

## **I. Clinical Protocol**

### **Personalized Medicine Based on Molecular Profiling of Pediatric and Young Adult Patients with Cancer (HUM00046018)**

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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 both in adults as well as in children 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 pediatric 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, their families and the clinicians. We have already shown the feasibility of such an effort in adults with refractory cancer in a similar pilot study conducted at the University of Michigan comprehensive cancer center.

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## PROTOCOL SUMMARY

<b>Title</b>	<b>Personalized Medicine Based on Molecular Profiling of Patients with Cancer</b>
<b>Objectives</b>	<p>Mechanism to profile the tumors of patients with cancer and create a clinical database for following outcomes to facilitate basic, clinical, and translational research. <b><i>This is a not a therapeutic study and is focused on tissue collection and tumor sequencing.</i></b></p> <ol style="list-style-type: none"> <li>1) To offer tumor sequencing to <b><u>patients with advanced or refractory cancer</u></b>. Patients may undergo routine procedure or tissue biopsy for sequencing in real time. Clinically significant results will be disclosed to patients and their clinicians.</li> <li>2) To facilitate <b><u>basic and translational research</u></b> that includes the correlation of biospecimens with corresponding clinical data, in order to develop and apply biomarkers for personalized medicine.</li> <li>3) To complete <b><u>Pilot phase</u></b> with 20 patients assessing benchmarks for tumor acquisition, time to sequencing results, and identification of informative genes.</li> </ol>
<b>Study Population</b>	Patients with advanced or refractory cancer who are considered eligible for clinical trials based on best medical practices in oncology
<b>Eligibility: Patients with Advanced or Refractory Cancer</b>	<p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1) A histologically or cytologically confirmed diagnosis of cancer</li> <li>2) Patients with any malignancy.</li> <li>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.</li> </ol> <p><b>OR</b></p> <p>Patients must have tumor suitable for biopsy (as assessed by trained specialists in Pediatric Surgery or interventional radiology) AND patients are medically fit to undergo a tissue biopsy or surgical procedure to acquire tumor tissue.</p> <ol style="list-style-type: none"> <li>4) Less than or equal to 25 years of age.</li> <li>5) Procedure-specific signed informed consent prior to initiation of any study-related procedures.</li> <li>6) Women and minorities are included in this protocol.</li> <li>7) Patients with multiple malignancies remain eligible.</li> <li>8) Patients with an inherited cancer syndrome or a medical history suggestive of an inherited cancer syndrome remain eligible.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1) It is the enrolling study physician's discretion to decide if a patient is not fit enough to undergo tissue biopsy.</li> <li>2) Patients who are incarcerated are not eligible to participate.</li> </ol>
<b>Screening:</b>	<p>Screening includes the following:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Complete History and Physical Exam.</li> <li><input type="checkbox"/> Review of medical records including pathology and molecular reports.</li> <li><input type="checkbox"/> <b>Either</b>, 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 <b>OR</b> the participant has had a review of radiological scans to</li> </ul>

	<p>determine if tumor is accessible for biopsy AND patient is considered medically fit to undergo a biopsy.</p> <ul style="list-style-type: none"> <li>□ Labs including: CBC with differential and Platelets, Comprehensive Metabolic panel, LDH, Ferritin, Uric acid, PT, INR, PTT..</li> </ul>
<b>Timeline</b>	<p><u>Genetic counseling:</u></p> <ul style="list-style-type: none"> <li>▪ Eligible participants receive genetic counseling as part of their informed consent.</li> <li>▪ Informed consent includes description of risk of genomic sequencing results, and includes patient preferences for disclosure.</li> </ul> <p><u>Specimens:</u></p> <ul style="list-style-type: none"> <li>▪ Blood, serum, buccal smears, saliva, and urine will be collected and frozen.</li> <li>▪ 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 <b>OR</b> patient will undergo tumor biopsy of an accessible lesion.</li> <li>▪ For patients with blood cell cancers such as leukemia, generally collection of peripheral blood and bone marrow samples will be sufficient.</li> <li>▪ Tumor specimens will be processed and frozen. Tumor specimens or blocks from a prior biopsy or surgery, if available, will be retrieved.</li> </ul> <p><u>Research Analysis:</u></p> <ul style="list-style-type: none"> <li>▪ Biopsies will be assessed for tumor content.</li> <li>▪ DNA and RNA from tumors will be sequenced.</li> <li>▪ After data is analyzed, a report with informative genes will be generated for review by the multi-disciplinary Sequencing Tumor Board.</li> <li>▪ Clinically significant results related to patient's cancer will be disclosed. Results will be validated in a CLIA-certified lab or sent to a CLIA-certified lab if pertinent testing exists.</li> <li>▪ 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.</li> <li>▪ 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.</li> <li>▪ Clinical outcomes are collected annual indefinitely.</li> </ul>
<b>Study size</b>	<ul style="list-style-type: none"> <li>▪ We will enroll 20 patients in the pilot phase to assess objective number three, and subsequently expand the study to enroll 100 patients per year, with annual increments of 35 patients per year.</li> </ul>
<b>Study follow up</b>	<ul style="list-style-type: none"> <li>▪ 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.</li> </ul>

## 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."*

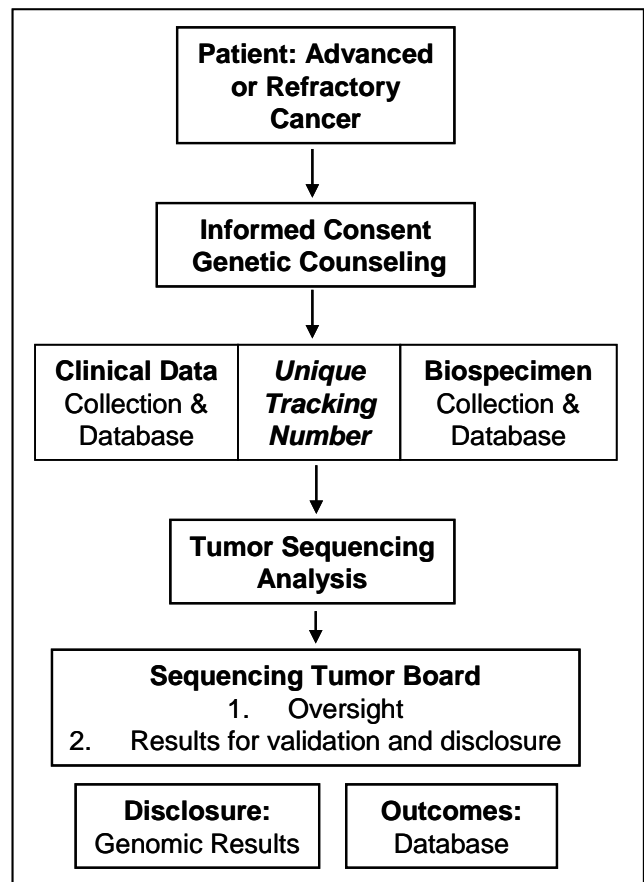
This is clearly evident in the clinical management of cancer where a “one size fits all” approach is not effective. Today, the promise of personalized medicine in cancer is rapidly moving forward and is supported by advances in genomics, proteomics, and metabolomics where cost efficient technologies to analyze DNA, RNA and other cellular components with high-throughput capacity enable thousands of molecular tests per experiment or per patient<sup>1 2</sup>. **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 clinicians.** 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 approach for tumor sequencing is currently not CLIA-approved. Clinical Laboratory Improvement Amendments (CLIA) provides for the standardization of clinical tests. Therefore, clinically significant results will need to be validated through a CLIA-certified lab before disclosure. 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 anticipate obtaining CLIA certification for next generation sequencing of tumors, so that results could be directly utilized.

## 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.

- **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/families may elect to contribute previously collected samples collected under another protocol, provided investigators from another existing



**Figure 1: Study Schema**

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.**
- **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)** 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.**
- We will implement this protocol in a **Pilot phase**, targeting enrollment of 20 patients. There are several challenges to implementing this, including obtaining quality tumor tissue and performing high quality sequencing and analysis in a reasonable period of time. This is further described in section 4 and section 13.
- 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**) 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

### 3.0 Background

Cancer is the second leading cause of death in the United States after heart disease<sup>3</sup>. The most common pediatric cancers in the United States are <sup>3</sup>acute leukemia, brain tumors, lymphoma, neuroblastoma and sarcoma. The most prevalent cancers are heterogeneous and can be characterized by multiple molecular aberrations (e.g. neuroblastoma, sarcoma and leukemia) 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<sup>4</sup>: 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. Gene function-based approaches identified several important signaling pathways strongly affecting tumor progression and treatment resistance in Neuroblastoma. In addition to the Trk family, the PI3K/Akt pathway, Ret, HGF/c-Met pathway and Src family kinases such as Fyn and

Shc family were reported to be closely associated with several prognostic factors and biological characteristics of neuroblastoma cells.<sup>5-8</sup> Because *MYCN* amplification is a strong poor prognostic factor, many researchers have been interested in searching for the genes transcriptionally regulated by the *MYCN* transcription factor to understand the molecular characteristics in tumors with and without *MYCN* amplification<sup>(33,34)</sup>

## **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<sup>9 10</sup>, 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<sup>11 12</sup>. Similarly, integrated genomic profiling has identified potential therapeutic targets in ALL, including aberrant cytokine receptor signaling mediated by rearrangements and mutation of *CRLF2* and *JAK2*.

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

Third, understanding the pharmacology of a drug is essential to delivering efficacious treatment<sup>13</sup>. 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<sup>14</sup>. Further, there are commonly prescribed drugs that influence CYP2D6 activity and could therefore negatively impact tamoxifen efficacy<sup>15-17</sup>. Similarly, There is a close phenotype–genotype relationship with a high risk of myelosuppression in *TPMT* homozygous-deficient ALL patients, accounting for 0.3% of the Caucasian population. Modulation of *TPMT* expression and activity was suggested following the discovery of variable number of tandem repeats in the promoter region of the *TPMT* gene<sup>18</sup>. Interestingly, the variability of 6-MP intracellular metabolism, investigated in only small ALL populations<sup>19 20</sup> was better explained when considering both *ITPA* and *TPMT* polymorphisms. 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<sup>21</sup>. For example, 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<sup>22</sup>. The trial screened 1500 patients to identify and treat 82 patients with ALK-rearranged cancer<sup>23</sup>. Interestingly, ALK may also be relevant in other cancers subtypes such as breast cancer and colorectal cancer (rearrangement)<sup>24</sup>, and neuroblastoma (mutation) where it occurs at a lower frequency<sup>25</sup>. Importantly, the same ALK inhibitor had clinical efficacy for patients with a rare inflammatory myofibroblastic tumor found to have the same ALK rearrangement<sup>26</sup>. This illustrates the importance of an individualized approach to cancer based on common or rare molecular aberrations rather than tissue of origin alone.



Recent studies have identified a number of novel genetic alterations in high-risk, 'BCR-ABL1-like' ALL patients. Ten percent of childhood high-risk ALL cases harbor activating mutations involving the pseudokinase and kinase domains of JAK1 and JAK2<sup>27</sup>. These mutations are transforming in vitro, and result in constitutive Jak-Stat activation of the mouse Ba/F3 hematopoietic cell line expressing the erythropoietin receptor transduced with mutant Jak alleles<sup>27-29</sup>. This transformation is abrogated by pharmacologic JAK1/2 inhibitors, suggesting that these agents may be a useful approach for treating patients harboring these mutations. The presence of JAK mutations is significantly associated with the presence of rearrangements resulting in dysregulated expression of CRLF2, the gene encoding the lymphoid cytokine receptor like factor 2, also known as the thymic stromal lymphopoietin receptor (TSLPR). These rearrangements were initially identified by Russell et al.<sup>30</sup> following screening of ALL cases for immunoglobulin heavy chain (IGH@) rearrangements. Two types of CRLF2 rearrangement have been identified: translocation of CRLF2, located at the pseudoautosomal region 1 (PAR1) of Xp/Yp into the IGH@ locus at 14q32.33, or an interstitial deletion of PAR1 that results in a form of promoter dysregulation, in which the first noncoding exon of P2RY8 is fused to the entire coding region of CRLF2<sup>31 32</sup>. Both rearrangements result in overexpression of CRLF2, which may be conveniently detected by flow cytometric analysis of leukemic cells. CRLF2 rearrangements are present in up to 7% of B-progenitor ALL cases, and are particularly common in ALL associated with Down syndrome (DS-ALL), where they are present in up to 60% of cases<sup>31 33</sup>. In both DS-ALL and non-DS-ALL, approximately half of CRLF2 rearranged cases have concomitant activating JAK mutations, suggesting that the two alterations cooperate in mediating downstream signal transduction and transformation. This is supported by co-immunoprecipitation experiments of CRLF2 and mutant JAK alleles, and the finding that Ba/F3 cells expressing interleukin-7 receptor alpha, the heterodimeric partner of CRLF2, are transformed following transduction with both CRLF2 and mutant alleles, but not by CRLF2 alone. In high-risk ALL, IKZF1 alterations, CRLF2 rearrangement and JAK mutations are frequently found together, and are associated with very poor outcome<sup>34 35</sup>. Consequently, there is great interest in the prospective identification of CRLF2/JAK mutations, and the development of therapies that specifically inhibit this signaling pathway. Together, these results have provided critical new insights into the biologic basis of a previously poorly understood subtype of high-risk ALL, but additional genetic alterations remain to be identified. Almost half of the CRLF2 rearranged cases lack a JAK mutation, and the nature of the cooperating lesions in these cases is unknown. Furthermore, only one-third of 'BCR-ABL1-like' cases harbor these alterations, and it is likely that additional mutations resulting in activation of kinase signaling pathways are present. This is supported by preliminary data from transcriptomic resequencing of 'BCR-ABL1-like' ALL cases using second generation sequencing approaches, which have detected novel rearrangements dysregulating ABL1 (NUP214-ABL1) and JAK2 (STRN3-JAK2) in high-risk B-progenitor ALL<sup>36</sup>.

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.

## Basic Science Research:

1. **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.
2. **Clinical Research: Rajen Mody, MD, MS** is the Clinical Director of Pediatric Oncology and the Principal Investigator (PI) of the Phase I-III of Children's Oncology Group (COG) clinical trials at the University of Michigan. He is also the PI for the pediatric oncology clinical database at the University of Michigan and has over 12 years of experience in conducting clinical trials in pediatric oncology.
3. **Clinical Cancer Genetics: Jeffrey Innis, MD, PhD**, is an expert in clinical cancer genetics and epidemiology.
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<sup>37</sup>. **Scott Kim, MD, PhD** is an Assistant Professor of Psychiatry and Co-Director of the **CBSSM**. Drs. Roberts and Kim 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. Mody, Pediatric 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<sup>38</sup>. 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.

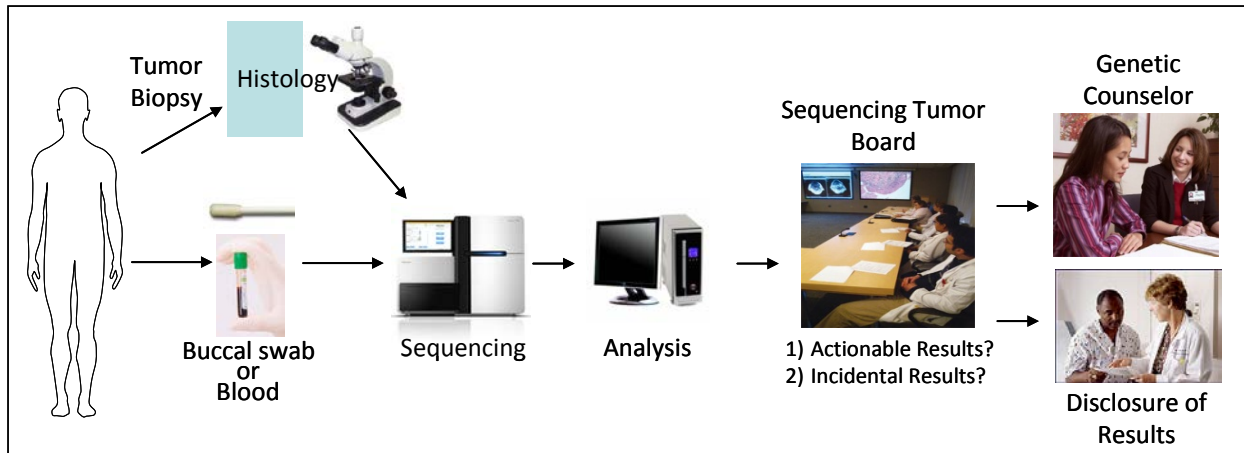
**Our Approach.** Biomarker research based on genomics has rapidly moved forward through the development of high throughput capacity and decreasing costs of nucleic acid sequencing ("next generation" sequencing)<sup>39 40</sup>. The **Michigan Center for Translational Pathology** has developed a pipeline for studying cancer using next generation sequencing of cancer<sup>41-43</sup>. We propose an "**integrative sequencing approach**" utilizing whole exome, transcriptome and 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<sup>44</sup>. In addition, our investigators recently reported the feasibility of such an approach in adults with cancer.<sup>45</sup> Our adult oncology enrolled patients with advanced or refractory cancer on to a pilot study who were eligible for clinical trials. For each patient, we performed whole-genome sequencing of the tumor, targeted whole-exome sequencing of tumor and normal DNA, and transcriptome sequencing (RNA-Seq) of the tumor to identify potentially informative mutations in a clinically relevant time frame of 3 to 4 weeks. Our pilot experience suggests that integrative high-throughput sequencing of patients with advanced cancer generates a comprehensive, individual mutational landscape to facilitate biomarker-driven clinical trials in oncology.

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<sup>46</sup>. They identified the RET oncogene as a novel target that could be treated with existing drugs or a through a clinical trial<sup>46</sup>.

**Sequencing Results.** The deliverable for tumor sequencing will be a genomic research report and basic discovery research. A multi-disciplinary Sequencing Tumor Board will provide oversight for the study and deliberate on sequencing results. For clinically significant sequencing results related to patient's cancer, results will be CLIA-validated through MCTP or other clinical genetic testing lab, and disclosed to patients/families and their referring oncologists. Those who elect to receive incidental findings and/or germ-line mutations, patients/families 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**



**Pilot.** In the first phase of establishing this mechanism for tumor sequencing in real time, the protocol is open to patients with advanced or refractory cancer being evaluated for possible Phase I clinical trials. Typically, patients would be referred to the Pediatric Phase I clinic (Dr. Mody,, Hutchinson, Yanik) or other oncologists, and offered participation in the study. We will assess benchmarks for tumor acquisition, time to sequencing results, and identification of informative genes (**Figure 3**). Further, this platform for tumor sequencing would be an asset to the development of upcoming clinical trials based on biomarkers. As we build and establish this mechanism, we plan to use the preliminary data to seek additional external funding to expand our existing infrastructure for basic and clinical research.

### 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.

- **Example 1: A boy with metastatic, relapsed neuroblastoma.** He undergoes liver biopsy and his tumor is found to have ALK mutation. He could be referred for additional CLIA-testing and potentially be treated with ALK inhibitors under clinical trial in our pediatric oncology unit.
- **Example 2: A little girl presents with rare form of leukemia (Juvenile Myelomonocytic Leukemia, JMML).** She enrolls on the protocol, and her malignant tissue is submitted for tumor sequencing. Basic science research efforts could lead to the development of novel molecular targets and therapies that could be one day helpful for a patient with a similar molecular and histologic diagnosis.

### 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/families 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 Pediatric Phase I Research Program (Rajen Mody).
- 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/families must be consented to this protocol in order to participate.
- Biospecimens are processed and banked through MCTP and MICHR (Arul Chinnaiyan, Ken Pienta).
- 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 someday be offered to all cancer patients/families. 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 initial results of our research studies will be sent to the referring physician. Our research results may find a result that can be confirmed with a clinically validated medical test. This is typically available through a genetic testing lab. These tests typically cost hundreds or thousands of dollars. If the patient and their physician decide to do any type of confirmatory testing, they or their insurance may be charged for the cost of a new sample collection or for laboratory tests to confirm the research results. Specifically, the University of Michigan will not participate in the decision whether to validate the research findings through a commercially available test.

## **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.
- 5) Younger than or equal to 25 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 avoid 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 after 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.
- 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).

- 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.

**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 cancer geneticist and board-certified genetic counselor 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/families will be provided a copy of the consent form for their records and have telephone and pager access to the Clinical Coordinator 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/families 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/families before enrollment<sup>47</sup>. Furthermore, patients/families 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/families. 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'/family 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/families 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**

<b>Disease Domain</b>	<b>Impact/Significance</b>	<b>Default</b>	<b>Decline Results?</b>	<b>Description</b>
<b>Cancer of Interest</b>	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
<b>Conditions other than cancer of interest</b>	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
<b>Other</b>	New/unanticipated issues	Determined by STB on case by case basis		Situations that do not readily fit into above categories; STB 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/families will be given the option to decline certain results<sup>47</sup>. Ultimately, patients/families 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)<sup>48</sup>. Therefore, the default consent is to disclose results to patients/families and clinicians for results related to “**Cancer of interest**”, which we designate as “not flexible,” since it is anticipated that patients/families 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/families 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/families 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 members**” 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.
- 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. Clinically significant results must be CLIA-validated before disclosure.
- 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 information or (2) informing the patient and physician about novel targets or new clinical trials.
- There will be no costs charged to participants/families for study participation.
- There will be no reimbursement to participants/families 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 will target the enrollment of 20 subjects. After the Pilot phase, this will be an open-ended study and there is no set limit to accrual.

### **6.9 Withdrawal from the Study**

Participants/families 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**

For subjects undergoing standard of care therapy, or enrolled in a clinical trial, who have not exhausted all possible therapeutic options, a tumor biopsy for research purposes will be obtained only in conjunction with a biopsy that is being performed for clinical care. For subjects with relapsed or refractory tumors for whom there is no therapeutic option outside of a clinical trial, a tumor biopsy may be performed for research purposes only. 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 through the Pediatric Phase I Research Program and the division of Pediatric Oncology. 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  $-80^{\circ}$  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. Three 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.

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

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

**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 Pediatric Surgery or 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. An H&E slide 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 -80°C 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/families 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/families 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 HIPAA regulations. Biospecimens will be linked to the clinical database with unique identification numbers without identifiers such as names, initials, or birthdates. Separately, the biospecimen database and clinical database will have minimal or no patient identifying information.

## **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<sup>49</sup>. The law protects people from discrimination by health insurers and employers on the basis of genetic information<sup>49</sup>.

## **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 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.

### **9.4 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**

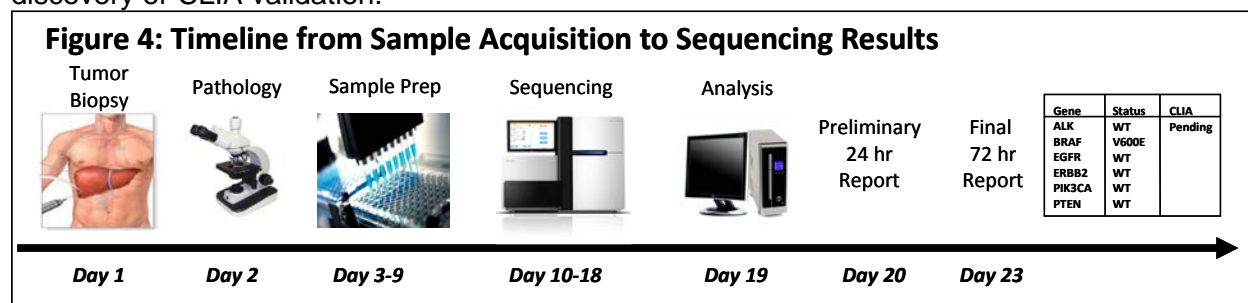
Participant samples and information will be used in diverse types of somatic and germ-line research. The main initiative will be to perform integrative sequencing of tumor specimens (transcriptome, exome, and whole genome sequencing) and a germline tissue control (exome sequencing). Additional studies 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<sup>41 42</sup> or known exons<sup>43</sup>. 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<sup>41 42</sup>. 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<sup>43</sup>. Whole genome sequencing, at 5x

coverage, allows a broad assessment of structural genomic variation. Together, this approach allows 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 transcriptome<sup>42</sup>, whole genome, and exome<sup>43</sup> 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.



**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)** 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 will review sequence results in weekly meetings in the context of each individual patient. 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<sup>50</sup>. There are several additional informative genes utilized in best clinical practices<sup>51 52</sup> and as targets in clinical trials which have been curated to our list. For example, there are over 20 locally available trials involving targeted therapies through UMCCC (Dr. Mody). Last, since nearly half of druggable genes are protein kinases, we have also included a comprehensive list of the human kinome<sup>53 54</sup>.



**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.<sup>55</sup> 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"<sup>50 56-60</sup>. Thus, we anticipate reviewing up to 80-100 mutations per case, but expect only a few variants to be informative or actionable.

**STB: 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 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 will discuss and address any safety or privacy issues that were raised for each patient. STB 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 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<sup>50 56-60</sup>. 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 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<sup>61</sup>, the STB will also review pertinent "negative" or wildtype findings for a Core list of genes (**Appendix 4**). In addition, the STB may also request additional information about the status of genes not reported at the STB 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 for review of these additional findings. Disclosure will depend upon the patient's informed consent selection.

**STB Operations.** The Study Coordinator and PI's will coordinate and manage the STB. 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 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, much like other cancer tumor boards, but this is not a requirement. For each case presented at the STB, 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<sup>51 52</sup>.

The STB 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/families 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<sup>62</sup>. 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 will review any pertinent germline findings and make the same category assignments.

**10.3 Implementation of STB Recommendations.** The Study Coordinator will summarize STB meetings and file these weekly reports, which will be reviewed by the Principal Investigators in monthly meetings. 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 (a cancer geneticist) will be present to disclose the results for them. The STB 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 (a cancer geneticist) 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 Pediatric Genetics Clinics at the University of Michigan, or by other medical geneticists geographically located closer to relevant family members.

**10.4 CLIA Validation.** The STB 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<sup>63</sup> 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<sup>64</sup>. 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 and clinical 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:

- 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](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 and/or Sameek Roychowdhury MD, PhD [Basic science and translational research]
- 2) Dr. Mody MD, Dr. Hutchinson, MD or *ad hoc* academic medical oncologists
- 3) Jeff Innis MD, PhD [Clinical research and genetics]
- 4) Jessica Everett, MS, Victoria Raymond, MS, or Jessica Long, MS [Genetic Counseling]
- 5) Scott Roberts, PhD or Scott Kim MD, PhD [Bioethics]
- 6) Clinical coordinator for the study: TBD
- 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

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

<b>Patient name (Last, MI, First)</b>	<b>Tumor type</b>
<b>Registration#</b>	<b>Date of biopsy</b>
<b>Date of birth</b>	

**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 <sup>1</sup> Gene <sup>n</sup>					

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](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 Institute

<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 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 by 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 wild type 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)?

<b>What GINA does</b>	<b>What GINA does not do</b>
<ul style="list-style-type: none"><li>▪ Prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums</li><li>▪ Prohibits an insurer from requesting or requiring that a person undergo a genetic test</li><li>▪ 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</li><li>▪ Prohibits employers from requesting, requiring, or purchasing genetic information about persons or their family members</li><li>▪ 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;</li><li>▪ remedies for violations include corrective action and monetary penalties</li></ul>	<ul style="list-style-type: none"><li>▪ Does not prevent health care providers from recommending genetic tests to their patients</li><li>▪ Does not mandate coverage for any particular test or treatment</li><li>▪ Does not prohibit medical underwriting based on current health status</li><li>▪ Does not cover life, disability, or long-term-care insurance</li><li>▪ Does not apply to members of the military</li></ul>

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## II. Informed Consent and Assent

# UNIVERSITY OF MICHIGAN

### CONSENT TO BE PART OF A RESEARCH STUDY

#### INFORMATION ABOUT THIS FORM

You, or your child, may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study. Parents or legal guardians, who are giving permission for a child, please note: in the sections that follow the word 'you' refers to 'your child'.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

#### 1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

**1.1 Study title:** Personalized Medicine Based on Molecular Profiling of Patients with Cancer

**1.2 Company or agency sponsoring the study:** None

**1.3 Names, degrees, and affiliations of the researchers conducting the study:**

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