SUMMARY OF CHANGES -- PROTOCOL

NCI Protocol #: 10323
Local Protocol #: Pending
Protocol Version Date: 07/21/2023

Protocol Title: Cancer Moonshot Biobank Research Protocol

I. Comments Requiring a Response (and discussed in the event of a teleconference) – Major Issues:

#	Section	Comments
1.	**Title Page**	Participating Organizations: • The NCTN Groups may not participate on this protocol. Please remove Alliance, ECOG-ACRIN, NRG and SWOG. • The NCORP / NCI Community Oncology Research Program does not exist as a rostered entity by itself and cannot be listed as a participating organization. While the intended participating individual NCORPs do not need to be further restricted to participating sites within each NCORP, the individual NCORPs intended to participate on this trial must be listed as participating organizations. **PI Response:** The NCTN groups are listed on the title page, but language has been provided stating that clinical sites must initiate stand-alone clinical study agreements with Theradex. Agreements with the NCTN groups will not be initiated with Theradex. There is no language about NCTN group participation so as to avoid confusion by participating NCTN sites. NCORP Community Sites and Minority/Underserved Community Sites along with affiliates or sub-affiliates will not be listed on the title page. NCORP affiliates or sub-affiliates are members of the NCTN group(s) and must also initiate a clinical site agreement with Theradex.

II. Recommendations– Administrative & Editorial Issues:

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td>1.</td><td>5.1</td><td>
Please delete the language within this section and replace it with the current CTEP protocol template language.

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.
• Investigator (IVR): MD, DO, or international equivalent,
• Non Physician Investigator (NPIVR): advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),
• Associate Plus (AP): clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
• Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
• Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th><th>AB</th></tr>
<tr><td>FDA Form 1572</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
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</table>

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>GCP training</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✓</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr>
</table>

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

• Addition to a site roster,
• Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
• Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
• Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, for this study, IVRs and NPIVRs must add the IRB number for Advarra, Inc. ((IRB00000971; FWA00023875) on their FDA Form 1572 to enroll a patient.

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

<u>PI Response:</u> This language has been incorporated</td></tr>
<tr><td>2.</td><td>5.1</td><td>It has been brought to our attention that CTEP has revised language around the Investigator and Research Associate Registration with CTEP. The CTSU is in the process of incorporating this and other applicable changes into the next version of the CTSU Support Logistical Language document. While the CTSU staff work on the next iteration of the CTSU Support Logistical Language document, please consider revising this section as indicated below (changes in red and blue).

~~Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually~~. Food and Drug Administration (FDA) regulations require</td></tr>
</table>

#	Section	Comments
		sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. **PI Response:** This language is part of an earlier recommendation, which has been incorporated
3.	5.2 IRB Approval	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** In addition, the Site-Protocol (PI) (i.e., the investigator on the IRB/REB approval) must meet the following ~~four~~ criteria t~~o complete~~ for the site to be able to have an Approved status following processing of the IRB/REB approval record: • ~~Holds~~ Have an active CTEP status; • ~~Active~~ Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster; • Includes the IRB number of the IRB providing approval (Advarra, Inc., IRB00000971; FWA00023875) in the Form FDA 1572 in the RCR profile, and • ~~Holds~~ Have the appropriate CTEP registration type for the protocol. **Additional Requirements** Additional site requirements to obtain an approved site registration status include: • An active Federal Wide Assurance (FWA) number; • An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); • An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and Compliance with all applicable protocol-specific requirements (PSRs). **PI Response:** This language has been incorporated
4.	5.2.1 Downloading Regulatory	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** Log in ~~on~~ to the CTSU members' website (https://www.ctsu.org) ~~using your CTEP-IAM username and password,~~

#	Section	Comments
	Documents	**PI Response:** This language has been incorporated
5.	5.2.2 Specimen Tracking System Training Requirement	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** • The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN, NCTN or NCORP study (either within CLASS, or via the procedure in place prior to CLASS), the training does not need to be completed again. ~~However, new versions of the Specimen Tracking System may require new training.~~ ~~Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time.~~ For questions about the training content or the tracking system itself, please contact STS Support at Theradex (STS.Support@theradex.com, ~~Theradex phone: 609-799-7580~~). **PI Response:** This language has been incorporated
6.	5.3.4 OPEN / IWRS	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** • ~~A valid CTEP-IAM account~~ • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; • To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type. • Have an approved site registration for the protocol prior to patient enrollment. **PI Response:** This language has been incorporated
7.	5.3.5 Special Instructions for Patient Enrollment	**Please revise within this section as shown, to reflect the updated CTEP protocol template language.** • The system is accessed through two Rave user roles: ~~"CRA Specimen Tracking"~~ "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and ~~the Biorepository~~ the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository). Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the ~~Rave/DQP tab.~~ ~~in the Data Management~~

#	Section	Comments
		~~section~~ Rave Home tab and then under Rave Resource Materials. **PI Response:** Part of this language has been incorporated, except for the language about the EET Biobank. The EET Biobank (Columbus, OH) is not utilized for this study. The Biorepository for this study is at Van Andel Institute (Grand Rapids, MI)
8.	7.6.3 Imaging Data	**According to our records 10323 uses TRIAD. Consider adding the following section from the CTEP protocol template, if applicable.** Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred. TRIAD Access Requirements: • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems. • Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR. • TRIAD Site User role on an NCTN, ETCTN, or other relevant roster. All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN. TRIAD Installation: To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/. This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration. For questions, contact TRIAD Technical Support staff via email TRIAD-

#	Section	Comments
		Support@acr.org or 1-703-390-9858. **PI Response:** Based on input from TRIAD staff supporting this study, most of the language has incorporated along with updates to submission address, email, and phone number for this study.
9.	11.2 Data Reporting	**Please revise as shown, to reflect the updated CTEP protocol template language.** Medidata Rave is ~~a~~ the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata: • ~~A valid account, and~~ • Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: • Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; • Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and • Rave Read Only ~~site staff~~ or Rave SLA role must have at a minimum an Associate (A) registration type. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. Upon initial site registration approval for the study in ~~Regulatory Supposrt System (RSS)~~ the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the

#	Section	Comments
		upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. Site staff ~~that~~ who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in ~~RSS~~ the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section ~~at www.ctsu.org/RAVE~~/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response:** This language has been incorporated
10.	11.2.3	**Please delete the language within this section and replace it with the current CTEP protocol template language.** **Data Quality Portal** The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or

#	Section	Comments
		delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website. To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count. **PI Response:** This language has been incorporated

III. Additional Protocol Changes by Principal Investigator:

#	Section	Comments
1.	Title Page	Updated roster of participating organizations.
2.	Title Page	Removed member from Project Oversight that is no longer part of study
3.	Version	Updated protocol version and date.
4.	2.1	Updated primary objective to state that patients may be enrolled at NCTN sites
5.	2.2.2	Qualified secondary objective to "up to 20%" for provision of biospecimens to PDMR.
6.	3.1, 3.2, 4.1.1	Updated eligibility criteria. Eligible melanoma patients include Stage III/IV. Metastatic castration-resistant prostate cancer changed to "metastatic prostate cancer" Provided additional clarification for eligible cancer types previously termed "Gastroesophageal Cancers". Included breast and ovarian cancers to list of eligible cancer types.
7.	3.4	New section describing the rationale for potentially initiating partnerships with existing biobanks or CROs to supplement enrollments, diagnoses, or treatments
8.	4.1.5	Provided clarity on the time frame between blood collection and participant enrollment based on clinical scenarios
9.	4.2.3	Improved language stating the use of certain anti-coagulants is allowed along with anti-platelet medicines. Discontinuation of anti-coagulants is per local site SOP.
10.	Figure 2	Updated Figure 2 to reflect new cancer types
11.	5.1	Updated language about investigator and research associate registration with CTEP
12.	5.2	Updated site registration details
13.	5.2.2	Updated specimen tracking system training requirements
14.	5.3.1	Updated consent and enrollment instructions Updated Figure 3 with current nomenclature for CRAs, the CLIA laboratory, and biomarker assay
15.	5.3.1, 6.3	Removed references to "PPE" portal and changed to "Engagement website"
16.	5.3.2	Updated instructions for using eConsent

#	Section	Comments
17.	5.3.3	Minor update to instructions for the Engagement website
18.	5.3.4	Updated language for OPEN/IWRS requirements
19.	5.3.5	Updated language for roles needed to access Rave.
20.	5.3.6	Clarified instruction to upload diagnostic pathology report into the Histology and Disease CRF in Medidata Rave
21.	6	Added references to NCTN sites in the patient and provider engagement section
22.	Figure 4, Figure 5	Removed second progression collection timepoint from each scenario. Clarified the timepoint when a patient is enrolled per scenario. Clarified when blood specimens are required or to collect if available. Clarified that On-Treatment tissue is not required for any clinical scenario.
23.	7.1, 7.2.3, 7.2.4, 7.3, 7.4, Appendix D	Replaced "normal" terminology with "adjacent non-tumor" to reflect that tissues samples near tumors do not fully represent normal tissue
24.	7.1	Clarified that the most critical collections are tissue and blood at the baseline and progression timepoints. Removed requirement for on-treatment tissue collection, to reduce protocol complexity. Added a qualifier in the clinical scenarios' diagrams for the timing of on-treatment blood collection ("standard of care follow-up visits for radiographic assessment of therapy responses"). Added post-treatment timepoint to allow sites to submit blood samples corresponding to this timepoint. Revised PDMR goal to "up to 20%" of participants.
25.	7.1	Further defined "Progression" as "as documented clinical evidence of increasing tumor burden by investigative analysis such as imaging studies, bone marrow analysis, increasing levels of tumor specific biomarkers etc"
26.	7.2.1	Improved instructions for submitting archival hematological malignancy samples
27.	7.2.3, 7.2.4	Fixed a typographic error to clarify that submissions with only one fresh tumor specimen will not be sequenced. Replaced "Oncomine" with "Biomarker" to indicate the next generation sequencing tests are not termed "Oncomine" Clarified that PDMR samples are only from baseline or progression timepoints

#	Section	Comments
28.	7.2.5	Clarified acceptable hematological malignancy samples and acceptable criteria
29.	7.2.6	Clarified that PDMR samples are only from baseline or progression timepoints. Clarified data submission for the "Social & Environmental Factors" CRF is prior to the patient going off study
30.	7.3	Improved instructions for Rave Specimen Tracking Process Steps to indicate the website to log into and the study to select
31.	7.6.2	Removed reference to Baseline Lesion CRFs
32.	7.6.3	Updated language for accessing TRIAD and TRIAD installation. Updated submission address, email contacts, and phone number
33.	7.6.5	Changed required interval for completing Follow-Up CRF to 6 months
34.	8.0; 8.3	For participant deaths, while on study, that are attributed to progressive disease (or not otherwise specified), sites are no longer required to submit adverse event information to CTEP-AERS
35.	9.1	Changed "endpoints 3-6" to "endpoints 2.2.3-2.2.6"
36.	9.2; Appendix J	Changed "Not reported or Unknown" to "Some Other Race" in accrual tables to accurately reflect how the 2020 Census is tabulated. Patients registered at enrollment in OPEN under "Not Reported" or "Unknown" will be tabulated as "Some Other Race."
37.	10.0	Clarified that the most critical collections are tissue and blood at the baseline and progression timepoints. Removed data requirements under Medical History.
38.	11.2	Updated requirements for accessing Rave
39.	11.2.3	Updated Data Quality Portal language to indicate this study does not use the Rave Calendaring functionality
40.	11.3	Updated the time frame for submission to public repositories from one month to three months. Added link to CMB study in dbGaP
41.	12.4	Added instruction when a patient withdraws from the study the BSS site staff need to complete the Off Study form in Rave
42.	Appendix A	Updated list of therapies granted regular (not accelerated) approval by FDA (as of 07/21/2023); included breast and ovarian cancers
43.	Appendix B	Updated Figure to include new cancer types
44.	Appendix C	Updated abbreviations

#	Section	Comments
45.	Appendix D	Updated list of acceptable archival specimens for hematological malignancies Addition of acceptable specimens for Post Treatment timepoint Clarified that the most critical collections are tissue and blood at the baseline and progression timepoints.
46.	Appendix F	Updated list of NMAv2 fusion genes
47.	Appendix H	Added in abbreviations for dMMR and MSI-H for PDMR exclusion criteria

NCI Protocol #: 10323

ClinicalTrials.gov Identifier: NCT04314401

TITLE: Cancer Moonshot[SM] Biobank Research Protocol

Corresponding Organization: Division of Cancer Treatment and Diagnosis (DCTD)
National Cancer Institute (NCI)

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Participating Organizations:

Alliance /Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
NRG / NRG Oncology
SWOG / SWOG Cancer Research Network
COG / Children's Oncology Group

Individual NCTN member sites, NCORP Community Sites, NCORP Minority/Underserved Community Sites, and affiliates/sub-affiliates are required to abide by all Protocol Specific Requirements (e.g. initiate a clinical study agreement with Theradex, utilize Advarra IRB).

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Lokesh Agrawal, PhD
Ping Guan, PhD
Abhi Rao, PhD
Veena Gopalakrishnan, PhD
Sean McDermott, PhD

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: R11 / Version 8.1 / July 21, 2023

TABLE OF CONTENTS

1. The Cancer Moonshot[SM] Biobank workflow outline

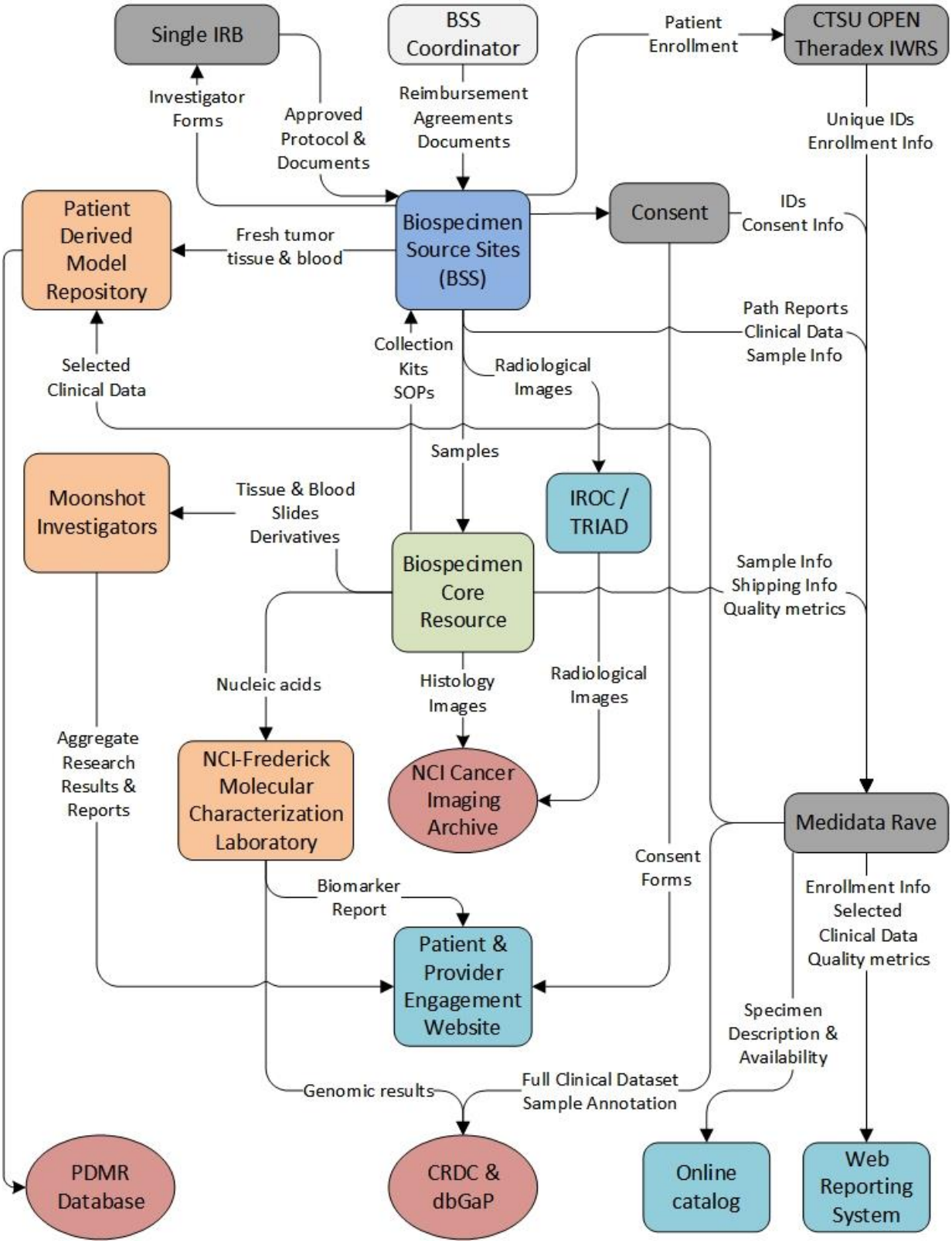


Figure 1. Cancer Moonshot[SM] Biobank Workflow Outline

Eligible study participants are identified, consented and enrolled at Biospecimen Source Sites (BSS) through patient and provider engagement activities. Biospecimens are procured at different timepoints during the course of cancer diagnosis and treatment. Clinical, radiology and pathology report data and biospecimen data are captured using case report forms (CRFs) and entered into Medidata Rave. Biospecimens are shipped either to the Biospecimen Core Resource (BCR) for processing and storage or directly to the Patient Derived Models (PDM) laboratory. Some tissue biospecimens are processed and analyzed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories with return of test results to providers for patient management. De-identified research data is deposited into the Cancer Research Data Commons (CRDC), The Cancer Imaging Archive (TCIA), the database of Genotypes and Phenotypes (dbGaP) and other potential NCI databases.

2. OBJECTIVES

2.1 Primary Objectives

2.1.1 To support current and future investigations into drug resistance and sensitivity and other NCI-sponsored cancer research initiatives through the procurement and distribution of multiple longitudinal biospecimens and associated data from a diverse group of cancer patients who are undergoing standard of care treatment at NCI Community Oncology Research Program (NCORP) sites and other NCTN sites.

2.2 Secondary Objectives

2.2.1 To provide a service of value to study participants and their medical providers through the performance of molecular profiling assays on tumor samples in a CLIA-certified laboratory and reporting of results to physicians and patients that they may opt to use in clinical management, including analysis of data for acquired resistance mechanisms.

2.2.2 To enable the development of patient-derived models such as cell lines and xenografts for cancer researchers through the provision of biospecimens from up to 20% of study participants to the NCI's Patient Derived Models Repository (PDMR), a national resource available to investigators (https://pdmr.cancer.gov/).

2.2.3 To develop and implement robust approaches in patient and provider engagement to improve understanding of biobanking and its relationship to cancer research and increase representation of minority and underserved study participants in cancer research. We define underserved populations in this protocol as populations that may encounter barriers to health care access, and who may experience disparities due to economic, cultural, and/or linguistic factors. These may include persons for whom English is a second language, persons with disabilities, rural populations, the elderly, racial and ethnic minorities, and more.

2.2.4 To develop increased capabilities in U.S. community hospitals and clinics for contribution to cancer research through biobanking activities.

2.2.5 To enable secondary research generated from the project through deposition of data in public repositories such as CRDC, TCIA, dbGaP and other potential NCI databases, including clinical, radiology and pathology data with an emphasis on treatment response and outcome data.

2.2.6 To provide residual biospecimens and associated data from the project to the cancer research community.

3. BACKGROUND

3.1 Purpose of Study

The Cancer Moonshot[SM] Biobank (CMB) aims to develop a national, networked biospecimen infrastructure that will serve the scientific needs of research projects including those funded by the NCI Cancer Moonshot Program. The CMB will deliver to investigators biospecimens and associated data from at least 1000 patients with locally advanced or metastatic solid tumors and hematologic malignancies undergoing standard of care therapy who represent the demographic diversity of the U.S. (Appendix A; Section 9.2). The study was initially designed to collect biospecimens to address the scientific requirements of the Cancer Moonshot-funded NCI Drug Resistance and Sensitivity Network (DRSN; https://nciphub.org/groups/drsn). The study now adds breast and ovarian cancer and plans to include up to 100-200 patients each with colorectal cancer (CRC), lung cancer (LCA), prostate cancer (PCA), gastroesophageal cancer (GEC), melanoma (MEL), breast cancer (BRCA), ovarian cancer (OV), acute myeloid leukemia (AML) and multiple myeloma (MML). DRSN investigators are working to learn more about specific molecular features of these cancers and to understand if there are molecular features within a particular cancer type or across cancer types that predict response or resistance to particular therapies. Future phases of CMB may include additional cancer types such as acute lymphoblastic leukemia (ALL), sarcoma (SARC), head and neck squamous cell carcinoma (HNSC), and central nervous system (CNS) origin. A broad range of biospecimens, primarily tissue and blood, will be collected from study participants at multiple longitudinal timepoints, with an emphasis on pre- and post-systemic therapy. Patients who consent to donate newly collected, non-archival biospecimens will have tumor tissue sent at baseline and/or disease progression (if applicable) to a CLIA-certified molecular profiling laboratory for test results that may help guide their care. Careful study site selection as well as patient and provider engagement strategies will be employed to enable participation from historically under-represented segments of the U.S. population. In general, the objective is to obtain formalin fixed tumor tissue for clinical next-generation sequencing (NGS) tumor testing as well as fresh frozen tumor tissue and blood for banking and distribution to researchers at two timepoints. Ideally, formalin fixed and fresh frozen tumor tissue as well as blood will be collected at baseline, on treatment and progression (Section 7.1). Archival formalin fixed and paraffin embedded (FFPE) tissue will also be accepted, provided that the tissue was collected within 5 years prior to initiation of one of the standard of care therapies listed in Appendix A, and that no more than 1 line of standard of care systemic therapy was administered from the date of archival material collection to the date of initiation of Appendix A therapy (Eligibility Criteria; Section 4.1).

3.2 Study Diseases

Cancer types include colorectal cancer (CRC, Stage IV), non-small cell or small cell lung cancer (LCA, Stage III/IV), prostate cancer (PCA, metastatic), gastroesophageal cancer (GEC) [to include gastric cancer NOS (Stage IV), esophageal cancer NOS (Stage IV), and adenocarcinoma of the gastroesophageal junction (Stage IV)], melanoma (MEL, Stage III/IV), invasive breast carcinoma (BRCA, Stage III/IV), high grade serous ovarian cancer (OV, Stage III/IV) [to include fallopian tube carcinoma, ovarian epithelial cancer, and primary peritoneal carcinoma], acute myeloid leukemia (AML), and multiple myeloma (MML). Patients should be undergoing

treatment for these cancer types with the commercially available therapies listed in Appendix A. Appendix A therapies may be administered as a singular/monotherapy or in combination with any other therapies that constitute an FDA-approved treatment regimen. Patients who are treated with other standard of care molecularly targeted therapies or immunotherapies per National Comprehensive Cancer Network (NCCN) guidelines are also of interest. After enrollment, patients may transition to a different standard of care therapy and remain in the study. Patients with mismatch repair deficient (dMMR) and/or microsatellite instability-high (MSI-H) CRC and small cell LCA are of particular interest for provision of fresh tissue samples to the PDMR.

3.3 Molecular Profiling Assay and Results Return

The Ion Torrent Oncomine Comprehensive Assay (OCA) and NCI-Myeloid Assay (NMA), NGS tumor tests, will be performed at the Frederick National Laboratory for Cancer Research (FNLCR) Molecular Characterization Laboratory (Appendices E and F). These tests are referred to as "Biomarker Tests" in communications for this study, based on current community consensus (https://www.commoncancertestingterms.org/). A report detailing a list of clinically relevant genomic alterations, narrative description of each genomic alteration and lists of standard of care therapies and clinical trials for each genomic alteration will be provided to medical providers and patients. Tumor NGS tests may be executed at one or two timepoints per patient, including at baseline and/or upon progression. Incidental findings will be reported to the provider (Reporting of Incidental/Secondary Findings; section 7.5.2; Appendix G). If insufficient tumor is obtained, repeat biopsies will not be performed for the sole purpose of performing these molecular profiling assays. Freshly obtained tissue that is collected on site in CMB-provided vials and processed at the Biospecimen Core Resource (BCR) will be used for clinical biomarker testing; archival material will not be used for clinical biomarker testing.

3.4 Partnership with Existing Biobanks and Contract Research Organizations

The Cancer Moonshot Biobank recognizes that a partnership with existing biobanks and contract research organizations (CRO) may be needed to supplement enrollments, biospecimens, specific cancer diagnoses, or treatments. Of particular interest for this initiative would be existing biobanks and CROs that have a long-term specific interest in a particular malignancy along with ongoing interactions with patients, health care providers and researchers in these diseases. Such partnerships will bring together separately funded and operated resources under a common program to facilitate Cancer Moonshot Biobank research. Federally funded biobanks as well as biobanks operated by non-profit or for-profit entities and medical institutions in the U.S. could be asked to participate in the Cancer Moonshot Biobank. NCI and Leidos Biomed will work to define and execute such partnerships. Existing Biobanks must meet the requirements set forth for the NCORP and NCTN sites, including but not limited to:

- intentional, broad consent of research participants to meet requirements of the NIH Genomic Data Sharing Policy
- agreement to participate in a single, central IRB review of research proposals for biospecimen utilization
- adequate and descriptive biospecimen collection data
- treatment, outcome, and other relevant clinical data

4. PATIENT SELECTION

4.1 Eligibility Criteria

4.1.1 Clinical presentation:

Is consistent with OR has been diagnosed with one of the following:

- Colorectal cancer: Stage IV
- Non-small cell or small cell lung cancer: Stage III/IV
- Prostate cancer: metastatic prostate cancer
- Gastric cancer, NOS: Stage IV
- Esophageal cancer, NOS: Stage IV
- Adenocarcinoma of gastroesophageal junction: Stage IV
- High Grade Serous ovarian cancer: Stage III/IV
- Invasive breast carcinoma: Stage III/IV
- Melanoma: Stage III/IV
- Acute myeloid leukemia
- Multiple myeloma

For the purposes of this study, re-staging is allowed.

4.1.2 Clinical enrollment scenarios:

Patient should fit in **one** of the following four clinical scenarios (a-d). Please refer to Appendix A regarding molecularly targeted therapy or immunotherapy that may be administered as a single/monotherapy or in combination with any other therapies that constitute FDA-approved treatment.

a. Undergoing diagnostic workup for one of the diseases listed in 4.1.1 for which **treatment will likely include** a new regimen of standard of care therapy indicated in Appendix A.

OR

b. **Scheduled to begin treatment with** a new regimen of standard of care therapy indicated in Appendix A.

OR

c. **Currently progressing on** a regimen of standard of care therapy indicated in Appendix A.

OR

d. **Currently being treated with** a regimen standard of care therapy indicated in Appendix A, without evidence of progression.

4.1.3 Requirements for fresh tissue biospecimen collections at enrollment:

For **clinical scenarios a, b, and c** above (4.1.2), **freshly collected tumor tissue or bone marrow (BM) aspirate** must be submitted at enrollment.

- For **clinical scenarios a and b**, the fresh tissue collection **must be prior to starting an Appendix A therapy**.

- For **clinical scenario a,** the biospecimen collection ***must be part of a standard of care*** medical procedure.

- For **clinical scenarios b or c,** the biospecimen collection ***may be part of a standard of care*** medical procedure

OR

The biospecimen collection ***may be part of a study-specific procedure*** ("research only biopsy"), when the patient has a tumor amenable to image guided or direct vision biopsy and is willing and able to undergo a tumor biopsy for molecular profiling (https://www.ncbi.nlm.nih.gov/pubmed/?term=30285529).

Note: For research-only biopsies, the biopsy must not be associated with a significant risk of severe or major complications or death; the procedure cannot be a mediastinal, laparoscopic, open or endoscopic biopsy; nor can the procedure be a brain biopsy; nor can the patient be under the age of majority as determined by each U.S. state.

4.1.4 Requirements for archival tissue:

For **clinical scenarios a and b** above (4.1.2), archival tissue as outlined below must be submitted IF AVAILABLE.

For **clinical scenarios c and d** above (4.1.2), archival tissue as outlined below is REQUIRED.

Pre-existing archival material (FFPE block, BM aspirate, or unstained slides) that:

i. Contains the cancer type for which the participant is enrolled, and
ii. Was collected no more than 5 years prior to initiation of a therapy listed in Appendix A, and
iii. Contains at least a surface area of 5 mm^2 and optimum surface area of 25 mm^2
or
3-5mL cryopreserved bone marrow aspirate to yield 200 million bone marrow mononuclear cells, and
iv. No more than 1 line of standard of care systemic therapy was administered from the

date of archival material collection to the date of initiation of Appendix A therapy.

4.1.5 Requirements for blood collection:

ALL scenarios require fresh blood collection at enrollment.

Blood collection for clinical scenarios a, b, and c must take place **within 1 week of fresh tumor specimen collection**.

Blood collection for clinical scenario d must take place **within 4 weeks of enrollment**.

4.1.6 Age 13 or older

4.1.7 Any sex and any gender.

4.1.8 ECOG Performance Status (PS) of 0, 1, or 2.

4.1.9 Ability to understand and willingness to sign an informed consent document. Consent may be provided by a Legally Authorized Representative (LAR) in accordance with 45 CFR 46.102(i).

4.2 Exclusion Criteria

4.2.1 Treated with or has already begun treatment with a non-standard of care therapeutic agent (investigational) in an interventional clinical trial.

4.2.2 Uncontrolled intercurrent illness that in the physician's assessment would pose undue risk for biopsy.

4.2.3 Use of full dose coumarin-derivative anticoagulants such as warfarin are prohibited. Patients may be switched to LMW heparin at physician discretion.

- Low molecular weight (LMW) heparin is permitted for prophylactic or therapeutic use.
- Factor X inhibitors are permitted.
- Use of anti-platelet drugs are permitted .

Stopping the anticoagulation for biopsy, bone marrow aspirate, or resection should be per site SOP.

A diagram describing enrollment scenarios is provided in **Figure 2** below and in Appendix B.

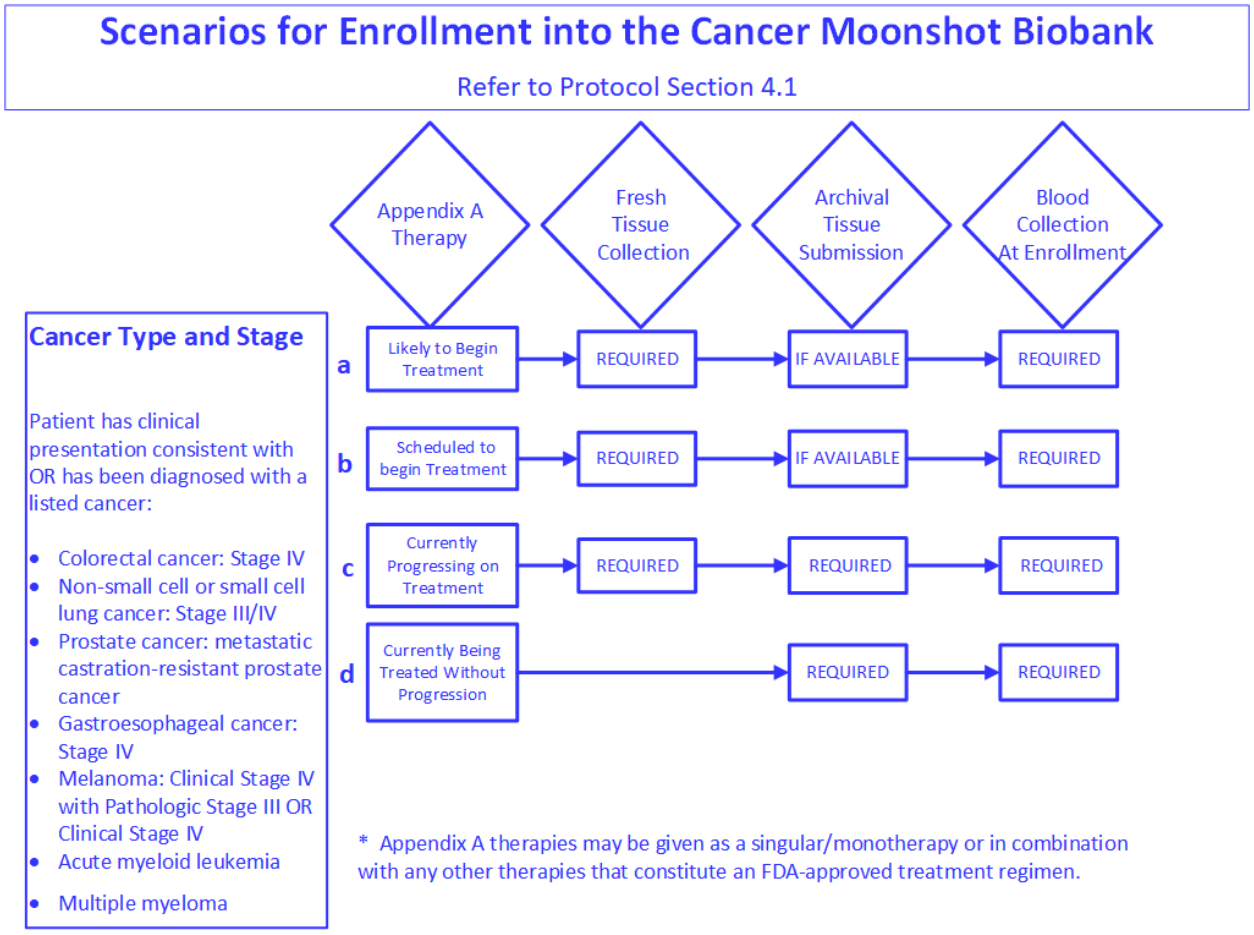


Figure 2. Diagram describing enrollment scenarios.

4.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

5. REGISTRATION PROCEDURES

All participating sites must open and maintain an approved regulatory status for this study. Sites will not be able to enroll patients if this study is not active at their site.

5.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR): MD, DO, or international equivalent,
- Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following :

- Addition to a site roster,
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL)
- In addition, for this study, IVRs and NPIVRs must add the IRB number for Advarra, Inc. ((IRB00000971; FWA00023875) on their FDA Form 1572 to enroll a patient.

In addition, for this study, IVRs and NPIVRs must add the IRB number for Advarra, Inc. ((IRB00000971; FWA00023875) on their FDA Form 1572 to enroll a patient.

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

5.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Since the CMB is a multi-site study, all sites must accept central IRB review. Advarra, Inc is the IRB (IRB00000971; FWA00023875) of record for the CMB. Advarra, Inc. will provide an Authorization Agreement and/or Oversight Waiver for each site prior to IRB review. All participating Investigators must add the IRB number for Advarra, Inc. on their FDA Form 1572 in their RCR profile if they plan to enroll patients.

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- Includes the IRB number of the IRB providing approval (Advarra, Inc., IRB00000971; FWA00023875) in the Form FDA 1572 in the RCR profile, and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization,
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and

Compliance with all applicable protocol-specific requirements (PSRs).

5.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org),
- Click on *Protocols* in the upper left of your screen,
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select DCTD, and protocol number 10323,
- Click on *Documents, Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided.

5.2.2 Protocol-Specific Requirements For 10323 Site Registration:

- IRB approval (All sites must have a documented approval letter from the IRB and IRB-signed CTSU IRB Certification Form).

- IRB-approved informed consent documents.

- eConsent Requirement:
  - All sites planning to consent patients must complete a one-time only training about the specific Medidata eConsent application and its use in CMB (Section 5.3.1) which is administered via the Compliance, Learning, and SOP Solutions (CLASS) system.
  - Training attendance will be monitored by CMB study staff through the CLASS system. For each site, at least one CRA or Site-Protocol PI must complete the training. *There is no need to submit a training completion certificate to the CTSU through the Regulatory Submission Portal.*
  - For questions about the training content, please contact CMB study staff at MoonshotBiobank@nih.gov.

- Clinical Site Agreement (CSA) Requirement:

- All sites must have executed a CSA with Theradex; attestation of the signed CSA will be communicated from Theradex to CMB study staff.

- Specimen Tracking System Training Requirement:
  - All site staff planning to do data entry in Rave for 10323 (i.e., Rave CRA or Rave CRA (LabAdmin) role) must complete the online specimen tracking training, which is administered via the Compliance, Learning, and SOP Solutions (CLASS) system.
  - Completion of this training is required for individual Rave CRAs/Rave CRA (LabAdmins) to receive Rave invitations for the study, i.e., to be able to access the study in Rave and enter data/manage specimen tracking.
  - A Rave CRA/Rave CRA (LabAdmin) at a site that receives site registration approval for 10323 (or is added to the site roster after it has received approval) will receive an automated email from CLASSHelpDesk@westat.com with the training assignment and instructions for accessing CLASS.
  - Completion of the training will be automatically communicated to the Regulatory Support System (RSS) and to Medidata Rave, and the individual will receive an invitation to 10323 in Rave. *There is no need to submit a training completion certificate to the CTSU through the Regulatory Submission Portal.*
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN, NCTN or NCORP study (either within CLASS, or via the procedure in place prior to CLASS), the training does not need to be completed again.

  For questions about the training content or the tracking system itself, please contact STS Support at Theradex (STS.Support@theradex.com).

  For questions or concerns about accessing the training in CLASS, please contact the CLASS Help Desk CLASSHelpDesk@westat.com.

5.2.3 Submitting Regulatory Documents

The CMB study staff will submit all required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

5.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration,* and
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

5.3 Patient Registration

5.3.1 Consent and Enrollment Requirements

Initial enrollment of a study participant will be conducted only when the patient fits the eligibility requirements of this protocol and informed consent has been obtained, which must be documented before any biospecimens may be admitted to CMB and subsequently used in research studies (Patient Consent; Section 12). Informed consent will be administered using electronic consent or paper consent. Paper consent will always be utilized for minor participants and may be utilized for adults when eConsent is not available, when an adult participant does not read English or Spanish in the provided eConsent, or for other reasons. Paper consent will be provided in multiple languages as requested by site staff.

Remote informed consent will be allowed for the study in line with the NCI Central IRB (CIRB) FAQ, "Frequently Asked Questions Regarding Remote Consent Procedures," at this website: https://www.ncicirb.org/content/frequently-asked-questions-regarding-remote-consent-procedures. See https://www.ncicirb.org/content/nci-cirb-information-about-covid-19 for more information. This may be used in order to limit contact and promote social distancing in response to COVID-19 containment measures. Before using these Remote Consent Procedures, sites must update their Study Specific Worksheet (SSW) or the Signatory Institution Worksheet (SIW) with the CIRB to state Remote Consent Procedures are used at their site.

For study participants utilizing electronic consent, Medidata eConsent is integrated with Medidata Rave and the steps below should be followed. Medidata eConsent will only be available for eligible adult participants. Medidata eConsent meets 21 CFR Part 11 requirements for electronic records and signatures.

1. The provider and/or coordinator will facilitate the consent process with study participants on a tablet using the Medidata eConsent application. Providers/coordinators will start the eConsent process by clicking on "+ Add Participant" and selecting the language (English or Spanish). The iPad will be transferred to the participant to begin the informed consent process.
2. Study participants will watch a video, completely read the informed consent form(s), and be able to flag sections in the informed consent document and/or HIPAA document and/or California Bill of Rights for which they require clarification.
3. Participants will need to complete a Knowledge Review section of five questions to gauge understanding of the study and informed consent form.
4. If the participant has flagged part(s) of the informed consent documents, the provider will review all flagged sections with the participant and resolve concerns. The participant will clear all the flags.
5. The participant will enter their name, gender (Male/Female), and date of birth. The participant or Legally Authorized Representative (LAR) will sign the informed consent form. If the LAR signs the form, the name and relationship to the participant is entered.
6. The participant will hand the tablet to the provider/coordinator who will log into the eConsent application.
7. If the participant cannot read, a Witness may sign the informed consent document(s) stating the document(s) have been read to the participant by study staff, discussed with the study staff, and the participant has been given an opportunity to ask questions. The Witness will enter their name prior to signature.
8. The provider/coordinator will countersign all informed consent document(s) using electronic signature through the Medidata eConsent application.
9. The provider will enter the eConsent Subject ID and consent date into the (Prerequisite) OPEN form and complete the registration form.
10. Once registered, the provider will complete study participant account creation in the Patient and Provider Engagement website by using the Patient ID generated by OPEN and entering the name and email address of the study participant.
11. The provider will download the PDF consent form from the e10323 eConsent dashboard and upload the consent document(s) to the study participant's account in the Engagement website.
12. The provider will provide a signed consent form to the study participant.
13. The Engagement website will automatically send an email to the study participant to activate their account.
14. Note that when the participant does not have an email address, the participant account cannot be created in the Engagement website, the consent document cannot be uploaded, and the Engagement website cannot send an email to the study participant.

For study participants not utilizing electronic consent, the steps below should be followed.

1. The provider will provide the participant with the paper consent document, either actual paper, or a PDF version of the document.
2. The participant will read the document and discuss any issue or concerns with the provider, either in person, or remotely by phone, email or other means of communication.
3. The participant will give back the signed document either in person, by mail, by secure email, or a secure application, etc.
4. The provider will countersign the document.
5. The provider will store the signed consent form document in accordance with the institutional practices; an electronic PDF version will be needed for step 8.
6. The provider will enter the consent information, such as indicating the patient was not e-consented, consent date, and informed consent version in the (Prerequisite) OPEN form and complete the registration form.
7. Once registered, the provider will complete study participant account creation in the Engagement website by using the Patient ID generated by OPEN and entering the name and email address of the study participant.
8. The provider will retrieve the PDF(s) stored in step 5 and upload the consent document(s) to the study participant's account in the Engagement website.
9. The Engagement website will automatically send an email to the study participant to activate their account.
10. Note that when the participant does not have an email address, the participant account cannot be created, the consent document cannot be uploaded, and the Engagement website cannot send an email to the study participant.

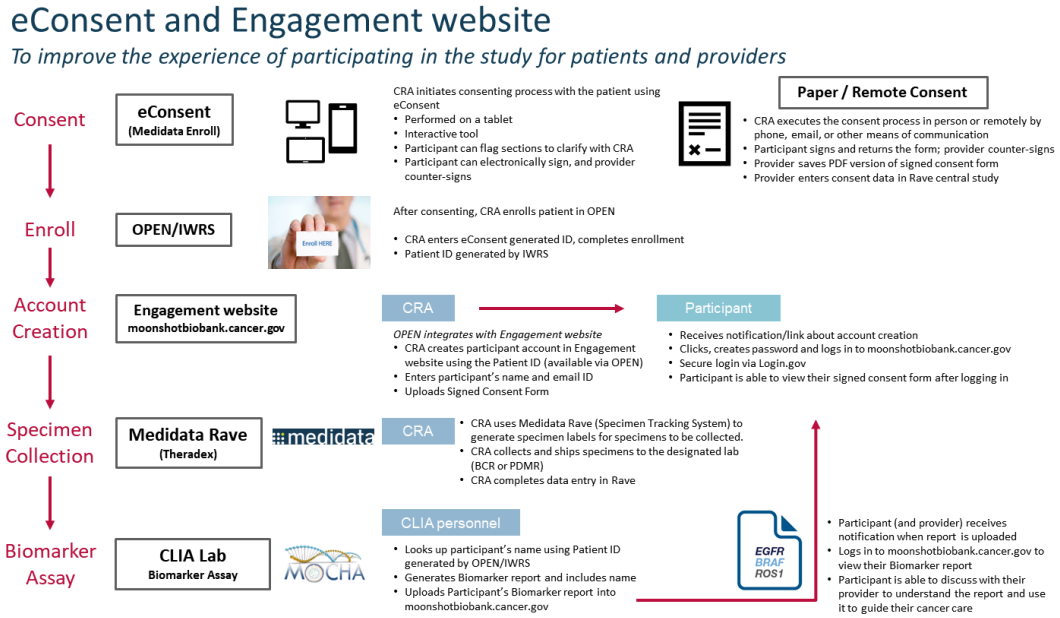


Figure 3. Consent and Enrollment Steps for Clinical Research Associates (CRAs).

5.3.2 Medidata Rave eConsent

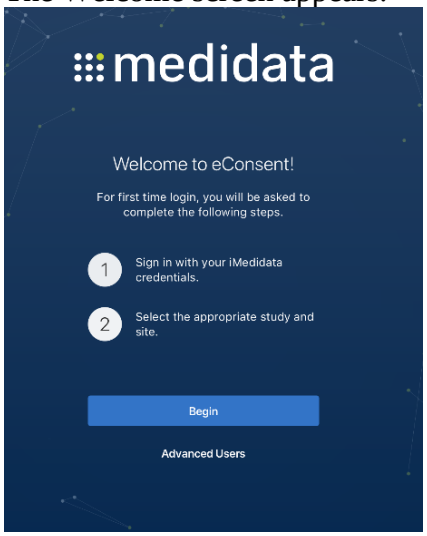
CMB will use the Medidata Rave eConsent application for eligible study participants. iPad tablets will be provisioned by INODE Ink, Inc and serviced by C3i Solutions. C3i will configure and remotely manage iPads, including rapid turnaround on replacement devices. Remote management and site support will be provided by VMWare AirWatch Enterprise Mobility Management software installed on each device, allowing for discrete controls on device usage, geolocation of lost devices, and remote lock-down, device erase and data utilization.

Devices will be under manufacturer's warranty and C3i will provide a full-service helpdesk 24/7/365 in 9 languages to support sites with any questions or problems with the devices. Devices with defects or issues which cannot be remotely managed may be returned to C3i and a replacement device cross-shipped to the site, configured for the site for use upon receipt.

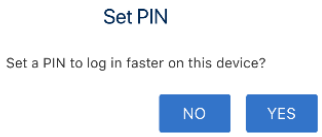
All Providers: First Time Login

1. Log into iMedidata and complete all required Medidata eLearning courses
2. Go to your iPad and press the iPad's home button (on the front of the iPad below the screen).
3. Activate the iPad's WiFi
   a. Tap the Settings icon
   b. Navigate to the Wi-Fi setting and select the name of your local Wi-Fi network
   c. Depending on your Wi-Fi security setup enter your username and password or the Wi-Fi password
4. Tap the eConsent app icon.

The Welcome screen appears.



5. Tap Begin.
6. Select Allow or Don't Allow for audit purposes.
7. Enter your iMedidata username and tap **Next**.
8. Enter your iMedidata password and tap **Sign In**.



9. Select YES to set a **PIN**.

10. Enter a PIN, using the keyboard on the iPad's touch screen.
11. Optional. Tap Skip this Step to opt out of setting a PIN.
12. Re-enter the PIN.
13. Optional. Tap Skip this Step to opt out of setting a PIN.
14. Select a **Study** (E10323).
15. Select a **Site** and tap **Enter**.
16. The main study screen appears. This screen displays important information about the study.
17. *Optional*. Tap **Documents** at the top-right of the screen to see details about these files.
18. Tap **Enter**.

The Subject List for your site appears.

<u>Subsequent Log In</u>

1. Tap the eConsent app icon on the iPad home screen.
2. Select your iMedidata username as the existing account.
3. *Optional*. Select **New User Login** to login as a different user.
4. Enter your iMedidata password or PIN and tap **Sign In**.
5. Tap **Enter**.
6. *Optional*. Tap Change Study/Site to change study or site.

The Subject List for your site appears.

Further instructional information is in the Knowledge Hub section of the Medidata website at https://learn.medidata.com/en-US/bundle/econsent/page/rave_econsent.html.

Sites with eConsent and/or iPad issues should contact Medidata at patientcloudsupport@mdsol.com

5.3.3 Engagement Website

User initialization for CRAs and providers

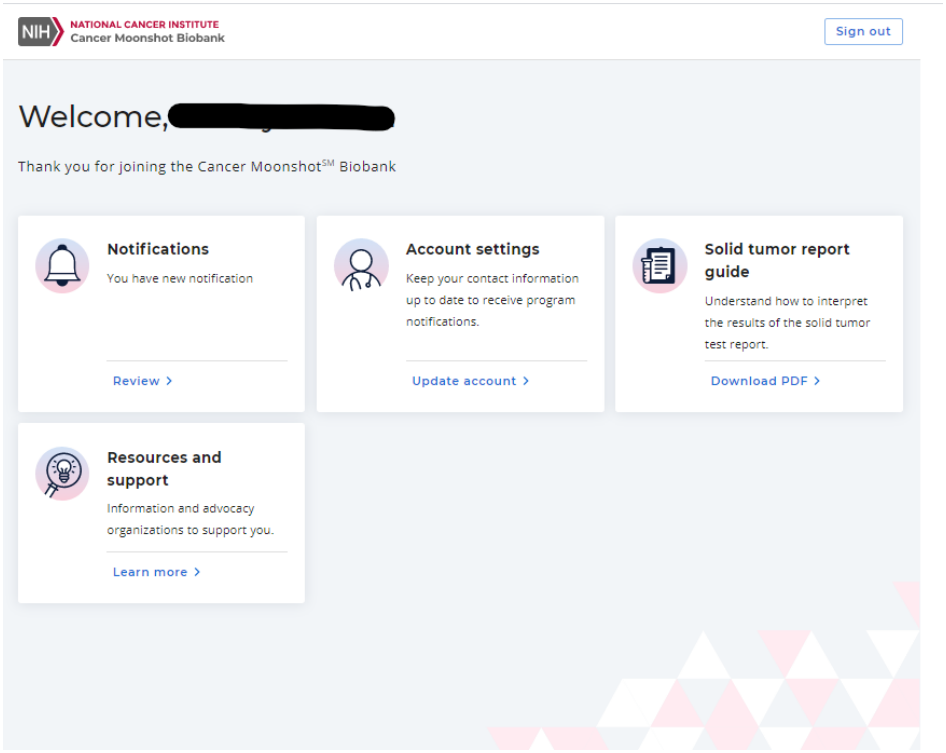
After the patient is registered in OPEN, the site registrar and the treating investigator will be classified in the Engagement website as the CRA and the provider, respectively. Information about the patient, such as the Rave Patient ID will be sent and associated with the CRA and the provider in the website.

Once the engagement website receives this information, it will check to see if the provider and the CRA have accounts on the website. If they are not already a user, then the system will send a welcome email to the CRA and/or the provider to invite them to initialize their account.

The CRA or provider must click on the activate account link or cut and paste the link to their browser and the user will be taken to the activate the online CMB account page.

The CMB uses login.gov to manage the user authentication. This allows for extra security, such as 2 factor authentication. If the user doesn't have a login.gov account, there is a link and instructions on how to create a login.gov account. Note that the email used in login.gov must be the same as the one associated with OPEN. Once a login.gov account is established, then the user can proceed to the Engagement Website login page, where they will enter their email and password that they used to create the login.gov account.

The user must then enter their 2-factor authentication, based on the choice made in setting up the account at login.gov. Options include a text message, secure code through an authentication application, USB security key, or a set of backup codes. After entering their 2-factor authentication, they will be taken to the home screen of the Engagement Website.

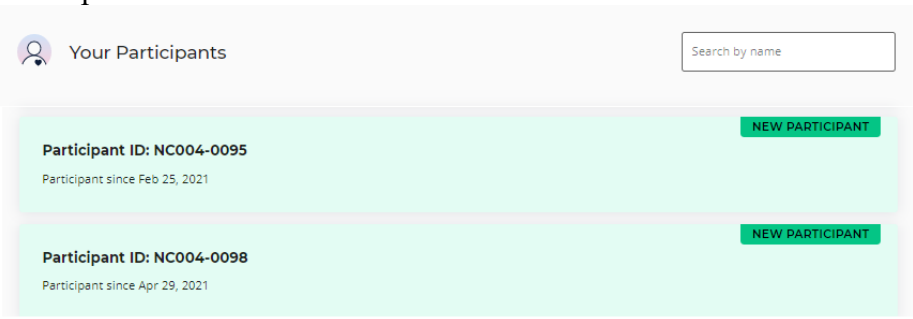


Engagement Website Home Page

User initialization for patients

The CRA will also receive an email that informs them when a new participant has joined the study.

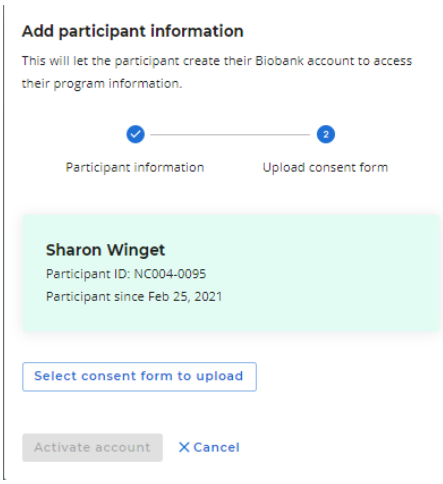
After the CRA clicks on the link and logs in to the site, they will be taken to their home page, as shown above. If they scroll down, they will be presented a list of associated participants, and the uninitialized participants will be shown with the Rave subject ID as defined in OPEN during the registration process. They will be also labeled as "New Participant".



To initialize the participant, the CRA selects the participant ID and then enters the participant's first name, last name and email address. Note that when the participant does not have an email address, the participant account cannot be created, the consent

document cannot be uploaded, and the Engagement website cannot send an email to the study participant.

The CRA can set the participant's language choice if necessary, and then select the "Save and continue" button. Then they will be prompted to upload a file for the signed informed consent.



The CRA then clicks the "activate account" button, and a welcome email will be sent to the participant at the email address entered in the step above.

The CRA should then get a page for that participant, where they can download the informed consent and biomarker test results, when one has been uploaded.

5.3.4 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.

Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient

transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.3.5 Special Instructions for Patient Enrollment

This Study will use the Site Registrar as the person responsible for activating a participant's account in the Cancer Moonshot Biobank's engagement website (moonshotbiobank.cancer.gov).

This Study will use the Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through two Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave Home tab and then under Rave Resource Materials .
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

5.3.6 Patient Enrollment Instructions

The following information will be requested:

1. Protocol Number (this study).
2. Investigator Identification.
   a.) Institution and affiliate name.
   b.) Investigator's name.
3. Consenting person's name.
4. Site Registrar's name.

5. Eligibility Verification: Patients must meet all of the eligibility requirements listed in Section 4.
6. Additional Requirements.
   a.) Patients must provide a signed and dated informed consent form. CMB will employ electronic consent (eConsent) using Medidata Rave eConsent for adult patients.
   b.) Written consent, assent, and parental permission forms will be available as a secondary method for adults who prefer paper format and adolescent patients as needed. All content regardless of electronic or paper format will be available in both English and Spanish.

Enrollment in this study happens through interactions between OPEN and IWRS. Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and the patient study ID. The UPID is associated with the patient and used each and every time the patient engages with this or any other STS protocol. The patient study ID is associated with the enrolling site, as well as the accession number of the patient's relative order of joining this protocol.

Immediately following enrollment, the institutional anatomic pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave into the Histology and Disease CRF. The report must include the protocol number, the surgical pathology ID (SPID), and the IWRS-assigned UPID for this study. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials and patient ID# for the study, from the institutional pathology report prior to submission.**

5.3.7 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6. PATIENT AND PROVIDER ENGAGEMENT PLAN

Patient and provider engagement is an integral component of CMB. For this study, patient and provider engagement is defined as the establishment of an ongoing trusting and mutually vested relationship between study participants, providers and CMB. Various outreach activities have been developed and implemented to engage cancer patients and their caregivers, medical providers, patient advocates and local communities that represent the patient populations that are served by contributing medical institutions. Specific local engagement projects currently and to be funded at participating BSS may include, but are not limited to, community advisory boards, focus groups, on-site workshops, educational events, development of culturally appropriate communication materials translated into languages spoken by participants by catchment area, and development of institutional frameworks for engaging and enrolling a diverse range of study participants. Several strategies will be employed to help meet study participant diversity goals as well as to support the longitudinal engagement of patients and providers within CMB. Through these efforts, CMB aims to help study participants develop an understanding and appreciation of their specific role in the project and their potential contribution to cancer research. We define underserved populations in this protocol as those that may encounter barriers to health care access or experience disparities due to economic, cultural, technological, geographic and/or linguistic factors. These may include persons for whom English is a second language, persons with disabilities, rural populations, the elderly, racial and ethnic minorities, and more. Our approach to address challenges to participation of medically underserved populations includes the selection of NCORP/NCTN Biospecimen Source Sites (BSS) who together will contribute to the Biobank's goals. For example, some NCORP/NCTN sites have high numbers of rural populations, others are "Minority/Underserved Community Sites" with patient populations comprised of at least 30% racial/ethnic minorities or rural residents, other sites emphasize a high level of adolescent and young adult research participants, and so on. In an effort to realize the Biobank's oversampling goals (Section 9.2), consideration was given when reviewing applications of sites serving large populations of minority patients diagnosed with PCA or MML. CMB will monitor accruals as part of regular study reviews, to ensure successful outreach, integration and longitudinal participation of diverse populations. Engagement activities for CMB include the components below.

6.1 BSS Local Engagement

To support NCORP/NCTN engagement activities relevant to CMB, limited funding is available through an application process. Proposed engagement is evaluated, selected by NCI and LBR and reimbursed by Theradex Oncology, which serves as the CMB BSS Coordinator. In addition to funding at selected sites, all NCORP/NCTN sites are expected to utilize their own pre-existing engagement infrastructure and personnel to aid in enrollment and retention of diverse study participants in the study. Of note, NCORP funds and supports existing working groups focused on disparities in research participation.

6.2 External Scientific Panel (ESP)

An ESP has been established that includes extramural experts selected by NCI to provide input on engagement activities and programs. ESP members include patient advocates, physicians,

scientists, communications experts and others with experience that aligns with CMB objectives. ESP members are professionals with a) a strong interest in working within diverse communities, including underserved populations; b) proven success in contributing to previous biobanking projects; c) knowledge of strategies and vehicles for building communication and trust with patients and/or providers; d) experience in longitudinal biobanking collection.; and e) awareness of implementation science approaches to disseminate and implement knowledge and lessons learned to all BSS. The ESP is working closely with NCI CMB leadership and its input will be shared with BSS to improve engagement efforts and address engagement challenges.

6.3 Patient and Provider Engagement Website

An online Patient and Provider Engagement Website is available in English and Spanish to support engagement efforts at http://moonshotbiobank.cancer.gov/. Through the website, study participants and providers will be informed of CMB activities and have access to resources that could be of benefit to them. Engagement website resources may include, but are not limited to: a) public information about the CMB; b) a secure login for patients and providers that provides the ability for patients to download copies of their signed consent documents and access to clinical biomarker reports for study participants and providers; c) general education videos and other materials related to biobanking and biospecimen donation; d) aggregate research results provided by CMB investigators; e) clinical trials information; f) enrollment data and patient demographics; and g) surveys distributed to study participants and providers to study use of the website and its resources. Appendix K includes the background and methods for the first planned survey as well as a list of questions to be administered to participants and/or providers via the Qualtrics survey platform. Results of the survey will be published and disseminated to the public through conferences, scientific journals, and online via community partnerships with advocacy organizations and others.

Traffic is directed to the Engagement website through BSS sites during site training, consent and enrollment, as well as through local engagement and the use of social media posts created in collaboration with the NCI Office of Communications and Public Liaison.

6.4 ELSI Study

The CMB may fund a single Ethical, Legal, and Social Implications (ELSI) study to explore various ELSI issues as the project launches and progresses. NCORP/NCTN sites will be invited to submit proposals for ELSI studies relevant to CMB. ELSI investigations might include research conducted through the Engagement website or other means on a multidisciplinary range of topics, such as user experiences of the eConsent platform, participant experiences in the program, usefulness of the clinical biomarker test provided by the program to providers and patients, and effects on treatment, if any, of the provided clinical biomarker test. Research results will not only be of benefit to CMB as they may also help guide and improve future programs and initiatives at NCI and will also likely be of interest to those in the extramural research community interested in ELSI in cancer research. The Office of Management Policy and Compliance and the NIH's Deputy Director for Extramural Research have determined that surveys of patients and providers, when survey results are analyzed and published, fit the federal definition of research and are therefore exempt from the Paperwork Reduction Act per the 21st

Century Cures Act. This exemption will allow the ELSI investigator to design and conduct surveys quickly during the course of the study without need for lengthy review by the Office of Management and Budget.

6.5 Social Media and Communications

CMB will utilize several avenues of communication to help create awareness of the project and provide research and general project updates throughout the life of the project. Communication platforms utilized will include posting to NCI social media accounts as well as content distribution through GovDelivery. Per guidance from Advarra IRB, communication materials developed by CMB that do not directly solicit enrollment or retention and posted on sites unaffiliated with the project which have been developed for viewership other than, or in addition to, potential subjects do not require prior IRB review. CMB may, in the future, enter into Memorandum of Understandings (MOU) with external organizations such as cancer advocacy organizations. These organizations may potentially distribute information about CMB through social media or other means. Terms for communicating about the project will be specified through MOUs developed by the HHS Office of General Counsel. Per guidance from Office for Human Research Protections regulations (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html) and Advarra IRB, such distribution of knowledge through external organizations would not constitute direct solicitation of enrollment or retention.

7. RESEARCH PLAN

7.1 Overview

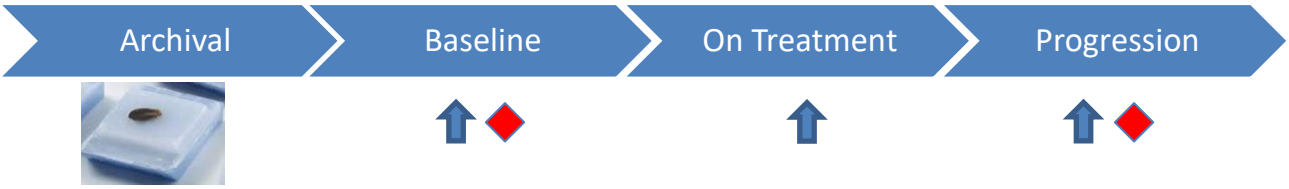
CMB will enroll patients meeting eligibility criteria (Section 4) who have signed informed consent. At enrollment and in an ongoing manner, biospecimens will be collected at multiple longitudinal timepoints (see **Figure 4;** Section 10; Appendix D). The most critical collections for the study are tissue and blood collected at baseline and progression timepoints. These longitudinal timepoints are relative to the time of patient enrollment, recognizing that patients with advanced cancers may already be well along in their treatment. Progression is defined as documented clinical evidence of increasing tumor burden by investigative analysis such as imaging studies, bone marrow analysis, increasing levels of tumor specific biomarkers, etc. Research biopsy procedures may be needed, that is, procedures scheduled for the sole purpose of collecting biospecimens for this study and not due to medical necessity. When available, archival material containing the cancer type for which the participant was enrolled will also be provided to the study. At enrollment, treatments must be standard of care per NCCN guidelines and may include molecularly targeted therapy and immunotherapy as well as FDA-approved combination regimens (Appendix A). Blood samples will be collected at all timepoints, when possible. All study participants will be followed at standard of care visits for therapy response, progression and survival for 5 years from the date of registration. The study site will check study participant's medical records from time to time (approximately every 6 months) to collect medical information for 5 years or longer. **Figure 5** illustrates four examples of possible enrollment and biospecimen collection scenarios that fulfill the research plan.

Tissue biospecimens may include core needle biopsies (CNB) and fine needle aspirates (FNA) as well as endoscopic or excisional biopsies, laparoscopic or open surgical resections. Additional biospecimen types such as bone marrow (BM) aspirates or biopsies will be collected for some cancer types (Appendix D). Whenever possible, adjacent non-tumor (ANT) tissue samples will also be collected. For up to 20% of study participants, additional blood and fresh tumor tissue from a biopsy or surgical resection at baseline and progression will be used for PDM development.

Figure 4. General Biospecimen Collection Plan

= Most important timepoints for biospecimen collection (tissue plus blood)

= Potential timepoints for biospecimen collection*



* For the purposes of this study, collection timepoints are defined as follows:

Archival: **Tissue** biospecimens collected prior to enrollment, up to 5 years prior to initiation of a therapy listed in Appendix A, with no more than 1 line of standard of care systemic therapy administered between the date of archival material collection and the date of initiation of Appendix A therapy (Section 4.1.4).

Baseline: Fresh (non-archival) biospecimen collection **(tissue plus blood)** prior to initiation of a therapy listed in Appendix A.
In the event that standard of care therapy is initiated while waiting for biomarker test results, such therapy is allowable for up to four weeks (28 days) prior to initiating biomarker test-informed Appendix A therapy (e.g., chemotherapy prior to ROS1 antagonist).

On Treatment: **Blood** biospecimen collection, when possible, at standard of care follow-up visits for radiographic assessment of therapy response.

Progression: Fresh (non-archival) biospecimen collection **(tissue plus blood)** following clinical and/or radiographic evidence of disease progression while on Appendix A therapy.
Progression is defined as documented clinical evidence of increasing tumor burden by investigative analysis such as imaging studies, bone marrow analysis, increasing levels of tumor specific biomarkers etc.

Post Treatment **Blood** biospecimen collection, when possible, at standard of care follow-up visits after Appendix A therapy has ended.

Ideally, enough fresh tumor tissue and blood will be collected at baseline and progression timepoints for a) banking and distribution to researchers and b) NGS tumor testing (biomarker testing). At minimum, fresh tumor tissue and blood will be collected at progression to pair with blood collected at enrollment and archival formalin fixed tumor tissue. Patients should be followed over time and biospecimens collected at future progression events if they occur.

Figure 5. Examples of possible enrollment and biospecimen collection scenarios that fulfill the research plan.

5a. Clinical enrollment scenario a.

Patient is undergoing diagnostic workup for one of the diseases listed in 4.1.1 for which treatment will likely include a new regimen of standard of care therapy indicated in Appendix A.

- Patient is enrolled at baseline timepoint.
- Fresh tissue and blood collections are required at enrollment.
- Archival tissue is submitted at enrollment when available.
- Fresh blood collections, timed with radiologic imaging events, are requested whenever possible at all on-treatment and post-treatment timepoints.
- Fresh tissue and blood collections are required at progression timepoint(s)

5b. Clinical enrollment scenario b.

Patient is scheduled to begin treatment with a new regimen of standard of care therapy indicated in Appendix A.

- Patient is enrolled at baseline timepoint.
- Fresh tissue and blood collections are required at enrollment.
- Archival tissue is submitted at enrollment when available.
- Fresh blood collections, timed with radiologic imaging events, are requested whenever possible at all on-treatment and post-treatment timepoints.
- Fresh tissue and blood collection is required at progression timepoint(s).

5c. Clinical enrollment scenario c.

Patient is currently progressing on regimen of standard of care therapy indicated in Appendix A.

- Patient is enrolled at progression timepoint.
- Fresh tissue and blood collections are required at enrollment.
- Archival tissue is required at enrollment.
- Fresh blood collections, timed with radiologic imaging events, are requested whenever possible at all on-treatment and post-treatment timepoints.
- Fresh tissue and blood collections are required if additional progression events occur.

5d. Clinical enrollment scenario d.

Patient is currently being treated with regimen standard of care therapy indicated in Appendix A, without evidence of progression.

- Patient is enrolled at on-treatment timepoint.
- Fresh blood collection and archival tissue is required at enrollment.
- Fresh blood collections, timed with radiologic imaging events, are requested whenever possible at all on-treatment and post-treatment timepoints.
- Fresh tissue and blood collections are required if additional progression events occur.

7.2 Biospecimen Collection

All biospecimens will be collected at BSS using BCR-provided kits according to pre-approved SOPs. General guidelines are given below. Further information about biospecimen collection, labeling, processing and shipment will be provided in the **CMB Protocol Laboratory Manual** (vol 1) posted on CTSU.

Sites are expected to have immediate access to the facilities and infrastructure to participate in the study as outlined in the Laboratory Manual. This includes but is not limited to appropriate personnel, anesthesiology, radiology, pathology, oncology and interventional radiology. In addition, sites must be able to follow the procedures for appropriate collection, handling, preservation and shipment of samples, as outlined in the Laboratory Manual.

Kits for the collection and shipment of biospecimens to the Van Andel Research Institute can be ordered online via https://pbc.vai.org/moonshot/. There are five kit types for #10323 – contents will be provided on the system website. Kits will include blood collection tubes, pre-filled containers for formalin fixation and fresh tissue transport, and cryovials for freezing and transporting frozen tissues. Please allow 5-7 days for receipt.

7.2.1 Archival Material Collection

Solid Tumors:

A pre-existing formalin-fixed paraffin-embedded (FFPE) tumor tissue (metastatic tissue preferred with optimal 70% tumor nuclei and minimal necrosis) block or at least 20 recently cut unstained sections on positively charged slides (4-5 microns thick) with a minimum surface area of 5 mm^2 and optimum surface area of 25 mm^2 will be submitted, if available. Tissue specimens of suboptimal size, cellularity or tumor content will require submission of more than one FFPE block.

The estimated age of the block(s) will be recorded with an upper limit of 5 years prior to initiation of therapy listed in Appendix A, assuming that no more than 1 line of standard of care systemic therapy was administered from the date of archival material collection to the date of initiation of Appendix A therapy.

Archival FNA samples may also be provided as smears and FFPE cell blocks **in addition** to the FFPE material outlined above.

The corresponding diagnostic anatomic pathology report and required clinical data for each tissue block must also be provided to confirm the cancer type for which the participant was enrolled.

If the BSS can only loan an FFPE block for a defined amount of time, the BCR will process and may return the sample within the required period by each site. In some cases, loaned FFPE blocks may be completely depleted by the BCR. Previously collected blood and fresh frozen tissue will also be submitted, if available. **Clinical biomarker testing will not be performed on archival material.**

MML and AML:

A tube containing 3-5mL cryopreserved bone marrow aspirate to yield 200 million bone marrow mononuclear cells will be submitted.

Or

A pre-existing formalin-fixed paraffin-embedded (FFPE) tumor tissue (metastatic tissue preferred with optimal 70% tumor nuclei and minimal necrosis) block or at least 20 recently cut unstained sections on positively charged slides (4-5 microns thick) with a minimum surface area of 5 mm^2 and optimum surface area of 25 mm^2 will be submitted, if available. Tissue specimens of suboptimal size, cellularity or tumor content will require submission of more than one FFPE block.

The estimated age of the block(s) will be recorded with an upper limit of 5 years prior to initiation of therapy listed in Appendix A, assuming that no more than 1 line of standard of care systemic therapy was administered from the date of archival material collection to the date of initiation of Appendix A therapy.

7.2.2 Solid Tumor Blood Collection

Peripheral blood will be collected, as listed below, at enrollment, whenever tissue is collected, and at on treatment timepoints that correspond to significant radiologic imaging events. If it is not possible to collect blood and tissue on the same day, matching blood may be submitted if it was obtained within two weeks before tissue collection. Blood samples corresponding to baseline tissue samples must be obtained prior to initiation of therapy listed in Appendix A. Blood samples may be collected (on treatment and synchronized with radiologic imaging if possible) independently of tissue collection.

If 40 ml of blood is available, the optimal collection order is as follows. If less blood is available, then one tube of each type is acceptable:

a) 2 x 10 ml – EDTA tubes (plasma and PBMC isolation).
b) 2 x 10 ml – Streck tube (cell-free nucleic acid and germline).

7.2.3 Solid Tumor Tissue Collection (Endoscopic or Excisional Biopsies and Surgical Resections)

Acceptable procedures for tissue biospecimen procurement include **medically necessary** mediastinoscopy, open surgery, laparoscopy, gastrointestinal endoscopy, bronchoscopy or craniotomy. No endoscopic or laparoscopic or open surgical procedure will be performed solely to obtain a biopsy for this protocol. FNA samples, including smears, rinses and FFPE cell blocks, will also be collected. Tissue will be collected that meets the following criteria:

1. Total ischemic time ≤ 1 hour whenever possible.

2. Tumor tissue:
   a) 2 samples – formalin (Biomarker and research FFPE).
      Clinical biomarker testing will <u>NOT</u> be performed if:
      - **only one sample is submitted,**
      - **samples measure less than 5 x 5 mm, or**
      - **if tumor content is < 10% as determined by the BCR.**
   b) 1 sample – fresh for PDM development (if available; baseline and progression; and meets eligibility criteria; Appendix H).
   c) 2-4 samples – fresh frozen on dry ice.
3. Adjacent Non-Tumor (ANT) tissue from surgical resections, if available – formalin and fresh frozen on dry ice (≤ 30 minutes).

Note: Ischemic time is the interval from cutoff of *in vivo* blood supply (devascularization) to ex vivo stabilization. It is not a requirement that these pieces be contiguous, however, they must have been collected from the same tumor nodule and as close in proximity to each other as possible.

Each sample should measure no greater than 1.0 x 1.0 x 0.5 cm.
For PDM development, each sample must measure at least 0.4 x 0.4 x 0.4 cm.

7.2.4 <u>Solid Tumor Tissue Collection (Needle Biopsies)</u>

Image-guided FNA followed by 16-18 gauge CNB with rapid on-site evaluation by cytology assessment is the preferred technique for percutaneous biopsy tissue procurement. Samples obtained through a bronchoscopy utilizing a 21g needle are also permitted. If fewer than 4-6 tissue cores are procured, then formalin fixed, fresh (PDM), and fresh frozen samples should be prioritized. FNA samples may be placed in the provided formalin cups.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be performed only if they are of low risk to the study participant as determined by the investigators and interventional radiologist. For recommended NCI developed standardized operating procedures regarding image-guided biopsies for this study, please see the Lab Manual.

The interventional radiologist should provide the investigator with an assessment of whether a lesion that is likely to yield enough material for molecular profiling can be found and biopsied with acceptable risk. Three main factors are considered: a) whether a suitable lesion (viable tumor) for biopsy is present (yield); b) whether the lesion selected for biopsy can be sampled to yield the required samples; and c) the expected level of risk of major complication to the patient (≤ 2% major complication to be eligible for biopsy). A pre-biopsy lesion scoring system (scale from 1-3) adapted from the one used by

Interventional Radiology at the MD Anderson Cancer Center will be used to assign a value to the interventional radiologist's assessment of the lesion. Briefly, the qualitative assessment criteria for the 3-point scale is as follows:

Pre-Biopsy Lesion Scoring Scale (courtesy MD Anderson Cancer Center)

Score Assigned	Likelihood of Yield	Reason for Score & Biopsy Disposition
1	Low (< 25%)	Reason: no target amenable to biopsy, high risk procedure. Biopsy disposition: should not be performed.
2	Uncertain (25-75%)	Reason: Uncertainty about success either due to technical challenges or lesion characteristics (e.g., small size, necrotic, sub-solid lesion, sclerotic, not FDG–avid, technically difficult biopsy). Sclerotic bone lesion usually low yield. Biopsy disposition: Communication with investigator for these types of lesions should occur to determine whether to proceed with biopsy.
3	High (> 75%)	Reason: viable tumor demonstrated on diagnostic imaging (enhancing lesion, growing lesion) that can be sampled aggressively. Disposition: Proceed with biopsy.

Contraindications to percutaneous biopsy include significant coagulopathy or anticoagulation treatment that cannot be adequately corrected, severely compromised cardiopulmonary function or hemodynamic instability, lack of a safe pathway to the lesion, inability of the patient to cooperate with, or to be positioned for, the procedure, and inability of the patient to provide informed consent.

Tissue will be collected, in optimal collection order, that meets the following criteria:

1. Total ischemic time ≤ 30 minutes whenever possible.
2. 4-6 cores measuring at least 1 cm in length:
   a) 2 cores – formalin (Biomarker and research FFPE).
      Clinical biomarker testing will <u>NOT</u> be performed if:
      - **only one sample is submitted,**
      - **samples measure less than 5 x 5 mm, or**
      - **if tumor content is < 10% as determined by the BCR.**
   b) 1 core – fresh for PDM development (if available; baseline and progression; and meets eligibility criteria; Appendix H).
   c) 2-3 cores – immediately fresh frozen on dry ice.
3. Adjacent Non-Tumor (ANT) tissue from surgical resections, if possible – formalin and fresh frozen on dry ice (≤ 30 minutes).

7.2.5 <u>Hematologic Malignancy Collection</u>

BM aspirates and BM biopsies are acceptable biospecimen types. Peripheral blood (PB) may be submitted if the patient has widespread disease burden.

Samples will be collected that meet the following criteria:

1. >20% tumor cells.
2. BM aspirates should be submitted in EDTA tubes from the first or second syringe pull, if possible, to ensure consistency. BM aspirates should be examined immediately for the presence of spicules.
3. BM biopsies must be submitted with a BM aspirate (BM aspirate will be used for clinical biomarker testing)
    - **Clinical biomarker testing will NOT be performed if only a BM biopsy is submitted, or if tumor content is < 20%.**

7.2.6 PDM Collection

If available and meets PDM eligibility criteria (Appendix H), matched blood and fresh tumor tissue biospecimens will be collected as described above for PDM development. Only send samples from **baseline and then progression** timepoints (archival, On Treatment, and Post Treatment are not acceptable timepoints for PDMR).

Designation of primary and metastatic sites and specific locations of collection within the body cavity should be noted. SOPs for detailed steps on collection, packaging, shipment, and communication with the PDMR are outlined and available in the CMB Laboratory Manual:

1. SOP-PDM100: Fresh Tumor and Blood Collection and Handling for Generation of Preclinical Models.
2. Participating site study staff must complete the "Social & Environmental Factors" CRF in Medidata Rave prior to the patient going off study.

Theradex will enter limited medical information into GeneMed, and a unique random ID (referred to as the PDX identifier) will be assigned by the GeneMed bioinformatics database. PDX identifiers will not be sent to the participating site that provided the sample. The limited medical data and molecular profiling data will be available at GeneMed through open access ONLY after being completely de-identified.

Initial processing of live cells (tumor tissue, circulating tumor cells) will be performed on biospecimens in which random PDX identifiers are still linked to the OPEN Registration ID in the GeneMed bioinformatics system; however, no manipulation of these cells beyond that essential to isolate, implant, culture, confirm presence of tumor cells, and/or preserve the specimens will be performed. No personally identifiable information (PII) of the enrolled patients will be stored in GeneMed.

Participating site study teams will register their patients in OPEN; to send specimens to the PDMR lab, the study teams will be required to provide limited medical information in order for the PDMR lab to prepare for specimen receipt and improve the likelihood of generation of preclinical models with the patient specimen. Upon sample arrival at the PDMR, the OPEN Registration ID will be discarded, and the sample assigned a PDX identifier using the GeneMed bioinformatics system. A link between the OPEN ID and PDX identifier will be present in the GeneMed bioinformatics database only for 10 days after biospecimen collection and data entry into GeneMed. Removal of the link at that

time will break the link between any information at the providing institution and the research samples at the PDMR. PDMR laboratory personnel working with the research sample will not have access to any confidential identifiable information.

PDX development and subsequent processing and analysis of samples will proceed in accordance with the established PDMR protocols. Since collection of longitudinal specimens is planned from a patient, the patient can remain on-study for this protocol and limited medical information uploaded after the last specimen is shipped. After shipment of the final specimen, the patient will be taken off-study and final de-identification completed by NCI-F/FNLCR honest brokers.

7.3 Biospecimen Tracking and Shipping

Chain of custody (documented continuity of possession and proof of integrity) must be initiated upon collection and maintained for all biospecimens submitted to CMB. The date and time of collection, identity of the personnel collecting the biospecimens and the shipping date must be entered into the Rave Specimen Tracking System (STS). Failure to update STS appropriately may result in delays in central assessments and reporting. Advance notice of shipments to the BCR and PDMR, including information regarding types of kits/containers, will be required.

NOTE: The corresponding diagnostic anatomic pathology report <u>MUST</u> be submitted with tissue biospecimens by the BSS for central confirmation of cancer type. The pathology report must state the disease diagnosis made by the local pathologist. If a new anatomic pathology report cannot be obtained, then the most recent available pathology report (identifying the malignancy) may be provided instead. **When available, molecular pathology reports should also be provided.**

For PDM development, biospecimens must be shipped on the same day as collection using FedEx Priority Overnight using only the provided shipping kits and fixed-temperature gel packs per the SOPs. Samples from multiple anatomic sites should be shipped in individual media jars per the SOPs.

Attention: Dan Danner
NCI-F/FNLCR
1073 Beasley Street, Building 1073 Fort Detrick
Frederick, MD 21702
Phone: 301 846-5748

For all other biospecimens, please ship collections to the address below using overnight courier (FedEx), early morning delivery option (FedEx Priority Overnight service is very strongly preferred):

Attention: Dan Rohrer
Van Andel Research Institute
333 Bostwick Avenue NE
Grand Rapids, MI 49503

Ph: 616.234.5122

Specimen Tracking System Overview and Enrollment Instructions

The following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 4.
- Additional Requirements:
  - Patients must provide signed and dated informed consent.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a patient study ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the Specimen Tracking System. The UPID contains no information or link to the protocol. IWRS will maintain an association between the UPID for the CMB, its IT systems and molecular characterization, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

Specimen Labeling

Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (to be added by hand)

Tissue Specimen Labels

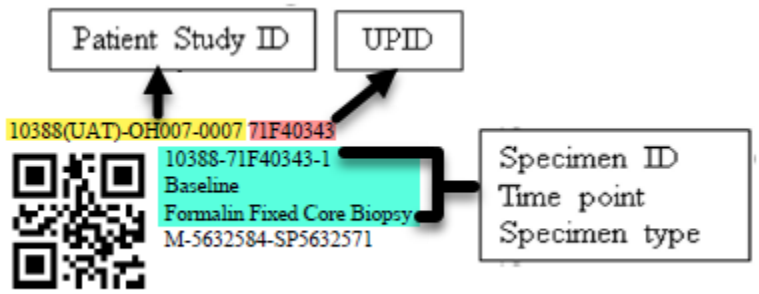
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or A for Adjacent Non-Tumor)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date and time (to be added by hand)

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

Example of Specimen Label

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. We recommend the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes three data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Adjacent Non-Tumor (A) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none

Space is provided at the bottom of the label for the handwritten date and optional time.

Rave Specimen Tracking Process Steps

Step 0: Log into Rave (https://login.imedidata.com/) via your CTEP-IAM account, then navigate to "**10323**" study, then select the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the **Baseline Medical History** form. For PDM eligible samples, complete the **Social & Environmental Factors** form. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time on each label.
- After collection, store labeled specimens as described in Section 7.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates, and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status**.

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. (Note that the pathology report from the site is required for patient clinical testing.) Be sure the printed copy includes the specimen label.

Step 6: Send email notification to recipient(s).

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

7.4 Pathology Quality Assessment at BCR

Pathology quality assessment will be conducted for tissue biospecimens submitted at each timepoint to verify diagnosis and if applicable, evaluate adequacy for biomarker testing (optimal 70% tumor nuclei with minimal necrosis). The BCR will create and archive whole slide images of representative tumor and adjacent non-tumor (ANT) tissue slides using an Aperio scanner and perform macrodissection to enrich tumor samples, if needed. If a sample does not contain any tumor, it will be stored as ANT tissue. If there is a discrepancy between the original anatomic pathology diagnosis and BCR pathology review, the treating investigator will be contacted by the BCR and the submitting site will determine next steps as deemed appropriate. All incidental morphologic findings will be recorded and reported back to the provider if clinically relevant.

7.5 Use of Biospecimens

All biospecimens collected and meeting study criteria will be shipped to, processed and stored at the BCR, with the exception of fresh samples shipped to PDMR (see Appendix H). The BCR will 1) evaluate and process samples for clinical testing and biobanking, and 2) process samples for approved investigator use. The BCR will coordinate shipment of biospecimens to all clinical

and research laboratories.

The BCR will provide samples and data to future unknown researchers who apply for access and are approved by the CMB sample and data access committee. A CMB biospecimen catalog is under development for public browsing and sample request, similar to other NIH biospecimen catalogs at NHLBI (BioLINCC), NIDDK, NCI (NCTN Navigator), NCI Specimen Resource Locator (https://specimens.cancer.gov/) and the GTEx sample catalog at the Broad Institute.

Researchers will be able to search the online Biocatalog for samples that meet their specific criteria. The Biocatalog will contain sample inventory information and annotation for samples stored at the BCR. CMB has contracted with Information Management Systems (IMS) to develop the catalog. NCI and extramural experts previously established the Common Biorepository Model, a standardized data structure for online searching of specimens, which will be considered in organizing the data structure for the Biocatalog.

All researchers will be able to view the policies regarding samples and data access and apply online for samples listed in the Biocatalog. Applications will be received on a rolling basis and reviewed quarterly by an Access Committee. The Committee will be newly established for the CMB project and will include individuals with expertise in oncology, bioethics, genomics, bioinformatics, statistical analysis and human subjects research. The Committee will be able to seek external, unbiased scientific and ethical expertise if the committee members lack the experience or qualifications to adequately evaluate a proposal. If the proposal is declined, there will be an appeals process, with the final decision made by the Committee.

The policies regarding sample access, including data sharing requirements for studies utilizing the samples, will be posted on the Biocatalog website and are summarized as follows. The proposed use of the samples and data must address a critical cancer research priority. The proposal must describe all methodological considerations and explain how the specific objectives of the project will be addressed and achieved. The proposal must also describe the researcher's material resource and infrastructure required to conduct the research as well as evidence they have funding. The applicants must agree to a Code of Conduct, modeled after the *All of Us* research program. The Code of Conduct will include language about following all applicable laws regarding sample and data use, and a declarative statement to not attempt to identify participants. The CMB will develop a pricing structure for accessing the samples, based on a cost recovery model for activities such as retrieval of the samples from storage, sample processing, preparation for shipping, and shipping costs.

The Access Committee will consider the scientific relevance and rigor of the proposed project, the funding that is available to the requestor to conduct the research, the number and type of samples requested, the suitability of the CMB samples to fulfill the research proposed, whether longitudinal/serially collected samples are requested, and whether there is sufficient statistical power to achieve the aims of the proposal. A Material Transfer Agreement (MTA) and Data Use Agreement (DUA) will both be required. The BCR will be required to carefully monitor and track the inventory to ensure that all samples from any one participant are not inadvertently depleted and provide this information to the Committee.

7.5.1 Biospecimen Processing at BCR

Blood
Whole blood collected in Streck tubes will be prepared and stored for plasma for future cell-free nucleic acid isolation and for distribution to qualified investigators. Whole blood collected in EDTA tubes will be prepared and stored for plasma, buffy coat and PBMC isolation. Additional analytes may be prepared as needed for distribution to qualified investigators.

Tissue
If tissue is received in formalin, the BCR will embed in paraffin. FFPE blocks will be sectioned at the BCR to generate a hematoxylin and eosin (H&E)-stained slide and if applicable, multiple 8 micron thick unstained curls. DNA and RNA will be co-extracted and stored as needed for distribution to qualified investigators. Fresh-frozen tissues will be stored in the vapor phase of LN2. Tissue biospecimens intended for clinical testing will be received and processed in the BCR (a CLIA certified and CAP accredited laboratory) and provided to a CLIA-certified NGS testing laboratory as outlined below.

Other
BM samples will be processed and stored at the BCR. Biospecimens intended for clinical testing must be received and processed in a CLIA certified laboratory and provided to CLIA-certified NGS testing laboratories as outlined below.

7.5.2 Next Generation Sequencing
The OCA and NMA clinical NGS tests will be performed at FNLCR to assess clinically relevant somatic tumor genomic alterations that may help guide patient management. The BCR will isolate nucleic acids from tumor samples and provide the analytes to FNLCR to perform the assays. FNLCR will deliver clinical reports to the study participant, treating physician and clinical research associate via the Engagement website or, if there is no participant account on the Engagement website, to the treating physician and clinical research associate by secure email (encrypted via NIH Secure Email and File Transfer Service). When a test is unsuccessful, a negative report is sent by secure email to the treating physician and clinical research associate.

Reporting of Incidental/Secondary Findings
For the OCA and NMA tests, paired normal tissue will not be used, so definitive abnormalities in germline tissues (heritable diseases) cannot be identified with any certainty. Some of the genes tested in the OCA and NMA assays on the patient's tumor could be tumor specific, but could also be in the patient's germline (and may be passed to subsequent generations). We have discussed this possibility with a committee of multidisciplinary experts (genetics, oncology, laboratorians, bioethicists). There is no consensus on what type of findings on a tumor sequencing assay would imply the presence/absence of germline mutation. The tumor findings will be communicated to the treating clinician with advice to consider germline testing if clinical and/or family history is consistent with the presence of such an abnormality and the patient provides consent for germline testing. Clinical germline testing is not available through this study. In many

cases, the medical significance of genetic variants is yet unknown. No genomic data will be shared with the patient other than the data from the targeted sequencing panel.

7.5.3 Sites Performing Correlative Study
The FNLCR Molecular Characterization Laboratory directed by Dr. Mickey Williams.

Attn: MoCha Samples/Shahanawaz (DJ) Jiwani
Leidos Biomedical Research
1050 Boyles Street
Building 459, Room 127
Frederick, MD 21702
PH: (301) 620-3914 (Dr. Jiwani)

7.6 Data Collection

7.6.1 Biospecimen Handling Data

The study collects information on biospecimen collection, processing, shipment, and storage conditions. This information is important to the study because variations in these preanalytical factors can affect analytical data. Select data pertaining to biospecimen handling (collection date and time, quantity, ischemic time, storage details, shipping information, etc.) and biospecimen processing (histology, pathology review, nucleic acid extraction, quality metrics) will be entered by BSS and BCR personnel, respectively, into Rave and BCR information management systems.

7.6.2 Clinical and Laboratory Data

The study collects extensive clinical data including longitudinal treatment data. This data is a critical companion to the biospecimens collected for the study, in order to support research that will include drug resistance and sensitivity research. Information on targeted and non-targeted therapy may impact genomic findings and future researchers' analyses. See Appendix I for definitions of targeted and non-targeted therapy.

Study participant demographics (race/sex/gender/ethnicity) and cancer diagnosis/staging will be entered in OPEN during enrollment by BSS personnel.

BSS personnel will enter additional data into Medidata Rave, including:

1) baseline medical history
2) alcohol/tobacco use and environmental/occupational exposures
3) non-targeted treatment, radiation, or surgery with response/outcome data for each
4) administration of Appendix A therapy/regimen with response/outcome data for each regimen
5) adverse events relating to biospecimen collection
6) bloodwork
7) surgical reports, pathology reports, imaging reports
8) biomarker test results (including previously performed tumor panel NGS tests,

IHC, FISH and PCR tests)

Additional data may be entered into Rave and/or other information management systems, if applicable, by BSS, BCR, and FNLCR personnel.

7.6.3 Imaging Data

The study collects radiological imaging data over the course of diagnosis and treatment, to correspond to the other clinical data collected along with data from biospecimen analysis. Any imaging acquired during standard of care is expected to be done under the site's own procedures and policies. Ideally, all submissions should be temporally associated with the collection of biospecimens (refer to Section 7.2). **Please do NOT submit any imaging not related to the patient's cancer management (emergency injuries, COVID-19 infection, etc.).**

Specifically, any imaging that falls into the following categories should be submitted, along with all applicable radiology/pathology reports:

1. Archival – any CT including PET/CT, MRI, and/or nuclear medicine scans, performed prior to enrollment, that led to or was performed concurrently to the diagnosis that established eligibility for this trial.
   a. AML or MML blood diagnosis may not have associated imaging.
   b. Film x-ray, ultrasound, and fluoroscopy are not required for submission.
   c. Do not submit imaging data that is dated more than 5 years prior to initiation of a therapy listed in Appendix A.
2. Baseline – most recent CT including PET/CT, MRI and/or nuclear medicine scans acquired prior to enrollment on study and initiation of a therapy listed in Appendix A.
3. On Treatment – any CT including PET/CT, MRI, and/or nuclear medicine scans acquired during standard of care treatment.
   a. Film x-ray, ultrasound, and fluoroscopy are not required for submission.
4. Progression – any CT including PET/CT, MRI, and/or nuclear medicine scans indicating disease progression or associated with stoppage of a therapy listed in Appendix A.
   a. Film x-ray, ultrasound, and fluoroscopy are not required for submission.

In addition, submit any of the following biopsy events with associated imaging using the time points listed above.

5. Biopsy – any imaging used for or during imaging-guided biopsy.
   a. Image before needle placement.
   b. Image with FNA or trocar needle in lesion.
   c. Image with core biopsy or trocar needle in lesion.
   d. **Biopsy report** (direct vision or image-guided) describing target lesion location (organ, laterality or segment if applicable and image number on pre-biopsy imaging if available).

Image data must be submitted according to the protocol requirements for ALL patients registered in OPEN, whether or not treatment is administered, including patients ultimately deemed to be ineligible. TRIAD is preferred for the submission of DICOM images; however, these methodologies are supported:

a. TRIAD-based (a PC with internet access and TRIAD software installation will be needed). The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail NCI10323@irocohio.org per the request by participating sites before their first data submission.

   TRIAD User Access Requirements:

   - Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
   - A registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
   - TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

   All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

   TRIAD Installation:

   To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/. This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration. For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

b. Web transfer-based (a PC with internet access and a web browser will be needed). (http://upload.IROCOhio.org or https://upload.wci.uc.edu)
   Any PCs with internet access and web browser (e.g., Chrome, Edge, Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail NCI10323@irocohio.org per the request by participating sites before their first data submission.
c. FTP transfer-based (a PC with internet access and any FTP software will be needed). Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately

through the specific trial e-mail NCI10323@irocohio.org per the request by participating sites before their first data submission.

d. Mail/CD Shipment-based (only if electronic transfer approaches cannot be achieved). Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's NCI ID number, study type, date of scans, and name of submitting institution.

Submit these data to:
Imaging Core Lab at IROC Ohio
Attn: NCI 10323
University of Cincinnati
Wright Center of Innovation
Digital Futures Building, Suite 310
3080 Exploration Ave
Cincinnati, OH 45206
Office: 513-556-7920

The radiology reports associated with the images should be de-identified and uploaded in the Literal Laboratory form and the findings for the corresponding assessment time point should also be entered in the Literal Laboratory form in Rave.

The complete imaging data set in digital DICOM format will be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) within no more than 14 business days upon the image acquisition completeness. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the imaging data is accepted by IROC Ohio.

Sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the NCI patient ID number (e.g., 23F60H0) and protocol number (e.g., 10323), respectively. DICOM tag dates and times cannot be altered prior to submission as they are used to put submissions into context regarding patient treatment. Additional changes to DICOM tags prior to submission impede further technical analysis and should be avoided whenever possible.
Resubmission may be requested in the event of over-anonymization.

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email NCI10323@irocohio.org to inform that the study has been submitted from the institution. IROC Ohio will notify site and NCI 10323 imaging committee within 2 business days of the data receipt, and then, within 3 business days following the data receipt, of the quality check report.

For any questions or problems about the data submission to IROC Ohio, please email NCI10323@irocohio.org or call +1-513-556-7920 for help.

7.6.4 Consent and Enrollment Data

Consent status and updates will be entered by BSS into Rave such that distribution of biospecimens and associated data can be managed appropriately.

7.6.5 Off-Study and Follow up Data

Follow up data will be entered into Rave every six (6) months after enrollment. If a patient goes off study, reasons will be provided in Rave.

8. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Complications associated with any biopsy or biopsy-related anesthesia or imaging procedures performed after enrollment to this study will be reported and tracked as protocol-related AEs. AEs not related to the biopsy or biopsy-related anesthesia or imaging procedures should **NOT** be reported in Rave or CTEP-AERS. Research staff should follow local policies for commercial AE reporting if needed. The following sections will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

8.1 Reporting Mechanisms

All AEs **must** be reported in routine study data submissions. Report AEs that are associated, or might be associated with the research biopsy procedure, including pre- and post- medication for the research biopsy procedure.

Routine reporting
Adverse events are reported in a routine manner at scheduled times during a study using Rave. For this study the Adverse Event CRF is used for routine AE reporting in Rave.

Expedited reporting
In addition to routine reporting, certain adverse events must be reported in an expedited manner through CTEP-AERS for timely monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions via Rave.**

8.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:
- Definite – The AE *is clearly related* to the biopsy.
- Probable – The AE *is likely related* to the biopsy.
- Possible – The AE *may be related* to the biopsy.
- Unlikely – The AE *is doubtfully related* to the biopsy.
- Unrelated – The AE *is clearly NOT related* to the biopsy.

8.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://ctepcore.nci.nih.gov/ctepaers/security/login).

The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the flowchart and tables below.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

8.3.1 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

8.3.2 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during study registration on all reports.

Note: A death on study requires both routine and expedited reporting ONLY if attributed to biopsy.

8.3.3 Definition of Research Biopsy-Related Toxicity

Research biopsy related toxicity will be defined as any ≥ Grade 3 toxicity or complication that is possibly, probably or definitely attributable to any research biopsy or research biopsy-related anesthesia or imaging procedures that occurs within 14 days. Research biopsy related toxicities which meet any of the following criteria must be reported in an expedited manner via CTEP-AERS:

1. Hospitalization for >24 (overnight observation will not be considered 'hospitalization' for this purpose).
2. An unplanned increase in level of care; hospitalization prolonged >48h.
3. Permanent adverse sequelae.
4. A life-threatening adverse event.
5. Death.
6. Other important medical events (IMEs) that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Table 1. Expedited Reporting Requirements for Research Biopsy-Related Adverse Events

<table>
<tr><td colspan="2"><u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria <u>MUST</u> be reported to the NCI via electronic submission within the timeframes detailed in the table below.</td></tr>
<tr><th>Grade 1 and 2 Timeframes</th><th>Grade 3, 4 & 5 Timeframes</th></tr>
<tr><td>Not required</td><td>15 Calendar Days</td></tr>
<tr><td colspan="2"><u>Expedited AE reporting timelines are defined as:</u>
o “15 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 15 calendar days of learning of the AE.</td></tr>
</table>

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The primary endpoint for this study is to procure, store and distribute longitudinal biospecimens and associated clinical data for current and future cancer research in order to elucidate molecular mechanisms of sensitivity and intrinsic or acquired resistance to standard of care systemic therapies, including immunotherapy. Cases will be grouped according to patient demographics, cancer type and treatment regimen. The secondary endpoints are to perform molecular profiling assays on tumor samples in a CLIA-certified laboratory and contribute data to the CRDC, TCIA, dbGaP and other potential NCI databases.

Statistical analysis for the primary and secondary objectives will be descriptive and will be analyzed for each BSS as well as study aggregate. We will summarize accrual and progress toward the primary and secondary objectives at interim monitoring meetings and upon completion of biospecimen collection by assessing the following endpoints:

1. Objective 2.1.1: The percentages of enrolled patients by cancer type and treatment regimen, as defined in Appendix A, overall and those who contribute samples to the PDMR, the clinical laboratory, and other approved investigators.
2. Objectives 2.1.1 and 2.2.3: The percentage of minority and underserved study participants accrued, as defined in the Planned Enrollment Report (Appendix J).
3. Objective 2.2.1: The percentage of enrolled patients for whom we are able to attempt molecular profiling (specimen quality assessment).
4. Objective 2.2.1: The percentage of enrolled patients for whom we are able to generate molecular profiling results (assay success percentage).
5. Objective 2.2.1: The percentage of enrolled patients for whom we are able to obtain samples at each longitudinal timepoint.
6. Objective 2.2.2: The percentage of collected biospecimens that are delivered to the PDMR.

Accrual endpoints 2.2.3-2.2.6 will also be assessed by patient demographics, cancer type and treatment regimen. The goal of interim monitoring will be to assess whether unexpected problems arise in the project.

9.2 Sample Size/Accrual Rate

At least 1000 study participants are expected to be enrolled, representing the diversity of the U.S. population based on the 2020 Census report (https://www2.census.gov/programs-surveys/decennial/2020/data/redistricting-supplementary-tables/redistricting-supplementary-table-04.pdf). A brief explanation of the derivation of the tables below is presented in Appendix J.

Overall Accrual goal: Ethnicity

Race	Ethnicity	Male	Female	Total
Any	Hispanic or Latino	94	94	188
Any	Not Hispanic or Latino	406	406	812
	Total	500	500	1000

Overall Accrual goal: Race

Race	Ethnicity	Male	Female	Total
White (alone)	Any	308	308	616
Black or African American (alone)	Any	62	62	124
American Indian and Alaska Native (alone)	Any	6	6	12
Asian (alone)	Any	30	30	60
Native Hawaiian or Other Pacific Islander (alone)	Any	1	1	2
Two or More Races	Any	51	51	102
Some Other Race	Any	42	42	84
	Total	500	500	1000

Since African Americans suffer the highest cancer incidence and mortality rates among all racial and ethnic groups, yet are persistently underrepresented in clinical trials and studies, CMB intends to oversample specific cancer types in which disparities are most pronounced and research progress in drug resistance and sensitivity could be significant. DRSN investigators studying PCA and MML indicated that biospecimens from African American patients as well as other minority groups would be of benefit since the majority of their current collections are derived from white (non-Hispanic) patients. Scientific questions of interest to DRSN investigators include molecular underpinnings of cancer incidence, therapy response and overall outcomes. Although the accrual targets below are ambitious, CMB will support patient-centric local engagement activities (Section 6) to facilitate these goals. If successful, this oversampling strategy could be applied to other cancer types in the future. A brief explanation of the derivation of the tables below is presented in Appendix J.

Oversampling Accrual goal: Ethnicity

PCA/MML		Accrual Goal	
Race	**Ethnicity**	**Number**	**Percent**
Any	Hispanic or Latino	28	18.7
Any	Not Hispanic or Latino	122	81.3
Total for each cancer type		150	100

Oversampling Accrual goal: Race

PCA/MML		Accrual Goal	
Race	**Ethnicity**	**Number**	**Percent**
White (alone)	Any	46	30.8
Black or African American (alone)	Any	50	33.3
American Indian and Alaska Native (alone)	Any	18	12.0
Asian (alone)	Any	18	12.0
Native Hawaiian or Other Pacific Islander (alone)	Any	18	12.0
Two or More Races	Any	-	-
Some Other Race	Any	-	-
Total for each cancer type		150	100

Observed cancer type/treatment percentages, percentages of patients receiving intervening therapies after fresh sample collection but before receipt of genomic results, underserved minority percentages, biospecimen quality percentages, assay success percentages, longitudinal sample percentages, and sample size will determine the width of 2-sided 95% confidence intervals calculated to estimate the true percentages, as demonstrated in the following table:

	Exact 2-sided 95% confidence interval for percentage			
Observed percentage	N=50	N=150	N=500	N=1000
10	(3.3, 21.8)	(5.7, 16.0)	(7.5, 13.0)	(8.2, 12.0)
20	(10.0, 33.7)	(13.9, 27.3)	(16.6, 23.8)	(17.6, 22.6)
30	(17.9, 44.6)	(22.8, 38.0)	(26.0, 34.2)	(27.2, 32.9)
40	(26.4, 54.8)	(32.1, 48.3)	(35.7, 44.4)	(36.9, 43.1)
50	(35.5, 64.5)	(41.7, 58.3)	(45.5, 54.5)	(46.9, 53.1)
60	(45.2, 73.6)	(51.7, 67.9)	(55.6, 64.3)	(56.9, 63.1)
70	(55.4, 82.1)	(62.0, 77.2)	(65.8, 74.0)	(67.1, 72.8)
80	(66.3, 90.0)	(72.7, 86.1)	(76.2, 83.4)	(77.4, 82.4)
90	(78.2, 96.7)	(84.0, 94.3)	(87.0, 92.5)	(88.0, 91.8)

To interpret this table, suppose, for example, that we are able to attempt molecular profiling on 90% of 400 enrolled patients at an interim monitoring timepoint. Then the 95% confidence interval for the percentage of specimen passing quality assessment is 86.6% - 92.8%. Similarly, we can interpret percentages for the other feasibility/accrual endpoints with 95% confidence as given in the table above.

9.3 Interim Monitoring

Analysis of results will be performed once every 3 months as biospecimens are processed. Information regarding biospecimen and assay quality, such as assay failure rate and reasons for failure, will be reviewed and actions put into place to remedy excessive failure rates. The distribution of demographics and cancer types will be monitored as patients complete screening.

CMB will apply enrollment modifications and perform protocol amendments as needed in order to meet the needs of specific NCI-sponsored cancer research initiatives, such as restriction on accrual of certain demographics, cancer types and/or standard of care treatment type.

9.4 Safety Monitoring

Safety monitoring is the responsibility of the study Co-PI. AEs are reported in a routine manner at scheduled times using Rave. In addition, expedited reporting through the CTEP-AERS mechanism is required for certain research biopsy-related AEs and death on study due to biopsy or specimen collection (Expedited Adverse Event Reporting; Section 8.3). After research biopsies are performed on the first 100 patients, a safety analysis will be performed to ensure that the incidence of biopsy-related serious adverse events (SAEs) ≤ 2%.

10. STUDY CALENDAR

* The most important collections are tissue and blood collected at baseline and progression

	Pre-Study Screening	Archival (Before Enrollment)	Baseline (Before Therapy) *	On Treatment	Post Treatment	Progression *
Informed Consent	X					
Performance Status	X					
Medical History[1]	X	X	X	X		X
Diagnosis / Staging[2]	X					
Re-Staging				X		X
Therapy[3]				X		X
Archival Biospecimens[4]		X				
Blood Collection[5]			X	X	X	X
Tissue Collection[6]			X			X
Anatomic Pathology Report for Diagnosis[7]	X					
New Pathology Report[6]				X		X
Molecular Pathology Reports[6,8]	X		X	X		X
Radiology Scans[6,9]	X		X	X		X
Adverse Event Evaluation			X	X		X

[1] Include baseline medical history, targeted and non-targeted treatment history with therapy assessment, social/environmental/occupational history, hematology information, procedure and operative reports.
[2] AML and MML patients must have completed standard exams (i.e., flow, cytogenetics) at screening.
[3] "Therapy" refers to the Appendix A treatment agent prescribed by the patient's physician, to be initiated after baseline biopsy (if applicable) is obtained; and the treatment actually received when progression was diagnosed. Includes treatment regimen and treatment summary.
[4] Archival biospecimen submission, meeting requirements in Section 7.2.1, is required if a patient, at the time of enrollment, is currently progressing OR being treated on a regimen containing an Appendix A therapy (see Section 4.1.2).
[5] New blood samples may be collected at any timepoint, synchronized with radiologic imaging. Please refer to CMB Protocol Laboratory Manual (vol 1) on CTSU for detailed description.
[6] When applicable.
[7] AML and MML patients must have diagnostic pathology report with blast cell determination
[8] Include previously performed tumor panel NGS tests as well as other biomarker and ancillary laboratory tests.
[9] Include any CT including PET/CT, MRI, and/or nuclear medicine scans.

11. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE, guidelines, and instructions for reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

11.1 Study Oversight

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical study, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other tissue procurement studies. The Protocol Principal Investigator and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

11.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type;
  - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role or Rave SLA must have at a minimum an Associates (A) registration type.

- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons

with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

11.2.1 Responsibility for Data Submission

It is the responsibility of the PI(s) at the site to ensure that all investigators at the NCORP/NCTN Sites understand the procedures for data submission and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Rave.

Data are to be submitted via to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the NCORP site to resolve. Monthly web-based reports are posted for review by the CTEP Principal Investigator for this protocol. Routine on-site audits are not planned. However, NCI reserves the right to conduct an on-site audit at any time in the event that there are concerns regarding data quality or patient safety.

CDUS data submissions will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The study's institutions are responsible for timely submission to CTMS via Rave, as above. Further information on

data submission procedures can be found at
http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11

11.2.2 Records Retention

All records pertaining to the study (including source documents) will be maintained for two years after study closure. Please contact CTEP prior to destroying any source documents.

11.2.3 Data Storage and Management

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary

table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

11.3 Data Sharing

As an NCI intramural Cancer Moonshot research project generating primary data, the CMB falls under the requirements of the NCI Cancer Moonshot Public Access and Data Sharing Policy ("CM Data Sharing Policy"). These requirements are in addition to the other NIH requirements referenced in the subsections below.

NCI Office of Data Sharing Supplemental Guidance to the CM Data Sharing Policy indicates that all data should be made publicly accessible as soon as possible, and no later than six months after a full, quality-controlled dataset has been produced. The CMB will provide clinical, genomic and imaging data on a rolling basis to the public repositories outlined in the following subsections, with a target of within three months from receipt of the data from the respective data provider to CMB submission into the public repository.

The CM Data Sharing Policy outlines requirements for the publications resulting from Cancer Moonshot research projects. The CMB data sharing processes are designed to enable investigators who use CMB data to meet these publication requirements, with respect to the public availability of the underlying data.

NCBI's Database of Genotypes and Phenotypes (dbGaP) will be used both to authorize investigators to access controlled CMB data and to distribute data as a publicly available database. CMB registered the project with dbGaP (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs002192.v1.p1). Registration will entail providing dbGaP with a certification from the CMB PI and Signing Official that, according to the IRB's review and approval of the patient consent, data may be distributed according to the processes described in this section.

NCI Cancer Moonshot Public Access and Data Sharing Policy
https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding/public-access-policy
NCI Office of Data Sharing Supplemental Guidance for Implementation of the NCI Cancer Moonshot Public Access and Data Sharing Policy
Available from NCI Office of Data Sharing

11.3.1 Clinical Data

Deidentified clinical data collected for this study will be made available to qualified investigators through secure methods. Clinical data collected in Rave will be submitted to dbGaP and/or CRDC by the CMB. Investigators will access clinical data via dbGaP. CMB is registered at dbGaP to facilitate this process.

Research projects using biospecimens from CMB are subject to the requirements in NIH policies for data sharing and public access to publications, listed below.

NCI Cancer Moonshot Public Access and Data Sharing Policy
https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding/public-access-policy

Final NIH Statement on Sharing Research Data
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html
http://grants.nih.gov/grants/policy/data_sharing/

11.3.2 Genomic Data

All genomic data collected in this study will be registered in dbGaP and stored in the CRDC, where controlled access is governed in accordance with the NIH Genomic Data Sharing Policy and other applicable guidelines. In particular, investigators who have agreed to the Data Use Agreement and are authorized by the dbGaP Data Use Committee will have access to all stored data on mutations and variants. Registration will occur via dbGaP.

Research projects using genomic data from CMB are subject to the requirements in NIH policies for data sharing and public access to publications, listed below.

NCI Cancer Moonshot Public Access and Data Sharing Policy
https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding/public-access-policy

NIH Genomic Data Sharing Policy
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html
http://gds.nih.gov/

Revised Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html
http://publicaccess.nih.gov/index.htm

11.3.3 Imaging Data

The data will physically reside at the NCI Cancer Imaging Archive (TCIA) (http://www.cancerimagingarchive.net/) and potentially at additional, future NCI imaging databases as part of the CRDC. The HIPAA compliant de-identified data will be publicly accessible via Internet web interfaces.

Research projects using image data from CMB are subject to the requirements of the NCI Cancer Moonshot Public Access and Data Sharing Policy.

NCI Cancer Moonshot Public Access and Data Sharing Policy
https://www.cancer.gov/research/key-initiatives/moonshot-cancer-

initiative/funding/public-access-policy

11.3.4 PDMR Data

Delinked clinical and genomic data will be stored in the NIH/NCI data system listed below.

PDMR Database: https://pdmdb.cancer.gov/pls/apex/f?p=101

11.4 Banking Translational Science Biospecimens for Future Research

Biospecimens stored in the BCR will be made available for NCI/DCTD-approved research projects. Please see Section 7.5 for more information on how biospecimens will be distributed to researchers. The BCR will not deplete a biospecimen unless written permission is received from the CMB PI or designee. Manual checks may occur at the time of distribution to confirm the amount available to the investigator. Once minimal amounts are reached, the CMB PI will be notified before biospecimens are distributed.

Sites can amend a patient's choice regarding the future use of the biospecimens at any time if the patient changes his or her mind; this information will be entered into Medidata Rave. At the time of biospecimen selection for project distribution, the most recent consent information stored in Medidata Rave will be determinative for distribution.

If the patient revokes permission to use the biospecimens, the BCR will destroy any remaining samples in its physical custody (i.e., biospecimens and derivatives, e.g., nucleic acids). When samples have already been distributed for research prior to revoking consent, recipients will be contacted with the request that the samples be destroyed per patient request; the program will not be able to guarantee such action on the part of recipients due to depletion of samples, etc. Analytical data derived from the patient's samples prior to revoking consent cannot be removed from research datasets in publications or databases. In some cases, NCI PDMR for example, the recipients of samples will have intentionally not maintained a link to a unique identifier for the participant and thus it would not be possible to request that PDM be destroyed or that distribution be discontinued. For additional details please see Patient Withdrawal (Section 12.4).

Patients and/or their providers may on occasion wish to locate remaining samples that could potentially be utilized for new clinical testing. CMB will make every attempt to locate such samples and when available send the samples back to the requestor, with the disclaimer if applicable that the sample may not have been processed and stored within a CLIA-certified laboratory.

11.5 Institutional Reimbursements

Institutions will be reimbursed, as per the contractual agreement, for study costs detailed in study-specific clinical services agreements (CSAs) executed with participating sites.

12. PATIENT CONSENT

Current FDA, NCI, state, federal and institutional regulations concerning informed consent, assent and authorization will be followed.

12.1 Patient Consent

Study participants or their legally authorized representative (LAR) must provide documented consent before their biospecimens may be admitted to the CMB and subsequently used in research studies.

12.2 Patient Assent for Participants Under the Age of Majority

Study participants who are under the age of majority (a person who has not reached the age where one is considered to be an adult, depending upon state law) must provide assent and there must be documented parental permission to enroll in CMB pursuant to regulatory requirements.

12.3 Legally Authorized Representative (LAR) for Decisionally Impaired Participants

For study participants who are decisionally impaired at the time of enrollment, or who become decisionally impaired during the course of the study, a LAR must be appointed pursuant to federal regulatory requirements and local law.

12.4 Patient Withdrawal

Study participants and their LAR may choose to leave the study at any time, upon request to their provider at the BSS or via the participant's individual secure login to the Engagement website. For patients less than the age of majority and persons with disabilities, the study site should be consulted regarding consent/assent for withdrawal. Sites must notify the CMB in the event of a participant-initiated withdrawal and complete the Off Study form in Rave.

As stated in Section 11.4, patient samples may include biospecimens and derivatives such as nucleic acids. If the patient revokes permission to use the samples, the BCR will destroy any remaining samples that are in the BCR's physical custody. When samples have already been distributed for research prior to revoking consent, recipients will be contacted with the request that the samples be destroyed per patient request; the program will not be able to guarantee such action on the part of recipients due to depletion of samples, etc. Analytical data derived from the patient's biospecimens prior to revoking consent cannot be removed from any research datasets in publications or databases. In some cases, NCI PDMR for example, the recipients of biospecimens will have intentionally not maintained a link to a unique identifier for the participant and thus it would not be possible to request that PDM be destroyed or that distribution be discontinued.

Patients may withdraw by communicating with study personnel at the site, using a project-specific SOP governing withdrawal, or online in the Engagement website. Three choices for withdrawal will be offered:

1. Complete Withdrawal: No further contact, no further collection of samples and data, and destruction of all samples and data at BCR. The program would additionally reach out to recipients of samples and request that remaining samples be destroyed.
2. Contact limited to electronic health record updates and sample use: No further contact, no further sample collection, but the patient allows the program to continue to get updates from their medical record and use their samples.
3. No future contact, continue to use samples: No contact of any kind, no further sample and data collection but previously collected data and samples can still be used.

APPENDIX A. ELIGIBLE CANCER TYPES AND SELECT LIST OF FDA-APPROVED THERAPIES

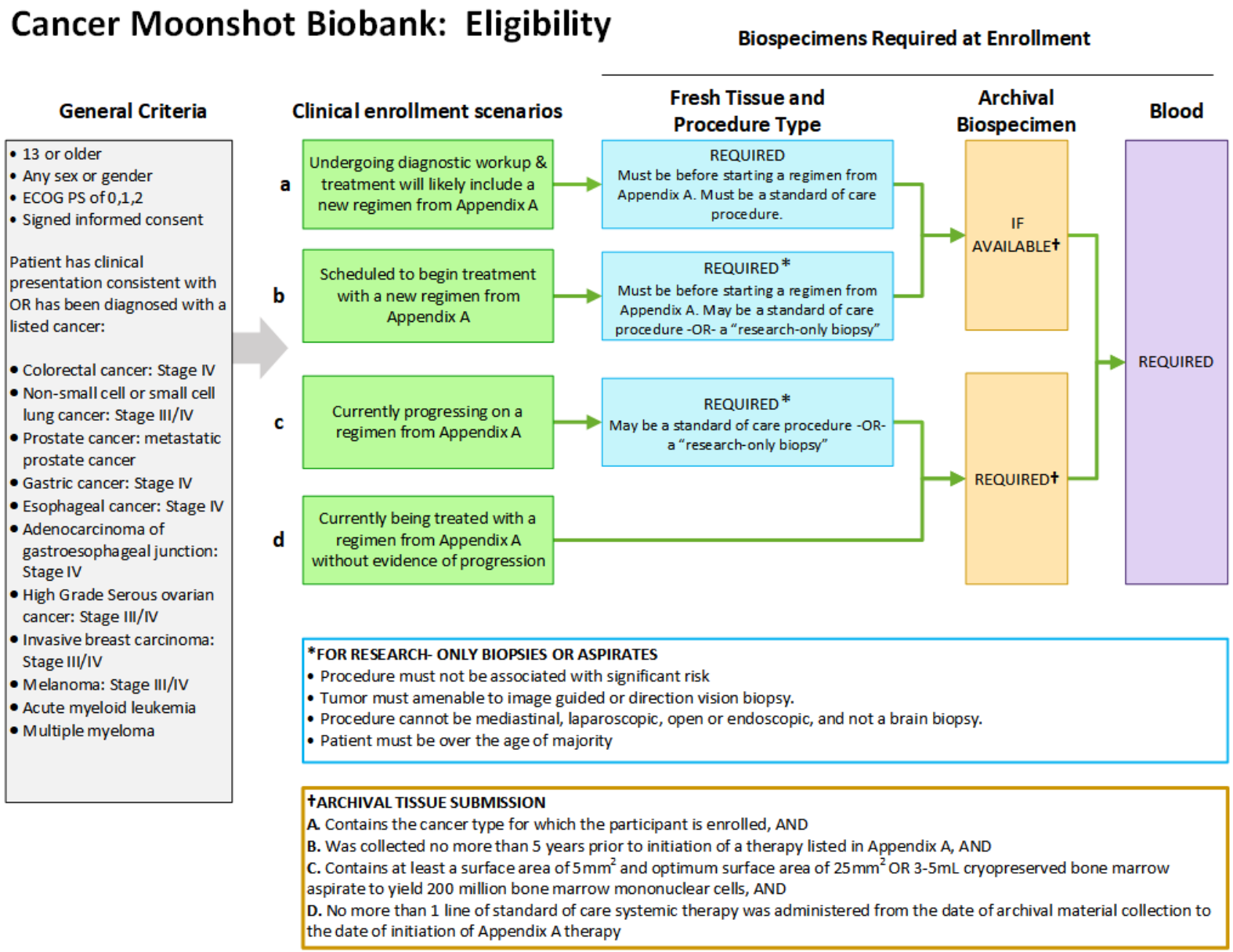
Therapies may be administered as a singular/monotherapy or in combination with any other therapies that constitute an FDA-approved (regular) treatment regimen.

Cancer Type	Therapy Targets	Drug Class	Drugs
Colorectal cancer (CRC)	EGFR	EGFR antagonists	cetuximab, panitumumab
	BRAF	BRAF antagonists	encorafenib + cetuximab
	VEGF	VEGF antagonists	bevacizumab, ramucirumab, regorafenib, ziv-aflibercept
	PD-1	PD-1 antagonist	pembrolizumab, nivolumab
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
Lung cancer (LCA; includes both small cell and non-small cell lung cancer)	ALK	ALK antagonists	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
	ROS1	ROS1 antagonist	crizotinib, entrectinib
	EGFR	EGFR antagonists	afatinib, erlotinib, gefitinib, osimertinib, dacomitinib
	PD-L1	PD-L1 antagonists	atezolizumab, durvalumab
	BRAF	BRAF antagonist	dabrafenib + trametinib
	PD-1	PD-1 antagonists	pembrolizumab, nivolumab, cemiplimab
	CTLA-4	CTLA-4 antagonist	ipilimumab, tremelimumab
	VEGF	VEGF antagonist	bevacizumab, ramucirumab
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
	MET	MET antagonist	capmatinib
	RET	RET antagonist	selpercatinib
Prostate cancer (PCA)	Androgen R	Androgen antagonists	abiraterone, apalutamide, enzalutamide, darolutamide, bicalutamide, flutamide, nilutamide
	GnRH	GnRH antagonist	relugolix, degarelix
	LHRH	LHRH agonists	leuprolide, goserelin, triptorelin
	PARP	PARP inhibitors	olaparib, talazoparib
	PD-1	PD-1 antagonists	pembrolizumab
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
	PSMA	PSMA inhibitor	lutetium Lu 177 vipivotide tetraxetan
	---	---	docetaxel, cabazitaxel
Gastroesophageal cancer (GEC; includes gastric cancer, esophageal	HER-2	HER-2 antagonist	trastuzumab, fam-trastuzumab deruxtecan-nxki
	VEGF	VEGF antagonist	ramucirumab
	PD-1	PD-1 antagonists	pembrolizumab, nivolumab

Cancer Type	Therapy Targets	Drug Class	Drugs
cancer, adenocarcinoma of GEJ)	NTRK	NTRK inhibitors	larotrectinib, entrectinib
	CTLA-4	CTLA-4 antagonist	ipilimumab
Breast Cancer (BRCA)	HER-2	HER-2 antagonists	trastuzumab, pertuzumab, margetuximab-cmkb, fam-trastuzumab deruxtecan-nxki, tucatinib, ado-trastuzumab emtansine, lapatinib
	PARP	PARP inhibitors	olaparib, neratinib, talazoparib
	PIK3CA	PI3K inhibitors	alpelisib
	mTOR	mTOR inhibitors	everolimus
	CDK 4/6	CDK 4/6 inhibitors	abemaciclib, palbociclib, ribociclib
	TROP2	TROP2 inhibitor	sacituzumab govitecan-hziy
	ER	ER degrader	elacestrant, anastrozole, exemestane, toremifene, letrozole, tamoxifen, fulvestrant
	PD-1	PD-1 antagonists	pembrolizumab
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
Ovarian Cancer (OV; includes ovarian epithelial cancer, fallopian tube carcinoma, primary peritoneal carcinoma)	PARP	PARP inhibitors	olaparib, niraparib, rucaparib
	VEGF	VEGF antagonist	bevacizumab
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
Melanoma (MEL)	BRAF	BRAF antagonists	dabrafenib, vemurafenib, encorafenib + binimetinib
	CTLA-4	CTLA-4 antagonist	ipilimumab
	PD-L1	PD-L1 antagonists	atezolizumab
	PD-1	PD-1 antagonists	pembrolizumab, nivolumab
	LAG-3	LAG-3 inhibitor	relatlimab
	MEK	MEK inhibitor	cobimetinib, trametinib
	NTRK	NTRK inhibitors	larotrectinib, entrectinib
Acute myeloid leukemia (AML)	FLT3	FLT3 antagonist	midostaurin, gilteritinib, quizartinib
	IDH1	IDH1 antagonist	ivosidenib, olutasidenib
	IDH2	IDH2 antagonist	enasidenib
	CD33	CD33 antagonist	gemtuzumab ozogamicin
	SMO	SMO antagonist	glasdegib
	BCL2	BCL2 inhibitor	venetoclax
Multiple myeloma (MML)	Proteasome	Proteasome inhibitor	bortezomib, carfilzomib, ixazomib
	CD38	CD38 antagonist	daratumumab, isatuximab-irfc

Cancer Type	Therapy Targets	Drug Class	Drugs
	SLAMF7	SLAMF7 antagonist	elotuzumab
	BCMA	BCMA antagonist	belantamab mafodotin
	CRM1	CRM1 antagonist	selinexor
	Immune	Immunomodulator	lenalidomide, pomalidomide

APPENDIX B. ELIGIBILITY FLOWCHART



APPENDIX C. KEY ABBREVIATIONS

AB	Associate Basic
AE	Adverse Event
AML	Acute Myeloid Leukemia
ALL	Acute Lymphoblastic Leukemia
ANT	Adjacent Non-Tumor
AP	Associate Plus
BBRB	Biorepositories and Biospecimen Research Branch
BCR	Biospecimen Core Resource
BM	Bone Marrow
BMP	Bitmap File Format
BRCA	Breast Cancer
BSS	Biospecimen Source Site
CAP	College of American Pathologists
CDUS	Clinical Data Update System
CDP	Cancer Diagnosis Program
CFR	Code of Federal Regulations
CI	Clinical Investigator
CIP	Cancer Imaging Program
CIRB	NCI Central Institutional Review Board
CLIA	Clinical Laboratory Improvement Amendments
CMB	Cancer Moonshot Biobank
CNB	Core Needle Biopsy
CNS	Central Nervous System
CRC	Colorectal Cancer
CRDC	Cancer Research Data Commons
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organizations
CSA	Clinical Site Agreements
CT	Computed Tomography Scan
CTCAE	NCI Common Terminology Criteria for Adverse Events
CTEP	NCI Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTMS	Clinical Trial Management System
CTSU	Cancer Trials Support Unit
DQP	Data Quality Portal
dbGaP	database of Genotypes and Phenotypes
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DICOM	Digital Imaging and Communications in Medicine
DO	Doctor of Osteopathic Medicine
dMMR	Deficient MisMatch Repair
DRSN	NCI Drug Resistance and Sensitivity Network
DTL	Delegation of Tasks Log

eConsent	Electronic Consent
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediamine Tetra Acetic Acid
EHR	Electronic Health Records
ESP	External Scientific Panel
ETCTN	Experimental Therapeutics Clinical Trials Network
ELSI	Ethical Legal and Social Implications
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FNA	Fine Needle Aspirate
FNLCR	Frederick National Laboratory for Cancer Research
FTP	File Transfer Protocol
FWA	Federal Wide Assurance
GEC	Gastroesophageal Cancer
GEJ	Gastroesophageal Junction
H&E	Hematoxylin and Eosin
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HNSC	Head and Neck Squamous Cell Carcinoma
IAM	Identity and Access Management
IC	NIH Institute and Center
IDE	Investigational Device Exemption
IMS	Information Management Systems
IND	Investigational New Drug
IRB	Institutional Review Board
IROC	Imaging and Radiation Oncology Core
IME	Important Medical Event
IVR	Investigator
IWRS	Theradex Interactive Web Response System
LAR	Legally Authorized Representative
LBR	Leidos Biomedical Research, Inc.
LCA	Lung Cancer
LPO	Lead Protocol Organization
MD	Doctor of Medicine
MEL	Melanoma
MML	Multiple Myeloma
MOU	Memorandum of Understanding
MRI	Molecular Resonance Imagery
MSI-H	Microsatellite Instability-High
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCORP	NCI Community Oncology Research Program
NCTN	National Clinical Trials Network
NGS	Next-Generation Sequencing
NHLBI	National Heart, Lung, and Blood Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney

NMA	NCI-Myeloid Assay
NPIVR	Non-Physician Investigator
OCA	Oncomine Comprehensive Assay
OPEN	Oncology Patient Enrollment Network
OV	Ovarian Cancer
PB	Peripheral Blood
PBMC	Peripheral Blood Mononuclear Cells
PCA	Prostate Cancer
PDM	Patient Derived Model
PDMR	NCI Patient Derived Models Repository
PDX	Patient-Derived Xenografts
PET	Positron Emission Imagery
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PPE	Participant and Provider Engagement
PS	Performance Status
QR	Quick Response Barcode
RCR	Registration and Credential Repository
REB	Research Ethics Board
RSS	Regulatory Support System
RUMS	Roster Update Management System
SAE	Serious Adverse Event
SARC	Sarcoma
sIRB	Single Institutional Review Board
SIW	Signatory Institution Worksheet
SOP	Standard Operating Procedure
SPID	Surgical Pathology ID
SSN	Social Security Number
SSW	Study Specific Worksheet for Local Context
STS	Rave Specimen Tracking System
TCIA	The Cancer Imaging Archive
TRIAD	Transfer of Images and Data
UPID	Universal Patient ID

APPENDIX D. BIOSPECIMEN AND DATA COLLECTION GUIDELINES BY CANCER TYPE

* The most important collections are tissue and blood collected at baseline and progression

Solid Tumors

Timepoint	Biospecimens	Images	Reports
Archival	• Blood EDTA and Streck tubes *if available* • Tissue FFPE or unstained slides Fresh frozen *if available* Adjacent non-tumor *if available*	H&E slide CT, MRI, PET	Clinical History Occupational History Radiology Pathology Biomarker Tests
Baseline *	• Blood EDTA and Streck tubes • Tissue Formalin fixed (2 cores) Fresh (1 core) PDM *if applicable* Fresh frozen (2-3 cores) Adjacent non-tumor (1 core) *if possible*	H&E slide CT, MRI, PET	Treatment Regimen Procedure Report Radiology Pathology Biomarker Tests
On Treatment	• Blood EDTA and Streck tubes • Tissue Formalin fixed (2 cores) Fresh frozen (2-3 cores) Adjacent non-tumor (1 core) *if possible*	H&E slide CT, MRI, PET	Treatment Assessment Procedure Report Radiology Pathology Biomarker Tests
Post Treatment	• Blood EDTA and Streck tubes	None	Treatment Assessment
Progression *	• Blood EDTA and Streck tubes • Tissue Formalin fixed (2 cores) Fresh (1 core) PDM *if applicable* Fresh frozen (2-3 cores) Adjacent non-tumor (1 core) *if possible*	H&E slide CT, MRI, PET	Treatment Summary Procedure Report Radiology Pathology Biomarker Tests

Hematologic Malignancies

Timepoint	Biospecimens	Images	Reports
Archival	• Blood EDTA and Streck tubes *if available* • BM Aspirate *if available* FFPE or unstained slides Fresh frozen *if available* Adjacent non-tumor *if available*	H&E slide CT, MRI, PET	Clinical History Occupational History Radiology Pathology Biomarker Tests
Baseline *	• Blood EDTA and Streck tubes • BM Aspirate Biopsy Fresh PDM *if applicable* Fresh frozen Adjacent non-tumor *if possible*	H&E slide CT, MRI, PET	Treatment Regimen Procedure Report Radiology Pathology *with blast cell information* Biomarker Tests
On Treatment	• Blood EDTA and Streck tubes • BM Aspirate Biopsy Fresh frozen Adjacent non-tumor *if possible*	H&E slide CT, MRI, PET	Transplant Report Treatment Assessment Procedure Report Radiology Pathology *with blast cell information* Biomarker Tests
Post Treatment	• Blood EDTA and Streck tubes	None	Treatment Assessment
Progression *	• Blood EDTA and Streck tubes • BM Aspirate Biopsy Fresh PDM *if applicable* Fresh frozen Adjacent non-tumor *if possible*	H&E slide CT, MRI, PET	Treatment Summary Procedure Report Radiology Pathology *with blast cell information* Biomarker Tests

APPENDIX E. GENES IDENTIFIED BY THE ONCOMINE COMPREHENSIVE ASSAY VERSION 3 PANEL NGS ASSAY

The Oncomine Comprehensive Assay version 3 (OCAv3) panel interrogates variants in 161 unique cancer-related genes. Within these genes, it interrogates >3,000 known mutations and polymorphisms in the 161 unique genes. It additionally reports non-hotspot mutations. These include any variant in a tumor suppressor gene that would be predicted to introduce a stop codon in the translated protein. The test identifies all variant classes including SNVs, small and large (≥3 bp) Indels, Copy Number Variants (CNVs), and Fusions. The list of genes interrogated by the panel is below.

Hotspot Genes (n=87)				Tumor Suppressor Genes with Deleterious Mutations (n=48)			Amplified Genes (n=47)			Fusion Driver Genes (n=51, 762 assays)		
AKT1	*ESR1*	*KIT* *	*PDGFRB*	*ARID1A*	*NF1* *	*STK11* *	*AKT1*	*FGFR2*	*TERT*	*AKT2*	*KRAS*	*RB1* *
AKT2	*EZH2*	*KNSTRN*	*PIK3CA*	*ATM* *	*NF2* *	*TP53* *	*AKT2*	*FGFR3*	*TSC1* *	*ALK*	*MDM4*	*RELA*
AKT3	*FGFR1*	*KRAS*	*PIK3CB*	*ATR*	*NOTCH1*	*TSC1* *	*AKT3*	*FGFR4*	*TSC2* *	*AR*	*MET*	*RET* *
ALK	*FGFR2*	*MAGOH*	*PPP2R1A*	*ATRX*	*NOTCH2*	*TSC2* *	*ALK*	*FLT3*		*AXL*	*MYB*	*ROS1*
AR	*FGFR3*	*MAP2K1*	*PTPN11*	*BAP1* *	*NOTCH3*		*AR*	*IGF1R*		*BRAF*	*MYBL1*	*RSPO2*
ARAF	*FGFR4*	*MAP2K2*	*RAC1*	*BRCA1* *	*PALB2*		*AXL*	*KIT* *		*BRCA1* *	*NF1* *	*RSPO3*
AXL	*FLT3*	*MAP2K4*	*RAF1*	*BRCA2* *	*PIK3R1*		*BRAF*	*KRAS*		*BRCA2* *	*NOTCH1*	*TERT*
BRAF	*FOXL2*	*MAPK1*	*RET* *	*CDK12*	*PMS2* *		*CCND1*	*MDM2*		*CDKN2A* *	*NOTCH4*	
BTK	*GATA2* *	*MAX* *	*RHEB*	*CDKN1B*	*POLE1*		*CCND2*	*MDM4*		*EGFR* *	*NRG1*	
CBL	*GNA11*	*MDM4*	*RHOA*	*CDKN2A* *	*PTCH1* *		*CCND3*	*MET*		*ERBB2*	*NTRK1*	
CCND1	*GNAQ*	*MED12*	*ROS1*	*CDKN2B*	*PTEN* *		*CCNE1*	*MYC*		*ERBB4*	*NTRK2*	
CDK4 *	*GNAS*	*MET*	*SF3B1*	*CHEK1*	*RAD50*		*CDK2*	*MYCL*		*ERG*	*NTRK3*	
CDK6	*H3F3A*	*MTOR*	*SMAD4* *	*CREBBP*	*RAD51*		*CDK4* *	*MYCN*		*ESR1*	*NUTM1*	
CHEK2 *	*HIST1H3B*	*MYC*	*SMO*	*FANCA*	*RAD51B*		*CDK6*	*NTRK1*		*ETV1*	*PDGFRA* *	
CSF1R	*HNF1A*	*MYCN*	*SPOP*	*FANCD2*	*RAD51C*		*CDKN2A* *	*NTRK2*		*ETV4*	*PDGFRB*	
CTNNB1	*HRAS*	*MYD88*	*SRC*	*FANCI*	*RAD51D*		*CDKN2B*	*NTRK3*		*ETV5*	*PIK3CA*	
DDR2	*IDH1*	*NFE2L2*	*STAT3*	*FBXW7*	*RB1* *		*EGFR* *	*PDGFRA* *		*FGFR1*	*PPARG*	
EGFR *	*IDH2*	*NRAS* *	*TERT*	*MLH1*	*RNF43*		*ERBB2*	*PDGFRB*		*FGFR2*	*PRKACA*	
ERBB2	*JAK1*	*NTRK1*	*TOP1*	*MRE11A*	*SETD2*		*ESR1*	*PIK3CA*		*FGFR3*	*PRKACB*	
ERBB3	*JAK2* *	*NTRK2*	*U2AF1*	*MSH2* *	*SLX4*		*FGF19*	*PIK3CB*		*FGR*	*PTEN* *	
ERBB4	*JAK3*	*NTRK3*	*XPO1*	*MSH6* *	*SMARCA4*		*FGF3*	*PPARG*		*FLT3*	*RAD51B*	
ERCC2	*KDR*	*PDGFRA* *		*NBN*	*SMARCB1* *		*FGFR1*	*RICTOR*		*JAK2* *	*RAF1*	

APPENDIX F. GENES IDENTIFIED BY THE NCI-MYELOID ASSAY

The NCI-Myeloid Assay runs on the Ion Torrent Genexus System, a fully automated next generation sequencing (NGS) platform that provides a turnaround time of <48 hours from specimen receipt to clinical reporting. The assay provides targeted coverage of hotspot gene mutations and fusions for accurate classification of myeloid disorders per WHO guidelines, covering 45 DNA genes and 35 fusion genes. The assay, which includes 93.3% of genes with mutations at >=3% frequency and 72% of genes with mutations at >1% frequency in AML, has been analytically validated at the Molecular Characterization Lab (MoCha).

Hotspot (28)		**Full gene (17)**		**Fusion (35)**	
• ABL1 • ANKRD26 • BRAF • CBL • CSF3R • DDX41 • DNMT3A • FLT3 • GATA2 • HRAS • IDH1 • IDH2 • JAK2 • KIT • KRAS	• MPL • MYD88 • NPM1 • NRAS • PPM1D • PTPN11 • SETBP1 • SF3B1 • SMC1A • SMC3 • SRSF2 • U2AF1 • WT1	• ASXL1 • BCOR • CALR • CEBPA • ETV6 • EZH2 • IKZF1 • NF1 • PHF6	• PRPF8 • RB1 • RUNX1 • SH2B3 • STAG2 • TET2 • TP53 • ZRSR2	• ABL1 • ABL2 • BCL2 • BRAF • CCND1 • CREBBP • EGFR • ETV6 • FGFR1 • FGFR2 • FUS • HMGA2 • JAK2 • KAT6A (MOZ) • KAT6B • KMT2A • KMT2A-PTDs	• MECOM • MET • MLLT10 • MRTFA (MKL1) • MYBL1 • MYH11 • NTRK2 • NTRK3 • NUP214 • NUP98 • PAX5 • PDGFRA • PDGFRB • RARA • RUNX1 • TCF3 • TFE3 • ZNF384

APPENDIX G. HEREDITARY AND GERMLINE MUTATIONS

The OCA and NMA assays examine tumor tissue only and do not examine normal (non-tumor) tissue. Mutations detected by the assay may be present only in the tumor, or in every cell of the body (including non-tumor cells). These tests also cannot tell whether a potential germline mutation causes or will cause a hereditary cancer syndrome. If the patient's history includes any one or combination of features suggestive of a possible hereditary cancer predisposition (such as, cancer arising at a young age, especially a cancer of a type unusual in younger patients; a personal history of multiple different types of cancers; or a significant cancer history among blood relatives, especially but not exclusively of the same type as the patient's) it is recommended that the physician arrange for the patient to meet with a genetic counselor and, if warranted, undergo the appropriate genetic test on normal (i.e. non-tumor) tissue (blood or cells brushed from the oral surface of the cheek) to check for a germline abnormality, regardless of the results of this research study.

Mutations in genes that are tested for by the OCA NGS Assay and that, when present in normal tissue, may be associated with hereditary cancer conditions are indicated (*) in the table in Appendix E. Listed genes were identified based on currently available published data about known associations with certain health issues. Results demonstrating a mutation in one of these genes may or may not be compatible with a germline mutation. Please refer to the publication "Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics" [Kalia SS et al. Genetics in Medicine volume 19, pages 249–255 (2017)] for further information.

APPENDIX H. NCI PDMR ELIGIBILITY CRITERIA

Exclusion Criteria

1. Patients with CRC that is not mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H).
2. Patients with complete response.
3. Patients with invasive fungal infections.
4. Patients with active and/or uncontrolled infections or who are still recovering from an infection.
   a.) Actively febrile patients with uncertain etiology of febrile episode.
   b.) All antibiotics for non-prophylactic treatment of infection should be completed at least 1 week (7 days) prior to collection.
   c.) No recurrence of fever or other symptoms related to infection for at least 1 week (7 days) following completion of antibiotics.
5. Patients with Human Immunodeficiency Virus (HIV), active or chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA) or known history of HBV/HCV without documented resolution.

APPENDIX I. DEFINITIONS FOR TARGETED AND NON-TARGETED THERAPY

- **Targeted Therapy:** Any therapy in Appendix A, received by the patient prior to enrollment and/or while on the study.
- **Non-Targeted Therapy:** Any therapy that is **not** in Appendix A, received by the patient prior to enrollment and/or while on the study. This includes non-Appendix A therapies that are given to the patient separately or as part of a regimen that includes targeted therapies.

APPENDIX J. DERIVATION OF PLANNED ENROLLMENT REPORT

All numbers were extracted from the 2020 Census reports. Accrual goals were based on race and ethnicity separately due to changes in race and ethnicity questions in the 2020 Census as compared to the 2010 Census. The percent male (50.0%) and female (50.0%) were split evenly since the 2020 Census had not reported gender and sex numbers. Data was sourced from the 2020 redistricting supplementary tables as per Public Law 94-171: https://www2.census.gov/programs-surveys/decennial/2020/data/redistricting-supplementary-tables/redistricting-supplementary-table-04.pdf.

The 2020 Census provides tabulation based on "Some Other Race." During registration in OPEN, and by extension Medidata Rave, the following Race options are available with more than one choice possible: White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Not Reported, and Unknown. Patients registered at enrollment in OPEN under "Not Reported" or "Unknown" will be tabulated as "Some Other Race."

Based on a reported percentage of Hispanic or Latino population (all races) of 18.7%, the CMB aims to accrue 188 Hispanic or Latinos (rounded up) and 812 Not Hispanic or Latinos. Similarly, based on White (alone) among Hispanic or Latinos (3.8%) or Not Hispanic or Latino (57.8%) combined for a total of 61.6%, the CMB plans to accrue 616 White (alone) participants. Other races are calculated similarly.

Percent of Population by Ethnicity and Race for the 2020 United States Census

Race	Hispanic or Latino (%)	Not Hispanic or Latino (%)	Total (%)	Male (%)	Female (%)
White (alone)	3.80	57.84	61.63	30.82	30.82
Black or African American (alone)	0.35	12.05	12.40	6.20	6.20
American Indian and Alaska Native (alone)	0.45	0.68	1.12	0.56	0.56
Asian (alone)	0.08	5.92	6.00	3.00	3.00
Native Hawaiian or Other Pacific Islander (alone)	0.02	0.19	0.21	0.10	0.10
Two or More Races	6.12	4.09	10.21	5.11	5.11
Some Other Race	7.91	0.51	8.42	4.21	4.21
Total	**18.73**	**81.27**	**100.00**	**50.00**	**50.00**

Oversampling Goals

The oversampling accrual targets for PCA and MML are also derived from the 2020 Census, and are calculated as follows:

a) Enrollment of at least 50 study participants of Black or African American descent (any ethnicity) for each cancer type to provide a more robust sampling size for research*.
b) Distribution of remaining 100 among other races.
    a. Decreased representation of White alone (any ethnicity) population by half (from 61.6% to 30.8%) for a total of 46 participants.
    b. Asian (alone), American Indian and Alaska Native (alone), Native Hawaiian or Other

Pacific Islander (alone) were split equally among the remaining 54 participants for 18 each.

c. Two or More Races and Not reported or Unknown will not be specifically targeted with respect to PCA or MML cancer types.

c) Hispanic or Latino (all races) remained at 18.7% for a total of 28 participants.

*CMB aims to provide investigators with longitudinal biospecimens to facilitate their research; therefore, no specific working hypothesis is being tested. We cannot determine at this point in time whether 50 study participants will offer sufficient statistical power for any particular study. The proposed sample size was derived to improve statistical power compared to overall enrollment targets while considering limited resources.

APPENDIX K. ENGAGEMENT WEBSITE SURVEY

The NCI Cancer Moonshot Biobank website survey is designed to evaluate the knowledge and experience of patients and healthcare professionals regarding usability of the Biobank engagement website and portal. The questionnaire is comprised of two sections, questions designed for patients and questions designed for healthcare professionals such as physicians and clinical research associates. All surveys will be anonymous and no PII will be collected. Collected information includes:

1. Demographics (age, sex, race, marital status, race/ethnicity, education, and income).
2. Provider practice information (occupation; specialty; practice setting; geography, i.e. rural or urban; practice services, i.e. on-site pathology, genetic counselor, or other)
3. Experience and satisfaction with Biobank website and portal and resources
4. Familiarity with biomarker testing among healthcare professionals
5. Electronic health records (EHR) use
6. Internet access among participants

Survey link: https://nci.az1.qualtrics.com/jfe/form/SV_78rY5TJOwKddtVs

Study Population

The target population are patients enrolled in the Cancer Moonshot Biobank study and healthcare professionals at participating Biobank program sites.

Recruitment and Screening

The healthcare team at participating Biobank hospitals and clinics will be encouraged to discuss the Biobank Patient and Provider Engagement (PPE) portal with eligible patients. The survey will be disseminated through the PPE portal to enrolled participants and healthcare providers who have activated their accounts.

Consent Process

Individuals will be presented with the informed consent screen which includes a description of the survey, the right to terminate participation at any point in time, security of the data, and how the survey information will be handled and used by the study. See "*Survey Screener Informed Consent*", below. Each respondent will be required to click the "NEXT" button to indicate that they have read the consent information and agree to continue. The respondent will not be allowed to enter the survey unless they click the "NEXT" button. By clicking "NEXT" to continue, respondents will give their implicit consent to participate. During the survey, respondents will be allowed to skip any question that they do not prefer to answer.

Research Methods

Data collection for this study will be conducted through an online survey developed and hosted on Qualtrics. Respondents will be invited to take the survey, comprised of both multiple choice and text entry questions. A study invitation, which includes the URL address for the survey, will be sent to eligible patient and provider participants through their Biobank portal accounts. Healthcare providers may also receive a link via email. Participants will be able to anonymously complete the survey at a location and time of their choice. The survey will take approximately 8 to 10 minutes to complete, and there will be no compensation provided to participants. The

questionnaire was independently evaluated by multiple members of the study team. All survey responses downloaded from Qualtrics will be anonymous and the study team will not collect or have access to any identifying information such as name or contact information.

Efforts will also be focused on disseminating study results, as well as potential future steps, through multiple avenues. Newsletters and press releases will be published on the Biobank engagement website and sent through the Biobank portal to update enrolled patients and healthcare professionals of the results of the survey, further demonstrating a vested interest in promoting patient and provider engagement. These results may also be disseminated to participating hospitals and clinics to share with staff and patients through their network and to patient advocacy organizations. Results will also be published to be disseminated to the wider community through reports, scientific journal articles, conference presentations, and social media.

Risks and Benefits of Participation

Risks

There is a small risk to the respondent's privacy. This risk is minimized by conducting data collection through Qualtrics, a cloud-based online survey tool, using a general survey URL sent to all participants and providers. Names or personal identifiers are not collected in the questionnaire and will not be included or mentioned in the results. Respondents may skip any question they do not wish to answer and/or may withdraw from completing the survey at any time without repercussion.

Benefits

There are no direct benefits to respondents, although respondents might benefit indirectly from the knowledge that they are providing valuable information to improve patient and provider engagement in biospecimen collection and cancer research.

Data Analysis Plans

Statistical analysis on both screener and survey data will be completed using statistical software such as SPSS or STATA. Analyses will include descriptive statistics for demographic characteristics and all major study variables.

Privacy, Data Storage, and Confidentiality

Names and contact information will not be collected by the survey or by Qualtrics. Survey responses will be secured on NCI servers and laptops with two-factor authentication. Access to data will be limited to personnel authorized to work on the project. The Biobank will have access only to respondent data, not names or other personally identifiable information. The data may be retained indefinitely.

Survey Screener Informed Consent

This following content screen will be shown to survey visitors to obtain consent to proceed prior to their starting the survey. Participant must click "next" to consent and begin the survey:

Welcome to the NCI Cancer Moonshot Biobank Survey!

We would like to know what you think about the Biobank engagement website and portal. This purpose of this survey is to understand how we can meet your needs and improve our efforts in providing resources to engage patients, caregivers, and healthcare professionals in biomedical research.

This survey will take about 8 - 10 minutes to complete. Your participation in this survey is voluntary. You may choose not to answer any question. You may also exit the web survey at any time. All information obtained from this study will remain anonymous and confidential and will be secured on NCI servers and laptops with two-factor authentication. Access to data will be limited to Biobank personnel authorized to work on the project.

If you have questions about this research, please contact us at Moonshotbiobank@nih.gov. If you have questions about your rights and welfare as a research participant, please call Advarra IRB at (877) 992-4724 or by email at adviser@advarra.com. Please do not include sensitive information or personal health information in your email.

If you agree to participate, please click "NEXT" to continue.

Thank you for your time!

Survey questions

Below are the survey questions to be administered to patients and/or providers:

2. Are you a patient or patient guardian?
   - ☐ Yes GO TO PATIENT/PATIENT GUARDIAN BLOCK (QUESTION 32)
   - ☐ No GO TO PROVIDER BLOCK (QUESTION 3)

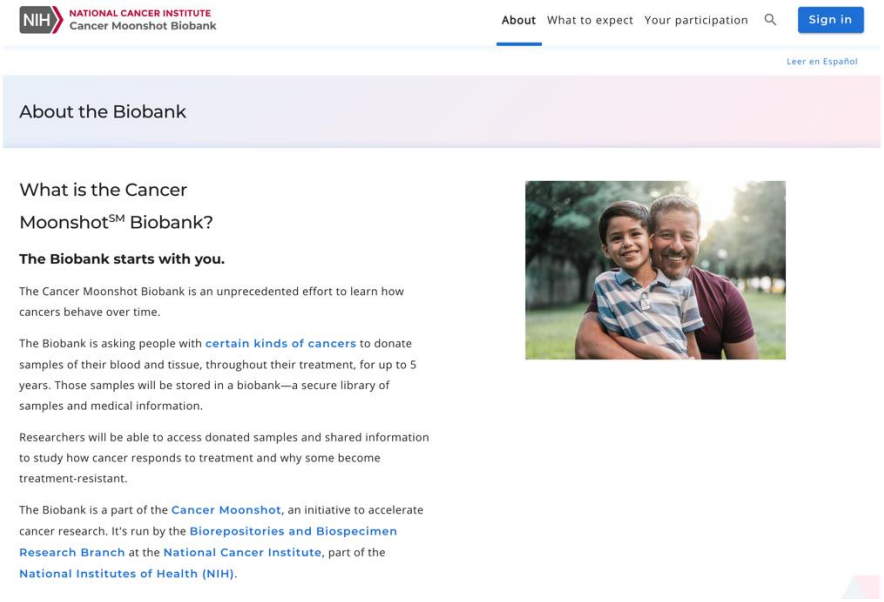
PROVIDER BLOCK

3. Please select your occupation:
   - ☐ Physician
   - ☐ Nurse Practitioner
   - ☐ Clinical Research Associate
   - ☐ Physician Assistant
   - ☐ Other (please specify): _____ TEXT FIELD. 50 CHARACTERS INCLUDING

SPACES.

Biobank PPE portal

4. Have you visited the **Biobank website?**



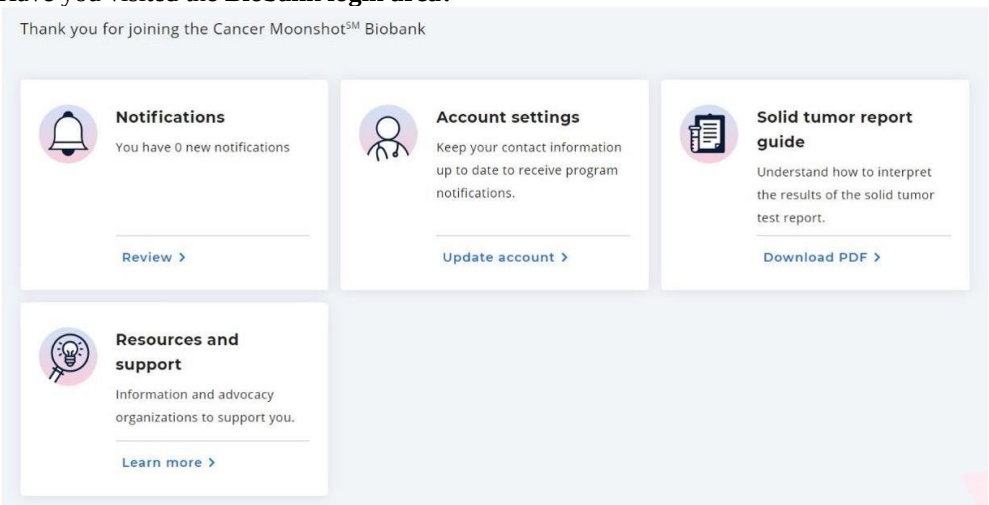
☐ Yes.
☐ No. SKIP TO QUESTION 7.

5. Have you used the **Biobank website** for any of the following reasons? Select all that apply.
   ☐ To find information about the Cancer Moonshot Biobank program.
   ☐ To find the location of a hospital participating in cancer research.
   ☐ To look for other medical research projects/clinical trials.
   ☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

6. Below are a number of statements regarding your satisfaction with the **Biobank website**. Please read each one and indicate to what extent you agree or disagree with each statement.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
This website is easy to use.	☐	☐	☐	☐	☐
I trust the information on this website.	☐	☐	☐	☐	☐
I can easily understand the information presented on the website.	☐	☐	☐	☐	☐
The language on the Biobank website made it easy to understand.	☐	☐	☐	☐	☐
I can find information I need easily and quickly on this website.	☐	☐	☐	☐	☐
Information on this website helps me have a better understanding of patient participation in cancer research.	☐	☐	☐	☐	☐
Information on this website makes me more confident in discussing cancer research with patients.	☐	☐	☐	☐	☐

7. Have you visited the **Biobank login area?**



☐ Yes.
☐ No. SKIP TO QUESTION 10.

8. Have you used the **Biobank login area** for any of the following reasons? Select all that apply.
☐ To activate a new patient account.
☐ To update contact information.
☐ To upload or view participant biomarker report.

☐ To view participant information.
☐ To view participant signed consent form.
☐ To view participant's provider contact information.
☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

9. Below are a number of statements regarding your satisfaction with the **Biobank login area.** Please read each one and indicate to what extent you agree or disagree with each statement.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
The website login area is easy to use.	☐	☐	☐	☐	☐
I trust the information in the website login area.	☐	☐	☐	☐	☐
I can find information I need easily and quickly in the website login area.	☐	☐	☐	☐	☐
I can easily understand the information presented on website login area.	☐	☐	☐	☐	☐
I understand the instructions on how to manage information through the website login area.	☐	☐	☐	☐	☐

10. Did you find the annotated sample biomarker reports helpful to understanding your patient's biomarker test results?

Sample reports and guides

Solid tumors

Sample biomarker report - solid tumors

View sample report

Guide to the biomarker report for solid tumors

View guide

☐Yes
☐No
☐Not applicable

11. Have you used the biomarker test results to help you make a decision about your patient's health?
    - ☐ Yes
    - ☐ No
    - ☐ Not applicable

12. In the past 30 days, how many times did you visit the Biobank website?
    - ☐ None
    - ☐ 1 to 2 times
    - ☐ 3 to 5 times
    - ☐ 6 to 9 times
    - ☐ 10 or more times

Familiarity with biomarker testing

13. Do you currently use biomarker testing as part of your duties?
    - ☐ Yes GO TO QUESTION 14
    - ☐ No SKIP TO QUESTION 16

14. In general, how often do you use a biomarker test for the following purposes?

	Never	Sometimes	Most of the time	Always	N/A
Provide diagnostic information	☐	☐	☐	☐	☐
Provide prognostic information	☐	☐	☐	☐	☐
Determine patient eligibility for clinical trials	☐	☐	☐	☐	☐
Inform treatment recommendations	☐	☐	☐	☐	☐
Provide patients with an understanding of their disease and guide decision-making.	☐	☐	☐	☐	☐

15. In general, how important was each of the following factors in your decision to use biomarker testing for a patient?

	Not at all important	Slightly important	Moderately important	Very important	N/A
Patient or patient family's preferences	☐	☐	☐	☐	☐
Test is covered by insurance	☐	☐	☐	☐	☐
Treatment covered by insurance	☐	☐	☐	☐	☐
Out-of-pocket expenses for treatment	☐	☐	☐	☐	☐
Out-of-pocket expenses for testing	☐	☐	☐	☐	☐

16. In general, how important was each of the following factors in your decision **not** to use biomarker testing for a patient?

	Never	Sometimes	Most of the time	Always	N/A
Biomarker testing was not recommended by clinical practice guidelines for the patient.	☐	☐	☐	☐	☐
Biomarker testing was not available at my practice.	☐	☐	☐	☐	☐
Biomarker testing was not covered by insurance.	☐	☐	☐	☐	☐
Reimbursement for biomarker testing was insufficient.	☐	☐	☐	☐	☐
I do not have the personnel and resources to obtain tissue for testing.	☐	☐	☐	☐	☐
I do not have the resources to interpret tests.	☐	☐	☐	☐	☐
I do not have enough time to order or review tests.	☐	☐	☐	☐	☐
Patient or patient family prefers not to use a biomarker test.	☐	☐	☐	☐	☐

17. In general, how confident are you in your ability to use biomarker test results to guide patient treatment and management?
    - ☐ Not at all confident
    - ☐ A little confident
    - ☐ Moderately confident
    - ☐ Very confident

18. In general, how confident are you in your ability to explain biomarker testing purpose and procedures to a patient?
    - ☐ Not at all confident
    - ☐ A little confident
    - ☐ Moderately confident
    - ☐ Very confident

19. In general, how often do patients initiate discussion about testing?
    - ☐ Always
    - ☐ Most of the time
    - ☐ About half the time
    - ☐ Sometimes
    - ☐ Never

20. In general, how often have you referred patients out for testing?
    - ☐ Always
    - ☐ Most of the time
    - ☐ About half the time
    - ☐ Sometimes
    - ☐ Never

Provider Electronic Health Records Use

21. Does your primary practice have the capability to share any health information with patients electronically?
    - ☐ Yes, through EHR/EMR GO TO QUESTION 22
    - ☐ Yes, through patient portal (separate from EHR) GO TO QUESTION 22
    - ☐ Yes, other electronic method GO TO QUESTION 22
    - ☐ No SKIP TO QUESTION 23

22. How long has your practice used EHR/EMR or patient portal?
    - ☐ Less than 1 year
    - ☐ 1 - 3 years
    - ☐ 4 - 6 years
    - ☐ More than 6 years

Specialty and Practice Information

23. What best describes your area of practice?
    DROP DOWN LIST OF SPECIALTIES: family medicine, geriatrics, general surgery, hospital medicine,

infectious disease, internal medicine, oncology, pathology, pediatrics, pulmonary, other

24. What is your practice setting?
    - ☐ Academic medical center or medical school
    - ☐ Medical center not affiliated with a medical school
    - ☐ Private practice
    - ☐ Group practice
    - ☐ HMO or integrated healthcare system
    - ☐ Other

25. How would you characterize the geography of your primary practice location?
    - ☐ Urban
    - ☐ Suburban
    - ☐ Rural

26. Are the following services present at your primary practice setting? Select all that apply.
    - ☐ On-site pathology
    - ☐ On-site genetic counselors
    - ☐ EMR alert to recommend biomarker test for a patient
    - ☐ Contracts with outside testing laboratories
    - ☐ Don't know

Provider demographics

27. What is your age? _____ NUMERICAL VALUES ONLY. MINIMUM VALUE =1. MAXIMUM VALUE =999.

28. How would you describe your gender?
    - ☐ Female
    - ☐ Male
    - ☐ Prefer to describe as: TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.
    - ☐ Prefer not to answer

29. What is your marital status?
    - ☐ Married or living with a romantic partner
    - ☐ Widowed
    - ☐ Divorced
    - ☐ Separated
    - ☐ Single

30. Are you Hispanic or Latino?
    - ☐ Yes
    - ☐ No
    - ☐ Decline to answer

31. What is your race? Do you consider yourself:
    - ☐ White
    - ☐ Black or African American
    - ☐ American Indian or Alaska Native
    - ☐ Asian
    - ☐ Native Hawaiian or Pacific Islander
    - ☐ Multiple races
    - ☐ Decline to answer

32. What is the highest grade or level of school you have completed?
    - ☐ Less than high school degree
    - ☐ High school graduate or equivalent (e.g., GED)
    - ☐ Some college but no degree
    - ☐ College graduate or more
    - ☐ Decline to answer

33. What is your combined annual gross (or pre-tax) income earned in the past year?
    - ☐ Less than $20,000
    - ☐ $20,000 to $34,999
    - ☐ $35,000 to $49,999
    - ☐ $50,000 to $74,999
    - ☐ $75,000 or more
    - ☐ Decline to answer

PATIENT/PATIENT GUARDIAN BLOCK

Internet access

34. Do you have Internet access at home?
    - ☐ Yes GO TO QUESTION 35
    - ☐ No SKIP TO QUESTION 37

35. What do you use to gain access to the internet? (Select all that apply.)
    - ☐ Smartphone
    - ☐ Laptop or desktop
    - ☐ Tablet
    - ☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

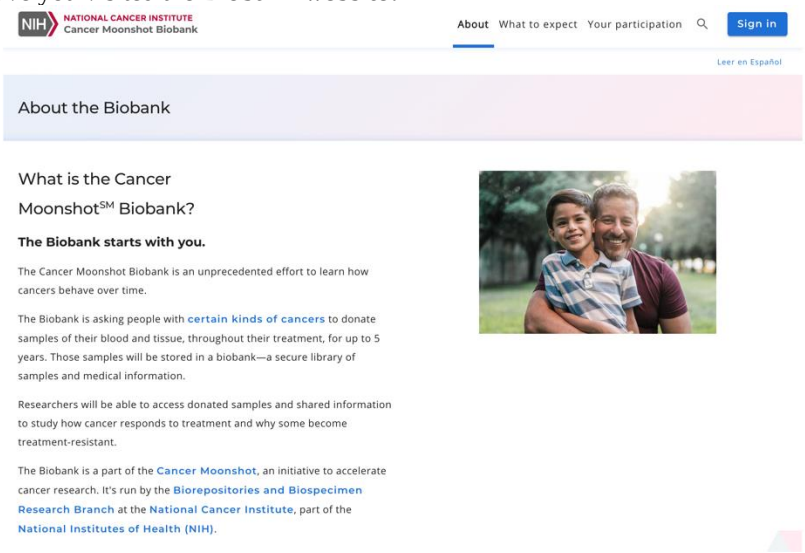
36. When you use the Internet, what kind of activities do you do online? (Select all that apply)
    - ☐ Email
    - ☐ Make purchases online
    - ☐ Read the news
    - ☐ Pay bills
    - ☐ Gather health information
    - ☐ Gather financial information
    - ☐ Search for work or employment
    - ☐ Entertainment (watch videos. listen to music, play games etc.)
    - ☐ Social media (Facebook, Twitter, Instagram etc.)
    - ☐ None of the above.

37. Which of the following, if any, are the reasons you do **not** access the Internet at home? (Select all that apply.)
    - ☐ Do not know how to use it.
    - ☐ Do not need it.
    - ☐ Do not want it.
    - ☐ It costs too much.
    - ☐ Use it at work or at school only.
    - ☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS

INCLUDING SPACES.

Biobank PPE portal

38. Have you visited the **Biobank website?**



☐Yes. GO TO QUESTION 39.
☐No. SKIP TO QUESTION 41.

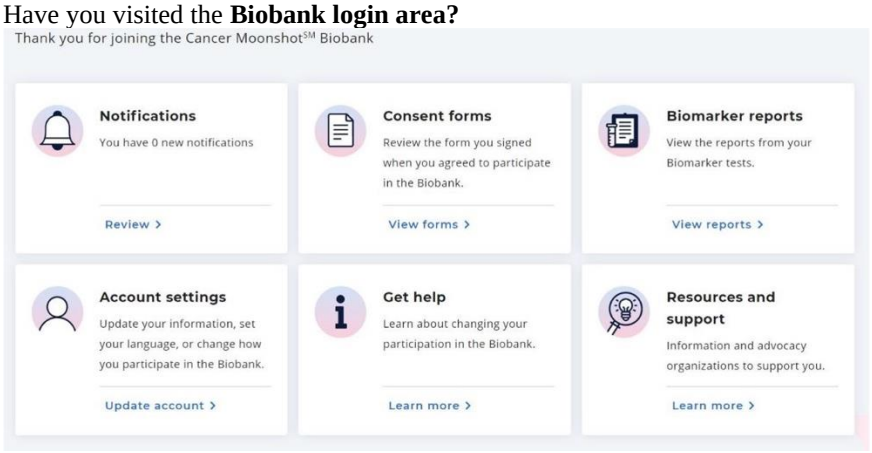
39. Have you used the **Biobank website** for any of the following reasons? Select all that apply.

☐To look up information about the Cancer Moonshot Biobank program.
☐To check eligibility to participate in cancer research.
☐To find the location of a hospital participating in cancer research.
☐To look for other medical research projects/clinical trials.
☐Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

40. Below are a number of statements regarding your satisfaction with the **Biobank website**. Please read each one and indicate to what extent you agree or disagree with each statement.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
The website is easy to use.	☐	☐	☐	☐	☐
I trust the information on the website.	☐	☐	☐	☐	☐
I can easily understand the information presented on the website.	☐	☐	☐	☐	☐
The language on the website made it easy to understand.	☐	☐	☐	☐	☐
I can find information I need easily and quickly on the website.	☐	☐	☐	☐	☐
Information on the website helps me have a better understanding of participating in cancer research.	☐	☐	☐	☐	☐
Information on the website helps me make informed decisions about participating in cancer research.	☐	☐	☐	☐	☐
Information on the website makes me more confident in discussing cancer research with others.	☐	☐	☐	☐	☐
The website prepares me for what happens if I decide to participate in cancer research.	☐	☐	☐	☐	☐

41. Have you visited the **Biobank login area?**



☐Yes. GO TO QUESTION 42.
☐No. SKIP TO QUESTION 44.

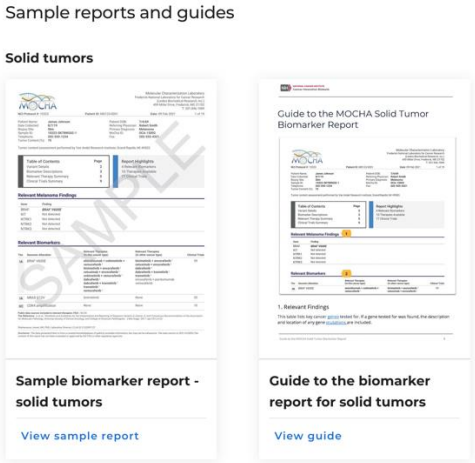
42. Have you used the **Biobank login area** for any of the following reasons? Select all that apply.

☐To update contact information.
☐To access biomarker test results.
☐To download signed consent form.
☐To view resources (finding a clinical trial etc.)
☐To change your participation in the program (close account or leave program).
☐To look for help.
☐Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

43. Below are a number of statements regarding your satisfaction with the **Biobank login area.** Please read each one and indicate to what extent you agree or disagree with each statement.

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
The website login area is easy to use.	☐	☐	☐	☐	☐
I trust the information in the login area.	☐	☐	☐	☐	☐
I can find information I need easily and quickly in the login area.	☐	☐	☐	☐	☐
I can easily understand the information presented on the login area.	☐	☐	☐	☐	☐
I understand the instructions on how to manage my information through the login area.	☐	☐	☐	☐	☐

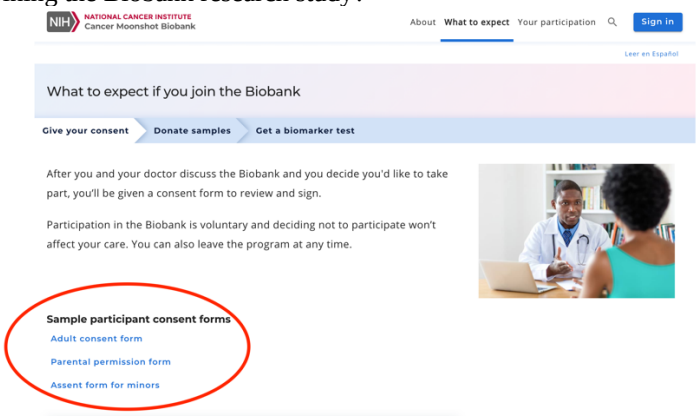
44. Did you find the annotated sample biomarker reports helpful to understanding your biomarker test results?



☐Yes
☐No
☐Did not use the sample biomarker reports.

45. Have you used your biomarker test results to help you make a decision about your health?
☐Yes
☐No
☐Have not received biomarker test results.
☐Did not get a biomarker test.

46. Did you find the sample participant consent forms helpful in understanding important information about joining the Biobank research study?



☐Yes
☐No
☐Did not use the sample participant consent forms.

47. In the past 30 days, how many times did you visit the Biobank website?
    - ☐ None
    - ☐ 1 to 2 times
    - ☐ 3 to 5 times
    - ☐ 6 to 9 times
    - ☐ 10 or more times

Electronic health record use

48. Do any of your healthcare providers (doctors, physician assistants, nurses, and other office staff) have a patient portal (MyChart, E-care, etc.)? Please note that this is not referring to the Biobank website.
    - ☐ Yes GO TO QUESTION 49.
    - ☐ No SKIP TO QUESTION 52.
    - ☐ Do not know SKIP TO QUESTION 52.

49. Do you use the patient portal (MyChart, E-care, etc.) provided by your healthcare provider (doctors, physician assistants, nurses, and other office staff)?
    - ☐ Yes GO TO QUESTION 50
    - ☐ No SKIP TO QUESTION 52

50. Why do you use the patient portal (MyChart, E-care, etc) provided by your healthcare provider (doctors, physician assistants, nurses, and other office staff)? (Select all that apply.)
    - ☐ Get test results.
    - ☐ Communicate with your healthcare provider.
    - ☐ Refill medications online.
    - ☐ Schedule appointments online.
    - ☐ Share your medical record with other healthcare providers.
    - ☐ Update your medical information.
    - ☐ Look for health information or resources.
    - ☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

51. In the last 30 days, how many times did you visit the patient portal (MyChart, E-care, etc) provided by your healthcare provider (doctors, physician assistants, nurses, and other office staff)?
    - ☐ None
    - ☐ 1 to 2 times
    - ☐ 3 to 5 times
    - ☐ 6 to 9 times
    - ☐ 10 times or more

52. If you have **not** accessed the patient portal (MyChart, E-care, etc), please select all that apply.
    - ☐ Prefer to speak to your health care provider directly.
    - ☐ Do not have a way to access the website.
    - ☐ Do not have a need to use the patient portal.
    - ☐ Concerned about the privacy or security of my medical records.
    - ☐ Other (please specify): _____ TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.

Patient demographics

53. What is your age? _____ NUMERICAL VALUES ONLY. MINIMUM VALUE =1. MAXIMUM VALUE =999.

54. How would you describe your gender?
    - ☐ Female
    - ☐ Male
    - ☐ Prefer to describe as: TEXT FIELD. 100 CHARACTERS INCLUDING SPACES.
    - ☐ Prefer not to answer

55. What is your marital status?
    - ☐ Married or living with a romantic partner
    - ☐ Widowed
    - ☐ Divorced
    - ☐ Separated
    - ☐ Single

56. Are you Hispanic or Latino?
    - ☐ Yes
    - ☐ No
    - ☐ Decline to answer

57. What is your race? Do you consider yourself:
    - ☐ White
    - ☐ Black or African American
    - ☐ American Indian or Alaska Native
    - ☐ Asian
    - ☐ Native Hawaiian or Pacific Islander
    - ☐ Multiple races
    - ☐ Decline to answer

58. What is the highest grade or level of school you have completed?
    - ☐ Less than high school degree
    - ☐ High school graduate or equivalent (e.g., GED)
    - ☐ Some college but no degree
    - ☐ College graduate or more
    - ☐ Decline to answer

59. What is your combined annual gross (or pre-tax) income earned in the past year?
    - ☐ Less than $20,000
    - ☐ $20,000 to $34,999
    - ☐ $35,000 to $49,999
    - ☐ $50,000 to $74,999
    - ☐ $75,000 or more
    - ☐ Decline to answer

END OF SURVEY