ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAQ152

COMET - Communication and Education in Tumor Profiling:

A Randomized Study of Pre-disclosure Genetic Education v. Usual Care in Tumor Profiling for Advanced Cancer and a Pilot Study of Remote Genetic Counseling for Participants with Potential Germline Mutations Identified on Tumor Profiling

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Rev Add 7

Version Date: May 14, 2019

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Rev. Add6

STUDY PARTICIPANTS

Step 1: Primary Intervention Study - RCT of Web-based Pre-disclosure Genetic Education v. Usual Care

US Sites Only
SWOG / SWOG
NRG / NRG Oncology
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
COG / Children's Oncology Group

Select Non-MATCH Expansion Sites: Please see Section 4.1.4.5 for more information.

Step 2: Secondary Genetic Counseling Substudy - Genetic Counseling for Incidental Germline Findings

US Sites Only
Select Participating Institutions: Please see Section 4.2.3.2 for detailed instructions and requirements.

Rev. Add5 **NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.**

ACTIVATION DATE
September 26, 2016
PRE-ACTIVATION DATE
August 15, 2016
Addendum #1 – Prior to Activation
Addendum #2 – 2/17
Addendum #3 – 7/17
Addendum #4 – 12/17
Addendum #5
Addendum #6
Addendum #7

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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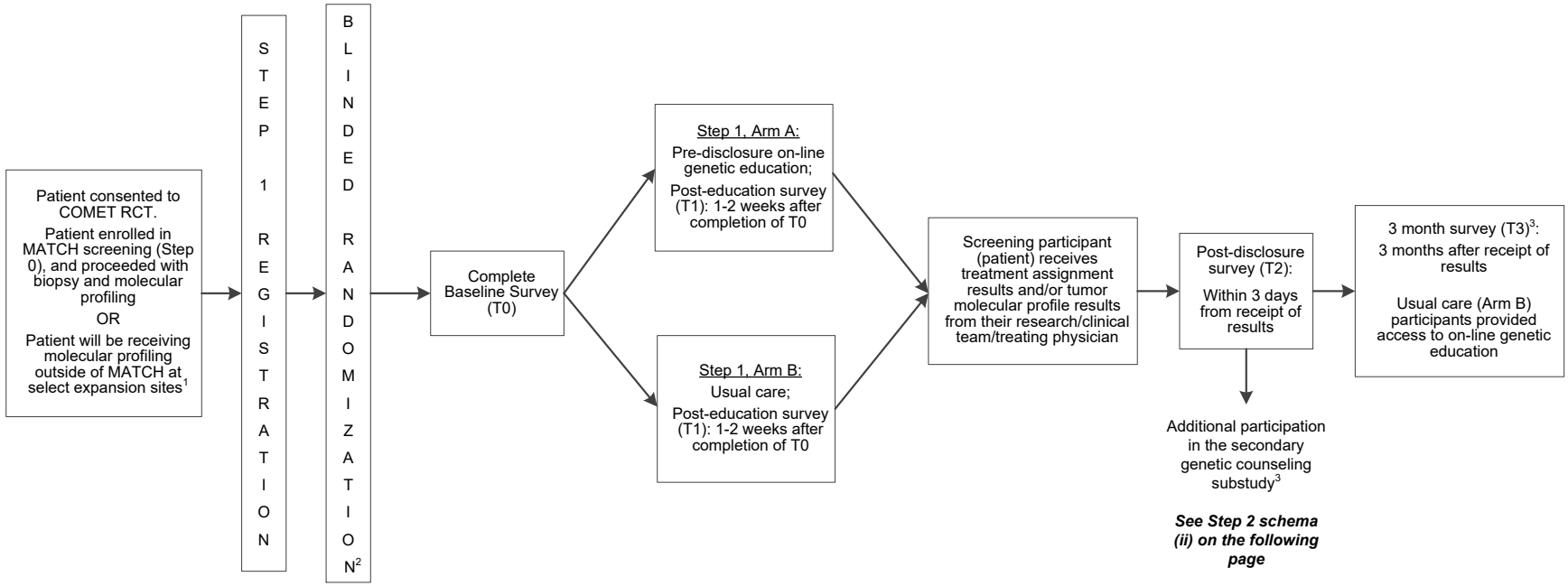
Schema

Step 1 - Primary On-line Genetic Education Study (RCT)

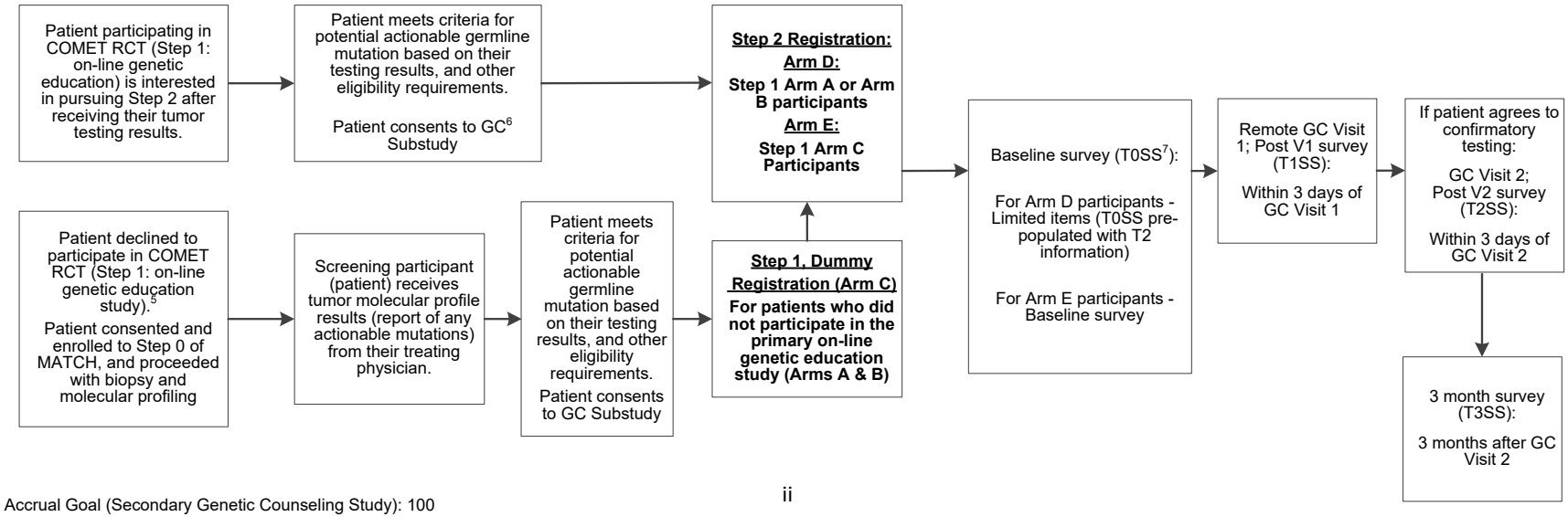


i

Accrual Goal (Primary On-line Genetic Education Study): 670

1. Select expansion sites only: See Section 4.1.4.5 for more information.
2. **Stratification Factors:**
   a. Gender: Male vs. Female
   b. Race: White vs. Others
   c. Age: ≤ 65 vs. > 65 years
   d. Education level: No College vs. College vs. Professional/Graduate
3. If patient is eligible for COMET Step 2 (secondary genetic counseling substudy) based on their testing results and the eligibility criteria, they can also continue on to participate in Step 2 in parallel with Step 1. The 3 month survey (T3) for Step 1 will still be requested, even if Step 2 is pursued.

Step 2 - Secondary Genetic Counseling Substudy[4]



ii

Accrual Goal (Secondary Genetic Counseling Study): 100

4. Select Participating Institutions Only: See Section 4.2.3.2 for instructions and requirements.
5. Please note, per Section 3.2.1.1, patients entering the study via an expansion site (see footnote #1 in the Step 1 schema) are only eligible for Step 2 if they participated in Step 1. They are not eligible for Step 2 via this path, without any prior participation in the study.
6. GC = genetic counseling
7. SS = substudy

1. Introduction

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1.1 Study Overview

The Communication and Education in Tumor Profiling (COMET) study consists of two major components, divided into two steps, each occurring by itself or sequentially. Only a subset of participants and select sites will participate in the Secondary Genetic Counseling Substudy.

1. Primary Intervention Study – Randomized Clinical Trial (RCT) of Web-based Pre-disclosure Genetic Education v. Usual Care (Step 1)

   A randomized substudy of pre-disclosure genetic education v. usual care in tumor profiling for advanced cancer

2. Secondary Genetic Counseling Substudy - Genetic Counseling for Incidental Germline Findings (Step 2)

   A pilot substudy of remote genetic counseling for participants with **potential** germline mutations identified on tumor profiling

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1.2 Hypotheses

1. The provision of web-based genetic education prior to receipt of tumor profiling results will be associated with greater increases in genetic knowledge and less increase in distress (Primary Intervention Study : RCT)
2. Participant factors, suggested by the Self-Regulation Theory of Health Behavior (SRTHB; e.g. test result, sociodemographic factors, health literacy, baseline knowledge or distress) will identify subgroups of patients who benefit more or less from the intervention (web-based pre-disclosure genetic education). (Primary Intervention Study: RCT)
3. The majority of participants with **potential** incidental germline mutations identified through tumor profiling will be willing to participate in: a) remote genetic counseling and b) genetic testing for **potential** germline mutations. (Secondary Genetic Counseling Substudy)
4. The uptake of remote counseling and testing among advanced cancer patients with **potential** germline incidental findings will be associated with patient factors (e.g. distress, uncertainty, family history, etc.) predicted by the Self-Regulation Theory of Health Behavior (SRTHB). Additionally, we hypothesize that remote pre- and post-test counseling with a genetic counselor will be associated with increases in knowledge, decreases in uncertainty and distress and increases in communication to at-risk relatives. (Secondary Genetic Counseling Substudy)

1.3 Background

1.3.1 Primary Intervention Study (RCT):

How and when to best communicate limitations of tumor profiling and the potential for incidental findings is unknown. Cancer has long been recognized as a genetic disease, driven and sustained by the accumulation of alterations in genes that code key signaling pathways[41-43]. With the advent of next-generation sequencing (NGS), in which multiple genes, even the entire genome, can be sequenced rapidly and at relatively accessible costs, we have entered an era of precision cancer care[3,43,44]. We can now readily identify numerous

acquired genetic aberrations in tumors, which can be used to identify targeted therapies with the hopes of improving patient outcomes[44].

The implementation of NGS in cancer care has raised a range of practical, ethical, and legal challenges for patients, providers, and the health care system as a whole[1,2]. As we move from "discrete" tests (e.g., single-gene or single-marker tests) to "bundled" (targeted sequencing of a panel of cancer genes) or "broad" tests (e.g., whole-exome or whole-genome sequencing), there is an increasing possibility of increasing confusion, distress or disappointment given the limitations of our current knowledge[13,46]. Equally important, tumor profiling has the potential to identify incidental germline findings[2,3,4]. In small qualitative studies, patients have reported confusion between somatic and germline testing and 71% reported potential psychosocial risks including unwanted information, germline implications for relatives and the potential for loss of hope with no actionable or targeted mutations based on testing[13]. Additionally, many patients have high expectations of benefit with tumor profiling and some experience disappointment if there are no actionable mutations are identified[14]. Additionally, while many patients report interest in incidental germline findings, some patients identify this as an additional burden, given a diagnosis of advanced cancer[14]. These studies highlight the potential risks and limitations associated with clinical implementation of tumor profiling in advanced cancer patients and the need to further understand patient outcomes and delivery models to enhance the benefits and minimize the risks of tumor profiling in cancer care[4].

Pre-disclosure (i.e. prior to the disclosure of test results to patients) genetic education has the potential to improve understanding, minimize negative responses to receipt of tumor molecular profile results and identification of incidental germline findings. How to best address these clinical challenges to benefit patients and their families remains unknown. The traditional approach to informed consent for germline genetic testing has been to share the risks, benefits and limitations of testing with patients prior to testing and to honor their preferences for receipt genetic information*. Recent guidelines from the Presidential Commission for the Study of Bioethical Issues and the American College of Medical Genetics suggest that the potential to identify incidental findings with tumor profiling be shared with patients in advance of testing so that they can consider and share their preferences for receipt of incidental germline information[1,7]. Yet, how to achieve this remains unknown, and there is pressing need for empiric studies to evaluate communication and delivery strategies[1,4]. Traditional provider-mediated genetic counseling is not feasible for every patient undergoing tumor profiling for therapeutic intent. Thus, if pre-disclosure education is required, alternative scalable models for provision of education and assessment of preferences will be needed as tumor profiling is widely adopted for the care of cancer patients.

In some settings the frequency of incidental findings may be relatively low[4]. For example, in the setting of tumor only sequencing (i.e. rather than paired tumor and germline platforms) a potential germline finding

may be identified but secondary germline confirmation would be necessary. This provides a second opportunity to assess patient preferences for germline findings. In this proposal, we hypothesize that pre-disclosure genetic education in this setting will improve understanding of germline implications and other risks, benefits and limitations of tumor profiling and reduce distress and uncertainty. Nonetheless, it remains possible that providing extensive genetic education and counseling at pre-disclosure may be overwhelming or lack salience for patients, and could even be associated with greater confusion and potential distress. Thus, we propose a randomized study to evaluate the relative advantages of on-line pre-disclosure education compared to usual care in order to address the pressing need for empirical studies to evaluate how to best communicate and deliver cancer genetic education and counseling in the setting of tumor profiling.

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1.3.2 Secondary Genetic Counseling Substudy:

How to best address incidental germline findings in the setting of clinical tumor profiling remains unknown. The implementation of NGS in cancer care has raised a range of practical, ethical, and legal challenges for patients, providers, and the health care system as a whole[1,2]. One of the most pressing challenges in the field is how to address incidental or secondary germline findings identified in advanced cancer patients undergoing tumor profiling for therapeutic intent[2-4]. Studies have shown that patients undergoing sequencing for therapeutic intent differ in their preferences for secondary germline information[5,6]. Obligations to intentionally interrogate germline data to return incidental findings in **potential** clinically important germline mutations (e.g. germline mutations with established clinical utility) remain uncertain. In recent clinical guidelines, the ACMG argued that laboratories intentionally seek and report clinically important germline findings in a list of detected gene mutation results[7]. Such an obligation to seek clinically important germline findings in the setting of tumor profiling has been debated, but there is a growing consensus that patients (in research and clinical settings) should be informed about the potential for incidental or secondary germline findings and that their preferences for these should be honored[1,8-10]. Yet, how to accomplish this in clinical patient care, and particularly in the setting of advanced cancer patients undergoing tumor profiling to inform therapeutic decisions remains unknown. Many have highlighted that additional research to evaluate outcomes and delivery models designed to honor preferences is crucial to this ongoing debate and the implementation of tumor profiling[1,8,11].

While the potential for germline findings has been greatly debated, many practicing clinicians are utilizing tumor profiling but report variable confidence in their genetic knowledge[12]. Additionally, there is variability in how clinicians describe tumor profiling and how frequently they discuss potential germline implications is unknown[4,12]. In small qualitative studies, patients have reported confusion between somatic and germline testing and 71% reported potential psychosocial risks including unwanted information, germline implications for relatives and

the potential for loss of hope with negative tumor profiling[13]. Additionally, while many patients report interest in incidental germline findings, some patients identify this as an additional burden, given a diagnosis of advanced cancer[14]. These studies highlight the need to both develop clinical care models which assist practicing physicians to facilitate identification of patients who may be candidates for further germline testing and to further evaluate how to best honor patient preferences for incidental or secondary germline information and the outcomes of identifying incidental germline findings among patients undergoing tumor for sequencing for therapeutic intent.

In light of the clear gap in knowledge concerning the risks for returning potential germline findings, any effort to provide this kind of information to patients should only be undertaken by an experienced team of genetic providers. Our team has experience with remote cancer genetic counseling with community sites in a NCI funded feasibility study (R21 CA164121: Bradbury, Bradbury et al. Utilizing remote real-time videoconferencing to expand access to cancer genetic services in community practices, JMIR, in press, 2015), and additional community sites in an ongoing randomized study of remote counseling v. usual care for cancer genetic testing (funded through the Basser Center for BRCA1/2 Research). These studies include both patients without cancer and patients with advanced cancer, specifically patients with metastatic breast cancer. Thus, the PENN telegenetic counselors have clinical experience counseling patients with advanced cancer at community sites and are sensitive to the unique issues facing patients with advanced cancer undergoing tumor profiling. Further, counseling patients with potential germline findings is within the scope of cancer genetic counseling practice. Additionally, the cancer genetics team at PENN has experience with cancer genetic counseling for patients with potential germline findings in tumor profiling both through COMET pilot work in metastatic breast cancer patients and other clinical tumor profiling, The PENN cancer genetics team and weekly case conference will be an additional resource for the genetic counselors participating in the COMET remote counseling substudy.

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1.4 Summary and Rationale for the Study

The study has been designed to address the need for empirical studies to evaluate how to best communicate and deliver cancer genetic education and counseling in the setting of tumor profiling.

1.4.1 Primary Intervention Study - RCT of Web-based Pre-disclosure Genetic Education v. Usual Care for Patients Undergoing Tumor Profiling for Cancer Treatment (Step 1):

The proposed randomized study will evaluate the utility of a scalable web-based pre-disclosure genetic education compared to the current usual care communication prior to receipt of tumor profile results. If this pre-disclosure education model successfully improves cognitive and affective responses to tumor profiling, it has the potential to be widely implemented in clinical care to benefit advanced cancer patients and their families. Given that COMET will recruit cancer

patients with a wide spectrum of tumor types and in both academic and non-academic centers, the web-based intervention and findings are expected to be broadly applicable to the advanced cancer population.

Additionally, secondary analyses evaluating groups that benefit more and less from the intervention will provide crucial data to enhance the intervention for future use in clinical practice. Even if the study finds no difference between intervention groups, these secondary analyses are likely to identify subgroups of patients who may benefit more from the intervention, or alternative modifications or interventions to maximize the benefits and minimize the risks associated with widespread clinical adoption of tumor profiling in cancer care. Thus, we expect this work to be highly relevant to clinical practice.

1.4.2 Secondary Genetic Counseling Substudy - Genetic Counseling for Incidental Germline Findings (Step 2):

The proposed genetic counseling substudy will evaluate the feasibility and preliminary outcomes of remote genetic provider mediated counseling for the subset of patients with potential germline mutations incidentally identified through molecular tumor profiling. If successful, this substudy will provide key preliminary data to support further research evaluating delivery models for potential incidental germline findings. While this may include remote counseling to provide access to genetic counselors for the subset of patients with incidental germline findings where additional germline testing is indicated, given a limited genetic counselor workforce and the anticipated broad application and use of tumor profiling in cancer care, alternative scalable models will need to be evaluated. These could include web-based delivery that could be combined with provider mediated counseling in select cases.

The proposed substudy seeks to evaluate patient preferences for, and outcomes of genetic counseling and testing in the setting of the identification of potential incidental germline findings, which are key first steps to developing scalable delivery models for the future. In related work and the proposed COMET randomized study of pre-disclosure genetic education, we have experience adapting provider mediated counseling and education to on-line patient-mediated delivery, providing expertise for the proposed subsequent research.

As an example, in the ongoing RESPECT study (R01-CA190871:Bradbury/Patrick-Miller), we have adapted provider-mediated tiered-binned pre-disclosure counseling for return of individual research results to an on-line genetic education followed by remote counseling with a genetic counselor at the time of result disclosure to address patient burdens associated with in-person visits. The ongoing multi-site RESPECT study will evaluate the outcomes of receipt of individual germline research results with this alternative delivery model. Thus, this genetic counseling substudy and the anticipated subsequent work are expected to contribute significantly to the ongoing debate over how to best communicate and deliver genetic

information with the delivery of tumor profiling in cancer care and how to honor patient preferences for incidental germline information.

1.5 Current Supporting Data

1.5.1 Primary Intervention Study - RCT of Web-based Pre-disclosure Genetic Education v. Usual Care (Step 1):

To address the need for empirical studies to evaluate how to best communicate and deliver cancer genetic education and counseling in the setting of tumor profiling, we have been conducting a pilot study of pre-disclosure genetic education delivered by a health educator among breast cancer patients undergoing tumor profiling on a related clinical trial (COMET Pilot Study). This genetic education is designed to educate patients regarding the benefits, risks and limitations of tumor profiling for cancer treatment, including the potential for incidental germline findings, which would need to be confirmed through additional germline genetic testing. In related studies evaluating germline multiplex testing for cancer susceptibility (R01 CA160847:Bradbury; R01-CA190871:Bradbury/Patrick-Miller), we have developed a novel tiered binned approach to genetic counseling and informed consent to address the increasing complexity of genetic testing in the era of multiplex and whole genome sequencing[15,44,46]. We have adapted the tiered binned approach for genetic education in the setting of tumor profiling for advanced breast cancer given the complexity of information and the need for efficient education in the setting of patients undergoing active treatment and testing for treatment decisions.

The goals of the COMET pilot study are:

1. To obtain patient feedback and conduct audiotape review of session to inform modifications to our tiered binned genetic education for tumor profiling and
2. To obtain preliminary outcome data to inform future studies evaluating outcomes of genetic education and counseling delivery models in the setting of tumor profiling.

While the original education was delivered via a health educator, this approach was chosen to maximize patient feedback regarding key elements and content. We had originally envisioned that it could be adapted for delivery by alternative modalities (e.g. print, web), if acceptable to patients. As an example, in the ongoing RESPECT study (R01-CA190871:Bradbury/Patrick-Miller), we have adapted provider-mediated tiered-binned pre-disclosure counseling for return of individual research results to an on-line genetic education followed by remote counseling with a genetic counselor at the time of result disclosure to address patient burdens associated with in-person visits. The ongoing multi-site RESPECT study will evaluate the outcomes of receipt of individual germline research results with this alternative delivery model.

To date, 25 breast cancer patients have enrolled in the COMET pilot study. 20 have completed genetic education and post-education

surveys. 14 have received results and have completed post-disclosure surveys.

Key preliminary findings relevant to this proposal include:

1. Many patients reported a limited understanding of the difference between germline and somatic genetics and the limitations of tumor profiling (e.g. the potential for no druggable targets).
2. Participants reported greater interest in web-based administration as an alternative to provider-mediated counseling than print materials. Patients reported advantages to web-based education included convenience, the ability to revisit information, faster access and the individual ability to select information to view. Many reported no disadvantages to a web-based alternative, while some identified losing the personal interaction, getting confused or not knowing what to view on a website.
3. Preliminary data suggests pre-disclosure genetic education may be associated with increases in knowledge and decreases in depression and general and state anxiety from baseline to post-disclosure.

In this pilot, there was no comparison arm, so changes in these outcomes need to be evaluated in a randomized study.

1.5.2 Secondary Genetic Counseling Substudy - Genetic Counseling for Incidental Germline Findings (Step 2):

In four NIH and foundation funded studies, we have been evaluating telephone and real-time videoconferencing counseling as alternative delivery models to increase the efficiency and improve access to genetic providers (R01 CA160847:Bradbury; R21-CA-164121:Bradbury) and for return of individual genetic research results (R01-CA190871:Bradbury/Patrick-Miller Conquer Cancer Foundation Advanced Clinical Research Award: Bradbury). These studies have established that remote counseling is a feasible alternative for further evaluation[15-17]. Benefits include expanded patient access to services and centralized provider expertise, particularly in the setting of a limited genetic counselor workforce. Communication protocols utilized in these ongoing studies will be adapted for use in the proposed genetic counseling substudy.

As described above, in our related studies utilizing telephone and videoconferencing to provide more efficient and accessible genetic services, particularly in populations where genetic providers are not available, we have found remote counseling to be feasible, acceptable to patient and providers and associated with increases in genetic knowledge and comparable affective outcomes to in-person counseling. Two recent randomized studies evaluating germline testing for *BRCA1/2* have reported similar findings[39,40]. Given related ongoing research and clinical activities in telegenetics, our genetic counselors are already licensed in several states with plan for licensure across over 20 states (Alzheimer's Prevention Initiative APOE4 Trial. 1UF1AG046150-01: Reiman. A randomized substudy of telephone versus videoconferencing disclosure of APOE genotype).

Thus, genetic provider licensure is not anticipated to be a barrier to implementation of this substudy.

2. Objectives

2.1 Primary Objectives

2.1.1 Primary Intervention Study: RCT (Step 1)

To evaluate the efficacy of web-based pre-disclosure genetic education (i.e. before receipt of tumor profile results) to:

a) Increase knowledge (genetic knowledge and knowledge of test benefits and limitations)

b) Decrease distress (anxiety, depression and cancer specific worry) compared to usual care services in patients undergoing tumor profiling for advanced cancer

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2.1.2 Secondary Genetic Counseling Substudy (Step 2)

To evaluate the uptake of:

a) Remote genetic counseling

b) Germline testing among advanced cancer patients with a **potential** clinically significant incidental germline mutation identified through tumor profiling

2.2 Secondary Objectives

2.2.1 Primary Intervention Study: RCT (Step 1)

To evaluate potential moderators suggested by the SRTHB (e.g test result, sociodemographic factors, health literacy, baseline knowledge or distress) to changes in:

a) Knowledge of genetic disease and test benefits and limitations

b) Distress in patients undergoing tumor profiling for advanced cancer

2.2.2 Secondary Genetic Counseling Substudy (Step 2)

To evaluate:

a) Factors associated with uptake of genetic counseling and germline testing

b) Cognitive and affective responses to confirmatory germline testing in advanced cancer patients with **potential** clinically significant incidental germline mutation identified in tumor profiling.

2.3 Exploratory Objectives

2.3.1 Primary Intervention Study: RCT (Step 1)

To explore:

a) Satisfaction and regret/disappointment related to tumor genetic test results

b) How to better deliver tumor genetic test results and germline information in the future

2.3.2 Secondary Genetic Counseling Substudy (Step 2)

To explore:

a) Behavioral responses (communication to others) to confirmatory germline testing in advanced cancer patients with potential clinically significant incidental germline mutation identified in tumor profiling

b) Satisfaction and regret/disappointment related to genetic counseling service or germline genetic test results

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria (Step 1) - Primary Intervention Study (RCT):

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_____ 3.1.1 Patients must be registered to the first screening step (Step 0) for the NCI-MATCH trial (EAY131) **OR** must be having tumor profiling for advanced cancer performed at or ordered by one of the select expansion sites described in Section 4.1.4.5.

_____ 3.1.2 Patients must speak English.

NOTE: The restriction to English-speaking participants is based on the challenges encountered in creating and/or translating web content for the Primary Intervention Study.

_____ 3.1.3 Patients must have web and e-mail access.

NOTE: The restriction to those with web and e-mail access is based on funding constraints for the costs associated with paper-based surveys.

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_____ 3.1.4 Patients in the MATCH trial must have not received his/her MATCH tumor genetic test results to be eligible to participate in COMET's RCT. Non-MATCH expansion site patients must have not received his/her results from tumor profile genetic testing to be eligible to participate in the COMET's RCT.

3.2 Eligibility Criteria (Step 2) - Secondary Genetic Counseling Substudy:

NOTE: Only available to patients from select participating sites (see Section 4.2.3.2 for instructions and requirements).

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_____ 3.2.1 Patients must meet the eligibility requirements in Section 3.1 (except for Section 3.1.3 and 3.1.4) and have had the results from their tumor genetic testing study shared with them.

3.2.1.1 Non-MATCH expansion site patients must have participated in COMET Step 1, the primary intervention study (RCT), in order to be eligible for Step 2.

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_____ 3.2.2 Patients must have a potential germline mutation, as determined by the NCI-MATCH tumor profiling assay or other clinical lab, and must meet one of the following criteria:

- Patient's tumor contains one of the following genetic variants: BRCA1, BRCA2, MLH1, MSH2, TSC1, TSC2, VHL, CDH1, CDKN2A
- Patient has an APC mutation and NOT colon cancer
- Patient has an APC mutation, colon cancer and a history of polyposis
- Patient has a PTEN mutation and NOT uterine cancer
- Patient has a TP53 mutation AND either a personal history of breast cancer diagnosed at age 65 or younger, OR a personal history of any other cancer diagnosed at age 40 or younger.
- Patient has a RB1 mutation with personal and/or family history of retinoblastoma or other associated RB tumor (e.g. soft tissue sarcoma, melanoma, PNET).
- Patient has a RET mutation with personal history of medullary thyroid cancer and/or family history of thyroid cancer.

3.2.2.1 Genes listed below require additional internal vetting by genetic counseling team.

TSC1/TSC2

1. All kidney cancers
2. Any cancer type with:
   a. Personal history of seizures or developmental delay, OR
   b. Personal history of renal tumors, OR
   c. Personal history of cardiac rhabdomyomas, OR
   d. Personal history of TSC-associated skin findings (shagreen patches), OR
   e. Personal history of TSC-associated brain tumors (SEGA)

CDKN2A

1. Personal and/or family history of melanoma < 60 years of age, OR
2. Personal and/or family history of pancreatic cancer, OR

3. Any cancer type with personal history >30 dysplastic nevi

STK11

1. NOT lung adenocarcinoma OR lung adenocarcinoma with history of small bowel or colon polyps (histopathology is *hamartoma* but confirmation is not requirement for eligibility)

VHL

1. Patient has Von Hippel-Lindau syndrome.

_____ 3.2.3 Patients must be able to speak English and hear by phone.

NOTE: The restriction to English-speaking participants is based on the availability of translators for the Secondary Genetic Counseling Substudy.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov .

CTSU Registration Procedures

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

IRB Approval:

NOTE: Sites must utilize the CIRB as their IRB of record to participate in EAQ152.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRB Manager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study

approval can be applied to those institutions. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EAQ152 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EAQ152
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For EAQ152 Site Registration:

- Sites must be willing to provide patient contact information to the Outcomes and Economics Assessment Unit (OEAU) located at Brown University.
- The Genetic Counseling Substudy is only available to patients from select participating sites (see Section 4.2.3.2 for instructions and requirements).

Checking Your Site's Registration Status:

Please refer to Section 4.1.4.4 for details on the EASEE-PRO system.

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website.

NOTE: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol study intervention prior to registration.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- The patient's highest education level has been obtained.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side 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.

4.1 Step 1 - Primary Intervention Study (RCT) Registration

4.1.1 Patient Registration Information

The following information will be captured at time of registration.

4.1.1.1 Protocol Number

EAQ152

4.1.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment

- Country of residence

4.1.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.3 Classification and Stratification Factors

4.1.3.1 Classification Factors:

- Primary Study (RCT) Participation: Yes vs. No.

4.1.3.2 Stratification Factors:

- Gender: Male vs. Female
- Race: White vs. Others
- Age: ≤ 65 vs. > 65 years
- Education level: No college vs. College vs. Professional/Graduate

4.1.4 Additional Requirements

4.1.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

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4.1.4.2 If the participant is coming from a clinical trial, the Protocol ID and case number of that trial must be indicated (e.g. for example, if the participant is registered to MATCH Step 0, then the Protocol ID would be EAY131 and the case number would be the MATCH assigned subject ID). If the participant is not coming from an associated clinical trial, the Protocol ID and case number should be left blank.

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4.1.4.3 Data collection for this study will be done through the Medidata Rave clinical data management system and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select

Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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 link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.1.4.4 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

Access to the study in EASEE-PRO is granted to all participants registered to the study through the OPEN registration system with a valid participant email address. Upon registration, an account verification email will be sent to the user with a link to activate their account. The user will be required to enter some verification information (e.g. DOB) in order to activate their EASEE-PRO account. Additionally, site persons with the appropriate roles in RSS will be granted access after IRB approval is obtained. In some studies, this access may allow CRAs to assist the participant accessing baseline surveys, educational materials, or other EASEE-PRO materials.

EASEE-PRO Participant Access:

To access EASEE-PRO, the participant must have an active EASEE-PRO user account. Upon registration to the study in OPEN, an account activation email will be sent to the address entered for the participant in OPEN eligibility checklist. This email address must be a valid email address for the participant. All participants in the COMET Study are required to have access to the internet and a valid email address to participate. (If the patient email address were entered incorrectly in OPEN, the CRA must contact the OEAU [COMET-help@stat.brown.edu] to manually correct the error.) To activate their account, users must click the link in the email and verify their account before they can login and complete surveys or

view web education materials. Once the account is activated, participants may login to the EASEE-PRO system through the OEAU-PRIDE web portal (https://pride.stat.brown.edu/Participant-Login). Upon login, users will be presented with a list of available surveys and materials they can view.

EASEE-PRO CRA Access:

To access EASEE-PRO, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. To login, CRAs will use their CTSU(IAM) credentials on the OEAU-PRIDE web portal (https://pride.stat.brown.edu/CRA-Login) using the familiar IAM interface. No e-learnings are required for use of this site.

The ECOG-ACRIN Outcomes and Economics Assessment Unit can be contacted for Patient Reported Outcome Questions via email at comet-help@stat.brown.edu. An EASEE-PRO instructional guide for both sites and patients can be found on both the E-A and CTSU websites.

Please see below for additional details on the EASEE-PRO system.

1) A secure environment for control of user records, information, and transactions (SECURIT): Provides a secure – limited access point for entering data into the restricted secure PII Database, for management of user data, creating user accounts, and reporting. The SECURIT web management interface requires the secure hypertext transfer protocol (HTTPS) to ensure encryption of transmitted data.

    a) PII database: is a dedicated secure limited access database, used to store protected PII.

        i) Secure: All communications to the PII database through SECURIT are encrypted. The database resides behind a firewall and cannot be reach from outside the OEAU.

        ii) Limited access: this database is restricted not only by username and password but is also restricted to specified internal OEAU computers by IP address, so that only authorized users logging in at the OEAU from pre-specified

computers may access/enter PII. At no time is outside access allowed to this database.

iii) Protected restricted PII (e.g. SSN) are encrypted at the time of data entry and double data entered for verification. All users regardless of their security level are blinded to this protected data, and it cannot be decrypted without the encryption key, housed in a safe, in a location separate from the OEAU. This type of data is generally collected for long term follow-up where it may be needed to be decrypted for select patients in order to search registries like the national death index to determine survival status of lost participants. In these instances, with appropriate approvals, the Database Administrator will decrypt this data in accordance with the approved retrieval specification.

b) User records: This functionality allows OEAU personnel, using specific computers within the OEAU, to create user records, enter user information into the PII database, and establish user web accounts in the separate user database. Allows the management of users and their data, including the ability to update a participant's preferred contact method, address, and participation status (e.g. no longer wishes to be contacted with respect to the PRO component of the study).

c) Information: This functionality allows the OEAU to record all participant contact, document any changes to the participant, and make any important notes related to the participant.

d) Transactions: SECURIT provides a reporting and monitoring interface to the PRO database, which is used to store non-PII patient reported survey responses.

i) Allows OEAU to monitor per patient form completion status using the tracking management facility. This facility reports on what data is currently expected from participants, CRAs, and the OEAU interviewers.

ii) Aggregate reporting: this series of reports allows the OEAU to monitor the distribution of patients over data completion methods and form completion methods (both overall and by site).

2) Database utility and control environment (PRO-DUCE): This utility interfaces with the main clinical database containing CRF/trigger data (Medidata RAVE), monitors the clinical database for events (eg., participant registrations, scheduled procedures, and other triggers) and establishes event scheduling. The system sets up e-mail reminders to CRAs, participants [and SMS text message reminders, when applicable to the study], and OEAU personnel to ensure timely completion of surveys.

3) Web entry systems (PROWESs): a Web site where participants complete online surveys

   a) PROWESs provides a front facing web portal for participants to complete questionnaires and have those results stored in the PRO database.

   b) Secure site using HTTPS and requiring a username and password login.

   c) On login, user is presented with brief instructions; including approx. time for completion, number of questions to be completed in this session, any important information regarding this survey (including help and contact information)

   d) PROWESs is a one-way interface, data cannot be returned from the PRO-DB to the user.

4) Valet Interface and data entry system (PROVIDES).

   a) The PROVIDES system is a web interface that allows site CRAs to act as a valet and enter a participant's responses to a survey into the PRO database should the survey be completed on paper. This allows Site CRAs to enter forms completed by the patient on site.

   b) Secure site using HTTPS and requiring a username and password login.

   c) Which forms can be entered is restricted by username, site affiliation, and role, thus Sites RAs can only enter surveys predesignated as on-site data collection surveys and only for their own patients.

   d) On login, user is presented with brief instructions; is requested to select the protocol, case number, timepoint and verify the case Id by providing the participant birthdate.

   e) PROVIDES is a one-way interface, data cannot be returned from the PRO-DB to the user.

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4.1.4.5 Only those select expansion sites listed in the associated study tool found on the ECOG-ACRIN and CTSU websites

will be permitted to enroll patients on the COMET study without prior involvement in the NCI-MATCH (EAY131) study.

To participate as a select expansion site for the Primary Intervention Study (RCT) and enroll patients unrelated to MATCH, sites must contact the study team for their review and approval.

- The designated CRA must send an e-mail to COMETstudy@uphs.upenn.edu with the following information:

  First and Last Name(s) of the Designated Contact(s) at your Institution
  E-mail address(es) for Designated Contact(s)
  Site Name
  CTEP Site ID
  Street Address
  City, State, Zip

NOTE: The person(s) identified as the Designated Contact(s) will be responsible for data entry in Rave in the event that the site participates.

Participation will require appropriate site staffing and resources to support the coordination of the non-MATCH tumor profiling arrangements and the study's requirements, including:

- Staff to identify, approach and consent potential participants.
- Staff to track survey completion and contact participants when a survey is late.
- Staff to identify when a participant has received their tumor genetic testing results and upload the test report into the Rave system.

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4.1.5 Registration of a patient to the COMET Ancillary Study Protocol does not relieve the registering investigator from adhering to correlative study requirements specific for the MATCH or other molecular profiling protocol and not specified by this ancillary protocol.

4.1.6 Patients assigned to the web-based education who do not view the website but complete baseline survey will still complete follow-up surveys.

4.2 Step 2 - Secondary Genetic Counseling Substudy Registration

Select Participating Institutions: Please see Section 4.2.3.2 for detailed information and instructions on how to express interest in participation.

4.2.1 Patient Registration Information:

4.2.1.1 Protocol Number

EAQ152

4.2.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.2.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.2.3 Additional Requirements

4.2.3.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.3.2 To participate in the Genetic Counseling Substudy, sites must contact the study team.

- The designated CRA must send an e-mail to EAQ152step2@jimmy.harvard.edu with the following information:

  First and Last Name(s) of the Designated Contact(s) at your Institution

  E-mail address(es) for Designated Contact(s)
  Site Name
  CTEP Site ID
  Street Address
  City, State, Zip

  NOTE: The person(s) identified as the Designated Contact(s) will be responsible for data entry in Rave in the event that the site participates.

All interested sites will be considered for participation in the substudy. Participation will require licensure assessment and licensure of the study team's genetic counselors (at the University of Pennsylvania), per state laws. Participation also requires a designated CRA to assist with testing requisitions, scheduling of remote counseling

appointments and ensuring communication with the treating provider, patient and medical team.

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4.2.3.3 For patients consented to the COMET Secondary Genetic Counseling Substudy, the responsible/designated CRA must fax the MATCH or other molecular profiling screening results report to the study team (Fax #: 215-573-1578), and discuss the results with the study team, including the genetic counselors at the University of Pennsylvania, over telephone.

4.2.3.4 Data collection for this study will be done through the Medidata Rave clinical data management system and the EASEE-PRO system. Please refer to Section 4.1.4.3 above for Rave access information.

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4.2.3.5 EASEE-PRO System:

Please refer to Section 4.1.4.4 above with the following modification: Participants who do not have internet access/e-mail may still participate in the Step 2 Genetic Counseling sub-study. For these participants only, site CRAs will need to complete a participant contact form and fax it to the OEAU so that the participant account can be activated manually within EASEE-PRO.

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4.2.3.6 Registration of a patient to the COMET Ancillary Study Protocol does not relieve the registering investigator from adhering to correlative study requirements specific for the MATCH or other molecular profiling protocol and not specified by this ancillary protocol.

4.3 Instructions for Patients who Do Not Complete Baseline Survey and/or Do Not Start Assigned Study Intervention

If a patient is randomized in the Primary Intervention Study (Step 1) but the baseline survey (T0) is not completed, patient is considered off study and no additional data will be requested and patients will not be available to register to the Secondary Genetic Counseling Substudy (Step 2).

Patients registered to Step 1 and further registered to Step 2, but who do not proceed with the genetic counseling, are to complete the requirements for Step 1. Specifically, Step 1 follow-up data will still be collected and must be submitted through Medidata Rave and the EASEE-PRO System according to the schedule in the ***EAQ152*** Forms Completion Guidelines.

For Step 2 participants, if the patient does not complete the baseline survey (T0SS) for Step 2, patient is considered off the substudy and no additional data will be requested for Step 2.

5. Methodology

5.1 Randomization

5.1.1 Primary Intervention Study - RCT of Web-based Pre-disclosure Genetic Education v. Usual Care (Step 1):

We will use a permuted block design for the randomization scheme. We will have 1:1 randomization between arms.

5.1.2 Secondary Genetic Counseling Substudy - Genetic Counseling for Incidental Germline Findings (Step 2):

Single arm pilot study (no randomization)

5.2 Interventions

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5.2.1 Primary Intervention Study (RCT) (Step 1):

As shown in the study schema, participants will be randomly assigned to web-based genetic education or a control group receiving usual care.

- Genetic education website (Arm A – intervention group):

  Upon completion of the baseline survey, Arm A participants will receive an access code to enter and complete the online education module. Adapted for COMET participants from the COMET pilot study materials, the module is designed to provide information on what can be learned through tumor testing, including the differences between genetic tumor changes and potential germline findings, and next steps including confirmation testing should a germline mutation be suspected. The module, which will be content and usability tested with patients of varied background and cancer diagnosis, features simple text, graphic, and video components.

  Arm A participants will be offered access to the web-based genetic education module at the study site following completion of the baseline survey, and will be able to revisit the site using any computer with web access, including a smart phone.

- Usual care (Arm B - control group):

  Participants in the usual care arm will not initially have access to the web-based genetic education. Rather their education will be consistent with usual care including conversations with the treating physicians, interaction with and information from clinical and/or MATCH research staff and any additional information they seek out through usual resources. This is intended as a “real world” comparison group. All usual care arm participants will be provided access to on-line genetic web education three months after receiving their tumor genetic testing results. These patients will be e-mailed a link to the website and a code to access the materials, which are viewable on any web-enabled device.

- Both Arms (A & B):

  Patients on both Arms A and B will be asked to complete a total of four surveys electronically (see Section 0). A baseline survey (T0) will be administered immediately following registration to COMET. A second survey (T1) will be administered following the intervention/usual care. An electronic link to the T1 survey will be emailed to all patients at 7 days following completion of the baseline survey (T0). A third survey (T2) will be sent to all patients within three days following their receipt of their tumor profile results. An electronic link to a fourth survey (T3) will be emailed to all patients three months following receipt of tumor profile results.

  All patients will receive periodic email reminders to complete surveys.

  We will coordinate COMET study activities closely with MATCH or other tumor profile procedures to ensure that surveys do not alter the treatment schedule. If participants have not completed surveys, this will not prevent next steps in their care or other tumor profile activities.

  We will test surveys and assess burden and completion rates. If there is evidence of burden, we will revisit length and prioritize outcomes and constructs of interest.

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5.2.2 Secondary Genetic Counseling Substudy (Step 2 – Arm D and Arm E):

As shown in the study schema, all participants who meet inclusion criteria and criteria for a potential germline mutation identified with molecular tumor profiling at a participating substudy site will be offered the study (up to accrual of 100 patients).

- Genetic Counseling:

  Patients who meet criteria for the remote counseling substudy will complete remote counseling visits and surveys as outlined in the study schema. Visit 1 will be standard pre-test counseling; if patients agree to confirmatory germline testing, Visit 2 will consist of result disclosure and review of implications for relatives, consistent with clinical standards in the field. Genetic counselors will be licensed to practice (if necessary) in the states where sites reside consistent with state laws. Similar to our other remote counseling studies, standardized counseling checklists will be utilized by genetic counselors to ensure fidelity to the communication protocols[15,17,18]. All sessions will be audiotaped to evaluate fidelity and to inform potential future modifications for alternative delivery models. Genetic counselors will collaborate with the patient's treating physician as they will be the ordering provider. Thus, test results and recommendations will be communicated to the patient's treating physician and genetic counselors will collaborate with the treating physician as needed. Implications of germline findings for relatives will be communicated to patients, including how relatives can obtain clinical genetic testing.

There will be no genetic counselors providing counseling services in the primary randomized study. A large number of genetic counselors from the PENN cancer genetics team will be involved in development of the web-based genetic education.

For the sub-study, we will utilize genetic counselors from the PENN cancer genetics team, as this pool of counselors has cultivated extensive experience in conducting genetic counseling with advanced cancer patients in the context of tumor profiling.

- Germline Genetic Testing:

  All confirmatory germline testing will be completed through a commercial CLIA-approved lab. The genetic counselor will provide recommendations for testing and the treating physician will be the ordering provider for clinical germline testing. The genetic counselor will disclose the genetic test results to patients during Visit 2 and will collaborate with the treating physician to provide recommendations for testing relatives.

- In summary, the Step 2 procedures for both Arm D and Arm E (per Section 6.2) will include the completion of up to 4 surveys and the associated interventions, as listed below:
  - All Step 2 participants will complete:
    - a baseline survey (T0SS)
    - a visit with a genetic counselor for germline mutation counseling (GC Visit 1)
    - a post GC Visit 1 survey (T1SS)
  - Additionally, if a participant agrees to confirmatory testing, this individual will also have:
    - a second visit (GC Visit 2) with a genetic counselor
    - a post GC Visit 2 survey (T2SS)
    - and a 3 month survey (T3SS)
  - For Arm D patients (i.e., those from Step 1 Arm A or Arm B), information taken from T2 (see Sec. 6.1) will be used to pre-populate T0SS, and only the remaining items in T0SS will need to be completed.

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  - Participants with email access will be directed to complete surveys online. Those without email access may complete paper surveys instead.

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5.2.3 Alternative pathway to Substudy (Step 1 - Arm C, then Step 2 – Arm E):

In an effort to reduce the length of time to recruitment and completion of the substudy, we have included an alternative pathway for entry therein.

- As indicated in the study schema, following enrollment in screening for MATCH, a subgroup of patients who receive their tumor molecular profile results (report of any actionable mutations) from their treating physician, and who meet criteria for potential actionable germlne mutation (AIM 2), will be consented to the

COMET substudy. These individuals will not be required to complete the main study (Step 1 - Arm A or B) to be eligible for the substudy (Step 2).

- Patients who are eligible and consent to participate in the substudy, and who were not enrolled on either Arm A or Arm B, will be registered to Arm C (Step 1; substudy only). These individuals will not participate in or complete any primary study (Arm A or B) education or surveys.
- Arm C participants will immediately be registered to Arm E (Step 2) and complete all of the Step 2 procedures (per Section 6.2), including the completion of up to 4 surveys and the associated interventions (see Section 5.2.2 above). For Arm E patients, the entire T0SS will be completed as the baseline survey.

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5.3 Patient Recruitment

All eligible patients will be recruited to Step 1 by MATCH site research staff at the time that they enroll in the MATCH Master (Screening) Protocol or will be undergoing clinical tumor profiling at a select expansion site.

Potential participants at expansion sites will be approached by site research staff after permission of the treating physician.

At sites participating in the Substudy (Step 2), potential Substudy participants will be identified according to the selection criteria (see Section 3.2). MATCH or other site research staff will notify potential participants, introduce the study and consent interested participants.

We will collaborate with the ECOG-ACRIN Underserved Populations Recruitment and Retention Subcommittee to develop recruitment strategies to facilitate the enrollment of a diverse sample of participants. Dr. Edith Mitchell is chair of this subcommittee, and she is also involved in an initiative to facilitate minority accrual to the MATCH trial ("Impact") and will contribute her expertise to facilitate diverse patient participation for the proposed COMET trial.

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5.4 PRO/QOL Data Collection Process

Patient completed outcomes:

Patients will be recruited at the time of registration into the COMET study. At the time of registration at the sites, the patient's contact information should be collected on the Patient Contact (PC) form by the site CRA for all participants who do not have email/internet access (Note: all RCT Step 1 participants are required to have email/internet and thus no PC should be collected for these individuals). The completed PC should then be fax it to the OEAU and stored in a secure locking file storage location. Participants with email/internet access will be asked to enter this information themselves directly into the OEAU servers when they activate their EASEE-PRO account. The contact information is stored in a Biostatistics Center (BC) database and **IS NOT** linked to the master ECOG-ACRIN database. The OEAU RA will not have access to the main ECOG-ACRIN database that contains screening results.

Administration of web-based questionnaires will be coordinated by the OEAU. Administration of the questionnaires will be triggered based on completion of study milestones.

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Questionnaire completion

Patients on Step 1, and those with e-mail access on Step 2, will be prompted to complete web-based forms via an e-mail. These e-mails will include a link to the web site for questionnaire completion. Each participant will be required to log in with their unique user ID and password to complete the requested instruments. The web site will reference a study-specific e-mail address and a toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance. All participant data will be stored on a secure server.

Because the timings of survey completion in relation to events lie in very narrow windows, patients who do not complete the web questionnaires within 3 working days of the initial request e-mail will receive additional e-mail reminders. These reminder e-mails, like the initial e-mail, will provide a link to the current surveys, ask the participant to confirm that they have been able to access the web site, and provide both the e-mail address and the toll free help number for support.

If patients still have not responded within 12 days of the original e-mail, the OEAU Research Associate may attempt to telephone the patient and administer the questionnaire over the telephone. If questionnaires are telephone-administered, they will be marked as such in the data base. All surveys, while desired within 3 days of the event, will remain available for participants until either the surveys are completed or they are off-study. Since the completion date is recorded for all surveys, the study team will be able to make relevant determinations for inclusion of this data in specific analyses. However, after telephone follow-up, no additional or extraordinary means will be employed to collect overdue/missing questionnaires.

Only participants on Step 2 without email access may complete paper survey. The timing of administration will be the same as the web-based surveys.

Participants unable to enter their survey responses may designate a “scribe” to relay their responses. Participants will be able to indicate whether the survey was filled in by the participant or the designated scribe.

5.5 Study Instruments

NOTE: All participants of the Genetic Counseling substudy will complete surveys as shown in the Study Schema. Surveys will evaluate the primary and secondary endpoints informed by our theoretical models grounded in the Self Regulation Theory of Health Behavior[18] and Diffusion of Innovation Theory[17].

The study instruments are as follows:

5.5.1 *Knowledge of Genetic Disease (T0-T3; T0SS-T3SS):*

This will be evaluated using an adapted version of the Cancer Genetics Knowledge Scale and clin seq knowledge scale [19-21]. Adaptations were made for Somatic Testing. This scale is composed of items evaluating the differences between somatic and germline testing (3 items); the limitations of somatic testing (7 items), the limitations of germline testing (3 items) and relationship between tumor testing and clinical trials (1 item).

5.5.2 *Knowledge of Germline (i.e. inherited) Genetic Disease (T0SS-T3SS):*

This will be evaluated using an 8-item scale adapted from the Cancer Genetics Knowledge scale (Cronbach's α=0.58-0.60)[21]. This scale includes items evaluating mechanism of inheritance (3 item), meaning of positive (2 items) and negative results (3 items).

5.5.3 *Health Literacy (T0 and T0SS):*

Health literacy is assessed using a 3-item scale for identifying patients with inadequate or marginal health literacy[49].

5.5.4 *Promis (assessments of emotional distress anxiety/emotional distress depression) (T0-T3; T0SS-T3SS):*

Emotional distress anxiety and depression are each assessed with the 4-item short Patient Reported Outcomes Measurement Information System (PROMIS), a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being[50, 51].

5.5.5 *State Anxiety (T0-T3; T0SS-T3SS):*

Measured with the 20-item State Inventory of the State-Trait Anxiety Inventory (STAI). The state scale is a sensitive indicator of transient or situational changes in anxiety (see Project 3, Section B.3.d)[24-27].

5.5.6 *Cancer Specific Distress (T0-T3; T0SS-T3SS):*

Measured using the Impact of Events Scale (IES)[28,29]. The 14 item IES is compromised of the Intrusion subscale (7 items) and the Avoidance subscales (7 items), which can be summed for the Total scale. Although the IES was developed to assess stress reactions following non-cancer-related traumatic events, it has more recently been utilized to assess response to cancer-related stressors, such as being at hereditary risk for cancer, which have been conceptualized as a continuous, rather than event-specific stressor [25,30,31]. Thus, the IES has been used in the context of learning of one's genetic status, to assess cancer-specific distress over time [25,26,31-34]. The IES has been validated in individuals experiencing many different kinds of stressors [28,29,35]. On the bases of our preliminary studies, we have chosen not to use one item that did not have good face validity in our population. Thus, our modified IES will include 14 items (7 Intrusion; 7 Avoidant).

5.5.7 *Uncertainty About Genetic Testing (T0-T3 for tumor; T0SS-T3SS for germline):*

Assessed using a 3-item scale adapted from the uncertainty subscale of the Multi-dimensional Impact of Cancer Risk Assessment Question (MICRA)[36]. This subscale has had high internal consistency in our related research (Cronbach's α=0.88)[18]. This instrument has been adapted to address both germline and tumor genetic testing.

5.5.8 *Perceived Utility of Genetic Testing (T0-T3 for tumor; T0SS-T3SS for germline):*

This novel construct was developed to evaluate patient perceptions of the utility of germline and tumor genetic information for various aspects of their life and the life of their family members. It is comprised of 10-items and has had high internal consistency in our related research (Cronbach's α=0.90)[18].

5.5.9 *Preferences for Germline (i.e. inherited) Risk Information and Delivery (T2 only):*

We will assess preferences for learning germline information querying patients about interest in germline information if additional testing was needed and in the hypothetical situation where germline information was available as part of somatic testing. We will also assess preferences for delivery of germline information assessing provider (e.g. with a genetic counselor, medical oncologist) and mode of delivery (e.g. phone, videoconference, web-based genetic portal).These will be novel items developed specifically for the purpose of this study.

The genetic counselor will make recommendations for testing and will work with the local oncologist to facilitate germline confirmation testing through a contract with a commercial lab (likely Ambry Genetics based on an existing relationships). The local oncologist will be the ordering doctor.

We will use the standardized remote counseling communication protocols utilized in related research (COGENT R01 CA160847:Bradbury, RESPECT R01 CA190871:Bradbury) and adapted for this context. Communication to at risk-relatives will be included in the standardized counseling protocols, which will be developed and finalized during the development period.

5.5.10 *Satisfaction with Receipt of Tumor Genetic Test Results (T2 only)*

This is a 9-item satisfaction with communication scale that evaluates participants' perceptions of their tumor profile test experience and of their experience receiving their tumor profile test results, including cognitive, affective and time/attention items. These scales were adapted for somatic testing[52, 53, 54].

5.5.11 *Preferences for Receipt of Tumor Genetic Test Results (T2 only)*

We will assess patient preferences for receipt of tumor profile test results, including queries related to the actual modes of sharing and receiving results, satisfaction with receiving results using these communication modes, and alternatives thereto. These will be novel items developed specifically for the purpose of this study.

5.5.12 *Satisfaction with Genetic Counseling Services (T1SS and T2SS only):*

Assessed with a 9-item satisfaction with communication scale items[27,36,37] utilized in our prior and related studies and has demonstrated high internal consistency (Cronbach's α= 0.73-80)[15,16].

5.5.13 *Regret and Disappointment Regarding Genetic Test Result (T2 and T3 for tumor; T2SS and T3SS for germline):*

Assessed with the 7-item Regret and Disappointment Scale (RDS) which has been utilized in the general population to assess regret and disappointment in decision making[48]. This instrument has been adapted to address both germline and tumor genetic testing.

5.5.14 *Communication about Germline (i.e. inherited) Genetic Test Results (T2SS, T3SS)*

Psychosocial intention (T2SS) will be assessed using a 4-item measure of intent to communicate genetic test results previously developed and utilized in our COGENT study to assess intent to share genetic test results with health care providers, family members and other third parties.

Performance of psychosocial behaviors (T3SS) will be assessed using a 4-item measure of communication of genetic test results as described in the psychosocial intention.

5.6 Survey Assessment Schedule:

Please refer to Section 0 for Step 1 - Primary Study Intervention: RCT and Section 6.2 for Step 2 – Secondary Genetic Counseling Substudy.

5.7 Duration of Participation:

Patients can withdraw consent at any time. The duration of participation is anticipated to be no more than 4-5 months for those patients participating in the Primary Intervention Study. For those participating in the Substudy (Step 2), participation on this part is expected to be no more than 1 month if participants don't opt to have confirmatory germline genetic testing, or no more than 4 months if participants do have confirmatory germline genetic testing. For those participating in both the Primary Study (Step 1) and the Substudy (Step 2), participation is expected to last no more than 5 months.

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5.8 Duration of Follow-up

For this protocol, all patients, including those who do not complete all steps, will be followed until the time of their last planned survey. Individual activity on the online genetic education web site will be followed through completion of all protocol therapy (if enrolled in MATCH).

In addition, all patients will be followed for survival per the standard ECOG-ACRIN follow-up schedule: at 3 months and 6 months after study entry.

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6. Study Parameters

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NOTE: All patients enrolled into Step 1 (including Arms A, B, and C) will be followed for survival per the standard ECOG-ACRIN follow-up schedule: at 3 months and 6 months after study entry.

Below is information specifically for patients enrolled into Arms A and B for the primary study.

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6.1 Step 1 - Primary Study Intervention: RCT – Arms A & B

NOTE: Patients on Arm C (see Section □□□□) will not participate in or complete any primary study (Step 1) education or surveys, and will immediately be registered to Arm E and complete all of the substudy (Step 2) procedures.

Survey Schedule:

Surveys	Baseline	Post-Genetic Education (1-2 weeks after completion of T0)	Post-MATCH or Clinical Tumor Test Results Received [A] (within 3 days)	3 Months After the Receipt of MATCH or Clinical Tumor Test Results [A]
T0	X			
On-line Genetic Education (T1)		Arm A		
Usual Care/Standard Genetic Education (T1)		Arm B		
T2			X	
T3				X

[A.] Refers to the written test report, not the notification of treatment assignment

Assessment Schedule:

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Primary Intervention Study (Step 1)						
Assessments [A]	**T0**	**T1**	**T2**	**T3**	**3 Months**	**6 Months**
Health Literacy	X					
Knowledge of Genetic Disease	X	X	X	X		
PROMIS Anxiety/Depression	X	X	X	X		
State Anxiety	X	X	X	X		
Cancer Specific Distress	X	X	X	X		
Uncertainty About Tumor Genetic Testing	X	X	X	X		
Perceived Utility of Tumor Genetic Testing	X	X	X	X		
Satisfaction with Receipt of Tumor Genetic Test Results			X			
Preferences for Receipt of Tumor Genetic Test Results			X			
Preferences for Germline (i.e. inherited) Risk Information and Delivery			X			
Regret and Disappointment Regarding Tumor Genetic Test Result			X	X		
Follow-Up[B]					X	X

A. Descriptions of individual measures (except for Follow-Up) are included in Section 5.5. All instruments will be included as a single survey for each timepoint.

B. All patients will be followed for survival per the standard ECOG-ACRIN follow-up schedule: at 3 months and 6 months after study entry.

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6.2 Step 2 – Secondary Genetic Counseling Substudy – Arm D and Arm E

NOTE: The designated CRA must fax the MATCH or clinical tumor screening results report to the study team and discuss the results with the study team over telephone (See Section 4.2.3.3).

Survey Schedule:

Survey	Baseline	Post-Remote Genetic Counseling [A] (within 3 days)	Post-Germline Testing Results Received [B] (within 3 days)	3 Months After Germline Testing Results Received [B]
T0SS[C]	X			
T1SS		X		
T2SS			X	
T3SS				X

A. Post-GC (Genetic Counseling) Visit 1, see schema for details

B. Post-GC (Genetic Counseling) Visit 2; see schema for details

C. For Arm D patients (i.e., from Step 1 Arm A or B patients), information taken from T2 (see Sec. 6.1) will be used to pre-populate T0SS, and only the remaining items in T0SS will need to be completed. The "Uncertainty" and "Perceived Utility of Genetic Testing" assessments in T2 are exceptions, and must be completed in T0SS for all patients. For Arm E patients (i.e. those from Step 1 Arm C), the entire T0SS will be completed as the baseline survey.

Assessment Schedule:

Secondary Genetic Counseling Substudy (Step 2)				
Assessment [A]	T0SS	T1SS	T2SS	T3SS
Health Literacy	X			
Knowledge of Genetic Disease	X	X	X	X
Knowledge of Inherited Genetic Disease	X	X	X	X
PROMIS Anxiety/Depression	X	X	X	X
State Anxiety	X	X	X	X
Cancer Specific Distress	X	X	X	X
Uncertainty About Germline (i.e. inherited) Genetic Testing	X	X	X	X
Perceived Utility of Germline (i.e. inherited) Genetic Testing	X	X	X	X
Satisfaction with Genetic Counseling Services		X	X	
Regret and Disappointment Regarding Germline (i.e. inherited) Genetic Test Result			X	X
Communication about Germline (i.e. Inherited) Genetic Test Results			X	X

A. Descriptions of individual measures are included in Section 5.5. All instruments will be included as a single survey for each timepoint.

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7. Statistical Considerations

The primary objective of the primary Intervention Study (RCT, Step 1) is to evaluate the efficacy of web-based pre-disclosure genetic education (i.e. before receipt of tumor profile results) on knowledge (genetic knowledge and knowledge of test benefits and limitations) and distress (anxiety, depression and cancer specific worry) compared to usual care services in patients undergoing tumor profiling for advanced cancer. The primary analysis will, thus, be based on patients who have survey data evaluable at both T0 (baseline) and T1 (post-genetic education) (or T2, post-disclosure of test results). Given the survey completion rate for both T0 and T1 is approximately 60% (as analyzed in May 2018), the accrual goal of the primary intervention study needs to be increased from 400 to 670 patients in order to maintain sufficient power for evaluating the effect of web-based pre-disclosure genetic education.

As MATCH has approached its goal of sequencing ~6000 patient tumors, this section incorporates changes to expand eligibility criteria (effective since Addendum #3) to allow patients from select sites who potentially undergo tumor profiling through non-MATCH assays and to increase the accrual goal (effective since Addendum #6). In this section, patients who enter COMET through MATCH Step 0 (prior to or after the activation of this addendum allowing for eligibility expansion) will be referred as the MATCH cohort, and other patients (who enter after the corresponding addendum activates) will be referred as the non-MATCH cohort.

7.1 Primary Study: Randomized Study of Web-based Pre-disclosure Genetic Education versus Usual Care (Step 1 – Arms A & B)

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NOTE: Patients on Arm C (see Section □□□□) will not participate in or complete any primary study (Step 1) education or surveys, and will immediately be registered to Arm E and complete all of the substudy (Step 2) procedures.

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7.1.1 *Primary endpoints* will include change in knowledge and distress (state anxiety, Promis anxiety, Promis depression and cancer specific distress) from baseline to post-education (T0 to T1) and baseline to post-disclosure (T0 to T2).

The following 10 analyses are of primary interest: change scores from T0 to T1, and T0 to T2 of each of the following five outcomes: knowledge, state anxiety, cancer specific distress, Promis anxiety and Promis depression, which correspond to 10 primary analyses. To account for the 10 primary analyses, A Bonferroni correction is considered here, setting the nominal p-value to declare statistical significance of $p< 0.005$ (5% Typical Type I error rate / 10 comparisons = 0.5% nominal p-value for declaring statistical significance). Preliminary data from the COMET pilot study (State Anxiety, IES-Total, Knowledge) is used to calculate power. As there was no preliminary data for Promis Depression/Anxiety in a similar setting, power calculation for these two measurements are based on data reported in Hinds et al. (2012). A sample size of 200 (with evaluable paired data) /arm is chosen here, which provides at least 85% power for all short-term outcomes (e.g. T0-T1) and changes in knowledge and cancer specific distress after receipt of tumor profiling results (e.g. T0-T2), using t test at two-sided 0.005 significance level.

With the completion rate for both T0 and T1 surveys at approximately 60% (as analyzed in May 2018) and the goal of evaluable sample size at 200/arm (at least for the analysis of changes between T0 and T1), the accrual goal of the primary intervention study needs to be inflated from 400 to 670 patients in order to maintain sufficient power for detecting proposed changes from T0 to T1 and changes in knowledge and cancer specific from T0 to T2 (as described in the preceding paragraph). With the completion rate for both T0 and T2 surveys at approximately 45% (as analyzed in May 2018), the projected evaluable sample size of 150 patients/arm can give the power of 72% for changes in knowledge and 95% for changes in cancer specific distress from T0 to T2. These 670 patients will be randomized 1:1 between the two arms, and the randomization will be stratified by gender, race, age (> 65 vs. ≤ 65), and education level. As of this analysis time, 320 patients have been enrolled into the primary intervention study. The current COMET accrual rate is approximately 15 patients per month (based on the last 3 months). Assuming 15, 20 or 25 patients per month (as more expansion sites are added over time) can be accrued to COMET from the select sites, it is expected to take 23, 17 or 14 additional months, respectively, to complete Step 1 accrual of 670 patients.

The original accrual plan posed a limitation on White patients at 80% of the accrual goal to ensure diversity of patients. Given that the accrual of this study might terminate early if the funding of this study ends, the accrual limitation on White patients is being lifted to ensure the maximal number of patients enrolled before funding ends.

Power for various sample sizes

Variable	Change score time period	Sample Size Per Arm	Power for p< 0.005, 2-sided	Change Score Group 1	Change Score Group 2	Standard Deviation Group 1	Standard Deviation Group 2
State Anxiety	T0 to T1	100	98%	2.71	-2.78	8.24	7.43
State Anxiety	T0 to T1	150	100%	2.71	-2.78	8.24	7.43
State Anxiety	**T0 to T1**	**200**	**100%**	**2.71**	**-2.78**	**8.24**	**7.43**
State Anxiety	T0 to T1	300	100%	2.71	-2.78	8.24	7.43
State Anxiety	T0 to T1	400	100%	2.71	-2.78	8.24	7.43
State Anxiety	T0 to T1	61	85%	2.71	-2.78	8.24	7.43
IES-Total	T0 to T1	100	100%	0.29	-1.78	1.70	3.19
IES-Total	T0 to T1	150	100%	0.29	-1.78	1.70	3.19
IES-Total	**T0 to T1**	**200**	**100%**	**0.29**	**-1.78**	**1.70**	**3.19**
IES-Total	T0 to T1	300	100%	0.29	-1.78	1.70	3.19
IES-Total	T0 to T1	400	100%	0.29	-1.78	1.70	3.19
IES-Total	T0 to T1	46	85%	0.29	-1.78	1.70	3.19
Knowledge	T0 to T1	100	97%	1.70	-1.50	6.11	3.02
Knowledge	T0 to T1	150	100%	1.70	-1.50	6.11	3.02
Knowledge	**T0 to T1**	**200**	**100%**	**1.70**	**-1.50**	**6.11**	**3.02**
Knowledge	T0 to T1	300	100%	1.70	-1.50	6.11	3.02
Knowledge	T0 to T1	400	100%	1.70	-1.50	6.11	3.02
Knowledge	T0 to T1	68	85%	1.70	-1.50	6.11	3.02
State Anxiety	T0 to T2	100	13%	-2.43	5.00	4.04	14.58
State Anxiety	T0 to T2	150	23%	-2.43	5.00	4.04	14.58
State Anxiety	T0 to T2	200	34%	-2.43	5.00	4.04	14.58
State Anxiety	T0 to T2	300	55%	-2.43	5.00	4.04	14.58
State Anxiety	T0 to T2	400	72%	-2.43	5.00	4.04	14.58
State Anxiety	T0 to T2	512	85%	-2.43	5.00	4.04	14.58
IES-Total	T0 to T2	100	79%	-1.00	-2.17	1.53	2.86
IES-Total	T0 to T2	150	95%	-1.00	-2.17	1.53	2.86
IES-Total	**T0 to T2**	**200**	**99%**	**-1.00**	**-2.17**	**1.53**	**2.86**
IES-Total	T0 to T2	300	100%	-1.00	-2.17	1.53	2.86
IES-Total	T0 to T2	400	100%	-1.00	-2.17	1.53	2.86
IES-Total	T0 to T2	114	85%	-1.00	-2.17	1.53	2.86
Knowledge	T0 to T2	100	48%	5.86	4.40	4.30	3.05
Knowledge	T0 to T2	150	72%	5.86	4.40	4.30	3.05
Knowledge	**T0 to T2**	**200**	**86%**	**5.86**	**4.40**	**4.30**	**3.05**
Knowledge	T0 to T2	300	98%	5.86	4.40	4.30	3.05
Knowledge	T0 to T2	400	100%	5.86	4.40	4.30	3.05
Knowledge	T0 to T2	194	85%	5.86	4.40	4.30	3.05

Power for Promis Depression and Promis Anxiety

With 200 evaluable patients per arm, there is 91% power to detect an effect size of 0.33 (as fraction of standard deviation), using t-test at two-sided significance level 0.005. Based on data from 92 children/adolescents, Hinds et al. (2012) reported standard deviation of 10.74 for Promis Depression and 12.5 for Promis Anxiety, respectively. Assuming the standard deviations for these two measurements in our proposed study are similar, the following table gives the absolute difference that can be detected with 91% power, under different assumptions for the correlation between the measurements across two timepoints, at two-sided significance level 0.005.

Variable	Correlation	Standard deviation of change	Effect size (as fraction of standard deviation)	Absolute difference	Power
Promis Depression	0.4	11.8	0.33	3.89	91%
Promis Depression	0.6	9.6	0.33	3.17	91%
Promis Depression	0.8	6.8	0.33	2.24	91%
Promis Anxiety	0.4	13.7	0.33	4.5	91%
Promis Anxiety	0.6	11.2	0.33	3.7	91%
Promis Anxiety	0.8	7.9	0.33	2.6	91%

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7.1.2 *Analysis Plan*

Outcome change scores (primary endpoints) between time points for each study participant will be calculated. Two-sample T-tests will be conducted first to evaluate whether there is any difference in outcome change scores (with respect to the primary endpoints) between MATCH patients and non-MATCH patients. If differences are observed, the analysis described below will be performed separately for each cohort.

Two-sample T-tests assuming unequal variances will be used for the primary analyses of the change scores between arms. An intention-to-treat approach will be used in which the effect between randomized arms is evaluated, regardless of any treatment crossover. In secondary analyses of the primary endpoints, demographic characteristics between the two arms will be evaluated using T-tests and Fisher's Exact Tests to investigate if the arms were unbalanced with respect to potential confounders. If any potential confounders (in particular age, race/ethnicity and health literacy) are found to have means/proportions that are different between the arms at a p-value of less than 0.1, we will examine the treatment effect in multiple linear regressions of the outcomes in which the randomized arms will be included as a binary (0/1) dummy indicator and all potential confounders that have a p-value < 0.1 will be included as covariates. These analyses will be repeated using the as-treated approach in which we compare differences between the interventions the patient actually received (for example, patients were randomized to the on-line pre-disclosure genetic education but instead received usual care).

There is no plan to perform interim outcome monitoring for this study. Participating patient will be at minimal risk given the nature of the study. The study will be closely monitored for feasibility (Section 7.1.4), and if feasible, information/data gathered would be useful and informative in patient care.

7.1.3 *Exploratory analysis* will be longitudinal changes in cognitive (e.g. genetic knowledge), affective (cancer specific distress, state anxiety, general anxiety and general depression, perceived utility, uncertainty). In these analyses, multiple linear or logistic regressions will be fit to investigate temporal changes in the randomization arm effect, using the Generalized Estimating Equations (GEE) to account for correlated data over time. Unstructured working correlation matrices for GEE will first be considered unless there are model convergence problems, in which case exchangeable working correlation matrices will be used instead. In the regressions, survey wave and the randomized arm will be included as dummy indicator (0/1 variables) covariates. As there are four survey time points, we include three dummy indicators for T1, T2 and T3. In analyzing the change of scores (T1-T0, T2-T0, T3-T0), two dummy indicators will be needed. We will also include interactions between the survey wave indicators and the arm indicator to see if the arm effect changes over time. We will also include potential baseline confounding variables that were not balanced between arms at a p-value < 0.1 (using T-Tests and Fisher's Exact Tests). These analyses will be repeated using the as-treated approach as well.

To evaluate potential moderators as described in Section 2, we will add relevant interaction terms to the GEE-estimated multiple linear and logistic regressions described above. Of most interest are interactions between the potential moderators (e.g. test result, sociodemographic factors, health literacy, baseline knowledge or distress) and the arm indicator.

Other exploratory endpoints include satisfaction and regret/disappointment related to tumor genetic test results, and how to better deliver tumor genetic test results and germline information in the future. Summary statistics will be provided and comparison may be explored between arms using T-Tests or Fisher's Exact Tests at two-sided significance level of 0.05.

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7.1.4 *Feasibility*

Monitoring enrollment on the primary study:

Accrual will be closely monitored after the addendum expanding eligibility criteria activates, A formal evaluation will start at 6 months after the addendum expanding eligibility criteria activates, allowing some time for the select sites to get ready for enrolling patients. If the rate of enrollment on Step 1 of EAQ152 is < 5 patients per month, the data will be discussed with the study team and the NCI to reevaluate the feasibility of the study.

Monitoring rate of compliance and questionnaire response:

Primary analysis will be based on randomized arms. Patients who have survey data at T0, and at least one of the follow-up timepoints

(T1 or T2), will be considered as evaluable. Among the first 100 patients who are enrolled on Step 1 for the primary study, if proportion of evaluable patients is < 60%, the data will be discussed with the study team and the NCI to re-assess the feasibility. Proportion of patients who cross-over, and proportion of the patients on Arm A who complete the web-based education, will also be reported.

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7.2 Secondary Germline Genetic Testing & Counseling Substudy (Step 2 – Arm D and Arm E)

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7.2.1

The *primary endpoints* for the substudy will be uptake of remote genetic counseling and uptake of clinical germline testing.

This substudy will be exploratory in nature. We will evaluate, separately, the proportion of individuals who complete a) remote genetic counseling and b) germline testing, among patients (whose hospital sites open accrual to COMET Step 2) with a **potential** clinically significant incidental germline mutation identified through MATCH or non-MATCH tumor profiling. The current COMET Step 2 accrual rate through MATCH is 1-2 patients per month. The substudy will stop patient accrual either when the accrual goal of 100 patients is met or 4 months after the primary study is closed to accrual (allowing the tumor profiling results to be returned back to the sites and so any remaining qualifying patients can be enrolled into the substudy), whichever is earlier.

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7.2.2 *Analysis Plan*

The proportions of individual uptake of remote genetic counseling and uptake of clinical germline testing will be calculated separately, along with the 95% confidence intervals.

Changes in knowledge and distress (state anxiety, general anxiety, general depression and cancer specific distress) from baseline to post-pre-test genetic counseling (T0SS to T1SS) and baseline to post-test for those who proceed with confirmatory genetic testing (T0SS to T2SS) will be described using descriptive statistics (e.g. means, standard deviations, proportions, 95% confidence intervals). Multiple linear regressions will be fit to further investigate temporal changes. Again, regression parameters will be estimated using GEE to account for correlated data over time. Unstructured working correlation matrices for GEE will be considered first unless there are model convergence problems, in which case exchangeable working correlation matrices will be used instead. In the regressions, survey wave as dummy indicator (0/1 variables) will be included as covariates. As there are three survey time points, we include two dummy indicators for T1 and T2 (leaving T0 as the baseline reference time period). We will also include potential baseline confounding variables in the models (e.g. age, sociodemographic variables).

Other exploratory endpoints include communication to others, satisfaction and regret/disappointment related to genetic counseling service or germline genetic test results. Summary statistics will be provided.

7.3 Gender and Ethnicity

Rev. Add6

7.3.1 Primary Study: Randomized Study of Web-based Pre-disclosure Genetic Education versus Usual Care (Step 1)

Assuming the number of enrolled patients will be approximately 670, based on the past 2 years of accrual to ECOG-ACRIN coordinated therapeutic studies by any participating group, excluding leukemia and myeloma, the anticipated accrual in subgroups by gender and race is as follows:

Racial Categories	Ethnic Categories				Total
	Not Hispanic/Latino		Hispanic/Latino		
	Female	Male	Female	Male	
American Indian or Alaskan Native	2	2	0	0	4
Asian	15	7	0	0	22
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Black or African American	28	25	0	0	53
White	275	291	15	10	591
Total	320	325	15	10	670

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Rev. 7/17

7.3.2 Secondary Germline Genetic Testing & Counseling Substudy (Step 2)

Assuming the number of treated patients will be approximately 100, based on the past 2 years of accrual to ECOG-ACRIN coordinated therapeutic studies by any participating group, excluding leukemia and myeloma, the anticipated accrual in subgroups by gender and race is as follows:

Racial Categories	Ethnic Categories				Total
	Not Hispanic/Latino		Hispanic/Latino		
	Female	Male	Female	Male	
American Indian or Alaskan Native	0	0	0	0	0
Asian	2	1	0	0	3
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Black or African American	4	4	0	0	8
White	42	44	2	1	89
Total	48	49	2	1	100

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

8. Electronic Data Capture

Please refer to the ***EAQ152*** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave (refer to Section 4.1.4.3) and the EASEE-PRO (refer to Section 4.1.4.4) system. Please refer to Section 5.4 for information on the PRO/QOL data collection process.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

9. Patient Consent and Peer Judgment

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

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Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]_____ [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]