetic risk assessment for adult-onset disorders[23]. Dr. Roberts will serve on the Sequencing Tumor Board and provide oversight of the study with respect to the psychosocial and bioethical components of this project.

Hypothesis: We hypothesize that sequence variation in the tumors of patients with advanced/refractory cancer will lead to measurable changes in therapeutic decision making

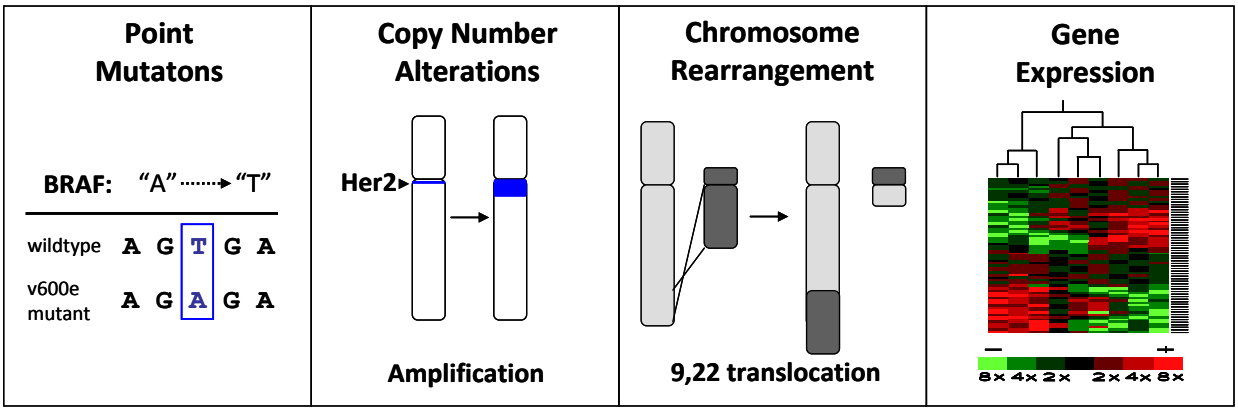
To address this, we propose a mechanism for individual tumor sequencing to identify genetic alterations that may guide the development of clinical trials based on biomarkers. Towards this goal, we have:
1) identified a target population of patients with cancer that could benefit from sequencing results,
2) developed a specialized flexible-default informed consent incorporating genetic counseling,
3) established a formal mechanism to interpret what results should be validated and disclosed to patients (Sequencing Tumor Board).

Implementing Personalized Cancer Medicine. To implement a mechanism for developing personalized cancer medicine based on molecular biomarkers, we propose to offer tumor sequencing to patients with advanced or refractory cancer. Tumor sequence data of such patients would create a mechanism for patient selection based on the molecular characteristics of their cancer in the design of upcoming clinical trials. Clinical oncology researchers at University of Michigan (Dr. Talpaz, Phase 1) could thereby design future clinical trials for druggable genes knowing that eligible patients could obtain correlative tumor sequence data. In addition, tumor sequencing creates opportunities for basic science research that can be correlated with clinical data and outcomes.

Feasibility. Recently, Von Hoff *et al*. reported a pilot study that demonstrated the feasibility and safety of individualized tumor analysis of patients with advanced cancer[24]. They evaluated 86 patients with refractory cancer, who underwent tumor biopsy and limited profiling of 62 genes or

druggable targets. Patients with druggable targets received matching therapy, while the remaining patients were treated with the clinician's choice. This molecular profiling approach, while limited in numbers, resulted in a longer progression free survival for 27% of patients compared to the prior failed regimen. Importantly, they demonstrated the feasibility of such a personalized strategy in real time. The main drawback of their approach was the limited number and types of genetic aberrations they could evaluate.

Figure 2: Classes of informative genetic information

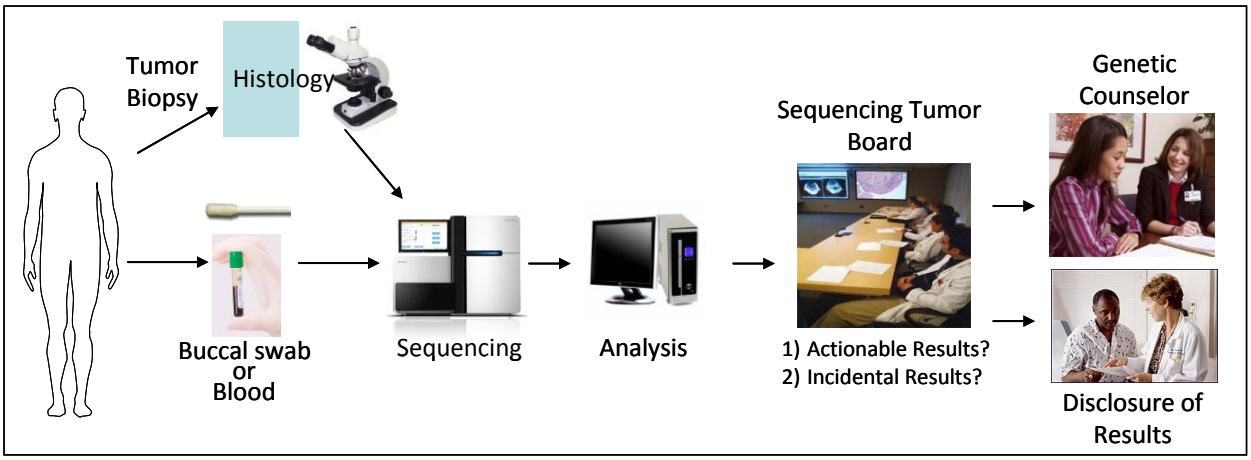


Our Approach. Biomarker research based on genomics has rapidly moved forward through the development of high throughput capacity and decreasing costs of nucleic acid sequencing ("next generation" sequencing)[25, 26]. The **Michigan Center for Translational Pathology** has developed a pipeline for studying cancer using next generation sequencing of cancer"[27-29]. We propose an **"integrative sequencing approach"** utilizing either ONCO1500 targeted gene panel, whole exome, transcriptome, or whole genome sequencing (at 5-fold coverage) to provide a comprehensive landscape of the genetic alterations in individual tumor specimens. This approach will enable the detection of point mutations, insertions/deletions, gene fusions and rearrangements, amplifications/deletions, and outlier expressed genes (**Figure 2**). Furthermore, we will identify certain germline alterations that may also be relevant. An advantage to this approach is that it is unbiased and could potentially provide information about as yet **unknown** genes or pathways important in cancer biology. Further, these data could support research in areas such as pharmacogenomics[30]. More recently, Jones *et al*. at the Genome Sciences Center (British Columbia Cancer Agency) reported a similar approach for whole genome and transcriptome sequencing of cancer in a patient with a rare, metastatic salivary gland adenocarcinoma of the tongue refractory to standard therapies[31]. They identified the RET oncogene as a novel target that could be treated with existing drugs or a through a clinical trial[31].

Sequencing Results. The deliverable for tumor sequencing will be a genomic research report and basic discovery research. A multi-disciplinary ~~Sequencing~~ Precision Medicine Tumor Board will provide oversight for the study and deliberate on sequencing results. For clinically significant sequencing results related to patient's cancer, if required for a study, results will be CLIA-validated through MCTP or other clinical genetic testing lab, and disclosed to patients and their referring oncologists. Those who elect to receive incidental findings and/or germ-line mutations, patients will be offered further follow-up and genetic counseling with a physician cancer geneticist and board-certified genetic counselor to discuss implications of these findings.

This resource could be instrumental in the design of upcoming clinical trials based on druggable molecular targets. However, this protocol does **not** specifically dictate course of action, nor provide validated prediction or prognosis for the given biomarkers. The protocol does provide a platform for linking basic biology with clinical outcomes to allow investigators at University of Michigan to collaboratively participate in translational research to develop prognostic and predictive biomarkers, or targets for potential therapies. We anticipate that the protocol would facilitate opportunities for translational research through additional collaborating clinical protocols.

Figure 3: Translation of Sequencing into Clinical Oncology Research



Ethical and Psychosocial Implications

If the clinical promise of such personalized medicine is to be realized, the psychosocial implications of genome sequence results must be better understood, effective health communication techniques developed, and ethical dilemmas addressed. Data are needed on how patients actually respond to sequence results in order to understand how this novel information affects the likelihood and extent of potential psychosocial benefits (e.g., positive behavior changes) and harms (e.g., misunderstanding, distress). An evidence-based plan for managing incidental findings and optimally presenting clinical or personally meaningful results based on ethical principles that incorporate patient viewpoints will need to be developed for genomic applications in clinical medicine. In addition, patient preferences for information may require physicians to consider not only the clinical utility of testing, but also how to address patients' "personal utility" values. By addressing the aforementioned needs, our surveys and interviews will bring much-desired evidence to the vigorous debate about the appropriate use of genomic sequence information in medicine.

Pilot. We have completed the pilot phase and enrolled 20 patients. We have met the planned endpoints that included assessing tumor acquisition, time to sequencing results, and identification of informative genes (see attached **Pilot Phase Progress Report**). Our success rate for tumor biopsy was 89%, there were no significant complications with the biopsies performed. The time from scheduled biopsy to Sequencing Tumor Board was 28 days on average. Further, we have identified informative genetic aberrations 100% patients that had complete analysis (The remaining three patients have analysis that is currently ongoing). Lastly, we have published this approach in ***Science Translational Medicine***, outlining the logistical challenges of this study[32].

3.4 Potential Benefits for Patients and Society

This protocol confers multiple long-term benefits to society by providing a mechanism for the collection of biospecimens and clinical data, which is a rate-limiting resource for translational studies that are designed to improve care of patients with cancer. In many cases, there will be no immediate, direct benefit to a patient who participates in this study. Here we offer three examples of patients that were evaluated in the pilot phase.

- ***Example 1: A man with metastatic well-differentiated neuroendocrine tumor of the thymus.*** He underwent biopsy of a neck or supraclavicular mass. Integrative Sequencing revealed a canonical activating mutation of the PIK3CA gene involved in the PI3K signaling pathway. This mutation if currently being targeted by clinical trials with inhibitors of PI3K and enriching for patients with this exact mutation. This mutation is a novel discovery for this disease, and would not otherwise have been found.
- ***Example 2: A man with metastatic prostate cancer.*** He underwent biopsy of an inguinal lymph node. Integrative sequencing revealed amplification and overexpression of the fibroblast growth factor receptor (FGFR1), which is currently being targeted in clinical trials.
- ***Example 3: A woman with cholangiocarcinoma*****.** She underwent biopsy of a liver metastasis. Integrative sequencing revealed amplification of the cyclin-dependent kinase 6 (CDK6), involved in cell cycle progression. This pathway is currently being targeted in clinical trials for inhibitors of CDKs.

Overall, these case examples demonstrate the study's ability to identify patients with molecular abnormalities that match therapies in clinical trials. It does not predict or provide proof of efficacy, but moreover it provides a means to **enrich** such trials and contribute to the **design** of upcoming trials at UMCCC.

3.5 Resources

This is a tremendous undertaking and represents a collaborative, multi-disciplinary effort at University of Michigan. Funding such an endeavor is outlined as follows:

- No additional fees are billed to patients for extra specimens collected outside the context of standard of care or for their tumor sequencing.
- For patients enrolled through the Phase I research program, biospecimen collection is funded through the Phase I Research Program and Comprehensive Cancer Center (Moshe Talpaz).
- For patients outside of Phase I, individual physicians who enroll patients may use separate discretionary funds or other resources to facilitate tissue collection, without additional cost to the patient.
- Existing IRB protocols at University of Michigan may collaborate with this tumor sequencing effort. Patients must be consented to this protocol in order to participate.
- Biospecimens are processed and banked through MCTP and MICHR (Arul Chinnaiyan).
- Tumor sequencing, data storage, and analysis is completed and funded through the MCTP (Arul Chinnaiyan).
- The Team is actively working to secure external funding to support this project including a U01 for Clinical Sequencing Exploratory Research submitted in March 2011 to the National Human Genome Research Institute (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-10-017.html).

4.0 OBJECTIVES

The primary objective of this protocol is to implement a mechanism for developing personalized cancer medicine based on tumor sequencing. We propose to offer sequencing to patients with

advanced or refractory cancer. We believe this approach will some day be offered to all cancer patients. Comprehensive sequencing of individual cancers contributes to missions of basic, translational, and clinical research with the shared goal of improving the lives of our patients.

1) To offer tumor sequencing to **patients with Cancer**. Patients undergo tissue biopsy for sequencing in real time.
2) To facilitate **basic and translational research** that includes the correlation of biospecimens with corresponding clinical data, in order to develop and apply biomarkers for personalized medicine.
3) To complete **Pilot phase** with 20 patients assessing benchmarks for tumor acquisition, time to sequencing results, and identification of informative genes.

The secondary objective of this protocol is to examine how patients and clinicians respond to tumor sequence results. Personalized cancer medicine based on tumor sequencing raises a distinct set of issues regarding health communication, implications for treatment, and effects on patients and family members. By investigating the patient and clinician perspective, we will facilitate integration of genomic sequencing into cancer care in an ethically informed and patient-sensitive manner.

1) Develop and evaluate techniques for optimal communication of sequencing information to patients.
2) Assess cancer patients' psychological and behavioral responses to genomic sequencing results.

5.0 ELIGIBILITY

5.1 Patient population

This protocol is designed to collect biospecimens with annotated clinical data from patients with advanced or refractory cancer.

5.2 Inclusion Criteria: (Must satisfy all criteria and either #3 or #4)

1) A histologically or cytologically confirmed diagnosis of cancer
2) Patients with any advanced or refractory malignancy.
3) Patients are undergoing standard of care surgeries or procedures where specimens will be first used for routine pathologic assessment and only then will leftover tissue be used for research purposes.

OR

4) Patients must have tumor suitable for biopsy (as assessed by trained specialists in interventional radiology) and Patients are medically fit to undergo a tissue biopsy or surgical procedure to get tumor tissue **OR** If Patients do not have a tumor suitable for biopsy but have another tissue available for molecular evaluation.
5) Older than or equal to 18 years of age.
6) Procedure-specific signed informed consent prior to initiation of any study-related procedures.
7) Women and minorities are included in this protocol.
8) Patients with multiple malignancies remain eligible.
9) Patients with an inherited cancer syndrome or a medical history suggestive of an inherited cancer syndrome remain eligible.

5.3 Exclusion Criteria:

1) It is the enrolling study physician's discretion to decide if a patient is not fit enough to undergo tissue biopsy.
2) Patients who are incarcerated are not eligible to participate.
3) Women who are pregnant.

5.4 Women of childbearing age.
For women of childbearing age, there are no screening requirements. We note that most patients entering this study are seeking eligibility for therapy or other clinical trial, in which case they are generally asked to avoiding becoming pregnant and even exercise some form of contraception by their medical oncologist. For women of childbearing age, their referring medical oncologist will discuss necessity or role for appropriate contraception. This is not part of the study activity, nor is it required for participation.

6.0 SUBJECT ENROLLMENT

6.1 Subject Recruitment. Patients or their legal guardians may receive a consent form and information sheet describing this protocol at their clinic visits, *via* postal mail or through secure electronic transmission. Clinical research coordinators and/or staff will be available by phone to provide information about the study to interested patients or their legal guardians. Patients can be approached by study personnel during their clinic visit(s).

6.2 Identification of Patients. Patients can be identified and contacted as follows:
1) Study personnel will identify returning patients with cancer for enrollment.
2) Staff at University of Michigan can identify patients in their outpatient and inpatient venues and refer them to the study.

6.3 Eligibility Screening. Eligibility screening will be conducted by the study staff including complete history and physical exam and review of medical records including radiological imaging. Criteria were described in **Section 5.0**.

Screening includes the following:
1) Complete History and Physical Exam (if having a research biopsy, to determine if medically fit for biopsy) Note: physical exam need not be repeated if performed by a co-investigator within 2 weeks of the research biopsy.
2) Review of medical records including molecular and pathology reports.
3) Patient is undergoing a routine standard of care procedure or surgery where specimens are first used for routine clinical pathologic assessment and leftover tissue be used for research purposes.

OR

Be a good medical candidate to undergo a tissue biopsy to get tumor tissue (as assessed by trained specialists in interventional radiology).

OR

If Patients do not have a tumor suitable for biopsy but have another tissue available for molecular evaluation.

4) Have previously collected tumor specimen from prior surgery or biopsy available (this is not required, but if available, tissue will be retrieved).
5) Labs including: PT, INR, PTT, and Platelets (if undergoing research tumor biopsy)

6.4 Enrollment of patients. Patients with cancer can be enrolled through a clinical team in which he or she is being cared for at University of Michigan. The team member should be an

investigator or co-investigator listed on the protocol. Alternatively, the clinical team can contact any of the investigators on the protocol who can proceed with assessing eligibility and completing enrollment.

6.5 Informed Consent. Informed consent will include a description of the study's purpose, medical implications, alternatives, and possible risks and benefits. A Clinical Investigator and/or study coordinator and board-certified genetic counselor (Jessica Everett, Victoria Raymond, et al.) will meet with eligible patients to discuss the study and provide genetic counseling about potential genomic risks and benefits. After meeting, potential study subjects will be encouraged to take additional time to consider their enrollment. Patients will be provided a copy of the consent form for their records and have telephone and pager access to the Clinical Coordinator/Study Investigator for any questions regarding the study. Those requesting additional time will be provided a copy of the consent form and must return a copy in order to enroll in the study. Participants may also complete the informed consent form remotely, and return their signed consent to study staff by mail. Staff will be available by phone or email to answer any questions for participants who chose to enroll in this manner. The consent status of each participant will be recorded by the Study Coordinator in the protocol registration database. Consenting subjects will be provided a copy of the form for their records.

An individual's decision to participate or not participate in this study does **not** affect their ability to participate in other research studies or the quality of care he or she receives. Contact information of those who do not wish to participate will be destroyed and/or removed from any relevant databases. An indication will be made in the database regarding this individual's desire not to participate in the study to ensure that this individual is not contacted regarding this study in the future.

6.6 Genomic Results. Due to the nature of genomic sequencing, there are unique features that must be explained to patients before enrollment[37]. Furthermore, patients will receive genetic counseling as part of informed consent, including discussion of possible return of results and privacy risk due to data sharing.

Explanation of Genomic Results. The potential number of findings involved through sequencing is varied and unpredictable, and therefore prioritization is necessary to process the volume of data and distill the results for patients. We considered that patients and family members, who are dealing with the difficult situation of advanced cancer, might prefer to focus on care of their disease rather than receive extraneous information that could be perceived as overwhelming and distracting. We do not have a proven, evidence-based way to implement the informed consent regarding patients' disclosure option preferences (indeed, that is why we need to study the issue); yet, we must adopt a reasonable practice in order to conduct this study. Our solution has been to develop a "provisional" model that is based on the following considerations (**Table 1**). **First**, from the patient's perspective, it makes sense to distinguish between results that inform management of the patient's specific cancer ("**Cancer of interest**") and those incidental results which may affect the patient's and/or their family member's risks of other conditions ("**Conditions other than cancer of interest")**. **Second,** the patients should be offered results based on best clinical judgment (i.e., offered a default option), but their preferences regarding incidental findings ought to be respected when possible (i.e., the default can be changed). We call this the **Flexible-Default Model of Informed Consent.**

Table 1: Provisional Informed Consent: Flexible Default Model

Disease Domain	Impact/Significance	Default	Decline Results?	Description

Cancer of Interest	Direct impact on care of current cancer	Disclose	Not flexible	Marketed treatment available Targeted clinical trial available
	Significance for biological family	Disclose	Flexible	Increased risk of cancer for biological family
	Significance is unknown	Not disclose	Not flexible	Mutation function or role unknown
Conditions other than cancer of interest	Potential medical impact	Disclose	Flexible	Clinically significant relative risk of disease or outcomes
	Significance for biological family	Disclose	Flexible	Significant implications for biological family decisions
	Significance is unknown	Not disclose	Not flexible	Mutation function or role unknown
Other	New/unanticipated issues	Determined by ~~**Sequencing Tumor Board (STB)**~~ **Precision Medicine Tumor Board (PMTB)** on case by case basis		Situations that do not readily fit into above categories; ~~STB~~ PMTB may need to create new categories

Flexible-Default Model of Informed Consent. Together with our bioethicist Dr. Kim, we have devised this model of informed consent where patients will be given the option to decline certain results[37]. Ultimately, patients should be offered results about their cancer based on best clinical judgment (i.e., default), but their preferences regarding incidental findings ought to be respected when possible (i.e., flexible)[38, 39]. Therefore, the default consent is to disclose results to patients and clinicians for results related to "**Cancer of interest"**, which we designate as "not flexible," since it is anticipated that patients who consent will expect these results. The default consent for **"Conditions other than cancer of interest"** is to disclose results. For the remaining categories of results that we consider "flexible", patients will be given an option to share their preferences and say "Yes" or "No" to these other results before they begin the study. The default for these categories is disclosure. However, if patients prefer they may decline such results at the time of consent. They will be asked for their preference for two simplified categories: A) "Results that may have significance for **biological family member**s" and B) "Results that are **not related to your cancer**, but may have potential medical impact for you". A genetic counselor and/or study investigator will assist the patient in completing this section of the informed consent. Categorization of findings is performed by the Sequencing Tumor Board as described later.

6.7 Details of Informed Consent

The consent forms will ensure that each participant understands and agrees to the following:

- The procurement of patient/donor biospecimens including standard of care procedures / surgeries OR tissue biopsy, tumor block retrieval, blood draw, buccal smear, and urine collection.
- The procurement of patient survey and interview responses, including consent to audio-record interview sessions.
- Consent includes genetic counseling, and explanation of potential benefits and risks of genomic results.
- The Genetic Information Nondiscrimination Act is explained (See Appendix 5).

- The collection, storage and use of patient/donor health information for research purposes by staff at UM.
- The linkage of patient/donor personal health information to the physical samples for research purposes by study personnel.
- There is no guarantee for success of tumor sequencing or clinical benefit from study participation.
- If clinically significant results regarding a patient's specific cancer are identified by the Sequencing Tumor Board, results will always be disclosed.
- Other clinically significant results will be disclosed (**default**), unless the patient indicates that they prefer to decline these findings on their informed consent. Those who elect to be re-contacted will be offered a referral to meet with a genetic counselor to discuss implications of these findings for their personal health and options for clinical genetic testing.
- Tumor sequencing is currently not CLIA-approved, but we anticipate obtaining CLIA certification in the future. If results will impact clinical decision-making, and are required by a clinical protocol, they will be CLIA-validated.
- This protocol does not mandate specific treatment decisions.
- Patients will be followed through medical records and sometimes phone contact for clinical updates until patients leave the study or time of death.
- Future contact from study personnel, either directly or through the patient/donor physician, for the purpose of (1) obtaining further clinical and survey information or (2) informing the patient and physician about novel targets or new clinical trials.
- There will be no costs charged to participants for study participation.
- There will be no reimbursement to participants for study participation.
- Biospecimen research will be conducted internally at UM, but may involve collaborations with other institutions or in some cases companies. Specimens will not be sold to any person or company for profit. Biospecimens shared with external companies or researchers will not contain identifying information.

6.8 Registration

Patients and subjects will be registered in the protocol registration database. Registration requires the following information:

1) Subject name and date of birth;
2) Date subject begins the study;
3) Subject full address and phone number;
4) Subject diagnosis;
5) Informed consent status;
6) Subject's **unique identification number** generated and assigned by registration database;
7) Subject's assigned specimen ID numbers; generated and assigned by registration database;
8) Contact information for subject specialty physicians and primary physicians;

Number of patients. The Pilot study enrolled 20 subjects. We have met the preset goals of the pilot, and now plan to continue enrollment an open-ended study and there is no set limit to accrual. In eResearch, we have indicated enrollment of 1000 patients.

6.9 Withdrawal from the Study

Participants can withdraw consent to participate in this study at any time. Specimens collected remain the property of the University of Michigan and are retained. If a patient request removal from their study, no further clinical data will be collected, but existing data will be retained. The

subject's privacy will be preserved. The subject's clinical information will be deleted from study databases, but will not be removed from complete analyses and datasets, and no new information will be collected from or about the subject. An indication will be made in the database regarding this individual's desire to withdraw from the study to ensure that this individual is not contacted regarding this study in the future. Clinical data collected as part of other research studies in which a patient is participating and does not withdraw consent will not be deleted or affected by withdrawal from this study.

7.0 BIOSPECIMEN COLLECTION

Specimens to be collected include a fresh tumor biopsy, previously obtained tumor specimens or blocks (if available), whole blood, serum, buccal smear, saliva, and urine. To ensure prompt collection and processing of samples, clinical visits and procedures will be coordinated with laboratory personnel from the Michigan Center for Translational Pathology (**MCTP**) and the Michigan Institute for Clinical and Health Research (**MICHR**).

- No additional fees are billed to patients for extra specimens collected outside the context of standard of care.
- Tissue biopsies will be arranged and funded through the Phase I Research Program and Comprehensive Cancer Center. This has been coordinated with the Department of Radiology.
- For patients outside of Phase I, individual physicians may use separate discretionary or research funds or resources to facilitate tissue collection, without additional cost to the patient.
- Except for tumor tissue, biospecimens will be collected at the beginning of the study after enrollment. No additional specimens will be collected unless patients are re-consented.

Exception 1: Patients who experience progression of their cancer, may elect to participate in the study again by undergoing a repeat tumor biopsy and specimen collection. They must sign a second informed consent.

Exception 2: Patients who have a tumor biopsy that fails to provide adequate tumor for sequencing, may choose to have a repeat tumor biopsy after signing the informed consent again.

7.1 Collection sites

Biospecimens may be collected through University of Michigan outpatient clinics and inpatient facilities. Previously collected tumor blocks, can be retrieved from other institutions or other clinical protocols interested in collaboration for tumor sequencing.

7.2 Biospecimens

Biospecimens will be collected at the beginning of the study. Tumor biopsy will be arranged and may occur typically during the first week depending upon on scheduling and availability. Biospecimens included in this protocol may be fresh, frozen or fixed. All biospecimens will be given a **specimen ID number** that is linked to the patient's **unique identification number**. This process can connect specimens to clinical data, but also protect confidentiality. Clinical data and biospecimens are collected and stored for future research. This is a necessity because translational research for development of biomarkers depends upon the correlation of basic research findings and clinical outcomes.

A) Blood

In most cases, blood samples will be drawn from patients scheduled to have venipuncture for routine clinical purposes. In some cases, when this is not possible, blood draws will occur at times other than those needed for routine clinical care. Generally, blood draws for research purposes will be 4 tablespoons of blood (amounts to 4-5 10mL tubes).

Exception 1: For some patients with leukemia or blood cell cancers who require leukaphoresis procedure as part of their routine clinical care, the leftover leukaphoresis product may be collected and banked for the study, since this is a blood product that is otherwise generally discarded.

Exception 2: Patients with blood cell cancers such as leukemia may experience evolution of their disease, such as development of resistance to therapies. Since blood draws are relatively non-invasive, these patients may be asked to undergo repeat blood draws over the course of their clinical care. Blood draws may not occur more than twice in a 21-day period.

Blood Processing. Generally, the processing and storage of blood samples will involve the following: blood will be drawn into one or more tubes that contain EDTA, heparin or citrate for the collection and stored as serum, white blood cells or whole blood. To preserve patient and donor confidentiality, samples are given a **specimen ID number**. Serum and white blood cells will be separated from other cellular components by centrifugation, allocated into tubes, catalogued, and frozen at –80° C or viably in liquid nitrogen freezers. Samples may be processed for DNA, RNA, and/or protein.

B) Urine
Urine collected from patients may contain small molecules that could serve as biomarkers for cancer. Urine studies may involve proteins, nucleic acids, or cells. Urine is self-collected fresh in a clean jar and aliquoted into 15 or 50 mL tubes.

Urine Processing. Up to six aliquots of up to 50 mL will be prepared and given a **specimen ID number**. Tubes will be centrifuged and then immediately frozen for future assays.

C) Buccal smear
Buccal smears are a source of normal tissue for comparison to tumor samples. Four buccal smears will be obtained at the time of diagnosis or at routine follow-up evaluations. Samples are given a **specimen ID number**.

Buccal Smear Processing. Swabs will be processed for nucleic acid and/or protein and stored at -20° C or -80° C respectively.

D) Saliva
Saliva is an excellent source of normal DNA and is collected using an Oragene kit. Samples are given a **specimen ID number**.

Saliva Processing. Saliva will be processed for nucleic acid and/or protein and stored at -20° C or -80° C respectively.

E) Previously collected and processed biospecimens
Fixed or frozen specimens may also be obtained from participants. In some cases, patients referred to University of Michigan clinics with a cancer diagnosis from outside hospitals will bring hematoxylin and eosin stained slides for routine review by pathologists. To preserve patient and donor confidentiality, samples are given a **specimen identification number** which will be

entered into the sample database. Authorized study personnel will contact the institution where tissue was already obtained and request the appropriate sample. Biospecimens collected under a previously existing IRB-approved protocol are also eligible for use in this study. A copy of the informed consent will be provided to such institutions to allow release of the tissue or cut slides for research purposes. To preserve patient and donor confidentiality, samples are given a **specimen ID** which will be entered into the sample database.

F) Standard of care procedures or surgery
Patients with advanced or refractory cancer who are undergoing standard of care procedures for diagnosis or treatment, will have tumor specimens first utilized for standard clinical pathologic assessment. If there is leftover tissue, these may be submitted for the study.

OR (if no standard of care procedure is planned)

G) Tumor tissue biopsy (solid or fluid)
Tumor tissue or fluids will be collected from patients through the least invasive approach. Patients will receive informed consent detailing risks and benefits of the specific procedure. Procedures will not involve general anesthesia.

The list of possible procedures includes but is not limited to:

- Percutaneous needle biopsy (Liver, Lung, Breast, Lymph node, Bone, Soft tissue mass)
- Lymph node biopsy
- Bone marrow biopsy and aspirate
- Thoracentesis for pleural fluid
- Abdominal paracentesis for peritoneal fluid

Procedure-specific consent. When patients undergo tumor biopsy, they will receive a routine clinical consent as provided by the health care professional who performs the procedure. Generally, this will be staff from the Department of Radiology. This consent process will describe the procedure, risks, benefits, and alternatives.

Tissue Biopsy Processing. Freshly excised tissue will be placed in OCT medium and frozen immediately at -80 C. H&E slides will be prepared for review by an MCTP pathologist to confirm and record tumor content of the biopsy. To preserve patient and donor confidentiality, samples are given a **specimen ID number**.

Repeat Biopsy. Patients who have progression of their cancer may choose to be re-consented for additional tissue procurement including tumor biopsy and other samples. This is subject to the same eligibility and consent requirements.

7.3 Specimen Storage and Disposal

Blood, serum, urine, saliva, and buccal samples will be stored in designated and secure facilities at University of Michigan. Generally, frozen tissue will be stored in secured -80ºC freezers. Storage and retrieval of fixed and paraffin embedded specimens will be handled using routine procedures of the Pathology Department affiliated with the hospital at which the specimen was collected.

Disposal of biospecimens will be considered under certain circumstances including but not limited to reduced specimen integrity, exhausted capacity or insufficient funds for long-term maintenance or storage of low priority biospecimens. Determination of the integrity and priority

of biospecimens is at the discretion of study personnel. The discarding of research specimens is also subject to any institutional policy and the informed consent under which the specimen was obtained.

7.4 Biospecimen collection risks to participants

Generally, tissues, blood, and fluids used under this protocol will be collected while the participant is already receiving routine clinical care, so that additional adverse risks will not be incurred due to the protocol.

- Blood draws may cause pain, redness, swelling, and/or bruising at the needle insertion site. Efforts will be made to collect the blood through a preexisting intravenous access, or at the time of a clinically indicated phlebotomy. The expected blood loss will be minimal.
- Buccal smears may rarely cause mucosal redness at the swab site.
- Urine collection will not cause any undue risks.

In general, tumor tissue biopsies or surgeries may cause **pain**, **inflammation**, **bleeding**, **swelling**, **scarring**, or **infection** at the site where the tumor tissue is removed. In addition, the following are biopsy-specific risks:

- Bone marrow aspirates or biopsies may result in nerve injury or aspiration needle breakage.
- Lymph node biopsies may result in nerve injury or lymphedema (persistent swelling).
- Thoracentesis may result in lung collapse or cardiac arrhythmias.

8.0 CLINICAL DATA COLLECTION

Clinical data may be collected from patients as part of ongoing care or as part of long-term follow up after treatment has been completed.

8.1 Type of Data Collected

Data collected will include patient identifiers such as name, date of birth, social security number, patient informed consent status, and patient clinical data, including tumor stage. These data are normally collected as part of providing clinical care at the Cancer Center. In general, data will be abstracted from medical records and the initial history and physical assessment. Routine clinical data may include information such as patient age, clinical evaluation, tumor stage, treatments, treatment outcomes, treatment toxicities, complications from disease or therapy, and long term follow up data. Participants will be asked to sign a medical record release form to allow retrieval of medical records for review and confirmation. The study calendar indicates follow up, and eventually patients will be followed annually until time of death. Participants will be given the opportunity to indicate their preferred means of contact, phone, mail, or email on the consent form.

8.2 Data Collection Methods

Clinical information generated from initial and follow-up patient visits to University of Michigan clinics will be abstracted from corresponding clinical records/databases and/or patient medical charts. For the collection of additional information such as personal and family medical history, patients with cancer may also receive surveys/questionnaires. In addition, if patients are routinely followed at outside hospitals, and if a patient has consented to participation in this protocol, clinical follow-up data will be obtained from the appropriate hospitals consistent with tumor registry practices. Medical record release forms (Appendix) will be obtained in such cases to obtain data from the outside clinic in compliance with all applicable regulations. Long term follow-up will generally be completed through review of medical records, but phone contact may be utilized if necessary.

8.3 Data Entry

Protocol registration and consenting information from all patients enrolled in this protocol will be captured and stored in a password protected database consistent with standard IRB and HIPPA regulations. Biospecimens will be linked to the clinical database with unique identification numbers and patient information in the clinical database will only be accessible by a small set of study personnel.

8.4 Risks to Participant

While it is possible that public knowledge of genetic factors could lead to patient/donor problems with health insurance, life insurance, or employment, the confidentiality of patient/donor identities will be strictly preserved under this protocol, minimizing such risks in this context. Furthermore, protections are afforded under the Genetic Information Nondiscrimination Act[40]. The law protects people from discrimination by health insurers and employers on the basis of genetic information[40].

8.5 Quantitative and Qualitative Data

A mixed-methods approach, using quantitative surveys and qualitative interviews, will be employed in order to examine how patients appraise and react to genomic sequencing results. Any efforts to improve communication with patients should start by understanding what problems currently exist. To gain such understanding, qualitative interviews will be conducted with up to 20 patients. The interviews will draw on the mental model approach to risk communication, a technique that identifies what people already understand about their health so that communications can focus instead on facts or relationships that people need to know, but are currently un- or misinformed about. Each patient in this sub-study will be interviewed (interview guides included in Appendix 6) by telephone at two points; each interview will last approximately 30-60 minutes. First, interviews will be conducted 1-2 days after the clinic visit or at a date preferred by the patient. This interview will focus on patient expectations about what testing will tell them and how such information might be used (e.g., to change their cancer treatment). Second, we will interview patients shortly after they have received their sequencing results to learn what they did or did not understand about their results and what changes to the communication process they would suggest. The interviews will be audio recorded in order to ensure the fidelity of the data. The goal is to identify problems, concerns, misconceptions, or desires that may inhibit effective understanding and use of the information patients receive as part of this study.

Furthermore, to guide the integration of genome sequencing into medical care, a greater understanding of patients' behavioral and psychological responses to their sequence results is needed. Self-reported survey data will be collected shortly after the clinic visit and the following disclosure of results. Patients will be provided surveys (Appendix 6) which can be completed at home. Each survey will take approximately 15 minutes to complete. A research assistant will contact the patient 1-2 days after the clinic visit to answer any questions the patient may have about the surveys and collect any responses to open-ended questions that the patients may want to provide over the phone instead of in writing. A self-addressed and pre-paid envelope will be given to the patient for the return of the surveys.

All survey and audio recordings will be kept confidential. The recordings will not be transcribed and personally identifiable information will not be recorded. A link list containing the patient's study identification number and the date of the interviews will be maintained until the data analysis phase in order to link a patient's first and second interviews. All data will be stored in a locked cabinet and/or in password protected files on a secure server.

9.0 MANAGEMENT AND ALLOCATION OF SPECIMENS AND DATA

To ensure prompt collection and processing of samples, clinical visits and procedures will be coordinated with laboratory personnel from the Michigan Center for Translational Pathology (**MCTP**).

9.1 Specimen Coding, De-identifying, and Tracking

All patient-derived materials will be tracked using a password-protected, secure, biospecimen management system through MCTP and MICHR. Detailed tracking of the specimens, consisting of storage location, retrieval and usage information, including distribution to collaborating investigators, will be maintained through this system. The specimen ID number will be used to uniquely identify biological samples during all aspects of experimentation so that the resulting data can be linked to specimens and patient's clinical data. Each participant has a unique identification number that can link their respective biospecimens and the clinical database.

9.2 Data Confidentiality and Security

The confidentiality of each patient record will be rigorously maintained using existing standards at University of Michigan Health Systems. Health Insurance Portability and Accountability Act (HIPAA) and state/federal government regulations for protecting patient privacy and security will be strictly maintained. No patient or subject-identifiable information will be given to third parties, including family members, unless that subject has given written or witnessed consent to do so. The results of the research studies may be published but subjects will not be identified in any publication.

In addition, the following steps have been taken to maintain confidentiality and security:

- Documents will be stored in a locked cabinet and locked office.
- Only authorized users from the protocol have access. When users leave the project or unit, access rights will be terminated.
- Databases will be password protected.
- Databases will be backed up electronically.
- Security software includes a firewall, anti-virus, anti-intrusion protection and are regularly updated on all servers and workstations.
- Paper or electronic media will be properly and safely disposed.

9.3 Data Processing and Storage

Protected health information is stored securely on University of Michigan servers behind firewalls that block access outside the institution. De-identified sequence data may be processed and/or stored on University of Michigan servers within the firewall or on remote servers with safeguards in place. Access is limited to a small set of authorized users via password control. Sequencing data files are de-identified for processing and do not contain patient or subject identifiers such as name, initials, date of birth, or medical record number. The files will contain identifiers such as library and sequencing run IDs, as well as a code assigned by the study coordinator. The code is not derived from patient or subject information and re-identification requires methods accessible only through the encrypted database.

All data transfers outside the University of Michigan firewall will be done over encrypted connections by authorized and authenticated personnel. For data processing and storage through HIPAA-compliant cloud providers, we will follow NIH security best practices as described in the following document:

http://www.ncbi.nlm.nih.gov/projects/gap/pdf/dbgap_2b_security_procedures.pdf

This includes encryption of data with tight control over the authentication keys, logging of account access with regular review of access logs, and regular scanning of software for known vulnerabilities.

9.4 Access to Biospecimens and Data for Research Purposes

Requests for specimens or data from investigators, collaborators and "outside" investigators will be considered by the Sequencing Tumor Board, and granted if specific criteria regarding scientific merit, feasibility of the work and patient confidentiality are met. The Committee chair or other designee will review and prioritize each request for data or specimen interrogation as it is made, which can be reviewed and discussed in monthly meetings. Collaborators are encouraged to formulate a formal research plan that can be reviewed by the Committee. Decisions made by the Committee will ensure timely specimen and data distribution, as well as data quality and confidentiality during collection and entry, are performed pursuant to the provisions of this protocol.

9.5 Specimen Property Rights

Specimens collected from participants are the property of University of Michigan and will remain at University of Michigan. Biospecimen research will be conducted internally at UM, but may involve collaborations with other institutions or in some cases companies. Specimens will not be sold to any person or company for profit. Biospecimens shared with external companies or researchers will not contain identifying information.

10.0 RESEARCH

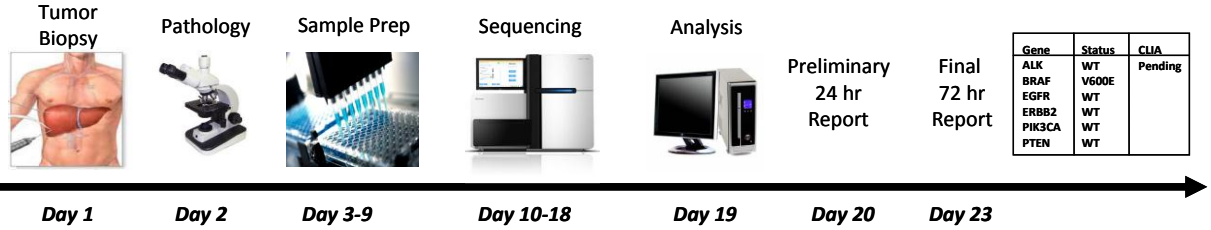
Participant samples and information will be used in diverse types of somatic and germ-line research. The main initiative will be to perform integrative sequencing of tumor specimens (ONCO1500 targeted gene panel, transcriptome, exome, or whole genome sequencing) and a germline tissue control (exome sequencing). Additional studies may be conducted using biospecimens and data, including but not limited to tumor biology studies, biomarker identification studies, drug target studies, genomics and proteomics studies, genetic susceptibility studies, drug development efforts, epidemiological studies, and outcomes studies.

10.1 Integrative Sequencing of Tumors

The current approach to mutation analysis involves high throughput massively parallel sequencing to identify genetic aberrations in all expressed transcripts[27, 28] or known exons[29]. Transcriptome or whole RNA sequencing entails capture and sequencing of those elements of the genome that are transcribed into RNA. Transcriptome sequencing can thereby generate data on gene expression, alternative splicing of RNA transcripts, novel RNA transcripts, and gene rearrangements[27, 28]. Exome sequencing entails capture and sequencing of exons on the DNA level. Exome sequencing can generate data on somatic mutations for all known exons and provide information about by copy number changes[29]. Whole genome sequencing, at 5x coverage, allows a broad assessment of structural genomic variation. ONCO1500 is a CLIA-certified laboratory developed test (LDT) designed to efficiently identify non-synonymous somatic mutations in a panel of 1500 genes with suggestive links to cancer. ONCO1500 exome sequencing identifies non-synonymous somatic mutations by comparing tumor versus matched normal tissue. These approaches allow comprehensive tumor sequencing for research and potentially clinical research purposes.

Methods. Generally, fresh tumor biospecimens or paraffin biospecimens will be collected and coordinated through MCTP and MICHR. A 5-micron section is taken from each frozen tissue block and will be evaluated by staff pathologists (MCTP) who will confirm tumor content and designate the % tumor associated with each specimen. Greater than 60% tumor cellularity will be required. Researchers will isolate genomic DNA, RNA, and protein for downstream applications and validations. Libraries for either ONCO1500, transcriptome[28], whole gnome, or exome[29] sequencing will be prepared as previously described, run on Illumina sequencers (HiSeq 2000), and analyzed in a period of 21-28 days (**Figure 4**). In some cases, additional sequencing methodologies may be employed such as genomic or standard Sanger sequencing for discovery or CLIA validation.

Figure 4: Timeline from Sample Acquisition to Sequencing Results



Research Analysis. Researchers will use the data set to assay for genetic alterations across a large number of genes important in cancer, including known or suspected oncogenes, druggable or "actionable" targets, and genes with proven clinical implications such as epidermal growth factor receptor (EGFR) expression or mutations. Researchers will also use the data set for exploratory research for discovery of novel cancer genes, pathways, or biomarkers. The results of the research studies may be published but subjects will not be identified in any publication.

10.2 Sequencing Tumor Board (Clinical Reporting)

Rationale. Interpretation of results necessitates expertise from multiple disciplines. We will employ a multi-disciplinary ~~**Sequencing Tumor Board (STB)**~~ **Precision Medicine Tumor Board (PMTB)** with expertise in clinical oncology, clinical genetics, pathology, genomics, bioinformatics, genetic counseling, psychology, and bioethics to deliberate on findings and provide oversight for the study. Variants will be filtered by the bioinformatics team through a pre-determined but flexible list of genes (Appendix 4). The ~~STB~~ PMTB will review sequence results in weekly meetings in the context of each individual patient. Primarily cases with clinically actionable findings will be presented at PMTB. If appropriate, and **based on the category and patient's informed consent for return of research results**, subsequent disclosure for somatic and germline results will occur through the patient's medical oncologist and genetics clinic, respectively.

Sequence Results in Cancer (Somatic). We have generated a pre-determined list of informative genes in cancer (**Appendix 4**). We considered genes "informative" if they have prognostic, predictive, or pharmacogenomic value OR if they are targeted in an ongoing clinical trial. The Sanger Institute maintains a Cancer Gene Census which is a catalog of genes (427) for which mutations have been causally implicated in cancer[41]. There are several additional informative genes utilized in best clinical practices[42, 43] and as targets in clinical trials which have been curated to our list. For example, there are over 40 locally available trials involving targeted therapies through UMCCC and Karmanos Cancer Institute (Drs. Talpaz, Lorusso). Last, since nearly half of druggable genes are protein kinases, we have also included a comprehensive list of the human kinome[44, 45].

Sequence Results in Human Disease (Germline). For informative genes in human disease, we have included genes from 1) Human Gene Mutation Database and 2) genes formally available as a clinical test at NCBI's GeneTests, which is used by professionals in clinical genetics[46-48]. This pre-determined list includes germline mutations that predispose individuals to cancer as well.

Drivers Versus Passengers. Over the course of a lifetime, somatic or cancer tissue can acquire selective advantage for specific gene mutations. Genes that are "driver" genes confer a selective growth advantage for cancer cells and typically involve genes implicated in cancer. In contrast, mutations in "passenger" genes do not confer a growth advantage, but are thought to be co-selected based on the presence of a driver gene. Recent large-scale genome and exome sequencing of several cancers has demonstrated that most cancers have up to 80-100 somatic sequence variants in the coding regions of the genome, and fewer than 15 are predicted to be possible "drivers"[41, 49-53]. Thus, we anticipate reviewing up to 80-100 mutations per case, but expect only a few variants to be informative or actionable.

~~STB~~ PMTB: Role. The Board will interpret sequencing results that will be processed, analyzed, and stratified for each patient. Variant stratification will occur before the weekly ~~STB~~ PMTB by the Bioinformatics Team (MCTP) and will be based on the pre-determined but flexible lists for informative genes (**Appendix 4**). The Board will interpret individual results and evaluate data classification and then determine the need for disclosure to the patient, consistent with result category and the preferences expressed by the patient in the informed consent. Further, the ~~STB~~ PMTB will discuss and address any safety or privacy issues that were raised for each patient. ~~STB~~ PMTB does not replace the function of traditional "tumor-specific" boards where an oncologic treatment plan is developed based on available evidence and expert opinion. Instead the ~~STB~~ PMTB deliberates on whether results have clinical impact and whether they should be disclosed.

Deliberation of Sequence Results. Recent large scale cancer genome and exome sequencing of several cancers has demonstrated that most cancers have up to 80-100 somatic sequence variants in the coding regions of the genome, and fewer than 15 are predicted to be possible "drivers" for cancer[41, 49-53]. Therefore, we anticipate reviewing up to 80-100 mutations per case, but expect only a few variants to be actually informative or actionable. The ~~STB~~ PMTB will review mutation "positive" findings for genes noted on the cancer gene list described above. Since the wildtype status for specific genes may be informative, e.g. wildtype K-ras in colorectal cancer[54], the ~~STB~~ PMTB will also review pertinent "negative" or wildtype findings for a Core list of genes (**Appendix 4**). In addition, the ~~STB~~ PMTB may also request additional information about the status of genes not reported at the ~~STB~~ PMTB meeting.

Over the course of the study, genes may be newly implicated as a target or informative variant in cancer. The predetermined gene lists will be updated at least every month and existing sequencing data will be queried for any new findings. If positive results are identified, these cases can be represented at ~~STB~~ PMTB for review of these additional findings. Disclosure will depend upon the patient's informed consent selection**.**

~~STB~~ PMTB **Operations.** The Study Coordinator, Co-Is, and PI's will coordinate and manage the ~~STB~~ PMTB. Representatives from University of Michigan with expertise in Clinical Oncology, Clinical Genetics, Translational Research, Genomics, Pathology, Bioinformatics, and Bioethics will be present for weekly meetings. In addition, additional *ad hoc* expertise in Clinical Oncology and Genomics may be requested depending on the patient and sequencing data presented. For example, the ~~STB~~ PMTB may elect to bring in an expert in clinical ovarian cancer and the PIK3CA pathway for a patient who has ovarian cancer. In addition, the referring medical oncologist will be encouraged to attend ~~STB~~ PMTB, much like other cancer tumor boards, but this is not a requirement. For each case presented at the ~~STB~~ PMTB, a Clinical Investigator will provide a standard clinical presentation of the patient and his or her cancer history based on the

clinical database. The patient's treatment options will be cross-referenced against standard recommendations including the patient's medical oncologist's assessment and national guidelines[42, 43].

The ~~STB~~ PMTB will classify results into categories of Impact or Significance based on **Table 1**. The category of "Direct impact on care of current cancer" will always be disclosed since that is the intrinsic purpose of participating in the study. The categories "Significance for biological family" and "Potential medical impact" (for conditions other than cancer of interest) will have a default of disclosure, but patients may change this default at the time of informed consent. "Significance unknown" includes variants whose role and function are not known and these results will not be disclosed since they do not have any clinical, biological familial, or "personal" meaning[55]. In some instances sequence variants may be associated with both a cancer and other medical condition, in which case mutations will be categorized as "both." Disclosure of results will depend on category assignments, the default status, and in some instances the patient's consent preference. Subsequently, the ~~STB~~ PMTB will review any pertinent germline findings and make the same category assignments.

10.3 Implementation of ~~STB~~ PMTB **Recommendations.** The Study Coordinator will summarize STB meetings and file these weekly reports, which will be reviewed by the Principal Investigators in monthly meetings. Referring oncologists will be invited to complete a brief survey (Appendix 6) regarding the return of tumor sequencing results to their patients. Clinicians will be contacted up to three times per patient to complete the survey. To ensure timely reporting, scheduling of disclosure for patients will be coordinated through the Study Coordinator.

Disclosure of Somatic Results. For somatic mutations, they will prepare a concise report (**Appendix**) summarizing the recommendations including description of impact/significance (**Table 2**) and CLIA validation in non-technical language with appropriate basic science and clinical oncology references. For somatic mutations, CLIA validation will occur in the MCTP CLIA/CAP Lab (Drs. Chinnaiyan & Kunju, MCTP). This report will be reviewed with the referring medical oncologist, who has the choice to disclose the results to their patient themselves. Medical oncologists routinely disclose results of somatic gene testing for genes such as K-ras, UGT1A1, Flt3, and C-kit. However, if referring clinicians are not comfortable or feel they lack the expertise, a Clinical Investigator will be present to disclose the results for them. The ~~STB~~ PMTB may also stipulate that genetic counseling is required for selected somatic results on a case by case basis.

Disclosure of Germline Results. For those who elect to receive results, the study coordinator will arrange for further follow-up with the Genetics Clinic (Dr. Stoffel) and a board-certified genetic counselor to discuss implications of these findings for their personal health and options for clinical genetic testing. For germline mutations, CLIA validation will occur through the Michigan Medical Genetics Laboratory (MMGL; a CLIA/CAP lab) directed by Dr. Innis, and validated results will be incorporated into the medical record. Some subjects with germline mutations may choose to have medical genetics evaluation and counseling, which will be provided by standard referral to the Adult or Pediatric Genetics Clinics (directed by Drs Stoffel and Innis, respectively) at the University of Michigan, or by other medical geneticists geographically located closer to relevant family members.

10.4 CLIA Validation. The ~~STB~~ PMTB will select sequencing results that require CLIA validation. Two University of Michigan CLIA/CAP labs will be available to validate "informative" results identified from tumor sequencing and include the MCTP CLIA/CAP lab (Drs. Chinnaiyan/Kunju) and the MMGL CLIA/CAP Lab (Dr. Innis). The MCTP CLIA/CAP lab will be

primarily dedicated to validating somatic alterations while the MMGL CLIA/CAP lab will be focused on validating germline alterations. All validation assays will be carried out based on previously optimized written protocols, standard operating procedures, and predefined reagents in accordance with prescribed CLIA guidelines. For all assays, the results will be assessed according to predefined ranges and cutoffs. For commercial kits, we will follow manufacturer's instructions. For in-house assays, the PCR results from test samples will be compared with the standard plots generated using a positive control for the corresponding assays. Similarly, mutation calling by sequencing will be based on comparison with positive control fragments obtained from an index sample or a synthetically produced positive control fragment with known sequence variations.

Other well characterized sequence variants involving actionable genes but without commercial assays will be confirmed by pre-validated assays developed in-house. An inventory of optimized quantitative real time PCR assays will be developed for all recurrent mutations or fusions encompassing the pre-determined gene list as described. Assay specific PCR primers flanking the fusion junctions or mutations will be designed using NCBI Primer Blast and will be obtained through overnight service from Integrated DNA Technologies (IDT). Two pairs each of primers will be designed for real time PCR and end point PCR respectively. Candidate mutations or fusions will be first validated by real time PCR and positive cases will be used to amplify PCR fragments, purified by Agencourt beads and subjected to Sanger sequencing using an 8-capillary 3500 or 24-capillary 3500xL Genetic Analyzer from Applied Biosystems, followed by analysis of the chromatograms using Sequencher 4.10.1 for mutation and zygosity calling (http://www.genecodes.com/) to confirm the aberrations.

10.5.1 Additional Research Studies

Additional studies may be conducted using biospecimens and data. The research is conducted in a de-identified manner except for knowledge of the patient's cancer subtype and outcomes. It is anticipated that as technologies evolve, this protocol will need to be amended to incorporate new, more efficient and cost effective methodologies. Additional studies included but not limited to:

1) Drug development efforts may include evaluation of:

- tumor cell sensitivity to experimental drugs
- compounds with the ability to counteract tumor drug resistance

2) Biomarker studies may include identification of:

- biomarkers that predict tumor sensitivity to drugs
- early detection biomarkers
- biomarkers that aid in tumor classification
- biomarkers that provide prognostic information about risk of recurrence
- methods to detect minimal residual disease

3) Tumor biology studies may include:

- immortalized cell lines may be generated from tumor tissues for future studies
- generation of primary tumor xenografts in experimental animals such as mice, to help carry out pre-clinical experiments with novel drugs
- knockdown or overexpression of genes in cell lines
- studies on circulating tumor cells from peripheral blood
- standard techniques for DNA, RNA, and protein such as immunohistochemistry, FISH, RT-PCR, western blot
- investigation of tumorigenesis mechanisms
- investigation of tumor invasion mechanisms

- investigation of apoptosis mechanisms
- investigation of signal transduction pathways
- investigation of cellular metabolic pathways
- investigation of tumor microenvironment
- investigation of tumor immunology
- phenotypic analysis
- analysis of tumor cell growth pathways
- study of drug sensitivity and resistance mechanisms

4) Genomics, epigenomics, metabolomics, and proteomics studies may include:

- next generation sequencing of DNA and RNA
- discovery and/or characterization of known and novel nucleic acids, proteins, and metabolites
- analysis of gene expression profiles and protein products in normal and cancer samples
- functional analysis of abnormal genes (DNA or RNA level) and proteins
- analysis of gene mutations, copy number changes, rearrangements
- identification of gene fusions
- analysis of RNA splicing / isoforms
- qualitative and quantitative gene expression
- analysis and characterization of coding and noncoding RNAs
- analysis of genomic or protein polymorphisms in normal and cancer samples
- identification of cancer causing genetic aberrations
- identification of cancer causing proteins
- analysis of germline mutations in hereditary cancers
- identification of somatic deletions, point mutations and amplifications

11.0 Statistics

The lead statistician for the protocol is Robert Lonigro who is part of MCTP. Statistical analysis will largely be limited to the tumor sequence data. Overexpressed genes will be identified from sequencing data by quantifying gene and exon expression using RPKM-normalized read counts[56] and comparing against corresponding measurements in benign reference samples. Copy number assessments will be using standard segmentation-based approaches such as the Circular Binary Segmentation algorithm[57]. Sequencing data will be qualified with standard quality scores and other validations when necessary.

12.0 Benefits and Risks

12.1 Benefits

In many cases, there will be no immediate, direct benefit to a patient who participates in this study. This study establishes a mechanism to profile the tumors of patients with cancer and create a clinical database to follow outcomes to facilitate basic, clinical, and translational research. ***This is a not a therapeutic study and is focused on tissue collection and tumor sequencing only*** We anticipate that this study could facilitate the design of future clinical trials based on informative sequencing results. This study will contribute to the general knowledge of cancer and has thereby has potential for benefits to society as a whole.

12.2 Risks

1) **Confidentiality**. **Personal identifiers** are removed from the biospecimen database, and are only connected to a participant's identity through a **unique patient identification number**. This layer of security will protect patient information per HIPPA and institutional standards, but also permit translational research. Access to files with patient identifiers and files with study

outcomes will be restricted to core staff with any exceptions to be approved by the principal and co-investigators. In addition to use of passwords and other security measures, all documents containing identifying information on individuals or physicians are considered confidential materials and will be safeguarded to the greatest possible extent.

2) Procedural risks. Risks of tumor biopsy are specific for each procedure but generally include **pain**, **inflammation**, **bleeding**, **swelling**, **scarring**, or **infection**. See section 7.0.

3) Genomic Results. These risks are discussed under Informed Consent.

12.3 Adverse Events

Definition: An adverse event (AE) is any untoward medical occurrence including the exacerbation of a pre-existing condition, in a clinical investigation patient that is **related to specific research procedure in the course of the collection of samples such as tissue biopsy for this protocol**.

Serious Adverse events (SAE) are defined as follows:

- Requires hospitalization
- Requires clinical evaluation
- Results in death
- Results in persistent or significant disability/incapacity

Adverse events will be reported by study personnel using the adverse event reporting form (Appendix 2) and evaluated by one of the study Co-Investigators. Adverse events will be reviewed every 3 months by the Biorepository committee.

13.0 DATA AND SAFETY MONITORING.

The **Sequencing Tumor Board** will work to protect the confidentiality of study data and ensure the safety of participants. This committee will include the Principal Investigators, data manager or designee, and other members of the study team involved with the conduct of the study. The Board will also consider factors external to the study, such as scientific developments that may have an impact on the safety of participants or ethics of the study. This will involve ongoing interpretation of data and discoveries at University of Michigan and in the literature.

1) The Sequencing Tumor Board will meet **weekly to monthly** (depending on patient enrollment):

- Review registration: retention of participants, adherence to protocol (potential or real protocol deviations)
- Review study accrual: enrollment rate relative to expectations, characteristics of participants
- Deliberation on sequencing results that are clinically significant and select results for CLIA Validation and subsequent disclosure
- Provide oversight to disclosure of results
- Validity and integrity of the data

2) In addition, the committee will meet **every month** to also discuss and review the following:

- Safety of participants (Adverse Events and Reporting)
  http://www.med.umich.edu/irbmed/ae_orio/ae_report_standard.htm
- Clinical Database
- Tissue Repository

- Resource Allocation and Access
- Overall scientific merit and ethics of study activities

Pilot phase assessment: After accruing 20 patients for the Pilot, the Principal Investigators will meet to review the following data:
1) Was tumor acquisition successful? (Quality DNA and RNA, acceptable tumor content?)
2) How much time passed from biopsy acquisition to sequencing results disclosure?
3) How many informative genes were identified per patient?

For each endpoint, the Team will assess what limitations were encountered, and develop alternative solutions to improve the process. The Team will provide an update with the IRB with proposed solutions and obtain necessary feedback to proceed with expanding the study in size and eligibility.

The internal Sequencing Tumor Board will be comprised of the following members with their respective expertise:
1) Arul Chinnaiyan MD, PhD [Basic science]
2) Moshe Talpaz MD, David Smith MD, Dale Bixby MD, PhD, Christoper Lao MD, [Translational and clinical research], or a*d hoc* academic medical oncologists
3) Elena Stoffel, MD, and/or Jeff Innis MD, PhD [Clinical research and genetics]
4) Jessica Everett, ~~Victoria Raymond~~, Kristen Hanson, , Michelle Jacobs, [Genetic Counseling]
5) Scott Roberts, PhD [Bioethics]
6) Clinical coordinator for the study: Lynda Hodges, Erica Rabban
7) Staff scientists from MCTP [Basic science / Bioinformatics]

The assigned data manager will summarize findings through *Data and Safety Monitoring Reports* (DSMR) every 3 months. The reports will be signed by the Principal Investigator or by one of the Co-Investigators. The reports will be filed with the IRB annually or more often if requested.

APPENDIX 1

Study Calendar												
	Timeline											
			Days after biopsy									
	1	2 to 5	7	14	21	28-35 Days	4 Months	8 Months	12 Months	18 Months	2 Years	Annual
Genetic counseling and Informed Consent	X					D						
Clinic Visit	X					D						
Complete History and Physical	X											
Review of radiological scans to determine if tumor is accessible for tumor biopsy	X											
Labs: PT, INR, PTT, Platelets	X											
Blood and Serum collection-C	X											
Urine collection-C	X											
Buccal smear, saliva collection	X											
Tumor Biopsy		X(A)										
Standard of care procedure or surgery		X(B)										
Tumor Block retrieval		X(C)										
Sequencing and Analysis			X	X	X	X						
Results Disclosure						D						
Clinical Data Updates (Phone and Medical Records)						X	X	X	X	X	X	X

A-Patients with advanced cancer will undergo tumor biopsy for research
B-Patients undergoing standard of care procedures or surgeries will have remaining specimens used for research
C-Patients will donate their previously collected tumor block from previous biopsy or surgery
D-If clinically significant results are found, disclosure will occur in a follow up clinic visit.

APPENDIX 2

ADVERSE EVENT REPORTING FORM

Patient name (Last, MI, First)	**Tumor type**
Registration#	**Date of biopsy**
Date of birth	

Date occurred:_____
Description of adverse event (Please describe in words):

Is this related to the protocol? Yes / No _____

Is this related to a tissue biopsy? Yes / No _____

Is this related to reporting of tumor sequencing? Yes / No _____

Is this considered a serious adverse event (SAE)?
[A SAE involves hospitalization, clinical evaluation, results in death, or results in persistent or significant disability/incapacity]

Reporting personnel:_____
Signature:_____

This report is to be brought to the attention of the one of the Co-Principal Investigators.

APPENDIX 3

SAMPLE MOLECULAR REPORT

Patient name (Last, MI, First)	**Tumor type**
Registration#	**Date of biopsy**
Date of birth	**Date of report**

Disclaimer: This report is a summary of selected genes and their aberrations based on sequencing. This report is based on an investigational protocol and the results therefore should be considered experimental, and may not have treatment implications.

Gene (Full name)	**Gene (abbreviation)**	**Point Mutation**	**Copy Number (Amplification, Deletion)**	**Gene Fusions**	**Transcript Expression**
Gene[1] Gene[n]					

Note: If additional analysis yields further information an amendment to the report will be issued.

Signature
Date
Contact information

Comments:

1. The sensitivity of this assay has not been defined. Results are limited in part to the quality of specimens, especially sample size and integrity.
2. The results are part of an investigational protocol, and are considered experimental.
3. Additional genetic aberrations are expected to be added to this list by the investigators.

References

1. …..

APPENDIX 4

GENES QUERIED

We have generated a pre-determined list of informative genes in cancer and human disease.

1) Sanger Cancer Gene Census
http://www.sanger.ac.uk/genetics/CGP/Census/
http://www.sanger.ac.uk/genetics/CGP/cosmic/

2) Best Clinical Practices in Oncology

A. American Society of Clinical Oncology
http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Clinical+Practice+Guidelines
B. National Comprehensive Cancer Network
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

3) Clinical Trials

A. University of Michigan Comprehensive Cancer Center
http://www.cancer.med.umich.edu/research/find-a-clinical-trial.shtml
B. Wayne State University's Karmanos Cancer Insititute
http://app-oncoreprod1.karmanos.org/sip/SIPControlServlet
C. Nationwide clinical trials
http://clinicaltrials.gov/

4) Human Kinome, http://kinase.com/human/kinome/

5) Human Gene Mutation Database
http://www.hgmd.cf.ac.uk/ac/index.php

6) NCBI's GeneTests
http://www.ncbi.nlm.nih.gov/sites/GeneTests

In addition, we have designated a Core list of genes that will be evaluated and reported for wildtype and variant results for each ~~STB~~ PMTB meeting. As new data and practices emerge, this list is subject to change over the course of the project and will be updated at least quarterly the team members of the Management Core, Project 1, and Project 2 combining expertise in clinical oncology, clinical genetics, cancer genomics, and bioinformatics.

Curated Genes of Interest: Status will be reported for wildtype or mutated genes							
Abl1	CD52	ERBB2	GNAQ	MDM2	NPM1	RET	TET2
Abl2		ERBB3	GNAS	MDM4	NRAS	RICTOR	TK1
ADA	CD70	ERBB4		MEN1	NTRK1	RUNX1	TMEM127
AKT1	CDA	ERCC1	HDAC1	MET	NTRK2	RUNX1T1	TNF
AKT2	CDH1	ERG	HIF1	MLH1	NTRK3		TOP1
AKT3	CDKN1A	ESR1	HRAS	MPL	PALB2	RRM1	
	CDKN1B	EZH2	HSPCA	MSH2	PDGFRA	RXRB	
ALK	CDKN2A	FBXW7	IDH1	MSH6	PDGFRB	SDH5	TOP2A

APC	CHK1	FGFR1	IDH2	MTHFR	PGR	SDHB	TOP2B
AR	CSF1R	FGFR2	IGFR1	MUTYH	PIK3CA	SDHC	TP53
				NF1	PIK3R1	SDHD	TSC1
ASNA	CTNNB1	FGFR3	IKBKE	NF2	PMS2		TSC2
ATM	CYP2D6	FGFR4	Jak2	NFKB1	POLA	SMO	TPMT
AURKA	DCK	FHIT		NFKB2	POLB	SOCS1	TXNRD1
AXIN2	DNMT1	FKBP9	Jak3	Nmyc	PTCH	SPARC	TYMS
BCL2	DPYD	FLCN	KIT	NOTCH1	PTEN	SPINK1	UGT1A1
BRAF	EGFR	FLT3	KRAS	NOTCH2	PTGS2	SRC	VEGFR1
BRCA2	EPHA3	FOLR2	MAP2K1	NOTCH3	PTPN11	SSTR1	VEGFR2
CD20	EPHA5	FRAP1	MAP2K2	NOTCH4	RAF1	STK11	VHL
CD25	EPHA6	GART	MAP2K4		RARA	SYK	WT1

APPENDIX 5

What is the Genetic Information Nondiscrimination Act (GINA)?

What GINA does	What GINA does not do
▪ Prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums ▪ Prohibits an insurer from requesting or requiring that a person undergo a genetic test ▪ Prohibits employers from using a person's genetic information in making employment decisions such as hiring, firing, job assignments, or any other terms of employment ▪ Prohibits employers from requesting, requiring, or purchasing genetic information about persons or their family members ▪ Will be enforced by the Department of Health and Human Services, the Department of Labor, and the Department of Treasury, along with the Equal Opportunity Employment Commission; ▪ remedies for violations include corrective action and monetary penalties	▪ Does not prevent health care providers from recommending genetic tests to their patients ▪ Does not mandate coverage for any particular test or treatment ▪ Does not prohibit medical underwriting based on current health status ▪ Does not cover life, disability, or long-term-care insurance ▪ Does not apply to members of the military

APPENDIX 6

1. Aim 4 Baseline survey

As a research participant in the Personalized Oncology through High-throughput Sequencing: Michigan Oncology Sequencing Center (MI-ONCOSEQ) study, you were offered DNA sequencing related to your cancer. We are interested in your opinions and experiences with the study, as well as your opinions about DNA sequencing studies in general.

This is the first of two brief surveys that you have been asked to complete. A follow-up survey will be mailed to you in several weeks. Each survey will take approximately 15 minutes to fill-out. Your participation is voluntary.

The goal of these surveys is to explore cancer patients' outlooks toward the DNA sequencing process. This survey will ask questions such as your reasons for joining the study, what information you think you will receive, and your knowledge of both the study and DNA sequencing in general. While some of the questions will ask you to think about scenarios that are hypothetical (made up), some of the information may relate to your life. You may also be asked questions about genetic test results that may be available in the future.

Your responses to the questions in this survey will not have any impact on your DNA sequencing results, nor will it change any of the choices you made when you consented to the study, or your cancer treatment. If you have questions or concerns about how these surveys are related to your DNA sequencing results, please contact Lan Q. Le at 734-615-2422 or lqle@umich.edu.

We thank you in advance for your participation. Your answers will help us understand DNA sequencing from the patient's point of view and how it can be used in the medical care of future patients.

1. There are many different reasons why people choose to participate in research studies. Can you please tell us in your own words why you are participating in this DNA sequencing study?

I am participating because…

_____

_____

_____

_____

_____

_____

_____

_____

2. Research studies are conducted to generate general knowledge. However, participants sometimes hope to gain personal benefits from the study. Can you please tell us in your own words what you are expecting to gain, if anything at all, from this DNA sequencing study?

I expect to gain…

_____

_____

_____

_____

_____

_____

_____

1. Listed below are some reasons why cancer patients might participate in DNA sequencing studies such as the MI-ONCOSEQ study. Please indicate how much you agree or disagree with the following statements.

I joined the MI-ONCOSEQ study:	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**
a. To contribute to cancer research.	☐	☐	☐	☐
b. To help researchers better understand how to treat my type of cancer.	☐	☐	☐	☐
c. Because my family encouraged me to participate.	☐	☐	☐	☐
d. To have more certainty about my type of cancer.	☐	☐	☐	☐
e. Because my doctor recommended the study to me.	☐	☐	☐	☐
f. To see if my DNA sequencing results could be used to help make cancer treatment decisions for me.	☐	☐	☐	☐
g. To learn about my genetic risk for diseases other than cancer.	☐	☐	☐	☐
h. Because I feel like I am helping other cancer patients.	☐	☐	☐	☐
i. To gain information that may be relevant to the health of my biological relatives.	☐	☐	☐	☐

2. Which statement from the above table best reflects the main reason why you joined the MI-ONCOSEQ study? In the blank space below, please write the letter (a-i) that corresponds with that statement.

_____

3. When you signed the informed consent form to participate in the MI-ONCOSEQ study, how well did you understand the following aspects of the study?

	I did not understand this at all				***I understood this very well***
a. What the researchers are trying to find out in this study.	1	2	3	4	5
b. The possible risks and discomforts of participating in the study.	1	2	3	4	5
c. The possible benefits to you of participating in the study.	1	2	3	4	5
d. How your participation in the study may benefit future patients.	1	2	3	4	5
e. What you will be told about your sequencing results and when you will be told.	1	2	3	4	5
f. What will happen to your blood and tumor tissue sample after your DNA sequencing is complete.	1	2	3	4	5
g. Overall, how well did you understand the study when you signed the consent form?	1	2	3	4	5

4. Listed below are some statements that a research participant like you might make when he or she joins the MI-ONCOSEQ study. We would like to know whether YOU agree or disagree with them.

   Some of these procedures and types of information are part of the MI-ONCOSEQ study, but others are not, and some may not even be possible. We are including the full list because we would like to learn about everything that YOU thought would happen as a result of enrolling in the study.

   Please indicate how much you agree or disagree with the following statements.

By participating in the MI-ONCOSEQ study, I am expecting…	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**
a. To learn more about the cause of my cancer.	☐	☐	☐	☐
b. To be told about clinical drug research studies that I may be eligible for.	☐	☐	☐	☐
c. To be able to enroll in a clinical drug research study.	☐	☐	☐	☐
d. To have a discussion with my doctor about my DNA sequencing results.	☐	☐	☐	☐
e. To be told about the gene changes found and what that means for my future.	☐	☐	☐	☐
f. To receive a list of gene changes found through the sequencing of my DNA.	☐	☐	☐	☐
g. To be given a written summary report about my DNA sequencing results.	☐	☐	☐	☐
h. To be told about the gene changes I have that may have implications for my biological relatives' risk of cancer.	☐	☐	☐	☐

5. Listed below are some concerns that research participants might have when they join DNA sequencing studies. Please indicate how much of a concern these are for you.

	Not at all concerned				**Extremely concerned**
a. The DNA sequencing results may **NOT** guide my current cancer treatment care.	1	2	3	4	5
b. The DNA sequencing results could give me information about my risk for other conditions that I may not want to know about.	1	2	3	4	5
c. The DNA sequencing results could give unwanted information about my biological relatives' risk of cancer.	1	2	3	4	5
d. The DNA sequencing results might be confusing or difficult to understand.	1	2	3	4	5
e. The DNA sequencing results might lead my doctor(s) to recommend things that I don't want to do.	1	2	3	4	5
f. The DNA sequencing results might make me worried or anxious.	1	2	3	4	5

6. Now we would like to ask you about the different types of DNA sequencing results that participants, like yourself, can receive from participating in a sequencing study. We do not know at this point whether you will have any of these types of results**.** We would just like to know your opinions about the type of results you could receive in the MI-ONCOSEQ study.

If the MI-ONCOSEQ study found DNA sequencing results **related to my cancer**, such as…

Type of results:	**I would receive these results automatically**	**I would receive these results ONLY if I said I wanted them**	**I would NOT receive these results**	**Not sure**
a. Results that could guide my current cancer treatment.	☐	☐	☐	☐
b. Results that help to explain my cancer but do NOT guide my current cancer treatment.	☐	☐	☐	☐

If the MI-ONCOSEQ study found DNA sequencing results that showed unexpected findings that were **unrelated to my current cancer treatment** but could still have potential impact on my health, such as…

Type of results:	**I would receive these results automatically**	**I would receive these results ONLY if I said I wanted them**	**I would NOT receive these results**	**Not sure**
c. Results that show that I am at an increased risk for a different type of cancer that is **not the focus of my current treatment**.	☐	☐	☐	☐
d. Results that show that I am at an increased risk for non-cancerous conditions that **can be treated effectively** (e.g., diabetes & heart conditions).	☐	☐	☐	☐
e. Results that show that I am at an increased risk for non-cancerous conditions that **cannot be treated effectively** (e.g., Alzheimer's disease).	☐	☐	☐	☐

f. Results that provide information about how I may respond to cancer medication.	☐	☐	☐	☐
g. Results that provide information about how I may respond to non-cancer medications.	☐	☐	☐	☐
h. Results that inform me that I may have a virus (e.g., HIV or HPV).	☐	☐	☐	☐

If the MI-ONCOSEQ study found DNA sequencing results that may have significance for my biological relatives, such as….

(Because you share many of the same genes with these relatives, your results may have implications for their health).

Type of results:	**I would receive these results automatically**	**I would receive these results ONLY if I said I wanted them**	**I would NOT receive these results**	**Not sure**
i. Results that show that I have a gene variant or gene change that is relevant for my relatives' risk of developing **cancer.**	☐	☐	☐	☐
j. Results that show that I have a gene variant or gene change that is relevant for my relatives' risk of developing **non-cancerous conditions.**	☐	☐	☐	☐

7. Now we would like for you to think ahead about the DNA sequencing results you might receive in this study. Please indicate whether you agree or disagree with the following statement.

	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
I believe I would be able to understand what my doctor tells me about my DNA sequencing results.	☐	☐	☐	☐

8. Overall, how would you rate your knowledge of genetics?

I do not know anything about genetics						***I know a great deal about genetics***
0	1	2	3	4	5	6

9. Prior to your participation in the MI-ONCOSEQ study, had you undergone genetic testing?

- ☐ Yes
- ☐ No

9.1 If yes, what kind of genetic testing did you have done?

(Select all that apply)

- ☐ Genetic testing for risk of cancer (such as *BRCA 1/2* testing for breast cancer)
- ☐ Genetic testing for risk of other conditions (such as testing for inherited heart conditions)
- ☐ Genetic testing related to pregnancy (such as prenatal testing)
- ☐ Genetic testing for medication response (such as tests that look for genetic variation linked to differences in how people respond to certain medications)
- ☐ Genetic testing you ordered from a private company that did not require permission from a doctor (such as genetic testing ordered online)
- ☐ Genetic testing as a part of a research study
- ☐ Other: _____

10. Prior to your participation in the MI-ONCOSEQ study, had you ever received genetic counseling?

- ☐ Yes
- ☐ No

10.1 If yes, with whom did you meet? (Select all that apply)

- ☐ Clinical geneticist (genetics doctor)
- ☐ Genetic counselor
- ☐ Oncologist (cancer doctor)
- ☐ Primary care provider
- ☐ Other: _____

11. The following questions ask about your current understanding of gene sequencing and cancer. Please indicate whether the following statements are true or false.

	True	False
a. Sequencing all of a person's cancer genes is a routine test that doctors can order for most people with cancer.	☐	☐
b. A doctor can tell a person their exact chance of developing cancer based on the results from gene sequencing.	☐	☐
c. Cancer gene sequencing may give people information about their chances of developing conditions other than cancer.	☐	☐
d. Even if a person has a gene variant or gene change that affects their risk of a certain type of cancer, they may not develop that cancer.	☐	☐
e. Once a gene variant or gene change is found that affects a person's risk of a cancer, that cancer can always be prevented or cured.	☐	☐
f. A person's health habits, like diet and exercise, can influence their risk of developing cancer.	☐	☐

12. Below is a list of statements that other people with cancer have said are important. Please indicate your response as it applies to the **past week.**

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
a..... feel sad.	0	1	2	3	4
b..... am satisfied with how I am coping with my cancer.	0	1	2	3	4
c..... am losing hope in the fight against my cancer.	0	1	2	3	4
d..... feel nervous.	0	1	2	3	4
e..... worry about dying.	0	1	2	3	4
f. ..... worry that my condition will get worse	0	1	2	3	4

13. Please circle a number between 1 (no distress) to 10 (extreme distress) that best describes how much distress you have had during the **past week**, including today.

No Distress										**Extreme Distress**
0	1	2	3	4	5	6	7	8	9	**10**

14. How often do you have someone (like a family member, friend, hospital/clinic worker or caregiver) help you read hospital materials?

None of the time				All of the time
0	1	2	3	4

15. How often do you have problems learning about medical topics because of difficulty understanding written information?

None of the time				All of the time
0	1	2	3	4

16. How confident are you filling out forms by yourself?

Not at all confident				Extremely confident
0	1	2	3	4

17. What is the highest level of education that you have completed?

- ☐ Grade school (up to grade 8)
- ☐ High school or GED (up to grade 12)
- ☐ Some college, no degree
- ☐ Associate or technical degree
- ☐ Bachelor's degree
- ☐ Master's degree
- ☐ Doctoral degree (e.g., PhD, MD)
- ☐ Don't know

18. How do you describe your ethnicity?

- ☐ American Indian/Native Alaskan
- ☐ Asian
- ☐ Black or African-American
- ☐ Hawaiian or Pacific Islander
- ☐ White
- ☐ Other: _____

Thank you for your participation! This concludes the first study survey. Please return your completed survey in the enclosed pre-paid envelope within 2 weeks.

Your participation was very valuable. The results from this survey will help us learn about patients' opinions on DNA sequencing testing and to improve future research.

We will mail the follow-up survey to you in several weeks.

2) Aim 4 Follow-up Survey

As a research participant in the Personalized Oncology through High-throughput Sequencing: Michigan Oncology Sequencing Center (MI-ONCOSEQ) study, you were offered DNA sequencing related to your cancer. You were also asked to complete two brief surveys. You completed the first survey several weeks ago and we are now asking you to complete the follow-up survey.

The goal of these surveys is to explore cancer patients' outlooks toward the DNA sequencing process. This survey asks about your thoughts, opinions, and experiences now that you have undergone DNA sequencing. This survey should take about 15 minutes to complete. Participation is voluntary

Some of the questions in this survey will ask you about scenarios and genetic test results that are hypothetical (made up), but some may relate to your life. **Your responses to the questions in this survey will not have any impact on the choices you made when you consented to the study or your cancer treatment.** If you have questions or concerns about how these surveys are related to your DNA sequencing results, please contact Lan Q. Le at 734-615-2422 or lqle@umich.edu

We thank you again for your participation. Your answers will help us understand DNA sequencing from the patient's point of view and how it can be used in the medical care of future patients.

1. In this section we would like to learn if any of the following events have occurred as a result of your participation in the MI-ONCOSEQ study. Some of these statements refer to things that happen to most participants in the study, while others describe things that may not happen to any participant. What we want to know is what has happened to YOU.

Please select the response that best matches your experience with the study.

	Yes	No	Not Sure
a. I have learned more information about my cancer.	☐	☐	☐

b. I have been told about clinical drug research studies that I am eligible for.	☐	☐	☐
c. I have been able to enroll in a clinical drug research study.	☐	☐	☐
d. I have had a discussion with my doctor about my DNA sequencing results.	☐	☐	☐
e. I was told about the gene changes that were found and what that means for my future.	☐	☐	☐
f. I was not told about my gene changes because I did not have any.	☐	☐	☐
g. I have obtained a written summary report about my DNA sequencing results.	☐	☐	☐
h. I have been told about the gene changes I have that may have implications for my biological relatives' risk of cancer.	☐	☐	☐

i. Anything else?

_____

_____

_____

Please reflect on the decision that you made to participate in the MI-ONCOSEQ study. Please choose the answers that best match how you feel about your decision to participate in the study.

2. In general, how satisfied are you with your decision to participate in this DNA sequencing study?

Not at all				**Extremely**
☐	☐	☐	☐	☐

3. I would make the same choice to have my DNA sequenced if I had to do it over again.

Strongly Disagree	Disagree	Neither	Agree	Strongly Agree
☐	☐	☐	☐	☐

4. Please circle a number between 1 (no distress) to 10 (extreme distress) that best describes how much distress you have had during the **past week**, including today.

No Distress **Extreme Distress**

0 1 2 3 4 5 6 7 8 9 10

5. Below is a list of statements that other people with cancer have said are important. Please indicate your response as it applies to the **past week.**

	Not at all	A little bit	Some-what	Quite a bit	Very much
a..... feel sad.	0	1	2	3	4
b..... am satisfied with how I am coping with my cancer.	0	1	2	3	4
c..... am losing hope in the fight against my cancer.	0	1	2	3	4
d..... feel nervous.	0	1	2	3	4
e..... worry about dying.	0	1	2	3	4

f. ..... worry that my condition will get worse.	0	1	2	3	4

6. There is an ongoing debate about whether researchers should return DNA sequencing research results to participants, and if so, what type of results should be returned. We are interested in your opinion about **what types of personal DNA sequencing results should be returned to study participants in general**.

In general, research results from DNA sequencing studies should be made available to participants…	**Definitely No**	**Maybe No**	**Maybe Yes**	**Definitely Yes**
a. For medical conditions that **can be** effectively treated (e.g., diabetes and heart conditions).	☐	☐	☐	☐
b. For medical conditions that **cannot be** effectively treated (e.g., Alzheimer's disease).	☐	☐	☐	☐
c. That may affect the participant's decisions about planning a family (e.g., whether they are carrying a genetic mutation for a serious illness like cystic fibrosis that could affect their children).	☐	☐	☐	☐
d. Whether the participant is likely to need higher or lower doses of **cancer medication.**	☐	☐	☐	☐
e. Whether the participant is likely to need higher or lower doses of **non-cancer medication**.	☐	☐	☐	☐

f. That have no medical significance but may tell the participant something of personal interest (e.g., about their ancestry).	☐	☐	☐	☐
g. For all of the available findings from the participant's genes.	☐	☐	☐	☐

7. Now we are interested in your opinion about **what types of personal DNA sequencing results you would want for yourself**.

If it was possible, I would want research results from DNA sequencing studies…	**Definitely No**	**Maybe No**	**Maybe Yes**	**Definitely Yes**
h. For medical conditions that **can be** effectively treated (e.g., diabetes and heart conditions).	☐	☐	☐	☐
i. For medical conditions that **cannot be** effectively treated (e.g., Alzheimer's disease).	☐	☐	☐	☐
j. That may affect my decisions about planning a family (e.g., whether I am carrying a genetic mutation for a serious illness like cystic fibrosis that could affect my children).	☐	☐	☐	☐
k. When it shows that I am likely to need higher or lower doses of **cancer medications**.	☐	☐	☐	☐
l. When it shows that I am likely to need higher or lower doses of **non-cancer medication**.	☐	☐	☐	☐
m. That have no medical significance but may tell me something of personal interest (e.g., about my ancestry).	☐	☐	☐	☐

n. For all of the available findings from my genes.	☐	☐	☐	☐

8. What do you think should happen when DNA sequencing results for research participants have health implications that may affect their biological relatives?

(Please circle all that apply)

a. The results are private to the research participant. They **should not be shared** regardless of the implications to others.

b. The results should be shared by the research participant with the relatives that he/she selects.

c. The results should be shared by the research participant with **all** his/her relatives.

d. The results should be shared by a research study team member directly with the research participant's relatives **BUT only with the research participant's consent.**

e. The results should be shared by a research study team member directly with the research participant's relatives and does **NOT need the research participant's consent.**

f. The results should be sent to the doctor of the relative(s) who may be affected **BUT only with the research participant's consent.**

g. The results should be sent to the doctor of the relative(s) who may be affected and this does **NOT need the research participant's consent.**

h. The results should only be offered to a family member if the family member requests them.

9. Sometimes a research participant dies before the DNA sequencing research results are available. What do you think should happen with this research information?

(Please circle all that apply)

a. The research results should NOT be given to any member of the family.

b. The research results should be offered upon request to any member of the family.

c. The research results should be offered upon request to the spouse or adult child(ren) only.

d. The research results should be published in the medical literature only.

e. Other_____

10. Which of these methods do you think are ACCEPTABLE ways for researchers to return DNA sequencing results to participants?

(Please circle all that apply)

a. Password protected, confidential Internet web site
b. Letter sent by mail
c. Email
d. Phone call
e. Phone call followed by a letter
f. Personal visit with a geneticist or genetics counselor
g. Personal visit with a member of the research team
h. Personal visit with the treating physician
i. Other _____
j. DNA sequencing results should not be returned to participants

11. What is the most PREFERRED way for researchers to return DNA sequencing results?

(Please circle one answer only)

a. Password protected, confidential Internet web site
b. Letter sent by mail
c. Email
d. Phone call
e. Phone call followed by a letter
f. Personal visit with a geneticist or genetics counselor
g. Personal visit with a member of the research team
h. Personal visit with the treating physician
i. Other _____
j. DNA sequencing results should not be returned

12. Since participating in the MI-ONCOSEQ study, have you received your DNA sequencing results?

☐ Yes

☐ No

12.1 If yes, how did you receive your results?

☐ My doctor discussed my results with me
☐ I received a written report of the results from my doctor
☐ I accessed a written report in my medical records
☐ Other: _____

I**f yes, PLEASE CONTINUE TO QUESTION 13**

If no, then STOP HERE.

If you have not received your DNA sequencing results then you do not need to answer the remaining questions. You have completed the survey.

Thank you for your valuable participation. The results from these surveys will help us learn about patients' opinions on DNA sequencing testing and improve future research.

Please return your completed survey in the enclosed pre-paid envelope within 2 weeks.

The following part of the survey asks about your DNA sequencing results.
If you DID NOT receive your DNA sequencing results you do NOT need to answer these questions.

Please think about the DNA sequencing results that you received.

13. Did your DNA sequencing results provide you and your doctor(s) with information that can be used to help select cancer-related treatment(s)?

- ☐ Yes
- ☐ No
- ☐ Not sure

14. Have changes been made to your cancer treatment because of your results?

- ☐ Yes
- ☐ No
- ☐ Not sure

15. Will changes been made to your cancer treatment because of your results?

- ☐ Yes
- ☐ No
- ☐ Not sure

16. Did your DNA sequencing results provide you and your doctor(s) with information that made you eligible for a clinical drug research study?

- ☐ Yes
- ☐ No
- ☐ Not sure

17. Have you tried to join a clinical drug research study because of your results?

- ☐ Yes
- ☐ No
- ☐ Not Applicable

18. Will you seek out a clinical drug research study because of your results?

- ☐ Yes
- ☐ No
- ☐ Not Applicable

19. Did your DNA sequencing results provide you and your doctor(s) with information about your cancer?

- ☐ Yes
- ☐ No
- ☐ Not Sure

20. Did your DNA sequencing results provide you and your doctor(s) with information that identified any of your biological family members of having an increased risk of cancer?

- ☐ Yes
- ☐ No
- ☐ Not Sure

21. Have any of your biological family members sought out medical advice because of your results?

- ☐ Yes
- ☐ No
- ☐ Not Applicable

22. Will any of your biological family members seek out medical advice because of your results?

- ☐ Yes
- ☐ No
- ☐ Not Applicable

23. Please describe any decisions you have made or actions you have taken as a result of receiving your DNA sequencing results.

_____

_____

_____

_____

_____

_____

_____

_____

24. Did you seek out any additional information about your DNA sequencing results?

☐ Yes

☐ No

24.1 **If yes**, have you used any of the following sources to learn more about your results?

(Please check all that apply)

☐ Books, brochures, or pamphlets
☐ Family member or friend
☐ Internet
☐ Magazines
☐ Medical journals
☐ Newspapers
☐ Radio
☐ Telephone hotlines
☐ Television
☐ Social media (such as Facebook)
☐ Other (please specify):_____

25. In general, how valuable were your results?

Not at all				Extremely
☐	☐	☐	☐	☐

26. Please explain why you thought your results were valuable or not.

_____

_____

_____

_____

_____

_____

27. Please indicate how strongly you agree or disagree with each statement.

	Strongly Disagree	Disagree	Agree	Strongly Agree
a. I feel certain that I understand my DNA sequencing results.	☐	☐	☐	☐
b. I am left with many questions and few answers about my DNA sequencing results.	☐	☐	☐	☐

28. Did you discuss your DNA sequencing results with anyone?

☐ Yes

☐ No

28.1 **If yes**, with whom did you discuss your results?

(Please check all that apply)

☐ My cancer doctor (oncologist)
☐ Another doctor besides my cancer doctor (please specify):_____
☐ A genetic counselor
☐ A nurse
☐ My spouse or partner
☐ My child(ren)
☐ Other family member(s)
☐ Friend(s)
☐ Co-worker(s)
☐ Other cancer patient(s)
☐ A support group
☐ Other (please specify):_____

29. Now we would like you to think about your experience with the doctor who discussed your DNA sequencing results with you. How did your doctor act and how did you feel when you received your results?

    Please indicate how strongly you agree or disagree with each of the following statements.

	Strongly Disagree	Disagree	Agree	Strongly Agree	Not Applicable
a. My doctor was able to explain the DNA sequencing results in a way that I could understand.	☐	☐	☐	☐	☐
b. My doctor discussed how my DNA sequencing results might affect my treatment.	☐	☐	☐	☐	☐
c. My doctor encouraged me to ask questions about my results.	☐	☐	☐	☐	☐
d. My doctor encouraged me to express any concerns I had about my results.	☐	☐	☐	☐	☐
e. My doctor made an effort to ensure that I understood my results.	☐	☐	☐	☐	☐

Thank you for your participation! This concludes the final study survey. Please return your completed survey in the enclosed pre-paid envelope within 2 weeks.

Your participation was very valuable. The results from this survey will help us learn about patients' opinions on DNA sequencing testing and to improve future research.

3. Physician Post PMTB survey

You referred this patient to the Michigan Oncology Sequencing Center (MI-ONCOSEQ) study who was recently discussed at Precision Medicine Tumor Board (PMTB). We are interested in learning about how sequencing information generated by this study is being used in clinical care. Once you have read the patient's MI-ONCOSEQ report, please answer the following questions. This brief survey should take you **less than 5 minutes** to complete. We thank you in advance for your time.

1. Did you attend Precision Medicine Tumor Board (PMTB) when this patient was presented?
   - ☐ Yes
   - ☐ No

[If "yes" to Q1]

1a. How useful was PMTB in providing clinically significant information about this patient?
   - ☐ Not at all useful
   - ☐ Somewhat useful
   - ☐ Very useful

[If "no" to Q1]

1b. What was your reasoning for not attending? ***(Select all that apply)***
   - ☐ Scheduling conflict
   - ☐ Did not think it was necessary for this patient
   - ☐ Was not aware of the meeting
   - ☐ Do not find PMTB a good use of my time
   - ☐ Other_____

2. Will you make any changes to this patient's cancer treatment based on PMTB and/or the MI-ONCOSEQ report?
   - ☐ Yes
   - ☐ No
   - ☐ Not sure

[If "yes" to Q2]

2a. What changes will you make? ***(Select all that apply)***

- ☐ Change this patient's current medications
- ☐ Change this patient's chemotherapy regimen
- ☐ Refer this patient to a clinical trial
- ☐ Refer this patient to the cancer genetics clinic
- ☐ Refer this patient to an oncologist of a different subspecialty
- ☐ Other_____

[If "no" or "not sure" to Q2]

2b. What is your reasoning? ***(Select all that apply)***

- ☐ There was not enough evidence or the results were not clinically significant
- ☐ This patient is responding well to his/her current treatment
- ☐ There are no locally available trials offering therapies that target the genomic alteration
- ☐ This patient is deceased*
- ☐ I am no longer in charge of this patient's care
- ☐ Other_____

***[If patient is deceased]**

2c. Would you share the genetic sequencing results (e.g., germline findings) with this patient's family if they requested it?

- ☐ Yes
- ☐ No
- ☐ Not Sure

-------- [If patient is deceased END survey here]---------

3. Will you share the genetic sequencing results with this patient?
   - ☐ Yes
   - ☐ No
   - ☐ Not Sure

[If "no" or "not sure" to Q3]

3a. What is your reasoning? ***(Select all that apply)***

- ☐ There was not enough evidence or the results were not clinically significant
- ☐ Tumor content was too low to yield results
- ☐ The results did not indicate that this patient is eligible for a clinical trial
- ☐ This patient is responding well to his/her current treatment
- ☐ This patient's health status is too poor to consider additional or alternative treatment
- ☐ I am not confident in my ability to accurately explain these results
- ☐ The interpretation of the findings might be different in the future as we learn more about cancer genetics I am no longer in charge of this patient's care
- ☐ Other_____

----------** If no to Q3 then the survey ends after Q3a**----------

[If "yes" to Q3]

3b. What is your reasoning for sharing these results? ***(Select all that apply)***

- ☐ To match this patient with a clinical trial
- ☐ To better inform this patient about his/her cancer

- ☐ To inform this patient about a new treatment option
- ☐ To inform this patient about results that may have health implications for his/her biological relatives
- ☐ This patient has the right to know his/her results
- ☐ This patient has requested to or is expecting to see the results
- ☐ Other_____

[If "yes" to Q3]

3c. How will you communicate these results?

- o Letter sent by mail
- o Email
- o Phone call
- o Clinic visit
- o Other_____

[If "yes" to Q3]

3d. When will you share these results with this patient?

- o Within a week of receiving the MI-ONCOSEQ report
- o At the next scheduled appointment I have with this patient
- o At a new appointment made specifically to discuss the results
- o When this patient's current treatment is no longer effective
- o I have already shared the results with this patient

Other_____

4. <u>Patient Interview Guides Clinic Visit Interview</u>

Starting Question: Tell me about different types of cancer.
What types of cancer do you know about?

___|___ General Information
___ How are cancers classified or put into groups?

___|___ Cancer Treatment Decisions
___ How do doctors decide what treatments to use for people with cancer?
___ Are there different types of cancer treatments?
___ What do doctors mean when they talk about targeted treatment for cancer?

Starting Question #2: Tell me about genomic sequencing of cancer patients.

___|___ Gene Mutations and Genomic Sequencing
- ___ How do gene mutations relate to cancer?
- ___ What is genomic sequencing?
- ___ How does genomic sequencing relate to cancer?
- ___ How might genomic sequencing change cancer treatment decisions?
  - ___ What, if anything, can genomic sequencing tell patients about the possible effectiveness of cancer treatments?
  - ___ What, if anything, can genomic sequencing tell patients about the possible side effects of cancer treatments?

___|___ Expectations and Communications
- ___ Why might a cancer patient like you want to participate in genomic sequencing?
- ___ How can the results from genomic sequencing be used?
- ___ What should patients expect to learn from genomic sequencing?
  NOTE: Ask followup questions (below) immediately if topic is mentioned, ask them at the end of the interview if not previously mentioned)

- ___ Is there anything else that patients might learn from genomic sequencing?
- ___ How likely do you think it is that you will learn something helpful from your genetic sequencing results?
- ___ How might genetic sequencing affect members of a patient's family?
- ___ Is there anything that might be discovered by genomic sequencing you would NOT want to be told about?
- ___ What choices do you have about genomic sequencing?
- ___ What information do you think appears in a patient's electronic medical record after genomic sequencing is done?

(Ask these followups only AFTER the above questions, if not already addressed)
- ___ Can you say more about what patients should expect to learn about their cancer from genomic sequencing?
- ___ Can you say more about what patients should expect to learn about cancer treatments from genomic sequencing?
- ___ Can you say more about what patients should expect to learn about their risk for other diseases from genomic sequencing?
- ___ Can you say more about what patients should expect to learn about their family members' risk of other diseases from genomic sequencing?

Follow-up Interview

Starting Question: Tell me about what has happened to you as a result of participating in this study.

___|___ Understanding
- ___ What does the phrase “genome sequencing” mean to you?
- ___ What is your understanding of why your genome sequencing was done?

___|___ Results and Effects
- ___ What have you learned about your results from your genome sequencing?
  - ___ If nothing/little: Why do you think you have not heard much about your genome sequencing?
- ___ Have you received anything in writing about your results?
- ___ What, if anything, was helpful from your results?
- ___ What, if anything, was NOT helpful from your results?
- ___ Did participating in this genomic sequencing affect your cancer treatment decisions?
- ___ Did your genetic sequencing have any effect on members of your family?

___|___ Alignment with Expectations
- ___ How has participating in this genome sequencing study compared to what you thought it would be like?
  - ___ Are there things you thought were going to happen that did not?
  - ___ Did anything happen that surprised you?
- ___ Is there anything you wish that someone had told you at the start of this study?
- ___ Is there anything that you learned from participating in this genome sequencing study that you now wish you had NOT been told?
- ___ What, if anything, confused you about your participation in this study?

___|___ Messages for other Patients
- ___ What should patients like you expect to learn from genomic sequencing?
- ___ What should patients like you NOT expect to learn?

5. Introductory Email to Physicians

Dear Dr. _____,
You referred a patient to the Michigan Oncology Sequencing Center (MI-ONCOSEQ, HUM#00046018) study who was recently discussed at the Precision Medicine Tumor Board (PMTB) meeting. As part of the research study, we are interested in learning about the process of disclosing genetic sequencing results to cancer patients. Once you have read the patient's MI-ONCOSEQ report, please answer this brief survey regarding the return of their results. You are asked to complete one survey for each patient that you referred. The survey should take you **less than 5 minutes** to complete.
By returning the survey, you are opting-in to having your response collected as part of the study. Your responses will be kept confidential and you may choose to not answer an individual question or skip any questions you want. Participation is completely voluntary and you can also choose to not take part. Refusal to participate will involve no penalty or loss of benefits which you are otherwise entitled. You can also stop participating at any time.
There are no direct benefits to you for completing this survey. However, future research may benefit both physicians and patients by the information we learn.
Although unlikely, there is the potential breach of privacy. To minimize this risk, all data will be kept confidential in password protected files and stored on a secure server. Your name and any other identifiable information will not be listed on the survey. Only a non-identifiable code with be used, and the answers to the survey will be kept separately to protect your privacy.
If you have questions about this survey, you can contact the Co-Investigator, Dr. Scott Roberts, University of Michigan School of Public Health, Department of Health Behavior and Health Education, 1415 Washington Heights SPH I Room 3854, Ann Arbor, MI 48109, (734) 763-7379, jscottr@umich.edu
We thank you in advance for your time.

6. Patient Interview Guides

Phone interview script: Patient interviews (audio recorded)

Hello, this is [insert your name] from the University of Michigan.
May I speak to _____?
Hello Mr/Mrs/Ms _____. I am a member of the MI-ONCOSEQ study team. During your clinic visit you indicated that we could contact you for a phone interview regarding your experiences with the study. Do you have time to speak with me right now?
□Yes
□No

IF YES

Thank you for taking the time to speak with me. This is the [first or second] of two phone interviews that you were selected and asked to take part in. This interview should take approximately 30-60 minutes to complete.
Before we begin, I want to remind you that you gave us permission to record these interviews when you signed the consent form. The recording may be used for the purpose of this research. These recordings will be kept confidential and we will not use your name once the recording begins. You can also ask us to stop the recording at any time during this interview.
Do you still agree to be audio recorded as a subject in this research study? □Yes □No
[Turn on recorder]
[Proceed to interview guide]

IF NO

Is there a better time for us to speak?
□Yes □No □Undecided
Interview Date: ____/____/_____ Time: _____ am pm

AFTER THE COMPLETION OF THE INTERVIEW

Thank you for taking the time to speak with me today.

Phone interview script: Following up on baseline written survey (no audio recording)

Hello, this is [insert your name] from the University of Michigan.
May I speak to _____?
Hello Mr/Mrs/Ms _____. We met [X] days ago at the University of Michigan Cancer Center. I am a member of the MI-ONCOSEQ study team and I am calling to follow up on the survey that was given to you at your clinic visit. Do you have a few minutes to speak with me?

☐Yes [Proceed to section below]
☐No [Proceed to page 3]

IF YES

Thank you for taking the time to speak with me. Have you had a chance to look at the survey?

[If yes] There are two open-ended questions at the beginning of the survey. May I ask you those questions over the phone?
[Proceed to baseline patient expectations and motivation questions below. Write down the patient's answers on the survey or a separate sheet of paper]

[If no] Do you mind turning to page [X] of the survey? There are two open-ended questions at the beginning of the survey. May I ask you those questions over the phone?
[Proceed to baseline patient expectations and motivation questions below. Write down the patient's answers on the surveyor a separate sheet of paper]

Questions:
1. There are many different reasons why people choose to participate in research studies. Can you please tell us in your own words why you are participating in this DNA sequencing study? I am participating because…
2. Research studies are conducted to generate general knowledge. However, participants sometimes hope to gain personal benefits from the study. Can you please tell us in your own words what you are expecting to gain, if anything at all, from this DNA sequencing study? I expect to gain…

[After the completion of the interview]
Thank you for taking the time to speak with me today. We greatly appreciate your participation in the study. Can you please complete the rest of the survey and mail it back to us within 2 weeks? Have a nice day.

IF NO

Is there a better time for us to speak?
☐Yes ☐No ☐Undecided
[If yes] Schedule an appointment for a return call
Interview Date: ____/____/_____ Time: _____ am pm
[If no] Thank you for your time. Can you please complete those questions along with the rest of the survey and mail it back to us within 2 weeks? Have a nice day.

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