DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Office for Human Research Studies

Protocol Front Sheet

DFCI Protocol No.: 12-078

1. PROTOCOL TITLE AND VERSION

Title: The use of sequencing to guide the care of cancer patients
Protocol Version No./ Date: Version 14/April 2015 **Sponsor Study Number:**

2. DF/HCC STUDY CONTACT INFORMATION

Primary Study Contact: Nelly M. Oliver **Email:** nelly_oliver@dfci.harvard.edu **Phone:** 617-582-8706

INVESTIGATORS: (List only those under DFCI IRB, *i.e.*, from institutions listed in Section 6 below)

Overall PI:	Levi A. Garraway, MD, PhD	**Phone:**	617-632-6689	**Institution(s):**	DFCI
Site Responsible PI:	Levi A. Garraway, MD, PhD	**Phone:**	617-632-6689	**Institution(s):**	DFCI

3. DRUG / DEVICE INFORMATION N/A:

☐ **Drug(s), Biologic(s)**:
Provided by:
IND Exempt: ☐ -or-
IND#: **Holder Type:** [pull down]
IND Holder Name:

☐ **Device(s) Name**:
Provided by:
IDE Exempt: ☐ -or-
IDE #: **Holder Type:** [pull down]
IDE Holder Name:

4. PROTOCOL COORDINATION, FUNDING, PHASE, MODE, TYPE ETC.

Regulatory Sponsor:
DF/HCC Investigator Stacy Gray, MD, AM

Cancer Related: Yes If yes:
Primary Disease Program:
Other
or
Primary Discipline Based Program:
Cancer Genetics

Funding/Support (check all that apply)**:**
☐ Industry:
☒ Federal Organization: NIH
Grant #: 1U01HG006492-04
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

CTEP Study: [pull down]

Phase: N/A

Multi-Center (i.e., non-DF/HCC site participation)**:**
No

Protocol Type: Other
If Ancillary, provide parent protocol #:

Protocol Involves (check all that apply as listed in the protocol document, even if not part of the research but is mandated by the protocol document)**:**

☐ Chemotherapy	☐ Hormone Therapy	☒ Medical Record Review
☐ Immunotherapy	☐ Vaccine	☒ Questionnaires/Surveys/Interviews
☐ Surgery	☐ Data Repository	☐ Radiological Exams
☐ Bone Marrow/Stem Cell Transplant	☐ Exercise/Physical Therapy	☐ Required Biopsy Study
☐ Cell Based Therapy	☒ Genetic Studies	☐ Human Embryonic Stem Cell
☐ Gene Transfer (use of recombinant DNA)	☒ Human Material Banking	☐ Quality of Life
☐ Radiation Therapy	☒ Human Material Collection	☐ Other:

5. SUBJECT POPULATION (also applies to medical record review and specimen collection studies)

Total Study-Wide Enrollment Goal: 400 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No

Total DF/HCC Estimated Enrollment Goal: 400 **Adult Age Range:** 18+ **Pediatric Age Range:**

Will all subjects be recruited from pediatric clinics? ☐ Yes ☒ No

If enrolling both adults and pediatric subjects, anticipated percent of pediatric subjects:

Retrospective Medical Record Reviews only (Please provide date range): from 1/1/2010 to 2/2/2015

6. DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Beth Israel Deaconess Medical Center (BIDMC)
☐ Beth Israel Deaconess Medical Center – Needham (BIDMC-Needham)
☐ Boston Children's Hospital (BCH)
☒ Brigham and Women's Hospital (BWH)
☒ Dana-Farber Cancer Institute (DFCI)
☐ Dana-Farber/New Hampshire Oncology-Hematology (DFCI @ NHOH)
☐ DF/BWCC in Clinical Affiliation with South Shore Hospital (DFCI @ SSH)
☐ Dana-Farber at Milford Regional Cancer Center (DFCI @ MRCC)
☐ Dana-Farber at Steward St. Elizabeth's Medical Center (DFCI @ SEMC)
☐ Massachusetts General Hospital (MGH)
☐ Mass General/North Shore Cancer Center (MGH @ NSCC)
☐ Mass General at Emerson Hospital – Bethke (MGH @ EH)

7. NON-DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Cape Cod Healthcare (CCH)
☐ Lowell General Hospital (LGH)
☐ New Hampshire Oncology-Hematology-P.A. (NHOH)
☐ Newton-Wellesley Hospital (NWH)
☒ Broad Institute
☐ Lawrence & Memorial Cancer Center in affiliation with Dana-Farber Community Cancer Care (LMCCC)

8. DF/HCC INITIATED STUDIES ONLY - INSTITUTIONAL PARTICIPANTS UNDER OTHER IRB (N/A:)

DF/HCC Multi-Center Protocols: (list institution/location)

DF/PCC Network Affiliates: (list institution/location)

Protocol Number: 12-078

Approval Date: 08/27/12 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 09/13/12 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OHRS Version Date
09/26/12	Correction: Consent Form replaced	N/A	N/A
01/24/13	Protocol, Consent Form and Front Sheet replaced due to Amendment # 1	01/14/13	01/24/13
02/04/13	Front Sheet updated (current version previously posted) Amendment #2	02/01/13	N/A
03/01/13	Correction Am #2: Front Sheet replaced	N/A	N/A
04/11/13	Protocol, Local Appendices, Consent Form and Front Sheet replaced due to Amendment #3	04/04/13	04/10/13
07/02/13	Protocol, Local Appendices A,C & D, Consent Form and Front Sheet replaced due to Amendment #4	06/19/13	06/25/13
07/31/13	Appendices C & D replaced due to Amendment #6; Protocol and Front Sheet replaced due to Amendment #7	07/17/13	N/A
08/20/13	Local Appendices replaced due to Amendment #8	08/08/13	n/a
08/22/13	Study renewal/ Consent Form footer replaced due to Continuing Review #1; *Note:* This CR has been given a 60-day extension. IRB Expiration Date: 10/21/2013	08/12/13	N/A
08/30/13	Protocol and Front Sheet replaced due to Amendment #9	08/21/13	n/a
10/17/13	Study renewal/ Consent Form footer replaced due to Continuing Review #1; *Note:* Due to previous IRB conditional approval, has met extension conditions and new IRB Expiration Date: 10/15/2014	08/12/13	n/a
01/07/14	Protocol, Front Sheet, Appendices C and D replaced; Local Appendices (Post-Consent Interview, Post-Disclosure Reminder Letter) added – due to Amendment #10	01/06/14	N/A
01/13/14	Protocol and Front Sheet replaced due to Amendment #11	01/08/14	N/A
03/24/14	Local Appendices replaced due to Amendment #12	03/20/14	n/a
04/08/14	Email Template added as a Local Appendix due to Amendment #13	03/27/14	N/A
08/12/14	Protocol, Front Sheet and Local Appendices (Appendices A to K) replaced; Appendix L added – due to Amendment #14	07/14/14	N/A
08/28/14	Protocol, Front Sheet, Appendix A and Appendix I replaced; Appendix M added – due to Amendment #15	08/13/14	N/A
10/01/14	Appendix I replaced due to Amendment #16	09/30/14	N/A
10/06/14	Correction: Protocol replaced due to incorrect version previously provided with AM 15	n/a	n/a
10/09/14	Study renewal / Consent Forms footer replaced due to Continuing Review #2	08/25/14	N/A
11/13/14	Protocol, Local Appendices and Front Sheet replaced due to Amendment #17	11/12/14	n/a
02/04/15	Protocol and Front Sheet replaced due to Amendment #18	01/23/15	N/A

03/24/15	Consent Form, Protocol and Front Sheet replaced; Appendix O added – due to Amendment #19	03/23/15	03/24/15
04/22/15	Appendix O replaced due to Amendment #21	04/21/15	N/A
04/29/15	Protocol, Consent Form and Front Sheet replaced due to Amendment #20	04/27/15	04/28/15
Date Posted	**Revised Sections**	**IRB Approval Date**	**OnCore Version Date**
08/19/15	Study renewal / Consent Forms footer replaced due to Continuing Review #3	07/27/15	07/28/15

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1.0 Abstract

The transformative medical potential of cancer genomic information has been made clear by the growing number of targeted agents that show remarkable efficacy against tumors whose salient genetic events confer heightened therapeutic vulnerability. Some mutations also identify tumors for which a therapy will be futile or even harmful. Many cancer genes harbor potentially "actionable" mutations at variable frequencies across a wide range of tumor types. These observations provide a compelling rationale for a paradigm wherein all therapeutically relevant tumor genomic alterations might be presented to physicians in a manner that guides "personalized" treatment.

Most tumors harbor a spectrum of genomic aberrations that govern their genesis and progression. Many such changes engender a heightened dependency on specific mutated proteins or altered cellular pathways for tumor growth and survival. Moreover, the past decade has witnessed a marked proliferation of developmental agents that target cancer vulnerabilities linked to genetic alterations. The ability to identify in advance the full spectrum of biologically and therapeutically relevant genetic alterations—and to render this information useful to clinicians—heralds a transformation in oncology that may dramatically improve outcomes for cancer patients.

The overarching goal of this protocol is to study the impact of sequencing in the clinical care of cancer patients. Findings from this study may uncover both somatic and germline genetic changes that impact the treatment, prognosis and susceptibility to cancer and non-cancer conditions. These findings may lead to improved strategies to treat and prevent cancer thus reducing the burden of cancer to society.

2.0 Background/Rationale and Potential Benefits

2.1 Background/Rationale

In the era of comprehensive genomic characterization, treatment decisions will increasingly be based on the genetic makeup of individual cancers (1-2). The steady expansion of targeted anticancer agents that are either FDA-approved or in development has called specific attention

to the importance of developing categorical approaches that pinpoint *in situ* the tumors most likely to respond. Knowledge of such alterations in the clinical and translational arenas—including mutations, chromosomal copy number alterations, and polymorphisms affecting drug metabolism—will undoubtedly facilitate individualized approaches to cancer treatment. Already, a small but growing number of targeted therapeutics have been deployed successfully based on key tumor genetic events, including all-trans retinoic acid against acute promyelocytic leukemias with t(15;17) (PML-RARa) translocations, traztuzumab against *ERBB2*-amplified breast cancers, imatinib in tumors containing mutations in *(BCR-)ABL* or *KIT*, and gefitinib or erlotinib in tumors harboring *EGFR* mutations (3-16). Newer kinase inhibitors targeting *BRAF* in melanoma and *ALK* in lung cancer have shown similarly promising results in clinical trials (17-19). However, systematic genomic characterization of cancers remains vastly underdeveloped in the translational and clinical oncology setting.

To bring comprehensive cancer sequencing into the clinical arena, we must engineer a robust process for distilling billions of data points into a handful of salient observations that are both interpretable and useful to clinicians and patients. Ideally, tumor genetic material from every cancer patient would be characterized for alterations in every actionable cancer gene. Such characterization would reveal the spectrum of genomic derangement across tumor types, the presence of mutations in unexpected contexts with potential therapeutic implications, and patterns of mutational co-occurrence that might direct treatment choice. Addressing this challenge requires technological and interpretive innovations that can procure the relevant genetic information from each tumor so that it might be linked to available treatment options. If widely obtained, such information might identify those patients most likely (or least likely) to respond to existing and emerging anticancer regimens.

The goal of this study is to speed the advent of personalized cancer medicine by implementing a framework for the application and clinical interpretation of cancer genome sequencing in human cancer. Dr. Garraway, the PI of this project, has been a leader in both cancer genomics and its adaptation for translational use. Previously, we developed and deployed OncoMap, a systematic mutation profiling platform based on mass spectrometric genotyping (20). This platform interrogates hundreds of actionable mutations in dozens of cancer genes (21), and forms the technology basis for the DFCI/BWH Personalized Cancer Medicine Partnership. Migration to sequencing is both a logical extension of this institutional effort and a substantial innovation that builds upon its strong foundation (22). Furthermore, the extension of this partnership to include the Broad Institute will bring a leading technological and analytical dimension. Upon completion, this research should open many new opportunities to link cancer genomics with clinical decision-making in a manner that improves the care of cancer patients.

After consent, patients with cancer who are being treated at DFCI will be enrolled into this clinical study wherein tumor and normal genomic DNA and/or RNA are procured and subject to sequencing, analysis, and interpretation. Sequencing studies will generally consist of whole exome sequencing (WES), but may also include whole genome sequencing, targeted (i.e. sub-exome) sequencing, and/or whole transcriptome sequencing. The majority of these sequencing studies will be conducted in research laboratories at DFCI and/or the Broad Institute, but may also include additional laboratories, including CLIA-approved sequencing facilities and/or commercial entities. For sequencing done in research laboratories, the resulting list of actionable alterations will be provided to a diagnostic CLIA lab for validation; the CLIA lab will independently query known actionable mutations using orthogonal approaches. All alterations detected in a CLIA-approved laboratory may be returned to the clinical team (with the patient's

consent) to inform the care of cancer patients. In parallel, we will conduct longitudinal surveys and qualitative interviews of patients and their oncologists at various points surrounding the informed consent, data delivery and decision-making processes in order to better understand how best to communicate the results of complex genetic studies to patients and physicians, and to help them use that information to choose the best treatment path.

2.2 Potential Benefits to subjects and/or society

This protocol creates a mechanism for the generation, interpretation, and clinical implementation of cancer sequencing. In some cases, patients who participate in this study will experience no direct benefits. In other cases, when patients or individuals test positively for certain known or suspected genetic abnormalities that are detected or confirmed in a CLIA-certified laboratory, they may choose to have their provider notified of these findings, and may choose to be treated with a drug that may potentially confer benefit or enroll in a clinical trial testing a relevant targeted therapy. This protocol will create a database of sequencing-detected alterations in cancer that can eventually serve as a roadmap for the development of new and more effective therapies or prevention approaches. This protocol will also provide guidance in devising ways to frame and communicate complex genomic results to patients and providers. Together, these advances will result in substantial societal benefit.

3.0 Objectives / Study Aims

The overall objective of this protocol is to develop a paradigm for the integration of germline and somatic genome sequencing into the care of cancer patients. We will perform sequencing analyses of tumor and normal tissue for research purposes, and will implement a framework for the application and clinical interpretation of parallel cancer and germline genome sequencing in patients with cancer. Specimens may also be analyzed for a variety of other research purposes. We anticipate that findings from this research will benefit some future patients and further our research capabilities. We will begin with two cancers as models: metastatic adenocarcinomas of the lung and colon.

This objective will be achieved through the following aims:

Specific Aim 1. To implement a production-scale platform for whole exome sequencing from archival (FFPE) material.

- To obtain tumor and germline specimens from patients with metastatic cancer who are receiving treatment at DFCI, beginning with metastatic lung and colon adenocarcinomas.
- To perform whole exome sequencing on these specimens in order to determine somatic and germline genomic alterations that may be relevant to the development or treatment of cancer
- To develop and implement an analytical and interpretive framework to prioritize clinically important genomic alterations

Specific Aim 2. To determine the clinical impact of somatic and germline whole exome sequencing in cancer patients.

- To determine the feasibility of whole exome sequencing of clinical cancer patients with advanced solid tumors, beginning with lung and colon adenocarcinomas**.**
- To establish a system of review and disclosure of results, including selected incidental results unrelated to the patients' cancer diagnoses, to physicians, patients, and their families

- To describe the impact of whole exome sequencing data on the medical management of patients with advanced solid tumors

Specific Aim 3. To describe the *impact* of information derived from somatic and germline whole-exome sequencing (WES) on cancer patients.

Cancer patients stand to benefit greatly from sequencing if genomic data identify highly effective therapies. However, patients may find genomic information difficult to understand, and they are vulnerable to psychological distress if faced with large amounts of uncertain information or with unanticipated incidental findings.

- We hypothesize that patients undergoing comprehensive tumor and germline genetic analysis will want to receive information about all potentially informative somatic and germline genomic variants (*Aim 3a*).
- Additionally, we will evaluate patients' understanding of disclosed genomic information (*Aim 3b*).
- Finally, we will characterize patients' test-related distress (*Aim 3c*).
- These questions will also be explored in depth using qualitative methods.

4.0 Study Design

This protocol is designed to facilitate the generation, interpretation, and clinical implementation of sequencing data from cancer patients during the course of their clinical care.

This protocol is designed to **be used along with DF/HCC Protocol 11-104 ("Research on Clinically Acquired Specimens")**. This protocol will use the same framework, infrastructure and databases established under 11-104 (CAMD, CRDR, CORIS, TDM, etc.). *DFCI patients who have not enrolled on 11-104 at the time of enrollment on this protocol will be asked concurrently to consent to participate in 11-104.*

Subject enrollment. Enrollment will be offered to patients who meet the eligibility criteria listed in Section 5.0. Consent may be sought at any time during the clinical care of the patient. Subjects will be identified through a coordinated effort between study personnel and the patient's treating oncologist. The study personnel will then approach eligible patients in person to facilitate study enrollment. In some cases, patients may contact one of the investigators directly. Although in some cases the identity of the subject may be known to one or more of the study investigators, specimens and all sequencing data will be encoded to protect the confidentiality of the subjects as described below.

Specimen collection. Patients' tumor tissue, bone marrow, and other biospecimens will be collected as part of their routine clinical care and/or as part of a separate research protocol, and therefore will not require any additional procedures except those required to obtain one additional tube of blood and/or a sample of saliva.

Specimen management. Specimens will handled as described in DF/HCC Protocol 11-104 ("Research on Clinically Acquired Specimens"), Strict patient confidentiality procedures will be followed, so that a patient's identity will not be publicly linked to any study results. Detailed biospecimen tracking and management procedures are described in section 10.

Research using specimens and/or data. Patient consent will permit some or all of the following: analysis of stored specimens, deposition of the resulting data in CRDR, linkage of these data to

clinical data stored in CORIS, banking of specimens or material derived from the specimens (e.g., DNA), sharing of de-identified genomic and survey data through centralized data warehouses (e.g., the NIH) or by controlled investigator-to-investigator mechanisms in a manner that does not include any patient identifiers, and possible future research on the specimens or their derivatives. Sequencing analyses may be linked to clinical information to determine if molecular data correlate with tumor behavior or patient outcomes using secure procedures described in this protocol and in 11-104.

Subject notification and participation. Experimental results may be made known to participants' providers if the results might influence their cancer care (e.g. treatment or clinical trial selection), or if participants consent to this notification, and if studies have been performed in a CLIA-certified laboratory (detailed in Section 6). As part of the consent process, patients will also be asked for preferences for germline test result disclosure. They will be asked to specify which types of germline genomic information they do or do not wish to be returned to them. Patient preferences for germline test-result disclosure will be provided to the study staff, and the patient's treating physician to ensure that patients only receive desired test results. Participants may change their preferences for test result disclosure at any time prior to receiving their results by completing a new consent form and indicating their updated preferences on the form.

During the consent process, patients will also be asked to designate a proxy who could be notified about a genomic variant with serious risk implications for the patient or for biological relatives in the event that the patient is no longer available to receive the information (e.g., if the patient becomes incapacitated or dies).

The duration of participation is variable. As part of the consent process, participants will acknowledge their understanding that participation in the study involves donation of their specimens for an unspecified duration. Other than acquisition of blood and/or saliva, participants will not undergo any further biological study procedures. However, data from research activities will be collected in an ongoing fashion unless the participant decides to be removed from this study. Instructions for withdrawal by participants are included in the consent forms. All participants will also be asked to fill out study-related surveys. A subset of patients will be invited to participate in in-depth in-person or telephone interviews.

5.0 Eligibility

5.1 Study Population

Participation in this protocol will be offered to any DFCI patients who are identified as oncology patients or patients suspected to have an eligible cancer diagnosis as defined by their providers. The project will begin with patients with metastatic adenocarcinomas of the lung and colon as detailed below.

5.1.1 Study Population For Cognitive Testing Of The Draft Baseline and Post-Disclosure Survey:

In the first phase of the project, the investigators (with the assistance of the DFCI Survey and Data Management Core (Survey Core)) will conduct cognitive testing of the draft survey instruments with approximately 5-10 Thoracic Oncology patients at DFCI who are not participating in Protocol 12-078.

5.2 Inclusion Criteria

Patients who have previously consented to DF/HCC Protocol 11-104 ("Research on Clinically Acquired Specimens"), 02-180 (lung cancer patients only), and/or are receiving clinical testing for *KRAS* mutations at BWH (colorectal cancer patients only) will be eligible for this study. Patients will be eligible if they:

1. have previously consented to DF/HCC Protocol 11-104 ("Research on Clinically Acquired Specimens"), 02-180 (lung cancer patients only), and/or are receiving clinical testing for *KRAS* mutations at BWH (colorectal cancer patients only)
2. have a diagnosis of advanced (stage IV) lung or colorectal adenocarcinoma (any histologic variant)
3. have a life expectancy of <u>at least</u> 6 months, as judged by their treating oncologist
4. have ECOG performance status (PS) of 0 or 1
5. have sufficient tumor genomic DNA available for exome sequencing, or can be extracted from existing tumor specimen, for whole exome sequencing and CLIA confirmation
6. have a treating oncologist who is participating in the physician study (protocol 12-249) that is a companion to this protocol
7. speak English (because study instruments are only available in English and Spanish)
8. consent to participate in this research study (patients who lack decision making capacity, and for whom proxy permission would be required, are not eligible to participate)
9. receive their cancer therapy at the Dana Farber Cancer Institute

In accordance with NIH guidelines, women and members of minority groups and their subpopulations will be included in this protocol.

To permit identification of eligible subjects (e.g., patients with sufficient tumor DNA available) and offer them the opportunity to participate in this study, we are requesting a waiver of HIPAA authorization to access potential study subjects' protected health information. This involves minimal risk and this study could not feasibly be conducted without such a waiver.

<u>5.3 Accrual</u>

It is estimated that a total of 200 lung cancer and 200 colorectal cancer patients will be analyzed. We expect about 50 in each group in year one, 75 in each group in year 2 and the final 75 in each group in year 3. It is possible that some enrolled patients will ultimately be unable to complete participation for many possible reasons (inadequate tissue, subject becomes much sicker more quickly than anticipated, etc.), so we will plan to accrue a total of 250 subjects in each group, stopping when we have 200 evaluable specimens and subjects in each cohort.

<u>6.0 Subject Enrollment</u>

<u>6.1 Enrollment of Patients</u>

Potentially eligible patients will be those who have consented to DF/HCC Protocol 11-104 ("Research on Clinically Acquired Specimens"), 02-180 (lung cancer patients only), and/or are receiving clinical testing for *KRAS* mutations at BWH (colorectal cancer patients only).

Potentially eligible patients will be identified through a coordinated effort between the study personnel (project manager (PM) and clinical research associates (CRAs)) and the patients' treating oncologists.

In order to determine whether a patient is likely to be eligible for the study, CRAs will routinely run a Business Objects report containing the following information: disease type, number of arrived appointments, 11-104 consent status, vital status, next appointment date, 03-189 consent status for colorectal patients and 02-180 enrollment status, KRAS testing status and EGFR testing status for thoracic patients. CRAs will then consult the LMR to determine disease stage, line of treatment, language spoken, that the patient is being treated at DFCI, ECOG status and that the patient has an Adenocarcinoma. If patients are determined to be potentially eligible per these criteria, CRAs will approach the treating physician to determine if life expectancy is at least six months, and whether or not the treating physician feels the patient is appropriate for the study. For those patients deemed potentially eligible up to this point, a lab technician will determine if they have sufficient DNA available to participate in the study. The study personnel will then approach eligible patients to invite them to participate in the study.

For patients whose only genetic testing has been through 11-104 we are requesting access to OncoTracker for the lab technician reviewing DNA/tissue availability for 12-078. This will greatly increase our ability to identify potentially eligible patients.

6.2 Patient Consent

Trained and qualified study personnel will provide potential participants with an opportunity to enroll in the study during clinic visits in a disease center or during an appointment with study staff. Staff will provide a full explanation of the study to the participant or their legal guardians, review the consent form, and answer any and all questions. Patients will be offered the chance to meet with a genetic counselor prior to consent or at any time during study participation.

Participants will then be offered an invitation to participate in the study, and those who elect to participate must sign the informed consent form (see Section 6.3). Subjects who request additional time to consider participation will be provided with a copy of the consent form and must return a copy of the signed consent form in order to enroll in the study.

Participants may also study the informed consent material away from the hospital and return their signed consent to study staff by mail or in person at next clinic visit. Study staff will follow-up with patients who have taken consent forms home by phone and/or at their next clinic visit. Staff will be available by phone to answer any questions for participants or their legal guardians who choose to enroll in this manner.

Participants must sign an informed consent form. Lack of response from an individual will be considered a passive refusal to participate. The consent status of each participant will be recorded by study personnel in the protocol registration database, and an individual's decision about participation will not affect their ability to participate in other research studies nor will it affect the care he or she receives at DFCI, BWH, and their affiliates.

Population of patients who participate in the cognitive testing of the survey instrument:

The study investigators will select approximately 5-10 thoracic oncology patients at DFCI who are not participating in the parent sequencing study, based on input from the patient's oncologist and patient availability. Drs. Martins or another member of the Survey Core will explain the purpose of the cognitive testing to potential subjects in person. Due to the fact that the cognitive testing presents minimal risk to participants and the fact that it does not include any procedures for which consent is required outside the research setting, we are asking for a waiver of the requirement for documentation of informed consent for the cognitive testing component of the study. We will provide patients with an information sheet prior to interview participation that outlines the purpose of the interview and elements of informed consent (Appendix A). Participants will be offered a $75.00 gift card as a thank you for their participation.

6.3 Consent Forms

6.3.1 Consent form content

Consent forms will be offered to patients to ensure that each consenting participant and/or legal guardian signatory understands and agrees to the following:

6.3.1.a. Required elements for study participation

- To allow research tests to be performed on the participant's tissues or fluids; to link the results of those tests to the participant's clinical information; and to store the participant's tissues and fluids and material derived from them (such as DNA) in secure areas for possible future research purposes.

- To provide one additional tube of blood and/or a sample of saliva for this study and to permit this material to be stored for possible future research purposes.

- To allow test results performed in a CLIA-certified laboratory to be returned to the participant's provider(s):
  - The following types of CLIA detected test results may be returnedto participants' providers with detailed annotations:
  -
    - Test results for somatic variants that may be used to modify treatment recommendations (e.g., EGFR mutations in lung cancer, KRAS mutations in colorectal cancer- somatic predictive variants which are actionable in principal, see Section 11.4.1)

    - Test results for somatic variants that may be used to identify possible clinical trials of genomically targeted agents (somatic predictive variants which are actionable in principal, see Section 11.4.1)

    - Somatic variants that confer **positive** prognostic implications (somatic prognostic which may or may not be actionable, see Section 11.4.1 and 11.4.2)

- Somatic variants that confer **negative** prognostic implications (somatic prognostic which may or may not be actionable, see Section 11.4.1 and 11.4.2)

- Test results from somatic variants that are of uncertain significance may be returned un-annotated and clearly labeled as variants of unknown significant.

- To allow medically significant results that may have an impact on family members to be returned to an individual designated by the study participant, should the participant be unable to receive such results in the future.

- To agree to complete study-related surveys and in-depth interviews.

- To permit the posting of the results of gene testing in centralized data warehouses (e.g., the NIH's dbGaP) in a manner that does not include any patient identifiers.

In the unlikely event that a participant has opted not to receive genomic test results but expert review of the genomic data deems that an identified genomic variant could have an immediate and substantial impact on the life or function of the patient or a close relative, the study team may decide to disclose the CLIA validated test result to the participant's physician who may then disclose the test result to the patient.

6.3.1.b. Optional elements of study participation

- Participants will be asked during the consent process to explicitly consent to or decline the return of any germline results to their DFCI providers that are judged by expert review (see Section 11.4) to be consistent with the categories below. For clarity, the description of these categories are separated below into cancer-related test results and non-cancer related test results.

  - Cancer Related Test Results

    - Germline variants in cancer risk genes (germline cancer risk variants which are actionable in principal, see Section 11.4.2)

    - Germline pharmacogenetic polymorphisms that impact chemotherapy or other cancer-related medications (germline cancer-related pharmacogenetic variants which are actionable in principal, see Section 11.4.2)

  - Non-Cancer Related Test Results

- Germline alterations that identify incidental findings of conditions or predispositions unrelated to cancer for which disease-modifying interventions are available, even if those interventions include only increased surveillance or avoidance of triggering exposures or behaviors (e.g., germline non-cancer conditions or risk variants which are actionable in principal, see Section 11.4.2)
- Germline alterations that identify conditions or predispositions unrelated to cancer for which no disease-modifying interventions are available (e.g., germline non-cancer conditions or risk variants that are not actionable, see Section 11.4.1 and 11.4.2)
- Germline pharmacogenetic polymorphisms that impact non-cancer related medications (germline non-cancer pharmacogenetic variants which are actionable in principal, see Section 11.4.2)
- Germline variants that identify incidental findings of carrier status for X-linked or recessive conditions (germline non-cancer carrier variants, see Section 11.4.1 and 11.4.2)

Withdrawal of consent, as well as partial withdrawal from selected components, is possible at any time at participant discretion. Upon request by a participant, his or her specimens and derivative material will be removed from research specimen repositories. (Material collected for clinical purposes will not be removed from clinically relevant archives e.g., Departments of Pathology.)

In addition, the consent documents make clear that "future research" tests on a participant's specimens may include tests that have not yet been designed, that the clinical utility of such tests are unknown and the results of such investigational tests will not automatically be made available to patients. Participants are informed that:

- Material obtained during surgery or by fluid collection belongs to the hospital at which such procedures take place. There will be no costs to subjects for specimen contribution and no reimbursement to subjects.
- In some cases, specimens may be shared with for-profit companies that are working with researchers on a specific research project. Specimens will not be sold to any person or company for profit. Specimens shared with external companies will not contain identifying information. Subjects will not benefit from any financial gain to the institutions or their investigators based on these projects.

6.3.2. Consent procedures

The patient must sign an informed consent form and will be provided with a copy of the form for their records.

6.4 Registration and Withdrawal

6.4.1 Procedures for subject registration

Consenting subjects will be registered with the Quality Assurance Office for Clinical Trials (QACT). Registration requires the following information: (i) name and telephone number of

person contacting protocol registration office; (ii) protocol name and number; (iii) date subject begins the study; (iv) subject name; (v) subject date of birth; (vi) subject ID number; (vi) subject address; (vii) subject diagnosis; and (viii) subject primary physician.

6.4.2 Study withdrawals

Participants may withdraw consent to participate in this study at any time. If a participant chooses to withdraw from the study, any remaining samples he/she contributed to research biorepositories will be discarded. However, data obtained prior to the participant's withdrawal from the study, including survey and interview data, will be kept. Samples essential for routine clinical care e.g., archived tissues in Departments of Pathology, will not be affected by study withdrawal. All efforts to safeguard the subject's privacy will be extended. An indication will be made in the database regarding this individual's desire to withdraw from the study to ensure that this individual is not contacted regarding this study in the future. Clinical data collected as part of other research studies in which a patient is participating and from which the patient does not withdraw consent will not be deleted or affected by withdrawal from this study. Additionally, a participant may withdraw selectively from particular components of the study.

7.0 Biospecimen Collection

7.1 Biospecimen Types

This protocol encompasses the identification of bodily fluids collected as part of clinical care including but not limited to blood, plasma, pleural and peritoneal effusions, cerebrospinal fluid, saliva, and urine. It also encompasses the identification of bodily tissues collected as part of clinical care including but not limited to buccal swabs, biopsies, aspirates, and tissue specimens such as malignant and non-malignant biospecimens from any organ including but not limited to muscle, skin, testes, uterus, ovaries, breast, bladder, kidney, lungs, prostate, brain, bone, and bone marrow. Biospecimens may be fresh, frozen or fixed. Finally, this protocol encompasses the collection of one additional tube of blood, and in some cases a saliva sample, that may not have been acquired as part of clinical care. These collections will occur as part of specific new activities covered by this protocol e.g., assessment of germline DNA sequences. Initial sequencing of the germline exome may be performed using DNA derived from blood or from saliva; confirmatory testing, if needed, will be performed using stored DNA extracted from blood.

7.2 Types of Biospecimen Donors

Biological specimens will be collected from patients with cancer or a history of cancer. In most cases, specimens will be collected from new and existing patients seen for treatment and follow up as part of the patient's routine clinical care and/or collected under a separate research protocol. The only exception is one additional tube of blood, with or without a sample of saliva, for germline genomic analyses, Other than this, specimen procurement will not require any extra or special procedures or effort by the participant.

7.3 Collection Sites

Biospecimens may be collected within DFCI clinics or the preoperative testing units, clinics, or inpatient facilities at BWH or Faulkner Hospitals. In some cases, samples required for this study may be requested from other hospitals or from medical practitioners.

7.4 Specimen Storage / Disposal

Generally, frozen tissue will be stored in secure -80C freezers at DFCI, BWH, or the Broad Institute, including secure freezers at DFCI's Harbor Campus site and the CHB Biorepository.

Storage and retrieval of fixed and paraffin-embedded specimens will be handled using routine procedures of the pathology department of the hospital at which the specimen was collected or the routine procedures of the bank storing these archived specimens. Blood samples will be stored in designated and secure facilities at DFCI (including the Harbor Campus), BWH, or the Broad Institute. Materials derived from these samples, such as DNA and RNA, may also be stored at these sites.

Disposal of biospecimens will be considered under certain circumstances including but not limited to reduced specimen integrity, exhausted capacity or insufficient funds for long-term maintenance or storage of low priority biospecimens. Determination of the integrity and priority of biospecimens is at the discretion of Specimen User Committees as defined in protocol 11-104. The discarding of research specimens is subject to relevant institutional policies and the informed consent under which the specimen was obtained.

7.6 Biospecimen Collection Risks to Participant

In general, patient tissues, blood, bone marrow, and fluids used in this protocol will have been collected for clinical care purposes, so that additional adverse effects or toxicities will not be incurred. Thus, risks experienced by subjects would be the same as those consented to as part of their usual medical care.

However, one procedure which is not part of routine patient care is called for under this protocol and may result in physical side effects, described below:

- Blood draws may cause pain and erythema and/or ecchymosis at the needle insertion site. Efforts will be made to collect blood through preexisting intravenous access or at the time of a clinically indicated phlebotomy. The expected blood loss will be minimal.

Occasionally, biological samples collected for research purposes will include excess tumor tissues and surrounding non-tumor tissue removed as part of a medical procedure that would otherwise have been discarded. Collection of these samples will not interfere with a patient's diagnosis or clinical care. When clinical specimens are used for the analyses described in this protocol, the pathologists who oversee collections of clinical specimen material will ensure that sufficient material remains for future clinical needs.

8.0 Survey and Interview Data Collection

8.1 Surveys

All participants will be asked to complete study-related surveys at two time points: at the time of informed consent (baseline survey) and approximately one month after disclosure of genomic test results (post-disclosure survey: two versions as detailed below).

Survey refinement and data collection: As noted above, in the first phase of the project, the investigators, with the help of the Survey Core, will conduct cognitive testing of the draft survey instruments with approximately 5-10 thoracic oncology patients at DFCI who are not participating in the parent sequencing study. This involves providing the interview participants with hypothetical testing scenario and then administering the draft survey instruments, assessing the survey questions, and the mode of administration (Appendix B). Standard questions used in cognitive testing include: "how did you arrive at your answer?"; "was that easy or hard to answer?"; "what does the term […] mean to you?"; and "Can you repeat the question I

just asked in your own words?". Drs. Martins, Gray and Joffe will revise the survey based on feedback and item-level statistics.

We will take a formal "pause" between the first 25-50 patients for a data review and safety check. Following the completion of approximately 50 baseline and post-disclosure surveys, the investigators will meet again to evaluate possible item reduction.

8.1.1 Survey Procedures

- Baseline Survey: The CRAs will work with participating oncologists to offer study participation to eligible patients and to obtain informed consent from those who wish to participate. When possible, consenting patients will complete the baseline survey in person (on a tablet computer or by pen and paper) at the time of consent. Alternately, they may take the survey with them to be completed, either online or with pen and paper, at a later time. We will mail a reminder letter and a copy of the baseline survey via regular mail or Federal Express Ground to all nonresponding participants who did not complete the baseline survey in person at the time of consent two weeks post-consent and four weeks post-consent. If necessary CRAs will telephone patients who did not respond to the 2nd reminder letter. An additional reminder and second copy of the survey will be sent out 2 weeks later (approximately 6 weeks post-consent). For patients who consent and provide an email address, survey links may also be sent electronically at two weeks post-consent, four weeks post-consent and six weeks post-consent. In addition, when patients who have not yet completed their baseline survey have regularly scheduled clinic visits, the CRAs will speak with them in clinic to remind them about the baseline survey and to offer them the opportunity to complete it electronically or in paper form while in clinic. Reminder mailings and contacts will be paused, based upon information from medical records or from treating clinicians, if patients become acutely ill or otherwise unable to complete survey materials. If reminders are paused, they will be resumed according to the every-two-week schedule described above if and when patients' clinical status improves. The baseline survey is expected to take no more than 15 minutes to complete.
- Post-Disclosure Survey: The study also includes patient surveys to be completed one month after a participant receives a disclosure of a sequencing-based finding from his or her primary oncologist. Through review of clinic notes and communication with the oncologist, study staff will identify the visit at which the oncologist disclosed the finding to the patient. Approximately one month later, they will contact the patient to request that she or he complete the one-month post-disclosure survey. Whenever possible, the CRAs will administer the one-month post-disclosure survey in person, at the time of a scheduled clinic appointment. Surveys will be mailed to all patients whom we are unable to approach in clinic (for patients who consent and provide an email address, survey links may also be sent electronically). The post disclosure survey is expected to take no more than 15 minutes to complete. Survey procedures will otherwise follow the steps outlined above for the baseline survey. There will be two versions of the post-disclosure survey. The primary post-disclosure survey will be administered to all participants for whom sequencing alterations have been identified and returned (either somatic or germline) (Appendix C - Previously Appendix A). A second version of the post-disclosure survey, which contains a sub-set of question from the primary post-disclosure survey, will be administered to participants who have received uninformative WES results (i.e.

no somatic or germline alterations that were worthy of CLIA validation and/or return) (Appendix D). The investigators will use information about the nature of the results, the medical record, the physician post-disclosure survey (outlined in Protocol 12-249), and direct communication with oncologists to determine which version of the post-disclosure survey is appropriate for each participant.

- Web-based vs. paper administration of surveys: As previously noted, surveys will be administered primarily via the web, but participants will also have the option of completing the survey on paper if they prefer to do so. The questions on the survey are identical, regardless of whether it is administered via the web or on paper. However, the instructional text throughout the survey will be adapted so that it is appropriate for & consistent with each specific format. For example, in the paper version of a survey, participants will be instructed to "check the one response" that best applies to them since check boxes are used for paper surveys, as per best practice. In contrast, on web surveys, radio buttons are used for single-choice question items while square boxes are used for questions where multiple responses may be selected. This means that in a web survey, the instructions will ask respondents to "mark the circle" that best reflects their response or to "select all that apply." The baseline survey submitted with this protocol is formatted with instructional text for a web survey, whereas the post-disclosure surveys submitted with this protocol are formatted with instructional text for paper administration so that there is an example of each type of instructional text.

DFCI Survey & Data Management Core staff will provide assistance with all aspects of survey data collection, including programming and maintenance of the web survey instrument and creating of a database to track patients' progress through the study.

8.1.2 Survey Measures

Baseline and post-disclosure survey measures are outlined in Table 1 (Baseline and post-disclosure survey questions, Appendix A).

Table 1	**Baseline**	**Post-disclosure**	
Covariates			
Socio-demographics	X		Standard Demographics and US Census
Performance Status	X	X	ECOG – Patient Self-Report version
Physical & Mental Health-related QOL – general & disease specific	X	X	EORTC QLQ – basic module
Brief health literacy	X		Brief Health Literacy
Subjective numeracy	X		Subjective Numeracy Scale
Attitudes about genetic testing	X		Attitudes about Genetic Testing
Experience with genetic testing	X		Experience w GT
Genetic knowledge	X		Knowledge of GT
Attitudes towards Genetics	X		Attitudes towards Genetics
Religiosity	X		Overall Religiosity from MMRS
Positive Religious Coping	X		Positive Subscale of Brief R-Cope
Decision-making preferences	X		Control Preferences Scale

Genetic Predisposition	X		Created
Outcome Measures			
Genomic information disclosure preferences	Elicited during consent		N/A
Understanding of disclosed genomic information		X	Based on Consent (see draft item in the proposed measures document)
Behavioral actions as a result of disclosed genomic information		X	Created for the study (see draft item in the proposed measures document)
Impact of genetic testing		X	MICRA and PAGIS support and certainty scales
Anxiety and depression	X	X	HADS
Information-sharing		X	HINTS
Motivations for Information Sharing		X	Family Communication Measure
Information-seeking		X	HINTS/CanCORS
Satisfaction with MD/ patient communication		X	Adapted HINTS; General Communication Subscale QOC
Decision Regret		X	Adapted from O'Connor

Covariates

All respondents will be asked to completed standard demographic questions that will assess their race, ethnicity, marital status, education level and their preferred language.

Performance Status will be assessed by the patient self-report version of the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (23). Respondents are asked to select which of 5 statements best reflect their current, overall level of physical function in relation to activities of daily living. Statements are scored from - 4 and an increase of 1 or more indicates a decline in overall physical function. The scale was developed by ECOG after reviewing criteria from many other cancer research groups. It is now the most widely used measure of performance status in cancer-related clinical trials. Basch and his colleagues (2005) successfully adapted the measure into a patient self-report scale (24). It is capable of discriminating between those patients who are eligible for a clinical trial and those who are not, as well as being able to predict whether patients are able to use an online self-report tool.

Quality of life in relation to overall physical functioning and symptoms will be assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ; 25). All respondents will receive the 30-item general questionnaire. For most of the questions, respondents are asked to indicate how often they experience a symptom (e.g., pain, shortness of breath) on a 4-point scale ranging from "not at all" to "very much". All EORTC-QLQ measures must meet evidence-based gold-standard criteria for psychometric validity and reliability prior to publication. As such, the overall measure has been shown to clearly identify patients with different levels of physical functioning as rated by their physicians.

General health literacy will be assessed using a 3-item brief measure developed by Chew et al. (26). Items are responded to a 5-point Likert scale varying from "all of the time" to "none of the time". These items have been validated against the Short Form Test Of Functional Health Literacy (STOFHLA) and the REALM (27). Analyses illustrate that these 3 items are effective at identifying individuals' with inadequate health literacy (ROC AUCs range from 0.66 - 0.84).

Subjective numeracy will be assessed using Fagerlin et al's Subjective Numeracy Scale (SNS) (28). Use of a subjective rather than an objective measure of numeracy may be more palatable to respondents. The SNS is correlated (r = 0.68) with other well-known objective measures of quantitative ability (29). In light of pilot data from Joffe's protocol 09-174 suggesting that scores based on a subset of items is highly correlated with the full 8-item scale scores, the SNS will be shortened by using 4 of the original 8 items.

Attitudes toward undergoing a genetic test will be measured using a measure developed by Michie et al. (30). Respondents are asked to rate their attitudes to undergoing a genetic test on a three 5-point scales: "a bad thing - a good thing," "harmful - beneficial," and "unimportant – important." In two studies of British undergraduates, the alpha coefficient of reliability was 0.79 for this scale. This instrument is scored by averaging the responses across the three items. Michie et al. investigated whether genetic information leaflets influence attitudes by comparing the impact of attractive, glossy leaflets from a credible source with the impact of less attractive black and white, unsourced leaflets (30). Results showed that those receiving the glossy leaflets had more positive attitudes toward genetic testing.

Experience with Genetic Testing will be assessed by a two items, one of which was originally developed & used by Sanderson et al. (31). This item asks respondents to indicate whether they have ever had a genetic test. Similarly, the PIs of this study have developed an additional question asking if patients are aware of any genetic conditions that affect their blood relatives. Response options to both items are yes, no and not sure.

Knowledge of genetic testing will be measured by adapting three questions from Furr et al's 5-item Genetic Knowledge Index (GKI) (32). Respondents are asked to indicate whether the statement is true, false, or whether they are not sure. Two items of the 5-item GKI are not used for the study; one because the answer was ambiguous and one because the item was inappropriate. Also, for one of the items used, the question was re-worded so the answer would be true as opposed to the other two items having an answer of false. Alpha measure of internal consistency is reported at 0.74 and the reliability statistic is near 0.70 for the full 5-item instrument. This instrument is scored by counting the number of correct responses.

Knowledge of genetic testing will also be measured using four questions from Singer et al. (33). Respondents are asked to indicate whether the statement is true, false, or whether they are not sure. In a study aimed at understanding whether attitudes toward genetic testing vary by race and ethnicity, Singer et al found a significant difference between African-Americans and Caucasians on a knowledge index counting the number of accurate responses to these five questions (notably, both groups correctly answered fewer than half of the questions). This instrument is scored by counting the number of correct responses.

Attitudes toward genetics are assessed using a 12 item attitude checklist which was adapted from a measure developed by Sanderson et al. (31). Participants are asked to check all of the words that reflect how they feel about genetics. The list of words includes four positive (excited, enthusiastic, optimistic, and hopeful), four negative (worried, concerned, pessimistic, and horrified), and four mixed-neutral (cautious, indifferent, mixed feelings, and confused) words. A principal components analysis with varimax rotation of the data from these words in a sample of 2000 adults from the United Kingdom yielded two factors that accounted for 30% of the variance. The four positive words all loaded on the first factor with values over 0.50. Thus, a count of these words (1 point per word selected) yields a Positive Attitude Score. Five words, worried, concerned, pessimistic, horrified, and cautious, all loaded on the second factor with

values over 0.40. A count of these words (1 point per word selected) provides a Negative Attitude Score. Interest in genetic testing was positively correlated with positive attitude towards genetics (r=0.253, p<.001) and negatively correlated with negative attitude towards genetics (r=-0.167, p<.001).

Individuals' overall level of religiosity will be assessed using 2-items from the Multidimensional Measure of religiousness/spirituality (MMRS). These items are scored on a 4-point scale ranging from "very religious" to "not religious at all". The MMRS is the product of a national working group that reviewed the constructs and measurement of religiosity/spirituality and their relation to physical and mental health outcomes. Data from the General Social Survey (GSS) show that these items for a unique domain that are reflective of overall religiosity (34).

The 3-item positive subscale of the Brief R-Cope will be used to measure individuals' positive religious/spiritual methods of coping (PRC) and dealing with life stressors (35). Items are scored on a 4-point scale ranging from "a great deal" to "not at all". Overall scored are derived from the sum of all items. The 3-items are derived from the longer Brief R-Cope and were selected because they have the highest factor loadings on the positive subscale on the longer measure. In a recent review of all studies between 2005 – 2010 using this measure, Pargament et al. (36) showed that the median internal consistency coefficient was 0.92 for PRC. Evidence of concurrent validity illustrates that the PRC subscale is positively correlated to psychological well-being, behavior coping, acceptance, happiness and self-esteem (correlations range from 0.20 – 0.66).

Decision Making Preference will be measured using the preferred-decision making item from the Control Preferences Scale (37). Respondents are asked to select the 1 statement (typically accompanied by a cartoon depicting the statement) that best reflects the role they prefer when making decisions about treatment for their cancer diagnosis. The 5 statements vary in the extent to which they are collaborative and are:

- ☐ I prefer to make the decision about which treatment I will receive.
- ☐ I prefer to make the final decision about my treatment after seriously considering my doctor's opinion.
- ☐ I prefer that my doctor and I share responsibility for deciding which treatment is best for me.
- ☐ I prefer that my doctor makes the final decision about which treatment will be used, but seriously consider my options.
- ☐ I prefer to leave all decisions regarding my treatment to my doctor.

These statements were developed using a modified Coombs unfolding task sort, the goal of which is to identify the normal distribution of ratings for the construct in question, in the population. Over the course of 20 years, numerous samples of Canadian and American patients, including those with cancer were used in the development & refinement of this scale. The language used in this scale was modified as a result of these studies. Recently (2011), DFCI's Survey and Data Management Core carried out cognitive interviewing with high-risk patients (including those with cancer); results for this item illustrated that even when unaccompanied by a cartoon, patients still found these easy to understand.

Genetic Predisposition will be measured using a series of questions drafted by the research team that ask about blood relatives and their history of cancer and diseases other than cancer.

OUTCOMES

Understanding of the disclosed genomic information will be assessed by up to (due to skip patterns) 16-items (broken into 6 section) developed by the Dr. Joffe and Gray. Items were developed to be concordant with information provided to patients both verbally and in writing during the consent process. Respondents are asked to read each statement and indicate whether the gene test information disclosed is ("yes") or is not ("no") reflective of the statement or whether they are unsure ("not sure").

Assessment of behavioral actions taken as a result of genomic information will be measured by an item that was developed by Drs. Joffe and Gray. This item queries participants about any changes to cancer treatment, enrollment in a clinical trial, and/or changes to any non-cancer related medications as a result of the gene tests done for this study. Participants will answer yes or no. A follow-up question asks them to document any other changes that they have made based on the results of the gene tests done for this study with a free text response option.

Impact of genetic testing is the primary outcome of the patient survey and it will be measured by the Multidimensional Impact of Cancer Risk Assessment (MICRA) (38). The MICRA is a validated, 25 item measure that assesses concerns and psychosocial consequences associated with genetic testing for cancer. Most items are completing using a 4-point likert scale ranging from "never" to "often". Domains elicited include uncertainty over test results, test-related distress, positive experiences associated with testing, decisional regret and cancer-related coping. A total score related to overall impact, as well as scores related to distress, uncertainty and positive experiences are yielded. The MICRA will be slightly adapted by using the words "gene test" instead of "testing" throughout to ensure that participants are able to clearly understand that we are interested in the impact of their gene testing results. This does not change the overall content of the measure in any way and is unlikely to have a detrimental affect on the psychometric properties of this measure. Five items of the MICRA will be dropped because they are related to developing cancer in the future/cancer prevention and thus are inappropriate for our patient population, all of whom will have a current diagnosis of cancer. All subscales of MICRA have been shown to significantly distinguish between women with the BRCA1/2 mutation and those without. Women with BRCA1/2 mutations also had higher mean total scores than those without the mutation. Internal consistency for each of the subscales was found to be $\alpha = 0.77$ or greater. We have embedded one additional question in the MICRA on regret about going through the gene testing process (in addition to the existing question that captures regret about getting test results; items 18 and 17 respectively) because we want to capture regret about the testing process as well as regret about receiving any test results.

Additional assessment of the impact of genetic testing will be measured using the certainty and support subscales of the Psychological Adaptation to Genetic Information Scale (PAGIS). The support subscale consists of 6 items that assess whether respondents are able to discuss their genetic tests with their family members. Internal consistency for this subscale is $\alpha = 0.82$. The certainty subscale consists of 6 items that assess the extent to which respondents' think that they understand their genetic test results ($\alpha = 0.77$). Questions are answered on a 6-point scale ranging from "strongly agree" to "strongly disagree". Items on each subscale were selected for

inclusion based on extensive testing among experts and patient populations and based on their factor loadings. Both subscales have been slightly modified to be relevant to the present study. The primary modification made is changing the word "gene" to "genetic test results".

State anxiety and depression will be measured with the Hospital Anxiety and Depression Scale (HADS) (39,40). HADS screens for mood disorders in medically ill patients; it focuses on subjective rather than physical symptoms, which may be confounded with illness. The scale consists of 14-items rated on a 4-point likert scale (response endpoints vary with items) and it yields scores for depression and anxiety. Factor analyses have shown a two-factor structure (depression and anxiety), across several studies, across both male and female cancer patients. It is positively correlated 0.70 with the Montgomery Asberg Depression Rating Scale (MADRS) in inpatients in Cancer or Internal Medicine and has an internal consistency reliability score of $\alpha = 0.90$ across both domains.

Information Sharing about genetic tests will be assessed through a single item from the Health Information National Trends Survey 4 (HINTS) modified by Drs. Gray & Joffe.

To assess motivations underlying information sharing, we will use items from the "motivations" domain of the Family Communications measure. Five items will be used to assess the importance of potential motivations underlying sharing of information with family members or relatives while 4 items will assess the motivations underlying why information **was not** shared with family members or relatives. This measure was developed using an interpersonal motivations model has been successfully used in research examining sisters' communication around BRCA1 And BRCA2 genetic test results.

Information Seeking about genetic tests will be assessed through single item from the Health Information National Trends Survey 4 (HINTS) modified by Drs. Gray & Joffe.

HINTS items are developed by a team of researchers with varying expertise, undergo rigorous cognitive testing and are then subjected to a pilot study before being included in HINTS proper (41).

Satisfaction with MD/Patient Communication will be assessed in two ways. First, 7 items adapted from HINTS 3 & 4 will be used to assess patient satisfaction with MD communication around the results of gene testing. These items will be answered on a 4-point scale ranging from "never" to "often".

Second, the general communication subscale of the quality of end of life communication scale (QOC) will be used to assess patients' perceptions of MDs general communication skills (42). This subscale consists of 6 items answered on a 0 – 10-point scale ranging from "very worst" to "very best". Studies in populations with cancer and other chronic illnesses has repeatedly confirmed the presence of this subscale. Internal consistency reliability of this scale is $\alpha = 0.91$. Convergent validity illustrates that scores on this subscale are positively associated with ratings of overall quality of communication, care and presence of treatment preference discussions (*r*'s range from 0.54 – 0.73).

Items adapted from HINTS 4 will be used to assess patient satisfaction with MD communication around the results of gene testing.

Decision Regret: The 5 item Decision Regret Scale by O'Connor and Brehaut (46,47) measures distress or remorse after a health care decision. Psychometric testing showed an alpha coefficient of 0.81-0.92. The scale correlates with satisfaction with the decision, decisional conflict, and overall rated quality of life. The scale has been used in the setting of prostate and breast cancer treatment (48), outcomes of genetic testing for melanoma risk and (49), hereditary breast-ovarian cancer risk testing (50).

Several items in the informative and uninformative post-disclosure surveys have been reordered to decrease the number of skip patterns and to ensure consistency between the paper and web-based survey versions. With the exception of item numbering, no changes have been made to the post-disclosure survey measures.

8.2 Interviews

Two sub-sets of participants will be invited to participate in in-depth interviews following informed consent and after test result disclosure.

The first sub-sample of 35 patients (5 pilot interviews, and 15 primary interviews with lung and colorectal cancer patients each) will participate in in-depth interviews following informed consent for germline and somatic sequencing.

A second sub-sample of 45 patients, stratified on the basis of test results disclosed (i.e., somatic, germline cancer-related, germline unrelated to cancer - see Section 11.4.1 and 11.4.2), will participate in in-depth interviews 1 month following disclosure. We will make an effort to ensure that at least 5 patients (of the 15 in each stratum) have lung cancer and at least 5 patients have colon cancer. All cancer patients who participate in qualitative interviews will be given a small monetary incentive to cover parking and a meal in the cafeteria. The samples for the post-consent and post-disclosure interviews will be selected on the basis of distinct criteria. It is possible, however, that some patients will meet the selection criteria for and participate in both sets of interviews.

8.2.1 Interview Procedures

All in-depth qualitative interviews will take place either in person at the time of patients' regularly scheduled clinic visits or, when necessary, by telephone. To decrease burden, patients participating in in-depth interviews following test result disclosure will be offered the option to complete the survey and interview during the same encounter. Dr. Elyse Park, the study's qualitative methodologist, will oversee the interview process. Interviews will be divided between Dr. Traeger, a post-doctoral fellow in psychology working under Dr. Park's supervision, and qualitative research staff from the DFCI Survey & Data Management Core. All interviews will be tape recorded and transcribed for analysis.

8.2.2 Interview Domains

- Informed Consent Interview: In the informed consent interview we will elicit participants' 1) attitudes regarding genetic testing, 2) assessment of the process of informed consent for germline and somatic sequencing, 3) understanding of the types of genomic information that may be disclosed following sequencing and the risk and benefits of learning sequence information, 4) exploration of preferences for disclosure of genetic information, and 5) additional motivations and/or concerns related to having gene sequencing. Interviewers will have a record of the disclosure choices that patients made during the consent process for sequencing and will probe for the reasoning underlying those choices. (Informed Consent

Interview Guide, appendix H) For participants who prefer to complete the post-disclosure interview by phone we will provide them with a copy of their disclosure choices prior to the interview. If the participant has given permission to email, study staff will email a copy of patient preferences to the participant; if the participant has not given permission to email, preferences will be mailed. As outlined in the Informed Consent Interview Guide participants will receive a $25 gift card for participating in post-consent interviews. For participants completing interviews by phone we may mail the gift cards with a thank you letter (see appendix N) for those patients who will not be returning to clinic within two weeks of having completed their interview. This letter will also be given to participants who are able to receive their gift cards in person during a clinic visit.

- Post-Disclosure Interview: In the post-disclosure interview we will elicit participants' 1) understanding of the types of genomic information that were disclosed, 2) understanding of the implications of disclosed sequence information for prognosis and treatment, 3) thoughts about the emotional impact of test result disclosure, 4) satisfaction with the decision to undergo testing, 5) satisfaction with doctor/patient communication, 6) thoughts about the impact of testing on the family, 7) thoughts about challenges encountered as a result of testing, and 8) thoughts on ways to improve the testing and result disclosure process (Post-Disclosure Interview Guide, to be submitted as an amendment at a later date).

8.3 Survey and Interview Data Collection Risks to Participants

There are minimal risks to participants from participation in the study-related surveys and interviews. The potential for loss of confidentiality of data collected exists. To minimize the potential for loss of confidentiality, we will employ multiple safeguards. All staff conducting surveys and interviews will be specifically trained for activities related to this project. Each participant will be assigned a unique study identification number that will be stored separately from personal identifiers. All data, including surveys, telephone recordings and transcripts, will be stored in locked file drawers. Access to data files containing personal identifiers will be secured with a password filing system and will be restricted to authorized study staff. All project file cabinets and computer databases will be secured in offices that are locked when not in use. No data regarding individual's responses will be provided to any third party. Data will be aggregated and summary reports will be generated without any personal identifying information.

If the patient has an elevated score on the anxiety or depression component of the HADS, the study team will notify the patient's physician so that she or he can take appropriate clinical action. This is clearly stated on the consent form so that the patient is aware of the plan to notify the patient's physician of elevated depression or anxiety scores.

9.0 Data Collection and Storage

Data Collection and Storage for all DFCI patients who are enrolled on this protocol will follow the procedures outlined in Section 8 of DF/HCC Protocol 11-104.

9.1 Data Collection: Subjects, Data Types, and Purpose

Sequencing data including whole exome, whole genome, sub-exome, and/or whole transcriptome data from specimens will be generated on all study participants. Clinical data will also be collected on all consenting patients. These data may be used for cancer-related research purposes by authorized investigators under the strict rules described in this Section

and elsewhere including protocol 11-104 and the CORIS protocol 10-460. In some cases, specimen data obtained in a CLIA-certified laboratory may be used by providers to inform decisions about therapy or clinical trial opportunities for individual patients.

9.2. Data Storage

All DFCI patients will have all data stored as described in DF/HCC 11-104 and 10-460. In particular, sequencing data may be stored in the Consented Research Data Repository (CRDR) as determined by the CRDR Oversight Committee and clinical data may be stored in CORIS. Associated sequencing and clinical data may be de-identified and transferred to a Transient Data Mart (TDM) as described in DF/HCC 11-104.

9.3 Data Sources

Data sources will include clinical information obtained from the electronic medical record at Dana-Farber Cancer Institute (for DFCI patients) as well as other sources described in protocol 10-460. Data sources for inclusion include all sequencing data and analysis performed at the Broad Institute, DFCI, or outside entity, including commercial entities. In addition, Clinical Research Coordinators on the study team in TOP and GI will obtain information from OncoTracker and the OncoPanel results viewer (protocol #11-104) and will therefore need access to both.

9.4 Data Collection and Risks to Participant

While it is possible that public knowledge of a participant's genetic factors could lead to problems with health insurance, life insurance, or employment, the confidentiality of participant identities will be strictly preserved under this protocol, minimizing such risks in this context.

Furthermore, protections afforded under the Genetic Information Nondiscrimination Act (GINA) will generally prohibit discrimination based on genetic information in connection with health coverage and employment. These protections apply to genetic research obtained as part of any study regardless of when it was conducted. However, GINA's provisions prohibiting such discrimination in employment do not apply to employers with fewer than 15 employees. Similarly, GINA's provisions do not prohibit discrimination based on genetic information by providers of life insurance, disability insurance, or long- term care insurance. The protections and limitations of GINA are described in the consent form in a manner consistent with current guidance documents.

State laws in Massachusetts also prohibit discrimination based on genetic information in health insurance, disability insurance, long-term care insurance and employment (but not to employers with fewer than 6 employees). State law protections are also described in the consent forms.

10.0 Specimen and Data Management, Access, and Oversight

10.1 Specimen Coding, De-Identifying, and Tracking

Specimen coding, de-identifying, and tracking for all DFCI patients who are participating in this study will be conducted as described in section 9.1 of DF/HCC Protocol 11-104. Specifically, all patient-derived materials that are not already stored in specimen archives will be tracked using caTissue, a centralized biospecimen management system. Detailed tracking of specimens and derivative material such as DNA and RNA, including storage location, retrieval, and usage information will be maintained through this database. The specimen ID number will be used to uniquely identify biological samples during all aspects of experimentation so that the resulting

data can be linked to specimen and clinical data. Researchers and staff who are not authorized to see PHI will be blocked from viewing PHI following HIPAA guidelines using role based access controls. Specimen-level clinical attributes such as tissue type, pathologic diagnosis, or grade, may also be stored with the specimens in CRDR.

10.2 Return of Research Results

When subjects provide specific consent, the results of CLIA-certified testing will be returned to their providers who may choose to share the results with consenting subjects at their discretion. In addition, CLIA-certified test results that are returned to subjects' physicians will be entered into the subjects' medical records. In most cases, there will be no obligation for reporting of results to subjects. However, exceptions may be made for results that are medically significant and actionable (*see section 11*).

Genomics experts on the study team and Study Investigators with ad hoc assistance from experts in the field as needed, will determine, when necessary, which results fall into this category (*see Section 11*). If necessary, confirmation of the results using a CLIA-certified test will be performed at no cost to the subject before releasing the information to that subjects treating oncologist. Subjects who provide consent for return of results will be informed that not all results will be returned to them e.g., non-significant, non-actionable results or results that are felt to have no clinical utility for the subject may not be returned. If medically significant and/or actionable germline genetic variants are revealed as a result of research testing and if they are confirmed by a CLIA-certified test and if the subject has consented to return of results to their provider, a report containing the results will be sent to the patient's provider. He or she will disclose the results to the patient according to his or her medical judgment and usual practice. If the subject is unable to receive results that have medical implications for family members, these results may be provided to a designate, provided that the subject has consented to this and has provided the name and contact information for the designate. These results will be returned to the designate using the subject's preferences documented in the signed consent form. Only those results matching the disclosure preferences of the subject will be returned to the designate, unless results are deemed to have an immediate and substantial impact on the life or function of the patient or a close relative.

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10.2.1 Risks Associated with the Return of Research Results to Participants

There is a chance that participants may experience psychological distress or anxiety as a result of receiving WES information, including disclosure of information about prognosis, inherited cancer susceptibility or incidental, non-cancer inherited diseases or carrier status. We will minimize psychological distress by eliciting participants' preferences for disclosure of germline genomic information which will then be fed back to the participants' treating oncologist. Disclosure of germline cancer susceptibility test and non-cancer related results will take place in coordination with the faculty and counseling staff in the cancer genetics and medical genetics groups, as needed. Additionally, any participants who indicate distress during test result disclosure, during the interviews and/or on the surveys will be referred to psychosocial clinicians working in the DFCI clinics at the discretion of their treating oncologist.

10.3 Data Confidentiality and Security

The confidentiality of each participant will be rigorously maintained using existing DFCI standards. Data access will be guided by institutional SOPs. HIPAA and state/federal government regulations for protecting patient privacy and security will be strictly observed.

Researchers and staff who are not authorized to see PHI will be blocked from viewing PHI following HIPAA guidelines using role based access controls. For example, as noted above, identifiers will be stripped from specimen data when they are transferred into the Clinical Database and Genomic Database. To further enhance security, linkage tables with identifying information in a separate secure file accessible only by dedicated study administrators, as described in Section 8.

No patient or subject identifiable information will be given to third parties, including family members, unless that subject has given written or witnessed consent to do so. The results of research studies may be published but subjects will not be identified in any publication.

Sequence data generated through this project will also be placed in NIH central data repositories. Samples will be sent only with a code number attached; directly identifiable information will not be shared with data banks or other investigators. There are many safeguards in place to protect this data. However, there may be a slight risk of loss of loss of privacy when sharing this information with these banks. Although we will do everything possible to protect the privacy of all data, we cannot absolutely guarantee its privacy or predict how genetic information will be used in the future.

If a participant contacts the study's project personnel, he or she will be informed of the status of the research without revealing specific findings.

10.4 Specimen Property Rights

Specimens collected from patients registered at DFCI, BWH, or other facilities are the property of those hospitals and will remain at those hospitals even if the staff members who obtained those specimens leave.

11.0 Laboratory Methodology / Data Analysis / Results

11.1 Specimen Processing and Requirements

After the patient provides consent, DNA/RNA that has previously been extracted will be located. One tube of blood will be drawn and/or saliva sample acquired as well, and genomic DNA will be extracted from the blood and stored in barcoded tubes. If necessary for additional tumor genomic DNA/RNA, tumor material will be acquired from the Department of Pathology at BWH. Designated optimal tissue block (i.e., highest volume of tumor, presence of tumor-enriched areas and documentation of pathologist's estimate of percentage of tumor cells) and corresponding H&E stained slide will be retrieved. The area of the block with highest tumor content will be collected either by coring with small caliber punches or by macrodissection of re-cut sections. Genomic DNA and/or RNA will be extracted from the tumor tissue and stored in barcoded tubes.

A portion of the DNA/RNA will be transported to the Broad Institute, the Center for Cancer Genome Discovery at DFCI, and/or an outside entity for sequencing. Another portion of the DNA will be retained in the BWH CLIA laboratory (CAMD) for clinical genotyping as needed, thereby enabling a direct comparison between CLIA lab findings and sequencing data when sequencing results are not generated in a CLIA environment. The remainder of the DNA will be stored a -20C. At present, ~500ng of tumor genomic DNA is required to do both whole exome sequencing (including DNA quantitation and quality control) and validation using CLIA-certified

OncoMap/OncoPanel. These DNA input requirements are expected to decrease during future study years.

11.2 Sequencing

Sequencing of tumor and normal material will be performed, which may include whole exome, whole genome, sub-exome, and whole transcriptome sequencing. The data will be used to assemble the incidence of somatic and germline genomic alterations, including (but not limited to) single nucleotide variants, small insertions/deletions, copy number alterations, rearrangements, pathogens, and epigenetic changes. Sequencing may be performed in research laboratories and CLIA-certified laboratories at the Broad Institute, DFCI, or third party entities, including commercial entities. 11.3 Analysis of Sequence Data

Relevant somatic and germline alterations will be identified by adaptation and modification of discovery-oriented algorithms in common use at the Broad Institute. We will also apply a series of computational algorithms that predict neutral, detrimental or activating variants. Upon completion, we will deliver a list of somatic and germline variants that perturb cancer genes and associated cellular pathways, many of which are targeted by existing or emerging anticancer agents.

11.4 Interpretation and Validation of Actionable Results

The results of sequencing will be subject to both computational analyses and evidence-based interpretation.. In addition, the Cancer Genomics Evaluation Committee (CGEC) has evolved over the course of the study. The Cancer Precision Medicine Tumor Board evolved out of the Cancer Genome Evaluation Committee (CGEC), the purpose of which was to review whole-exome sequencing results for patients enrolled in the CanSeq project and make decisions about return or results. The CGEC process allowed rich and informative discussions pertaining to many interesting germ line and somatic variants. The lessons learned allowed the CanSeq team to implement a series of modifications that could make the process educational for the larger DFCI/BWH community. Based on feedback and encouragement from the original CGEC membership, the decision was made to evolve into a more "classic" tumor board whose mission is to elicit salient insights from illustrative or challenging cases in which tumor profiling might alter treatment or management.

This evolution also allowed for the development of guidelines for return of straightforward CanSeq results based on CGEC practice and the evolving field of genomics. These guidelines have been developed in collaboration with the CGEC, expert reviewers and study investigators.

Straight-forward results that will be returned to the clinical team include somatic alterations with clear therapeutic implications as per the literature in the following categories (Predictive – FDA-Approved therapies and Predictive-Clinical Trials – Levels A through D) and those with clear prognostic and or diagnostic implications (see table 11.4.1). Somatic alterations with unclear therapeutic implications in the categories of Predictive –Level E) will be candidates for referral to expert review when evidence in the literature is incomplete orconflicting. Upon referral, these variants will be reviewed by a minimum of two members of the Expert Review Committee. If the Expert Review Committee does not reach a consensus, the case will be presented to the tumor board for further discussion. The expert review committee is comprised of members of the

CanSeq executive committee with expertise in the following areas: genomic science, medical oncology, pediatric oncology, medical genetics, genetic counseling, pathology, bioethics, and bioinformatics.

We will apply more stringent criteria for the return of germline variants. Germline variants in the following categories will be returned to the clinical team (see table 11.4.2):

- Cancer risk mutation – Known, expected or likely pathogenic
- Carrier state – Known pathogenic
- ACMG genes (see appendix L- ACMG table)- Known pathogenic, expected or likely pathogenic depending on the gene, as listed in the ACMG table
- Pharmacogenomic variants (not currently returning but may ultimately return) – Known polymorphism that influences drug metabolism
- Variant of unknown significance in a gene directly related to the indication/type of cancer (e.g. VUS in APC in colorectal cancer patent)

An initial assessment based on agreed-upon guidelines will be made by a board certified medical geneticist on our expert review committee. All reports on results that have not previously been vetted by the expert review committee will be circulated to committee members and reviewed by at least one reviewer in addition to the primary reviewer (at least 2 expert reviewers) before being returned to the clinical team.

Findings will be provided to the clinical care team if they are felt to be potentially actionable or if they provide information about disease or disease risk, pharmacogenetic polymorphisms, prognosis or disease carrier status. , who will have access to patients' preferences for disclosure of genomic results and will only receive germline results that are in line with patient preferences, will then decide how to disclose test results to their patients. Additionally, we have parallel and complementary systems of disclosure for germline and somatic test results due to the fact that somatic and germline tests impact patients and their families in profoundly different ways. As part of the study, a genetic counselor is available to help disclose such results to patients and their families as needed.

11.4.1 Categorization of somatic genetic alterations

PREDICTIVE IMPLICATIONS:

FDA-approved - There is a **validated association** between this alteration and response/resistance to this FDA-approved agent **for this indication**

Level A - This alteration is used or has been used as an **eligibility criterion** for clinical trials of this agent or class of agents

Level B - There is **limited clinical evidence** (early or conflicting data) for an association between this alteration and response/resistance to this agent or class of agents in this tumor type

Level C - There is clinical evidence for an association between this alteration and response/resistance to this agent or class of agents in **another tumor type ONLY**

Level D - There is **preclinical evidence** for an association between this alteration and response/resistance to this agent or class of agents

Level E - There is an **inferential association** (based on homology, computational data, structural information, or pathway involvement) between this alteration and response/resistance to this agent or class of agents

CATEGORY:	LEVEL A	LEVEL B	LEVEL C	LEVEL D	LEVEL E
Prognostic	There is a **validated association** between this alteration and prognosis in this tumor type	There is **limited evidence** for an association between this alteration and prognosis in this tumor type			
Diagnostic	There is a **validated association** between this alteration and diagnosis in this tumor type	There is **limited evidence** for an association between this alteration and diagnosis in this tumor type			

Genetic alterations are placed into these categories based on their known clinical/medical relevance and the degree of association between genotype and phenotype. We anticipate that over the course of this study, the specific content of these categories will evolve as more information becomes available on the clinical and biological impact of specific genomic alterations. Genomic alterations in the Predictive category, include those with known predictive findings that have proven clinical utility (e.g. *EGFR* mutation in NSCLC). For many alterations in this category there are established tests in the BWH CLIA lab or commercially available kits/vendors that can be used to validate the findings if not already sequenced in a CLIA-certified laboratory. We also expect to find novel mutations in genes with known clinical relevance for which there is a targeted agent available in the context of a clinical trial (e.g. novel *BRAF* mutation in NSCLC with a BRAF inhibitor available through a clinical trial), or known

actionable mutations for which there is an FDA approved targeted agent for a different indication (e.g., KIT mutation in thymic carcinoma and imatinib use off-label).

An institutional registry will allow us to capture outcome data on the efficacy of FDA-approved agents for genomically defined subsets of patients. Several members of the CGEC are in the process of designing clinical trials for patients based on somatic genetic alterations. In addition, we may identify alterations that are theoretically targetable (e.g. an activated kinase) but for which no therapy (kinase inhibitor) exists.

Prognostic genomic variants may also be identified through WES. While it is highly unlikely that somatic WES will identify diagnostic genomic alterations that call into question the patient's primary diagnosis, if this does occur such alterations may be discussed by the tumor board and confirmed (if not already sequenced in a CLIA-certified laboratory) and returned to treating physicians as appropriate. Given the study inclusion criteria, all enrolled patients will have a defined diagnosis (lung or colorectal cancer), thus limiting the likelihood that sequencing will provide additional diagnostic information.

11.4.2 Categorization of germline genetic alterations

Similarly, the germline genetic alterations will be divided into 4 categories by the genomics experts on the study team. The alterations will be further characterized as meeting criteria for clinical validity and/or clinical utility, as defined below. Alterations that are judged not to meet the criteria for clinical validity or clinical utility will be considered variants of unknown significance.

Table 2

Type of Test	Clinical Validity	Clinical Utility
I. Cancer risk mutation	• Evidence confirms association of marker with elevated cancer risk	• Evidence supports improved health outcomes based on prevention or early detection strategies
II. a. Pharmacogenomic variant related to cancer treatment	• Evidence confirms association of marker with a phenotype/ metabolic state that relates to drug efficacy or adverse drug reactions	• Evidence supports improved cancer-related health outcomes based on drug selection or dosage
II. b. Pharmacogenomic variant not related to cancer treatment	• Evidence confirms a association of marker with a phenotype/ metabolic state that relates to drug efficacy or adverse drug reactions	• Evidence supports improved health outcomes, unrelated to cancer, based on drug selection or dosage

III. Incidental finding of genetic predisposition or condition, unrelated to patient's cancer	• Evidence confirms association of marker with disorder	• Evidence supports improved health outcomes based on early intervention • Provision of information may be useful for personal or clinical decision making to the patient or his relatives
IV. Carrier state	• Known association of gene variant with monogenic disorder (may be autosomal dominant, recessive or X-linked)	• Evidence supports improved health outcomes based on early intervention for affected offspring • Availability of information useful for personal or clinical decision making

The categorization of genetic alterations outlined for germline mutations is modeled on the framework that has been outlined by The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG). EGAPP is an independent panel that has developed and implemented an evidence-based, systematic process for evaluating genetic tests and other genomic technologies (43).

Guidelines for return of germline results are outlined on page 26.

In addition, if considering whether a test result with clinical utility should be validated and potentially returned, expert reviewers will consider the following factors (http://evidence.personalgenomes.org/guide_impact_score):

- Participants' preferences as captured during the informed consent process for this study
- Severity of disease
- Disease treatability or preventability (i.e., the nature and efficacy of medical interventions that might be taken)
- Nonmedical actions that patients might take based on knowing their test results
- Penetrance (i.e., how likely the variant is to cause the associated disease or phenotype)
- Strength of the evidence supporting clinical validity and utility
- For carrier states, the nature of the inheritance and likelihood that offspring would be affected by the genetic condition

Category I alterations includes genomic variants related to cancer risk. Tests in this category will vary in their known effect size and, given the criteria outlined above, genomic experts on the study team will be more likely to recommend validation and possible return of results for genomic variants that have a high penetrance and high relative risk (e.g. relative risk (RR) of greater than 4 as defined in the published literature) than it will for variants that have moderate to low penetrance and moderate to low relative risks (e.g. variants that have a relative risk of 2-

4 or less than 2 as defined in the published literature).

Category II alterations include pharmacogenetic variants that predict altered drug metabolism for drugs that are cancer-related (Category IIa, e.g. *DPD* deficiency and 5-fluorouracil toxicity) and for drugs that are not cancer-related (Category IIb, e.g. Cyp 2C9 and warfarin metabolism)..

Category III alterations include those that predict risks for a non-cancer-related disease for which there is a medical intervention (e.g. *LPL* mutations in familial combined hyperlipidemia and early statin initiation) as well as for non-cancer-related disease for which there is well established clinical validity, no known medical intervention(s) related to risk reduction/disease prevention, but for which there is evidence that disclosure of test results might be useful for personal decision making (e.g. Alzheimers disease). Input from the committee can be enhanced by integration with established gene risk alleles published in Online Mendelian Inheritance in Man. We also may find actionable mutations in unusual contexts, and we anticipate that such variants may constitute a significant focus of the tumor board’s deliberations.

Category IV alterations include genomic alterations related to disease carrier state and consist of alterations in genes related to monogenic disorders that are inherited in an autosomal dominant, autosomal recessive, or x-linked manner (e.g. cystic fibrosis or x-linked severe combined immunodeficiency syndrome).

The remainder of alterations will not have established clinical validity and will not be discussed by the tumor board.

We anticipate that over the course of this study, the specific content of these categories will evolve as more information becomes available on the clinical and biological impact of specific genomic alterations.

11.4.3 Recommendation to validate alterations in a CLIA laboratory

When not already sequenced in a CLIA-certified laboratory variants falling into the return category per the guidelines outlined in section 11.4 will undergo confirmation in a CLIA laboratory and, if confirmed, the results will be returned back to the treatment team. Genomic alterations that are not felt to warrant validation in a clinical laboratory (if not already sequenced in a CLIA-environment) will be stored in the CRDR or Genomic Database for future use. For all patients who have identified germline alterations, we will synchronize test result validation and disclosure with the genetic counseling services available through our cancer-risk evaluation and medical genetics programs upon request by treating oncologist.

Going forward, most sequencing will have been conducted in a CLIA-certified laboratory (such as those part of the OncoMap or 02-180 panel or under the Broad Institutes CLIA platform). Alterations identified in this way would not need to be re-validated in a CLIA laboratory. However, the process for expert review\ and disclosure of results would remain the same.

11.4.4 CLIA validation of alterations

If sequencing has not been conducted in a CLIA labotory, tenomic findings identified as potentially actionable will need to be confirmed in a CLIA laboratory before being returned to physicians and patients. The DNA from the specific tumor and germline samples will have

already been isolated and prepared and reside at the Center for Advanced Molecular Diagnostics at BWH (CAMD). For category I somatic mutations, many of the clinical assays already exist and are being utilized as part of OncoMap or Oncopanel. Patients who have consented to DF/HCC 11-104 or 02-180 will also have their tumor simultaneously analyzed by ongoing clinical genotyping efforts. In order to develop new clinical assays, we will expand and/or modify existing OncoMap/OncoPanel (Sequenom mass spectroscopy) assay or develop pyrosequencing, Sanger sequencing, ASO-PCR, lightscanner melt curve analysis or PCR/fragment length analysis assays at the BWH CLIA laboratory (CAMD). These assays will include those for both germline genetic variants (currently not being tested at BWH) and novel potentially clinically significant somatic findings (either in new genes or new mutations in genes currently being tested). To develop new assays, we will follow the procedures currently used in the CLIA CAMD laboratory for test development and validation. The genomic alteration (e.g. point mutation, insertion/deletion, internal tandem duplication, etc.) is reviewed and the most cost-effective and efficient methodology is selected. Appropriate primers and/or probes are designed and tested on both normal and identified positive control (mutated) DNA. The optimized assay is then validated by documenting within-run and between-run precision, accuracy, sensitivity, and specificity. Once the assay has passed these validation steps, it will be considered a clinical test and applied to the identified DNA specimen. Over the last 3 years, the CAMD has developed, validated and implemented several assays into clinical use. Examples include *KRAS* and *BRAF* mutation testing (by pyrosequencing), *JAK2* codon 617 testing (allele-specific PCR), *EGFR* exon 19 analysis (PCR-capillary electrophoresis), and HPV genotyping (PCR-RFLP analysis). In addition, they have taken the OncoPanel research test and implemented this into a clinical test.

For some mutations (e.g. BRCA1), there may be only one clinical laboratory (Myriad Genetics) in the U.S. that can perform testing due to patent rights. Most clinical laboratories that perform germline testing will not accept DNA for testing and require a primary blood specimen. In these instances, we will inform the physician and patient that the whole exome sequencing identified a finding that warrants further investigation. The patient would be referred to a genetic counselor to decide whether they want clinical testing and, if so, a primary specimen would be sent to the CLIA laboratory for testing and reporting.

For copy number alterations identified from sequencing, a parallel process is in place to develop and validate fluorescence in situ hybridization (FISH) probes. FISH probes will be obtained from either commercial sources (Abbott Molecular) or developed using bacterial artificial chromosomes (BACs) covering the appropriate gene of interest and obtained from the Children's Hospital Oakland Research Institute (Oakland, CA). Centromeric probes will be used as a control to determine whether the copy number alteration represents a true amplification or polysomy. The FISH analyses will be performed using established methods and 100 nuclei per specimen will be scored. The BWH cytogenetics laboratory has previously developed, validated and implemented FISH testing including evaluation of *ALK* rearrangements in NSCLC.

11.5 Statistical Analysis Plan

Specific Aim 1. To implement a production-scale platform for whole exome sequencing from archival (FFPE) material.

Analysis of somatic and germline sequencing data will be performed as described in Sections 11.3 and 11.4 above.

Specific Aim 2. To determine the clinical impact of somatic and germline whole exome sequencing in cancer patients.

Aim 2a. The sample size for this study is 400 patients (200 lung cancer, 200 colorectal cancer). The sample size is primarily driven by the cost of whole exome sequencing. Despite this limitation we will still be able to assess the feasibility of WES from FFPE specimens. Periodic assessments of failure rate and concordance with CLIA-validated testing will be performed to monitor yield and evaluate discrepancies over the course of the project. Analyses will be descriptive.

To evaluate the feasibility of WES of clinical cancer patients, we will calculate failure rates and tabulate the cause of failures (e.g. DNA degradation, failures in the WES process) over the course of the study, in order to iteratively modify the relevant steps in the protocol to drive down the failure rate. If we evaluate 50 patients at each assessment, there is good precision to estimate the failure rate assuming a 5% rate (CI width of 14%).

To evaluate the concordance, we will only compare whether findings obtained in the CLIA laboratory are also obtained by WES to determine whether all genomic alterations currently being assayed by OncoMap or OncoPanel can also be captured by WES. Since WES is more sensitive than allelotyping (OncoMap/OncoPanel)) we expect that there may be instances where a mutation is detected by WES that is missed by OncoMap/OncoPanel. For determining the genotype at a specific locus (wild type or mutant allele), the concordance of WES and current clinical genotyping may be relatively high, although the concordance is not known specifically and may vary by locus. Based on preliminary data, we anticipate the concordance at each single locus will be relatively high (e.g. 99.9%), and estimate a small chance of at least one discrepancy over 43 loci (4%). To illustrate precision to estimate the discrepancy rate, 95% CIs were calculated for a range of hypothetical concordance rates assuming data are available for at least 95% of patients (190 lung, 190 CRC). With a sample size of 50, there is good precision (CI width 13.2%) and high precision with a sample size of 100 (CI width 8.8%) with a 4% discrepancy rate.

Table 3:

concordance rate at a single locus				any discrepancy over 43 loci			
rate	95% CI			rate	95% CI		
	n=50	n=100	n=190		n=50	n=100	n=190
99.0%	89.4-99.9%	94.6-100.0%	96.3-99.9%	35.0%	21.2-48.8%	25.7-45.2%	28.0-42.0%
99.5%	89.4-99.9%	94.6-100.0%	97.1-100.0%	23.0%	11.5-36.0%	15.2-32.5%	16.9-29.3%
99.9%	89.4-99.9%	94.6-100.0%	97.1-100.0%	4.0%	0.5-13.7%	1.1 - 9.9%	1.5 - 7.4%

Aim 2b. The number and nature of findings will vary by disease; thus the initial description will be by cancer type for both somatic and germline changes. Analyses of genomic findings will be

descriptive (e.g. the proportion of patients who have any category I findings that are not revealed through routine clinical testing, average number of category I and II findings). Patient data will be pooled to determine the number and fraction of unique genomic findings from Specific Aim 1 that are judged by the CGEC or expert review to need confirmation in a CLIA laboratory.

Aim 2c. Patients will be classified as having somatic findings that lead to a clinical action ("actionable" item), including those already being captured by OncoMap. We will evaluate the proportion of patients having an actionable item among those with a somatic finding. If the failure rate is 5%, we expect there will be data for 380 patients (190 lung, 190 CRC). We estimate a moderate proportion of patients will have a somatic finding (30% EGFR mutation in lung; 40% KRAS, BRAF, PIK3CA in CRC). Assuming these rates, we estimate there will be 133 patients with a somatic finding (57 lung, 76 CRC). The proportion of actionable items may be higher with WES, however it is difficult to know at this time how much higher it will be. Assuming there are 57 lung cancer patients and 76 CRC patients with a somatic finding, there will be adequate power (80%) to detect a 19% difference in the proportion of an actionable item in the lung cohort (e.g. 30% vs. 49%) and a 17% difference in the CRC cohort (e.g. 40% vs. 57%) based on a 2-sided 0.05 level 1-sample test for binomial proportions.

Aim 2c will also collect data on instances where knowledge of genomic data led to use or avoidance of existing therapies or enrollment into a clinical trial (change in treatment). We will determine the proportion of patients with a novel finding (not currently captured by OncoMap or Oncopanel) that are CLIA validated and lead to a change in treatment, pooling data over patient cohorts as a way to evaluate the overall impact of sequencing. The change in treatment proportion and 95% CI will be determined. As it is difficult to estimate the proportion of patients who will have a novel finding, we estimated the precision over a range of plausible proportions assuming there are data for 380 patients (190 lung, 190 CRC). As shown in Table 4, there is good precision if at least 20% of patients have a novel finding (CI width at most 23%).

Table 4. Precision to estimate the likelihood of a change in treatment among patients having a novel finding.

Proportion of patients having a novel finding	Number of patients having a novel finding	Width of 95% CI for proportion having a change in treatment
5%	19	47%
10%	38	33%
20%	76	23%
30%	114	19%
40%	152	16%

Specific Aim 3. To describe the *impact* of information derived from somatic and germline whole-exome sequencing (WES) on cancer patients.

The first analytic task will be to evaluate measurement quality and generate descriptive statistics. Our second analytic task will be to re-express/transform variables and explore the

relationships between variables. The third analytic task will be summarization of data and hypothesis testing. If appropriate, we will use standard techniques such as sensitivity analyses or multiple imputation to handle missing data. Our general approach to data analyses includes:

- estimating proportions and CIs
- evaluating mean values at each time point, as well as mean changes in scores over time (i.e., disclosure – follow-up) using standard methods (descriptive statistics, 1-sample, 2-sample t-tests or Wilcoxon tests), and
- exploratory regression modeling (e.g. linear or logistic) to describe relationships between endpoints, type of result (see categories above: prognostic somatic variant, germline cancer risk, etc.), and patient and physician characteristics as appropriate.
- Tests will be 2-sided with α=0.05; precision estimates are based on 95% CIs, and detectable effects refer to 80% power with a t-test.

Aim 3a: To test the hypothesis that patients will want to receive information about all potentially informative somatic and germline genomic variants. Patients' interest in potentially informative variants is thought to be relatively high overall, but may vary somewhat by disease and type of result. Using data obtained during the consent process, we will determine the proportion of patients indicating a preference for information about all potentially informative variants overall, by cancer type, and by type of result. We expect data for most patients enrolled in Years 1-3, and good precision to estimate proportions by patient subgroups (width of CI: 14% within each disease cohort).

Aim 3b: To evaluate patients' understanding of disclosed genomic information. At the post-disclosure time point, each patient will be asked to report his or her understanding of the genomic information that is returned by the oncologist during the disclosure visit (e.g., type of result). Each patient's response will be compared with information reported by his or her oncologist (collected in the companion physician survey). We will determine the proportion of patients whose responses are consistent with their oncologist's report (i.e., agreement rate), with rates described by type of result and cancer type.

Data are expected for at least 200 patients, given the possibility of loss to follow-up or of physician non-response. With 100 patients in any subgroup of interest, there is good precision to estimate the agreement rate (width of CI 20%), and precision is still reasonably good with a subgroup of 80 patients (width of CI 23%).

Aim 3c: To characterize patients' test-related distress after disclosure of genomic information. Patients' distress will be assessed at the post-disclosure survey using the MICRA distress subscale. Some patients may have little test-related distress, whereas others may score higher (e.g., if testing reveals adverse prognostic information or information about inherited cancer or non-cancer risk).

We will summarize test-related distress at the post-disclosure time point by type of result. Secondary analyses will include summaries of the HADS by time point to describe general distress over time, and correlation between the HADS and MICRA at the post-disclosure time point.

Data at follow-up may be unavailable for some patients who are unable to complete the visit due to their advanced disease. We will examine baseline characteristics (follow-up visit vs. no follow-up visit) to evaluate the potential for bias. In addition to complete case analysis, sensitivity analyses (e.g., using weighted methods (44)) may occur to evaluate bias.

It is difficult to predict how many patients will have received each type of result, although it is likely that at least 10-20% will have received somatic information that is potentially actionable. In

published data , with MICRA subscale scores normalized to a 0-100 point scale, a SD=23.9 for test-related distress was reported among women who were informed that they had a BRCA1/2 mutation (variability among those who tested negative was substantially smaller, SD=4.1).(33) We may observe a higher SD in this project, as we anticipate a more heterogeneous sample of patients (e.g., 20% higher, SD=28.7). To illustrate the precision for the mean, the widths of 95% CIs are listed in Table 5 for a range of sample sizes and potential SDs associated with the underlying measure. If the SD is relatively low (scenario A), there is high precision to estimate the mean within a group. If the SD is higher (scenario B & C), the width of the CI will be less than 12% with 100 patients and less than 15% with 60 patients.

Table 5: Precision to estimate mean test-related distress in a single group

	Scenario A	Scenario B	Scenario C
Group Size	SD=4.1	SD=23.9	SD=28.7
50	2.3	13.2	15.9
60	2.0	12.1	14.5
80	1.8	10.5	12.6
100	1.6	9.4	11.3

Table 6 shows the ability to detect differences in mean test-related distress between 2 groups (e.g., those who do vs. do not receive test results with adverse prognostic implications), using a 2-sided 0.05 level t-test. Detectable differences are given in SD units and in terms of absolute differences under three hypothetical scenarios.

Table 6: Detectable differences in test-related distress, comparing two groups of equal size

		Scenario A	Scenario B	Scenario C
Group Size	Detectable difference in SD's	SD=4.1	SD=23.9	SD=28.7
30	0.75	3.1	17.9	21.5
40	0.67	2.7	16.0	19.2
50	0.60	2.5	14.3	17.2
60	0.55	2.3	13.1	15.8
70	0.51	2.1	12.2	14.6
75	0.50	2.1	12.0	14.4
80	0.46	1.9	11.0	13.2
90	0.43	1.8	10.3	12.3
100	0.41	1.7	9.8	11.8

Qualitative Analysis Plan: Drs. Gray, Joffe and Park will read all transcripts for completeness. Transcripts will be uploaded into NVivo 8; educational attributes will be coded for each participant. Analysis of the patient data will be conducted using content analysis to explore the domains outlined above (45). Each interview will be coded independently by a Survey Core staff member and by Dr. Traeger. The coders will extract themes and codes through this iterative process, and then code responses for frequency, intensity, and extensiveness. Biweekly coding

meetings involving Dr. Park, Dr. Traeger, and the Survey Core qualitative interview staff will be held throughout the duration of the study. Kappa coefficients will be generated on an ongoing basis to assure a consistent level of agreement (Kappa>0.80). Coding discrepancies will be evaluated and resolved through an iterative process at coding meetings. Within-subject analyses will be conducted to compare participants’ responses across the 2 post-disclosure interviews. Across all participants, analyses will also be stratified by educational level and disease site. Drs. Gray and Joffe will participate in coding meetings every other month, to contribute to the analysis process and give clinical feedback on data interpretations.

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13.0 Appendices

- Appendix A - Measures for Patient Baseline
- Appendix B – Email Notification to Patients to Complete Baseline Survey
- Appendix C– Measures for Patient Post-Disclosure Survey in the Setting of Uninformative Sequencing Results
- Appendix D – Measures for Patient Post-Disclosure Survey in the Setting of Informative Sequencing Results
- Appendix E – Training plan for CRCs
- Appendix F – Patient Baseline Reminder Letter
- Appendix G – Patient Post-Disclosure Email Invitation and reminder email
- Appendix H – Patient Post-Disclosure Reminder invitation and reminder letter
- Appendix I – CanSeq Patient Informed Consent Interview Guide
- Appendix J – Patient Information brochure
- Appendix K- Post-Disclosure email introduction
- Appendix L – ACMG Guidelines
- Appendix M – Patient Preferences Communication
- Appendix N – Gift Card Thank You Letter
- Appendix O – Patient Post-Disclosure Interview

DANA-FARBER CANCER INSTITUTE

Patient ID:

CanSeq

Thank you for agreeing to participate in the CanSeq research study.

For each of the questions below, please select the one response that best applies to you.

There are no right or wrong answers. The information you provide will be strictly confidential.

1. From the list below, please mark the box next to the statement that best describes your current level of physical ability and activity.

☐	I am fully active and able to carry out activities the same as before my cancer diagnosis, without any restrictions.
☐	I have difficulty with physically strenuous activity but I am able to walk and carry out work that is light or based in one location; such as light house-work or office-work.
☐	I can walk and take care of myself, but I am not able to carry out work activities; I am up and about more than half the hours that I am awake.
☐	I am capable only of limited self-care and spend more than half the hours that I am awake in bed or in a chair.
☐	I am completely disabled, cannot carry on any self-care, and am totally confined to a bed or chair.

2. We are interested in some things about you and your health. Please answer the following questions by marking the box that best applies to you.

	Not at all	A little	Quite a bit	Very much
a. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	☐	☐	☐	☐
b. Do you have any trouble taking a long walk?	☐	☐	☐	☐
c. Do you have any trouble taking a short walk outside of the house?	☐	☐	☐	☐
d. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
e. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

3. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Were you limited in doing either your work or other daily activities?	☐	☐	☐	☐
b. Were you limited in pursuing your hobbies or other leisure time activities?	☐	☐	☐	☐
c. Were you short of breath?	☐	☐	☐	☐
d. Have you had pain?	☐	☐	☐	☐
e. Did you need to rest?	☐	☐	☐	☐
f. Have you had trouble sleeping?	☐	☐	☐	☐
g. Have you felt weak?	☐	☐	☐	☐
h. Have you lacked appetite?	☐	☐	☐	☐
i. Have you felt nauseated?	☐	☐	☐	☐
j. Have you vomited?	☐	☐	☐	☐
k. Have you been constipated?	☐	☐	☐	☐

4. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Have you had diarrhea?	☐	☐	☐	☐
b. Were you tired?	☐	☐	☐	☐
c. Did pain interfere with your daily activities?	☐	☐	☐	☐
d. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	☐	☐	☐	☐
e. Did you feel tense?	☐	☐	☐	☐
f. Did you worry?	☐	☐	☐	☐
g. Did you feel irritable?	☐	☐	☐	☐
h. Did you feel depressed?	☐	☐	☐	☐
i. Have you had difficulty remembering things?	☐	☐	☐	☐
j. Has your physical condition or medical treatment interfered with your family life?	☐	☐	☐	☐
k. Has your physical condition or medical treatment interfered with your social activities?	☐	☐	☐	☐
l. Has your physical condition or medical treatment caused you financial difficulties?	☐	☐	☐	☐

For the following questions please mark the number between 1 and 7 that best applies to you.

5. How would you rate your overall health during the past week?

Very poor ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 Excellent

6. How would you rate your overall quality of life during the past week?

Very poor ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 Excellent

Patient ID:

Now we would like to know more about how you are **currently** feeling. For each statement below, please choose 1 response that best describes your current feelings.

7. I feel tense or 'wound up':

- ☐ Most of the time
- ☐ A lot of the time
- ☐ From time to time, occasionally
- ☐ Not at all

8. I still enjoy the things I used to enjoy:

- ☐ Definitely as much
- ☐ Not quite so much
- ☐ Only a little
- ☐ Hardly at all

9. I get a sort of frightened feeling as if something awful is about to happen:

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

10. I can laugh and see the funny side of things:

- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

11. Worrying thoughts go through my mind:

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ From time to time, but not too often
- ☐ Only occasionally

12. I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

13. I can sit at ease and feel relaxed:

- ☐ Definitely
- ☐ Usually
- ☐ Not Often
- ☐ Not at all

14. I feel as if I am slowed down:

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

15. I get a sort of frightened feeling like 'butterflies' in the stomach:

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite Often
- ☐ Very Often

16. I have lost interest in my appearance:

- ☐ Definitely
- ☐ I don't take as much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

17. I feel restless as if I have to be on the move:

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

18. I look forward with enjoyment to things:

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

19. I get sudden feelings of panic:

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

20. I can enjoy a good book or radio or TV program:

- ☐ Often
- ☐ Sometimes
- ☐ Not often
- ☐ Very seldom

Next, we'd like to ask you some questions about your experience with and beliefs about genetic testing.

For each of the following items, please mark the number between 1 and 5 that best describes your attitude about having a genetic test.

For me a genetic test is...

21. a. A bad thing ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 A good thing

b. Beneficial ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 Harmful

c. Important ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 Unimportant

22. Before you joined this CanSeq study, did you ever have a genetic test to find out if you are at increased risk for a disease?

☐ Yes
☐ No
☐ Don't Know

23. As far as you know, is each of the following statements about genetics and genetic testing true or false, or are you not sure?

	True	False	Not Sure
a. If a person has a genetic mutation for a disease, the person will always get the disease.	☐	☐	☐
b. Only mothers can pass on genetic diseases.	☐	☐	☐
c. People can be healthy even if they have a genetic mutation for a disease.	☐	☐	☐
d. Genetic testing can be used in adults to find out if they have a greater than average chance of developing certain kinds of cancer.	☐	☐	☐
e. Genetic testing can be used in adults to find out if they have a greater than average chance of developing depression.	☐	☐	☐
f. Genetic testing can be used in adults to predict whether a person will have a heart attack.	☐	☐	☐
g. Genetic testing can be used during pregnancy to find out whether the baby will develop sickle cell disease or cystic fibrosis.	☐	☐	☐

25. Please select 1 statement that best reflects the role you prefer when making decisions about treatment for your cancer.

- ☐ I prefer to make the decision about which treatment I will receive.
- ☐ I prefer to make the final decision about my treatment after seriously considering my doctor's opinion.
- ☐ I prefer that my doctor and I share responsibility for deciding which treatment is best for me.
- ☐ I prefer that my doctor makes the final decision about my treatment after seriously considering my opinion.
- ☐ I prefer to leave all decisions regarding my treatment to my doctor.

The questionnaire is almost complete. For the next section, we would like to know a little more about you.

26. How often do you have problems learning about your medical condition because of difficulty understanding written information?
- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

27. How confident are you filling out medical forms by yourself?
- ☐ Extremely
- ☐ Quite a bit
- ☐ Somewhat
- ☐ A little bit
- ☐ Not at all

28. How often do you have someone (like a family member, friend, hospital/clinic worker or caregiver) help you read hospital materials?
- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ None of the time

29. How good are you at working with fractions?

Not at all good					Extremely good
☐	☐	☐	☐	☐	☐
1	2	3	4	5	6

30. How good are you at working with percentages?

Not at all good					Extremely good
☐	☐	☐	☐	☐	☐
1	2	3	4	5	6

31. When reading a newspaper, how helpful do you find tables and graphs that are part of the story?

Not at all					Extremely
☐	☐	☐	☐	☐	☐
1	2	3	4	5	6

32. When people tell you the chance of something happening, do you prefer that they use *words* ("it rarely happens") or *numbers* ("there's a 1% chance")?

Always prefer words					Always prefer numbers
☐	☐	☐	☐	☐	☐
1	2	3	4	5	6

33. To what extent do you consider yourself a religious person?
- ☐ Very religious
- ☐ Moderately religious
- ☐ Slightly religious
- ☐ Not religious at all

34. To what extent do you consider yourself a spiritual person?
- ☐ Very spiritual
- ☐ Moderately spiritual
- ☐ Slightly spiritual
- ☐ Not spiritual at all

35. Think about how much you try to understand and deal with major problems in your life. To what extent does each of the statements below reflect the way you cope?

	A great deal	Quite a bit	Somewhat	Not at all
a. I think about how my life is part of a larger spiritual force.	☐	☐	☐	☐
b. I work together with God as partners to get through hard times.	☐	☐	☐	☐
c. I look to God for strength, support and guidance in crises.	☐	☐	☐	☐

36. What is your religion? *Please check all that apply.*
- ☐ Protestant (*please specify denomination*):_____
- ☐ Catholic
- ☐ Jewish
- ☐ Born-again or Evangelical Christian
- ☐ Mormon/Latter-day Saints
- ☐ Muslim
- ☐ Buddhist
- ☐ Hindu
- ☐ Unitarian Universalist
- ☐ No religion
- ☐ Atheist
- ☐ Other religion (*please specify*):_____

37. Do you consider yourself Hispanic, Latino/a or Spanish?

☐ No
☐ Yes →

If yes, please select the primary group you belong to from the list below:

- ☐ Mexican (from Mexico), Mexican American, Chicano
- ☐ Puerto Rican
- ☐ Cuban
- ☐ Dominican
- ☐ Other (*please specify*): _____

38. What is your race? *Please check all that apply.*

☐ White	
☐ Black or African American	
☐ American Indian or Alaska Native →	Please tell us the name of your enrolled or principal tribe:
☐ Japanese	
☐ Chinese	
☐ Other East Asian →	Please select your primary East Asian Group below: ☐ Korean ☐ Vietnamese ☐ Taiwanese ☐ Other (*please specify*): _____
☐ South East Asian or Indian →	Please select your primary South East Asian racial group below: ☐ East Indian ☐ Filipino ☐ Vietnamese ☐ Laotian ☐ Guamanian or Chamorro ☐ Hmong ☐ Thai ☐ Pakistani ☐ Cambodian ☐ Other (*please specify*): _____
☐ Native Hawaiian or other Pacific Islander	
☐ Other →	*Please specify:*

39. What is your preferred language?

- ☐ English
- ☐ Spanish
- ☐ Other (*please specify*): _____

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

- ☐ None
- ☐ Some grade school (grades 1 to 7)
- ☐ Grade school graduate (grade 8)
- ☐ Some high school (grades 9 to 12)
- ☐ High school graduate or GED
- ☐ Post high school training other than college (vocational, technical, etc.)
- ☐ Some college or Associates degree
- ☐ College graduate
- ☐ Master's degree
- ☐ Doctoral degree

41. As of today, what is your employment status?

- ☐ Employed more than or equal to 32 hrs/wk
- ☐ Employed less than 32 hrs/wk
- ☐ Employed, but on medical leave
- ☐ Full-time student
- ☐ Part-time student
- ☐ Unemployed, seeking work
- ☐ Homemaker
- ☐ Unable to work due to disability
- ☐ Retired
- ☐ Other (*please specify*):_____

42. From the list below, please choose the response that best reflects your current marital status.

- ☐ Legally married or registered domestic partners
- ☐ Living with a partner to whom you are not married
- ☐ In a serious relationship but not living with a partner
- ☐ Single
- ☐ Separated
- ☐ Divorced
- ☐ Widowed
- ☐ Other (Please specify): _____

42a. Some people who join this study are hoping that the sequencing results will help answer questions that they have about their health or their family's health. We cannot promise that the sequencing results will answer your questions. However, if you do have questions you are hoping the study will answer, please use the space below to tell us about them (optional).

_____

_____

_____

Finally, we would like to ask you some questions that will help us to understand whether cancer and other diseases might run in your family.

43. Have you had more than 10 colon polyps in your lifetime?
- ☐ Yes
- ☐ No
- ☐ Don't Know

44. Are your ancestors of Ashkenazi Jewish descent?
- ☐ Yes
- ☐ No
- ☐ Don't Know

45. Are you adopted?

☐ No → **Please continue to next page.**

- ☐ Yes
- ☐ Don't Know

46. Do you have information about your biological family?
- ☐ No → **That is all the questions we have. Thank you very much for completing our survey.**
- ☐ Yes

Please continue to next page.

Answer the remaining questions to the best of your ability, based on information you may have about your *BLOOD* relatives.

Think about your ***biological MOTHER***.

47. How many sisters does (did) your MOTHER have? _____

48. How many brothers does (did) your MOTHER have? _____

Think about your ***biological FATHER***.

49. How many sisters does (did) your FATHER have? _____

50. How many brothers does (did) your FATHER have? _____

51. Do you believe that an *increased risk of developing cancer* runs in your family?
    - ☐ Yes
    - ☐ No
    - ☐ Don't Know

52. Complete the following table to the best of your ability, for any of your *CLOSE BLOOD RELATIVES* who have ***had cancer***. Please list which family member(s) have had cancer, what type(s) of cancer(s) they have had, and ***the approximate age*** at which their cancers were diagnosed (For example: "60's"). If you do not know the type of cancer or age when diagnosed, please indicate 'don't know.'

    A list of cancers appears on the last page of this questionnaire.

    Close blood relatives include: Mother, Father, Daughter, Son, Sister, Brother, Half-sister, Half-Brother (note mother or father's side)**

Relationship to you (** see list above)	Type of cancer	Approximate age when cancer was diagnosed
Example: Sister	Breast	60's

53. Please complete the following table to the best of your ability, for any of your EXTENDED FAMILY MEMBERS who are *BLOOD RELATIVES* and have ***had cancer***. Please tell us which family member(s) have had cancer, what type(s) of cancer(s) they have had, and ***the approximate age*** at which their cancers were diagnosed (For example: "60's.") If you do not know the type of cancer or age when diagnosed, please indicate 'don't know.'

    A list of cancers appears on the last page of this questionnaire for your reference.

    Extended family members include: Aunt, Uncle, Grandmother, Grandfather, Niece, Nephew, Female Cousin, Male Cousin.**

Relationship to you (** see list above)	Mother's or father's side	Type of cancer	Approximate age when cancer diagnosed
Example: Aunt	Mother's side	Breast	60's

54. Do you believe that an *increased risk of developing a disease other than cancer* runs in your family?
    - ☐ Yes
    - ☐ No
    - ☐ Don't Know

55. List any hereditary (genetic) diseases ***other than cancer*** that run in your family. Some examples are: Cystic fibrosis, Fragile X, Gaucher's disease, Hemochromatosis, Homocysteinuria, Huntington's disease, Muscular Dystrophy, Neurofibromatosis, Sickle-cell Anemia, Tay Sachs disease, and Thalassemia.

    _____ _____

56. Other conditions may be common in families but are not strictly "genetic", meaning that we cannot identify one gene that explains their pattern in the family. Examples include high blood pressure, diabetes, dementia (Alzheimer's and others), and alcoholism. Please list any conditions that are common in your family.

    _____ _____

    _____ _____

THANK YOU FOR COMPLETING OUR SURVEY!

Survey and Data Management core
qualitative and quantitative research

List of Potential Cancers

Type of Cancer/Tumor/Malignancy	Type of Cancer/Tumor/Malignancy
• Lung Cancer	• Colon Cancer
• Head and Neck Cancer: o Larynx o Mouth o Palate o Throat o Tongue	• Other Gastrointestinal cancer: o Esophagus o Stomach o Small Intestine o Rectum o Anus o Appendix o Gall bladder/ Biliary tree o Liver
• Breast Cancer (including DCIS)	• Pancreas • Pancreas Islet Cell
• Male Genito-Urinary: o Prostate o Testis o Other	• Female Genito-Urinary: o Cervix o Endometrium (uterus lining) o Uterus o Ovary o Fallopian Tube/Peritoneum
• Kidney	• Bladder
• Hematologic (Blood/Immune): o Leukemia o Hodgkin's Disease o Lymphoma o Myeloma o Waldenstrom's Macroglobulinemia	• Sarcoma: o Bone (Osteosarcoma) o GIST o Soft Tissue Sarcoma (includes Leiomyosarcoma, Liposarcoma, other)
• Skin Cancers: o Melanoma o Basal Cell o Sebaceous Adenoma o Squamous Cell	• Brain Tumors: o Glioblastoma/Astrocytoma o Medulloblastoma o Hemangioblastoma
• Endocrine/Hormonal: o Adrenal gland (cortex) o Carcinoid (lung or abdomen) o Paraganglioma or Pheocromocytoma o Thyroid	

Appendix B: Email Notification to Patients to Complete the Baseline Survey

Dear [Insert First Name Last Name],

We spoke with you during a recent clinic visit about our study "The Use of Sequencing to Guide the Care of Cancer Patients." Thank you for agreeing to participate in this study.

We are now writing to ask that you take a moment to complete the baseline survey for this study. You may have already started to complete this survey during your visit to the clinic.

You can access this survey at:

[To the IRB: URL and logon information to be determined]

You may reply to this email at CanSeq@DFCI.HARVARD.EDU if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Follow up Email Notification to Patients to Complete the Baseline Survey

Dear [Insert First Name Last Name],

We recently sent you an email asking you to complete the baseline survey for our study, "The Use of Sequencing to Guide the Care of Cancer Patients." According to our records, we have not yet received your completed baseline survey. We are now writing to ask that you complete the survey at your earliest convenience.

You can access this survey at:

[To the IRB: URL and logon information to be determined]

You may reply to this email at CanSeq@DFCI.HARVARD.EDU if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Patient ID: _____

DANA-FARBER CANCER INSTITUTE

CanSeq

A number of months ago you agreed to participate in a research study to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells. This study is called the CanSeq study.

For each of the questions below, please check the one response that best applies to you, unless instructed differently.

Remember, there are no right or wrong answers. The information you provide will be strictly confidential.

1. During your appointments in the last month or two, do you remember your doctor telling you about the results of your CanSeq gene sequencing?

   ☐ Yes
   ☐ No ⟶ Go to Question 10, Page 6.
   ☐ Not sure ⟶ Go to Question 10, Page 6.

2. In your own words, please describe the results of your CanSeq gene sequencing.

_____
_____
_____
_____
_____

Patient ID: _____

We understand that, during a recent clinic visit, your doctor told you that the results from your CanSeq gene sequencing did not provide any information that would affect your health or cancer treatment at this time. We will call these **"uninformative gene sequencing test results."** Your answers to the remaining questions will help us learn more about patients' experience of receiving uninformative test results.

3. The questions below are about some specific responses you may have had after receiving your CanSeq gene sequencing test results. Please check one box in each row to tell us whether you had each response *never, rarely, sometimes*, or *often* in the past week.

In the past week, how often have you...	**Never**	**Rarely**	**Sometimes**	**Often**
a. Felt upset about your gene sequencing test results.	☐	☐	☐	☐
b. Felt sad about your gene sequencing test results.	☐	☐	☐	☐
c. Felt anxious or nervous about your gene sequencing test results.	☐	☐	☐	☐
d. Felt guilty about your gene sequencing test results.	☐	☐	☐	☐
e. Felt relieved about your gene sequencing test results.	☐	☐	☐	☐
f. Felt happy about your gene sequencing test results.	☐	☐	☐	☐
g. Felt a loss of control.	☐	☐	☐	☐
h. Had problems enjoying life because of your gene sequencing test results.	☐	☐	☐	☐
i. Been uncertain about what your gene sequencing test results mean about your health.	☐	☐	☐	☐
j. Been uncertain about what your gene sequencing test results mean for your child(ren) and/or family's health.	☐	☐	☐	☐
k. Thought about how your gene sequencing test results have affected your work or family life.	☐	☐	☐	☐
l. Felt concerned about how your gene sequencing test results will affect your insurance status.	☐	☐	☐	☐
m. Had difficulty talking about your gene sequencing test results with family members.	☐	☐	☐	☐
n. Felt that your family has been supportive during the gene sequencing testing process.	☐	☐	☐	☐
o. Felt satisfied with family communication about your gene sequencing test results.	☐	☐	☐	☐
p. Worried that the gene sequencing testing process has brought about conflict within your family.	☐	☐	☐	☐

Patient ID: _____

Please continue to tell us about specific responses you may have had after receiving your CanSeq gene sequencing test results.

In the past week, how often have you...	Never	Rarely	Sometimes	Often
q. Felt regret about getting your gene sequencing test results.	☐	☐	☐	☐
r. Felt regret about going through the gene sequencing testing process.	☐	☐	☐	☐
s. Felt that your gene sequencing test results have made it harder to cope with your cancer.	☐	☐	☐	☐
t. Felt that your gene sequencing test results have made it easier to cope with your cancer.	☐	☐	☐	☐

4. Have you shared the fact that the results from your CanSeq gene sequencing did not provide any new information about your health or cancer with any family members?

   ☐ Yes ⟶ *Go to Question 5, below*
   ☐ No ⟶ *Go to Question 7, Page 4.*
   ☐ Not applicable, I do not have any close family members with whom I could share the results from my gene sequencing ⟶ *Go to Question 8, Page 5.*

5. From the list below, please select everyone in your family with whom you have discussed the fact that your CanSeq gene sequencing did not provide any new information about your health or cancer. ***Please check all that apply.***

   ☐ My spouse or partner
   ☐ My child(ren)
   ☐ My sibling(s)
   ☐ Other family member(s) (*please specify:* _____)

6. For each of the reasons listed below, please select the number between 1 “not at all important” and 5 “extremely important” that best reflects how important this reason was when making your decision to share your results with your family members.

	Not at all important 1	2	3	4	Extremely important 5
a. To obtain emotional support.	☐	☐	☐	☐	☐
b. To get advice about decisions regarding possible treatments.	☐	☐	☐	☐	☐
e. Because my family member(s) asked/wanted to know.	☐	☐	☐	☐	☐

When you are finished with question 6, please skip to Question 8, Page 4.

7. For each of the reasons below, please select the number between 1 “not at all important” and 5 “extremely important” that best reflects how important this reason was to your decision not to share your results with your family members.

	Not at all important				**Extremely important**
	1	**2**	**3**	**4**	**5**
a. I was concerned about sharing my medical information with family member(s).	☐	☐	☐	☐	☐
b. I was having difficulty dealing with my gene sequencing test results.	☐	☐	☐	☐	☐

8. From the list below, please select everyone outside of your family with whom you have discussed the fact that your CanSeq gene sequencing did not provide any new information about your health or cancer. ***Please check all that apply.***

☐ Another doctor besides your cancer doctor (please specify): _____
☐ A genetic counselor
☐ A nurse
☐ Friend(s)
☐ Co-worker(s)
☐ Other cancer patient(s)
☐ A support group
☐ Other (*please specify*_____)
☐ I did not discuss these results with anyone outside my family

9. Think about when your doctor(s) explained the fact that your CanSeq gene sequencing did not provide any new information about your health or cancer. To what extent...

	Not at all	A little	Quite a bit	Very much
a. Did your doctor(s) encourage you to ask questions about the results of your gene sequencing?	☐	☐	☐	☐
b. Did your doctor(s) encourage you to express any concerns you had about the results of your gene sequencing?	☐	☐	☐	☐
c. Did your doctor(s) make an effort to ensure that you understood what the results of your gene sequencing meant for you?	☐	☐	☐	☐
d. Did your doctor(s) make an effort to ensure that you understood what the results of your gene sequencing meant for your family?	☐	☐	☐	☐
e. Did you find the doctor's explanation of the results of your gene sequencing easy to understand?	☐	☐	☐	☐

Patient ID: _____

Now we would like to know more about how you are **currently** feeling. For each statement below, please mark 1 response that best describes your current feelings.

10. I feel tense or 'wound up':

- ☐ Most of the time
- ☐ A lot of the time
- ☐ From time to time, occasionally
- ☐ Not at all

11. I still enjoy the things I used to enjoy:

- ☐ Definitely as much
- ☐ Not quite so much
- ☐ Only a little
- ☐ Hardly at all

12. I get a sort of frightened feeling as if something awful is about to happen:

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

13. I can laugh and see the funny side of things:

- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

14. Worrying thoughts go through my mind:

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ From time to time, but not too often
- ☐ Only occasionally

15. I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

16. I can sit at ease and feel relaxed:

- ☐ Definitely
- ☐ Usually
- ☐ Not Often
- ☐ Not at all

17. I feel as if I am slowed down:

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

18. I get a sort of frightened feeling like 'butterflies' in the stomach:

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite Often
- ☐ Very Often

19. I have lost interest in my appearance:

- ☐ Definitely
- ☐ I don't take as much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

20. I feel restless as I have to be on the move:

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

21. I look forward with enjoyment to things:

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

22. I get sudden feelings of panic:

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

23. I can enjoy a good book or radio or TV program:

- ☐ Often
- ☐ Sometimes

☐ Not often ☐ Very seldom

24. This next set of questions is about how good your doctor is at talking about certain important issues like becoming very ill. For these questions, the answer choices are on a scale of 0 to 10, where 0 means your doctor is the very worst you could imagine, and 10 means your doctor is the very best you could imagine.

When talking with your cancer doctor about important issues like becoming very ill, how good is he/she at:

	Very worst 0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Very best 10**
a. Using words that you can understand?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
b. Looking you in the eye?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
c. Answering all your questions about your illness and treatment?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
d. Listening to what you have to say?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
e. Caring about you as a person?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
f. Giving you his/her full attention?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
g. Asking about the things in life that are important to you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
h. Respecting the things in life that are important to you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
i. Overall, how would you rate this doctor's communication with you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Patient ID: _____

25. Finally, we would like to ask you some questions about you and your health. Please answer the following questions by marking the box that best applies to you.

	Not at all	A little	Quite a bit	Very much
a. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	☐	☐	☐	☐
b. Do you have any trouble taking a long walk?	☐	☐	☐	☐
c. Do you have any trouble taking a short walk outside of the house?	☐	☐	☐	☐
d. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
e. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

26. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Were you limited in doing either your work or other daily activities?	☐	☐	☐	☐
b. Were you limited in pursuing your hobbies or other leisure time activities?	☐	☐	☐	☐
c. Were you short of breath?	☐	☐	☐	☐
d. Have you had pain?	☐	☐	☐	☐
e. Did you need to rest?	☐	☐	☐	☐
f. Have you had trouble sleeping?	☐	☐	☐	☐
g. Have you felt weak?	☐	☐	☐	☐
h. Have you lacked appetite?	☐	☐	☐	☐
i. Have you felt nauseated?	☐	☐	☐	☐
j. Have you vomited?	☐	☐	☐	☐
k. Have you been constipated?	☐	☐	☐	☐

Patient ID: _____

27. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Have you had diarrhea?	☐	☐	☐	☐
b. Were you tired?	☐	☐	☐	☐
c. Did pain interfere with your daily activities?	☐	☐	☐	☐
d. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	☐	☐	☐	☐
e. Did you feel tense?	☐	☐	☐	☐
f. Did you worry?	☐	☐	☐	☐
g. Did you feel irritable?	☐	☐	☐	☐
h. Did you feel depressed?	☐	☐	☐	☐
i. Have you had difficulty remembering things?	☐	☐	☐	☐
j. Has your physical condition or medical treatment interfered with your family life?	☐	☐	☐	☐
k. Has your physical condition or medical treatment interfered with your social activities?	☐	☐	☐	☐
l. Has your physical condition or medical treatment caused you financial difficulties?	☐	☐	☐	☐

For the following questions please mark the number between 1 and 7 that best applies to you.

28. How would you rate your overall health during the past week?

Very poor ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 Excellent

29. How would you rate your overall quality of life during the past week?

Very poor ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 Excellent

30. From the list below, please mark the box next to the statement that best describes your current level of physical ability and activity.

☐	I am fully active and able to carry out activities the same as before my cancer diagnosis, without any restrictions.
☐	I have difficulty with physically strenuous activity but I am able to walk and carry out work that is light or based in one location; such as light house-work or office-work.
☐	I can walk and take care of myself, but I am not able to carry out work activities; I am up and about more than half the hours that I am awake.
☐	I am capable only of limited self-care and spend more than half the hours that I am awake in bed or in a chair.
☐	I am completely disabled, cannot carry on any self-care, and am totally confined to a bed or chair.

Thank you very much for completing our survey.
We really appreciate your time and effort.

Survey and Data Management core
qualitative and quantitative research

Patient ID: _____

DANA-FARBER CANCER INSTITUTE

CanSeq

A number of months ago you agreed to participate in a research study to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells. This study is called the CanSeq study.

For each of the questions below, please check the one response that best applies to you, unless instructed differently.

Remember, there are no right or wrong answers. The information you provide will be strictly confidential.

1. During your appointments in the last month or two, do you remember your doctor telling you about the results of your CanSeq gene sequencing?

   ☐ Yes
   ☐ No ⟶ Go to Question 20, Page 9
   ☐ Not sure ⟶ Go to Question 20, Page 9

2. Think back to the conversations you have had with your doctor(s) in the last month or two about one or more of your CanSeq gene sequencing test results. Did any of these results provide you and your doctors with information that is ***related to your cancer***?

   ☐ Yes
   ☐ No
   ☐ Not sure

3. In your own words, please describe the results of your CanSeq gene sequencing that were ***related to your cancer***:

_____
_____
_____
_____
_____

Patient ID: _____

The results of your CanSeq gene sequencing tests may have provided you with more than one piece of information.

4. Did any of the CanSeq gene sequencing test results that were ***related to your cancer*** provide you and your doctors with information that might…

	Yes	Not Sure	No
a. Be used to help select cancer-related treatment(s)?	☐	☐	☐
b. Qualify you for a clinical study of a research drug?	☐	☐	☐
c. Tell you that you have a ***better than average*** prognosis (outlook) for your type of cancer?	☐	☐	☐
d. Tell you that you have a ***worse than average*** prognosis (outlook) for your type of cancer?	☐	☐	☐
e. Identify you, and possibly your family members, as having an ***increased risk*** of developing cancer?	☐	☐	☐
f. Tell you about how your body handles chemotherapy or other cancer medications?	☐	☐	☐

5. Now please think back to the conversations you have had with your doctor(s) in the last month or two about your CanSeq gene sequencing test results. Did any of these results provide you and your doctors with information that was ***not related to your cancer***?

☐ Yes
☐ No
☐ Not sure

6. In your own words, please describe the results of your CanSeq gene sequencing that were ***not related to your cancer***:

_____
_____
_____
_____
_____

7. Did any of the CanSeq gene sequencing test results that were ***not related to your cancer*** provide you and your doctors with information that might...

	Yes	Not Sure	No
a. Identify you, and possibly your family members, as having a condition, or having an increased risk of developing a condition, ***other than cancer*** that ***can*** be treated?	☐	☐	☐
b. Identify you, and possibly your family members, as having a condition, or having an increased risk of developing a condition, ***other than cancer*** that ***cannot*** be treated?	☐	☐	☐
c. Tell you about how your body handles ***non-cancer- related*** medications?	☐	☐	☐
d. Identify you as carrying a gene alteration for a ***non-cancer-related condition*** that you might pass on to a child?	☐	☐	☐

8. Did your doctor tell you about any results from your CanSeq gene sequencing that **do not** affect your health or cancer treatment at this time?

☐ Yes
☐ No
☐ Not sure

9. Based on the results of your CanSeq gene sequencing tests, have you taken any of the following actions?

	Yes	No
a. Made any changes to your cancer treatment?	☐	☐
b. Enrolled in a study of a research drug (clinical trial)?	☐	☐
c. Made changes to any non-cancer-related medications?	☐	☐

10. Have you made any other changes based on the results of your CanSeq gene sequencing tests?

☐ No
☐ Yes (*please describe below*)

_____
_____
_____
_____

Patient ID: _____

11. The questions below are about some specific responses you may have had after receiving your CanSeq gene sequencing test results. Please check one box in each row to tell us whether you had each response *never, rarely, sometimes*, or *often* in the past week.

In the past week, how often have you...	**Never**	**Rarely**	**Sometimes**	**Often**
a. Felt upset about your gene sequencing test results.	☐	☐	☐	☐
b. Felt sad about your gene sequencing test results.	☐	☐	☐	☐
c. Felt anxious or nervous about your gene sequencing test results.	☐	☐	☐	☐
d. Felt guilty about your gene sequencing test results.	☐	☐	☐	☐
e. Felt relieved about your gene sequencing test results.	☐	☐	☐	☐
f. Felt happy about your gene sequencing test results.	☐	☐	☐	☐
g. Felt a loss of control.	☐	☐	☐	☐
h. Had problems enjoying life because of your gene sequencing test results.	☐	☐	☐	☐
i. Been uncertain about what your gene sequencing test results mean about your health.	☐	☐	☐	☐
j. Been uncertain about what your gene sequencing test results mean for your child(ren) and/or family's health.	☐	☐	☐	☐
k. Thought about how your gene sequencing test results have affected your work or family life.	☐	☐	☐	☐
l. Felt concerned about how your gene sequencing test results will affect your insurance status.	☐	☐	☐	☐
m. Had difficulty talking about your gene sequencing test results with family members.	☐	☐	☐	☐
n. Felt that your family has been supportive during the gene sequencing testing process.	☐	☐	☐	☐
o. Felt satisfied with family communication about your gene sequencing test results.	☐	☐	☐	☐
p. Worried that the gene sequencing testing process has brought about conflict within your family.	☐	☐	☐	☐

Patient ID: _____

Please continue to tell us about specific responses you may have had after receiving your CanSeq gene sequencing test results.

In the past week, how often have you...	Never	Rarely	Sometimes	Often
q. Felt regret about getting your gene sequencing test results.	☐	☐	☐	☐
r. Felt regret about going through the gene sequencing testing process.	☐	☐	☐	☐
s. Felt that your gene sequencing test results have made it harder to cope with your cancer.	☐	☐	☐	☐
t. Felt that your gene sequencing test results have made it easier to cope with your cancer.	☐	☐	☐	☐

12. For each statement below, please check the box that best reflects your response.

	Agree	Somewhat agree	Somewhat disagree	Disagree
a. It's hard for me to talk about my gene sequencing test results with my relatives.	☐	☐	☐	☐
b. It's hard for me to talk about my gene sequencing test results with my friends.	☐	☐	☐	☐
c. I feel satisfied with my communication with my family about what my gene sequencing test results mean for me.	☐	☐	☐	☐
d. It makes me feel better to talk to my loved ones about my gene sequencing test results.	☐	☐	☐	☐
e. My relatives are supportive when I tell them about my gene sequencing test results.	☐	☐	☐	☐
f. My friends are supportive when I tell them about my gene sequencing test results.	☐	☐	☐	☐
g. I understand how I came to have the gene alteration(s) described in my gene sequencing test results.	☐	☐	☐	☐
h. I understand the health risks my relatives face because of my gene sequencing test results.	☐	☐	☐	☐
i. I feel certain I understand the meaning of my gene sequencing test results.	☐	☐	☐	☐
j. I understand the chances I have of passing gene alteration(s) along to my children.	☐	☐	☐	☐
k. I feel I can explain to other people what my gene sequencing test results mean.	☐	☐	☐	☐
l. I feel confused because I have been given different explanations of what my gene sequencing test results mean.	☐	☐	☐	☐

13. Have you shared the results from your gene sequencing with any family members?

- ☐ **Y**es ⟶ *Go to Question 14, below*
- ☐ No ⟶ *Go to Question 16, Page 7.*
- ☐ Not applicable, I do not have any close family members with whom I could share the results from my gene sequencing ⟶ *Go to Question 17, Page 7.*

14. From the list below, please select everyone in your family with whom you have discussed your CanSeq gene sequencing test results. ***Please check all that apply.***

- ☐ My spouse or partner
- ☐ My child(ren)
- ☐ My sibling(s)
- ☐ Other family member(s) (*please specify:* _____)

15. For each of the reasons listed below, please select the number between 1 "not at all important" and 5 "extremely important" that best reflects how important this reason was when making your decision to share your results with your family members.

	Not at all important				**Extremely important**
	1	**2**	**3**	**4**	**5**
a. To obtain emotional support.	☐	☐	☐	☐	☐
b. To get advice about decisions regarding possible treatments.	☐	☐	☐	☐	☐
c. To provide information about my relative's risk of having this gene alteration(s).	☐	☐	☐	☐	☐
d. To encourage my relative(s) to do genetic testing.	☐	☐	☐	☐	☐
e. Because my family member(s) asked/wanted to know.	☐	☐	☐	☐	☐

When you are finished with question 15, please skip to Question 17, Page 7.

16. For each of the reasons below, please select the number between 1 “not at all important” and 5 “extremely important” that best reflects how important this reason was to your decision not to share your results with your family members.

	Not at all important 1	**2**	**3**	**4**	**Extremely important 5**
a. I was concerned about sharing my medical information with family member(s).	☐	☐	☐	☐	☐
b. I was having difficulty dealing with my gene sequencing test results.	☐	☐	☐	☐	☐
c. I felt guilty about having this gene alteration(s).	☐	☐	☐	☐	☐
d. I felt worried about having this gene alteration(s).	☐	☐	☐	☐	☐

17. From the list below, please select everyone outside of your family with whom you have discussed your CanSeq gene sequencing test results. ***Please check all that apply.***

☐ Another doctor besides your cancer doctor (please specify): _____
☐ A genetic counselor
☐ A nurse
☐ Friend(s)
☐ Co-worker(s)
☐ Other cancer patient(s)
☐ A support group
☐ Other (*please specify*_____)
☐ I did not discuss these results with anyone outside my family

18. Have you used any of the following sources to learn more about your CanSeq gene sequencing test results? ***Please check all that apply.***

☐ Newspapers
☐ Books, brochures, pamphlets
☐ Medical journals
☐ Magazines
☐ Radio
☐ Telephone hotlines
☐ Social media (such as Facebook)
☐ Television
☐ Internet
☐ Other (*please specify*_____)
☐ I did not seek any information about my gene test results

Patient ID: _____

19. Think about when your doctor(s) explained your CanSeq gene sequencing test results to you. To what extent...

	Not at all	A little	Quite a bit	Very much
a. Did your doctor(s) encourage you to ask questions about the results of your gene sequencing?	☐	☐	☐	☐
b. Did your doctor(s) encourage you to express any concerns you had about the results of your gene sequencing?	☐	☐	☐	☐
c. Did your doctor(s) make an effort to ensure that you understood what the results of your gene sequencing meant for you?	☐	☐	☐	☐
d. Did your doctor(s) make an effort to ensure that you understood what the results of your gene sequencing meant for your family?	☐	☐	☐	☐
e. Did you find the doctor's explanation of the results of your gene sequencing easy to understand?	☐	☐	☐	☐

Patient ID: _____

Now we would like to know more about how you are **currently** feeling. For each statement below, please mark 1 response that best describes your current feelings.

20. I feel tense or 'wound up':

- ☐ Most of the time
- ☐ A lot of the time
- ☐ From time to time, occasionally
- ☐ Not at all

21. I still enjoy the things I used to enjoy:

- ☐ Definitely as much
- ☐ Not quite so much
- ☐ Only a little
- ☐ Hardly at all

22. I get a sort of frightened feeling as if something awful is about to happen:

- ☐ Very definitely and quite badly
- ☐ Yes, but not too badly
- ☐ A little, but it doesn't worry me
- ☐ Not at all

23. I can laugh and see the funny side of things:

- ☐ As much as I always could
- ☐ Not quite so much now
- ☐ Definitely not so much now
- ☐ Not at all

24. Worrying thoughts go through my mind:

- ☐ A great deal of the time
- ☐ A lot of the time
- ☐ From time to time, but not too often
- ☐ Only occasionally

25. I feel cheerful:

- ☐ Not at all
- ☐ Not often
- ☐ Sometimes
- ☐ Most of the time

26. I can sit at ease and feel relaxed:

- ☐ Definitely
- ☐ Usually
- ☐ Not Often
- ☐ Not at all

27. I feel as if I am slowed down:

- ☐ Nearly all the time
- ☐ Very often
- ☐ Sometimes
- ☐ Not at all

28. I get a sort of frightened feeling like 'butterflies' in the stomach:

- ☐ Not at all
- ☐ Occasionally
- ☐ Quite Often
- ☐ Very Often

29. I have lost interest in my appearance:

- ☐ Definitely
- ☐ I don't take as much care as I should
- ☐ I may not take quite as much care
- ☐ I take just as much care as ever

30. I feel restless as I have to be on the move:

- ☐ Very much indeed
- ☐ Quite a lot
- ☐ Not very much
- ☐ Not at all

31. I look forward with enjoyment to things:

- ☐ As much as I ever did
- ☐ Rather less than I used to
- ☐ Definitely less than I used to
- ☐ Hardly at all

32. I get sudden feelings of panic:

- ☐ Very often indeed
- ☐ Quite often
- ☐ Not very often
- ☐ Not at all

33. I can enjoy a good book or radio or TV program:

- ☐ Often
- ☐ Sometimes
- ☐ Not often

☐ Very seldom

34. This next set of questions is about how good your doctor is at talking about certain important issues like becoming very ill. For these questions, the answer choices are on a scale of 0 to 10, where 0 means your doctor is the very worst you could imagine, and 10 means your doctor is the very best you could imagine.

When talking with your cancer doctor about important issues like becoming very ill, how good is he/she at:

	Very worst 0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Very best 10**
a. Using words that you can understand?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
b. Looking you in the eye?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
c. Answering all your questions about your illness and treatment?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
d. Listening to what you have to say?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
e. Caring about you as a person?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
f. Giving you his/her full attention?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
g. Asking about the things in life that are important to you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
h. Respecting the things in life that are important to you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
i. Overall, how would you rate this doctor's communication with you?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Patient ID: _____

35. Finally, we would like to ask you some questions about you and your health. Please answer the following questions by marking the box that best applies to you.

	Not at all	A little	Quite a bit	Very much
a. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	☐	☐	☐	☐
b. Do you have any trouble taking a long walk?	☐	☐	☐	☐
c. Do you have any trouble taking a short walk outside of the house?	☐	☐	☐	☐
d. Do you need to stay in bed or a chair during the day?	☐	☐	☐	☐
e. Do you need help with eating, dressing, washing yourself or using the toilet?	☐	☐	☐	☐

36. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Were you limited in doing either your work or other daily activities?	☐	☐	☐	☐
b. Were you limited in pursuing your hobbies or other leisure time activities?	☐	☐	☐	☐
c. Were you short of breath?	☐	☐	☐	☐
d. Have you had pain?	☐	☐	☐	☐
e. Did you need to rest?	☐	☐	☐	☐
f. Have you had trouble sleeping?	☐	☐	☐	☐
g. Have you felt weak?	☐	☐	☐	☐
h. Have you lacked appetite?	☐	☐	☐	☐
i. Have you felt nauseated?	☐	☐	☐	☐
j. Have you vomited?	☐	☐	☐	☐
k. Have you been constipated?	☐	☐	☐	☐

Patient ID: _____

37. During the past week:

	Not at all	A little	Quite a bit	Very much
a. Have you had diarrhea?	☐	☐	☐	☐
b. Were you tired?	☐	☐	☐	☐
c. Did pain interfere with your daily activities?	☐	☐	☐	☐
d. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	☐	☐	☐	☐
e. Did you feel tense?	☐	☐	☐	☐
f. Did you worry?	☐	☐	☐	☐
g. Did you feel irritable?	☐	☐	☐	☐
h. Did you feel depressed?	☐	☐	☐	☐
i. Have you had difficulty remembering things?	☐	☐	☐	☐
j. Has your physical condition or medical treatment interfered with your family life?	☐	☐	☐	☐
k. Has your physical condition or medical treatment interfered with your social activities?	☐	☐	☐	☐
l. Has your physical condition or medical treatment caused you financial difficulties?	☐	☐	☐	☐

For the following questions please mark the number between 1 and 7 that best applies to you.

38. How would you rate your overall health during the past week?

Very poor						Excellent
☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7

39. How would you rate your overall quality of life during the past week?

Very poor						Excellent
☐	☐	☐	☐	☐	☐	☐
1	2	3	4	5	6	7

40. From the list below, please mark the box next to the statement that best describes your current level of physical ability and activity.

☐	I am fully active and able to carry out activities the same as before my cancer diagnosis, without any restrictions.
☐	I have difficulty with physically strenuous activity but I am able to walk and carry out work that is light or based in one location; such as light house-work or office-work.
☐	I can walk and take care of myself, but I am not able to carry out work activities; I am up and about more than half the hours that I am awake.
☐	I am capable only of limited self-care and spend more than half the hours that I am awake in bed or in a chair.
☐	I am completely disabled, cannot carry on any self-care, and am totally confined to a bed or chair.

Thank you very much for completing our survey.
We really appreciate your time and effort.

Survey and Data Management core
qualitative and quantitative research

Appendix E – Training Plan for CRCs

Training plan for Clinical Research Coordinators (CRCs)

All Clinical Research Coordinators (CRCs) who will be involved in obtaining consent from patients will need to undergo formal training. This training will include:

 A formal training session. This small -group training session will be led by the genetic counselors who are co -investigators on the study, and will include an educational/didactic portion, role plays, and a Q+A period.

 Written training materials. These materials have been developed and assembled by the genetic counselors on the study.

 Weekly attendance at study meetings.

 Hands-on training for the consent process conducted by the genetic counselors. For each new CRC, the first consent process will be performed by one of the genetic counselors while the CRC observes. Subsequently, the genetic counselor will observe 2 additional consent processes performed by the CRCs. At this point, if the genetic counselor judges that the CRC is adequately prepared, the CRC will be able to independently lead subsequent consent discussions. However, genetic counselors will be available to all patients considering participation who wish additional discussion with a genetic counselor before making their decisions.

Appendix F – Patient Baseline Reminder Letter

Dear Mr./Mrs. (insert last name) ,

We recently approached you during your clinic visit to complete the baseline survey for our study, "The Use of Sequencing to Guide the Care of Cancer Patients." Thank you for taking the time to talk with us. According to our records, we have not yet received your completed baseline survey. We understand how busy you may be at this time, and would greatly appreciate it if you would please complete the survey at your earliest convenience.

You may return your completed survey in the enclosed postage paid envelope or bring it with you to your next clinic visit.

If you have any questions please contact Nelly Oliver at 617-582-8706 or CanSeq@dfci.harvard.edu.

Thank you for your consideration,

Stacy Gray, MD, AM
617-632-6049

Appendix G: Patient Post-disclosure Email Invitation

Dear [insert FN, LN],

A number of months ago you agreed to participate in a research study, "The Use of Sequencing to Guide the Care of Cancer Patients" to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

We understand that your cancer doctor recently discussed the result of the gene sequencing with you. We are now writing to ask that you take a moment to complete the enclosed survey. This survey asks about your experience learning the results of your gene sequencing from your physician.

You can access this survey at:
[To the IRB: URL and logon information to be determined]

You may reply to this email at CanSeq@dfci.harvard.edu if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617-632-6049

Post-Disclosure Reminder Letter

Dear [insert FN, LN],

A number of months ago you agreed to participate in a research study, "The Use of Sequencing to Guide the Care of Cancer Patients" to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

We recently approached you during your clinic visit or emailed you a survey asking about your experience learning the results of your gene sequencing from your physician. We are now writing to ask that you take a moment to complete the follow-up survey which asks about your experience learning the results of your gene sequencing from your physician. You may have already started to complete the survey during your visit to the clinic.

You can access this survey at:
[To the IRB: URL and logon information to be determined]

You may reply to this email at CanSeq@dfci.harvard.edu if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617-632-6049

Appendix H: Patient Post-disclosure Invitation

Dear [insert FN, LN],

A number of months ago you agreed to participate in a research study, "The Use of Sequencing to Guide the Care of Cancer Patients" to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

We understand that your cancer doctor recently discussed the result of the gene sequencing with you. We are now writing to ask that you take a moment to complete the enclosed survey. This survey asks about your experience learning the results of your gene sequencing from your physician.

You may return your completed survey in the enclosed postage paid envelope or bring it with you to your next clinic visit.

If you have any questions please contact Nelly Oliver at 617-582-8706 or CanSeq@dfci.harvard.edu.

Thank you for your consideration,

Stacy Gray, MD, AM
617-632-6049

Post-Disclosure Reminder Letter

Dear [insert FN, LN],

A number of months ago you agreed to participate in a research study, "The Use of Sequencing to Guide the Care of Cancer Patients" to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists used a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

We recently approached you during your clinic visit or mailed you a survey asking about your experience learning the results of your gene sequencing from your physician. We are now writing to ask that you complete the survey at your earliest convenience.

You may return your completed survey in the enclosed postage paid envelope or bring it with you to your next clinic visit.

If you have any questions please contact Nelly Oliver at 617-582-8706 or CanSeq@dfci.harvard.edu.

Thank you for your consideration,

Stacy Gray, MD, AM
617-632-6049

My name is _____ and I am working with the researchers and doctors on the "CanSeq study." As you may remember, in this study, we are using a type of genetic testing called "gene sequencing."

(*Show patient copy of his/her consent form)*: This is the consent form that you signed when you agreed to take part in the CanSeq study. Do you remember talking with your doctor or the research staff about the CanSeq Study?

- If yes: great, thanks.
- If no: Would you like to take a few minutes to review this form?
    - *If patient doesn't recall study after reviewing the consent form, say:* "I understand. If you have questions about the CanSeq study, please talk with your cancer doctor about it. Thank you very much for your time."
    - *End interview.*

To briefly summarize, in the CanSeq study, we are sequencing the genes in your cancer cells. The purpose of this sequencing is to see if there are gene changes in your cancer cells that your doctors can use to help select your cancer treatments.

We are also sequencing the genes in your normal cells. When we sequence the genes in your normal cells, we might also find changes related to health problems other than cancer.

We want to ask about your experiences with deciding to have gene sequencing in the CanSeq study.

The interview will take about 45 minutes. Is this a good time to do the interview? (*If not, try to reschedule with patient*)

Please let me remind you that the interview is completely voluntary. If at any time during this interview you would like to stop, please tell me. Also, you can choose not to answer questions.

Your name will be kept confidential, and we won't share your name or other identifying information with anyone outside our research team.

To thank you for your participation, we will offer you a $25 gift card at the end of the interview.

Do you have any questions?

Before we start, I would like to remind you that we are recording these interviews so that we can make sure that we capture what patients are telling us. Is it okay with you that I record the interview?

--*if yes:* Thank you. After I turn on the recorder, I will ask you to tell me again that you agree that I can record the interview.
--*If no:* I understand. Because it's important for our research that we have recordings of our interviews, we won't be able to continue with the interview today. Thank you for your time, and for your participation in the CanSeq study.

Turn on recorder

Now that I have turned on the recorder, can you tell me whether you agree that I can record this interview?

Thank you.

In this interview, I would like to ask you about a few things: First, your decision to have gene sequencing in the CanSeq study; second, your understanding about the genetic information that might be found; and finally, how much of this genetic information you want to be told.

We'll start with the first.

Section One: Informed consent to participate in CanSeq

I will ask you what it was like for you to decide to have gene sequencing in the CanSeq study.

Please think back to the time when your cancer doctor and the CanSeq research staff talked with you about the possibility of participating in the CanSeq study.

1. Can you tell me in your own words what you think gene sequencing is?
2. What were the main reasons why you agreed to have gene sequencing?
3. Were there any reasons why you considered NOT agreeing to have gene sequencing?
4. Please think about the conversations that you had with your cancer doctor and the research staff about gene sequencing.
    a. What did you think about the amount of information that you were given? Why?
5. Was there anything about gene sequencing, as part of the study, that you found hard to understand?
    a. *If yes*: What did you find hard to understand?

b. *Optional probe*: Is there something that your cancer doctor or the research staff could have done to help you to better understand gene sequencing? *If yes, what?*

As part of the study, all potential participants were given the chance to speak with a genetic counselor.

6. A genetic counselor is a person who helps people decide whether or not to have genetic testing and then helps them understand the results of the tests. Did you speak with a genetic counselor before you decided to have gene sequencing in the study?

    a. *If yes*: Please describe what this was like.

        i. *Optional probe*: Was talking with a genetic counselor helpful or not helpful? Please explain

7. Did you speak with anyone else about gene sequencing before you decided to join the study?

    a. *Optional probe:* Anyone from your family? What did you discuss?

    b. *Optional probe:* Any friends? What did you discuss?

    c. *Optional probe:* Any other doctors besides your cancer doctor? What did you discuss?

    d. *Optional probe:* Any other patients? What did you discuss?

8. Did you look up any information about gene sequencing before agreeing to have gene sequencing in this study? Why/why not?

    a. *If yes*, what sources of information did you look at?

    b. Did you find this information helpful or not helpful? Why/why not?

Section Two: Types of information that might be found through gene sequencing

Now I would like to ask you what you understand about the different types of information that might be found through gene sequencing – of both cancer cells and normal cells.

Let's start with cancer cells.

9. Please explain, in your own words, what you and your doctors might learn from sequencing the genes in your <u>cancer cells</u>.

a. *Probe:* Are there any (other) ways in which the results of gene sequencing on your cancer cells might be helpful to you? Please explain.

b. *Probe:* Are there any (other) ways in which the results of gene sequencing on your cancer cells might be harmful to you? Please explain.

Now let's talk about the information from your normal cells

10. Please explain, in your own words, what you and your doctors might learn from sequencing the genes in your <u>normal cells</u>. (Probe to elicit as many responses as possible.)

    a. *Probe:* Is there any (other) way in which the results of gene sequencing on your normal cells might be helpful to you? Please explain.

    b. *Probe:* Is there any (other) way in which the results of gene sequencing on your normal cells might be harmful to you? Please explain.

11. Is there any way in which the results of gene sequencing on your normal cells might be helpful to your children or blood relatives? Please explain.

12. Is there any way in which the results of gene sequencing on your normal cells might be harmful to your children or blood relatives? Please explain.

Section Three: Reasons for preferences regarding return of results

Let's now look at the copy of the consent form that you signed. Please turn to page [insert relevant page number here].

The results of gene sequencing on your cancer cells may provide you with some new information. I'm going to ask you how you'd feel about getting some of this information.

13. How do you think you would feel if you received a gene test result that could help your doctor to choose a clinical study of a research drug?

14. How do you think you would feel if you received a gene test result that that meant that you had a **better** than average prognosis, or outlook, for your type of cancer?

15. How do you think you would feel if you received a gene test result that meant that you had a **worse** than average prognosis, or outlook, for your type of cancer?

Now I'm going to ask about how you decided which types of genetic information you wanted the CanSeq researchers to share with you and your doctor.

Here is a series of questions that you answered, regarding which results you would or would not want the CanSeq researchers to share with your doctors and you (*point to*

appropriate place in consent form). I am going to ask you the reasons for some of your responses.

16. You said that you (would/would not) want to be told that you had an increased risk of developing certain cancers. Can you explain why?

17. You also said that you (would/would not) want to be told about any gene test result that might tell you about how your body handles chemotherapy or other cancer medications. Can you explain why?

The next set of choices on the consent form is about results from gene sequencing that are unrelated to cancer.

18. You said that you (would/would not) want to be told that you had an increased risk of developing a condition, other than cancer, that **can** be treated. Can you explain why?

19. You said that you (would/would not) want to be told that you had an increased risk of developing a condition, other than cancer, that **cannot** be treated. Can you explain why?

20. You also said that you (would/would not) want to be told about a gene test result that might tell you about how your body handles medications that are not related to cancer treatment. Can you explain why?

21. Only for patients with children: Finally, you said that you (would/would not) want to be told that you carry a gene alteration for a condition that's not related to cancer and that you might pass on to a child. Can you explain why?

22. Thinking back to the decisions you made about which types of results you would want back, was it easy or difficult to make these decisions? Why/why not

Now I would like to ask you a few questions about what doctors and researchers should do when they discover gene sequencing results that they don't understand very well.

Often, when gene sequencing is performed on patients' cells, the meaning of some of the results is very uncertain. When this happens, doctors are not sure what the uncertain results mean. For example, they may be unsure whether the results could have any effect on patients' treatment. Or they may be unsure whether the results have any meaning for patients' or their family members' risk of developing disease in the future.

If doctors receive uncertain results, they might decide to ignore them or share them with patients,

23. Imagine that the meaning of some of your gene sequencing results was very uncertain. Do you think you would want *your doctor* to be given those uncertain results? Yes or no?

    a. Why/Why not?

24. Do you think *you* would want to be given those uncertain results? Yes or no?
    a. Why/Why not?

Section Four: Final Thoughts

Now I have a few more questions to ask you before we finish the interview.

25. Is there anything that you're hoping to learn from your gene sequencing that we haven't already discussed?

26. Do you have any concerns about your gene sequencing that we haven't already discussed?

27. Would you recommend gene sequencing to another cancer patient? Why/Why not?

28. We are planning to develop new educational materials to help people as they make decisions about receiving gene sequencing results.

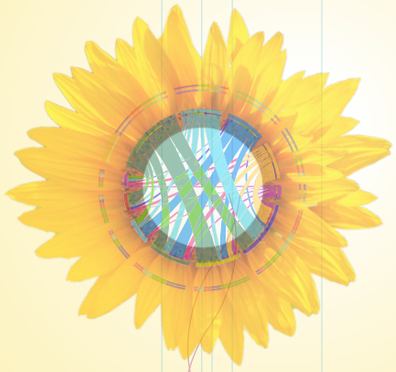
    a. Would additional educational materials have been helpful to you when you were making your decisions? Why or Why not?

    b. How willing would you have been to review educational materials in the following ways? For each of the following options, please tell me if you would be not willing at all, be somewhat unwilling, be neither willing or unwilling, be somewhat willing, or be very willing?
        i. Through a website where you can choose the information that you want to review?
        ii. In a pamphlet or booklet?
        iii. By teleconference in your home (interacting with a health educator on a computer screen)?

29. Before I close, I wanted to check in to see if any of these questions were upsetting?

30. Do you have any questions or additional comments?

Thank you for taking the time to do this interview with me today! We really appreciate your willingness to help us learn from your experiences in the CanSeq study.



People who are considering gene sequencing are asked to make some important decisions about the kind of results they want to receive.

The "right" decisions are the ones that feel most comfortable to you.

CAN HELP YOU THINK IT THROUGH.

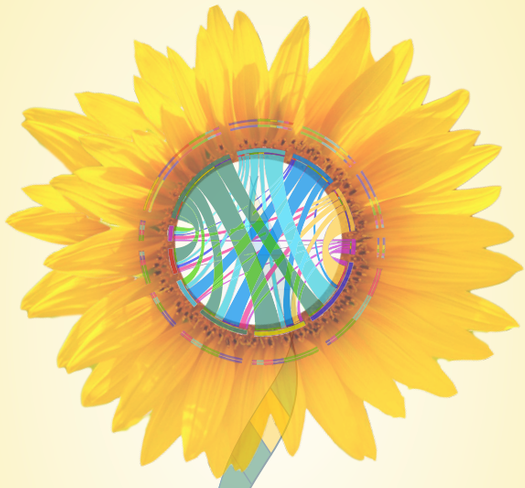
LEARN MORE. GET SUPPORT.

CanSeq@dfci.harvard.edu

Produced by
DF/HCC Health Communication Core
HealthCommCore.org

CANCER GENE SEQUENCING

THINKING IT THROUGH



THE CANSEQ STUDY

DANA-FARBER CANCER INSTITUTE

BROAD INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

THE EXCITEMENT AND PROMISE OF GENE SEQUENCING IS BEING ABLE TO TARGET CARE TO A PERSON'S SPECIFIC CANCER.

THE CANSEQ STUDY LOOKS at all of your genes, including the ones in your cancer cells. Because of this, sequencing can produce many kinds of results, both about your cancer and about other possible health issues.

YOUR DOCTOR OR A GENETIC COUNSELOR

WHAT MIGHT GENE SEQUENCING MEAN FOR YOU?

THE CANSEQ STUDY USES GENETIC SEQUENCING TO IMPROVE CANCER CARE.

WAYS SEQUENCING MAY HELP YOU

We study cancer genes to learn if they can predict response to treatments. That means gene sequencing results could:

- Affect your cancer treatment directly—for example, show how your cancer might respond to specific drugs and dosages
- Show if your cancer can be treated with a new therapy as part of a clinical trial
- Tell you about your prognosis (outlook)

You will also be helping us learn how to improve the future care of patients with cancer.

WHAT TO BE AWARE OF

Your sequencing results may or may not directly benefit you. Test results may:

- Not offer any helpful information
- Tell you about other health risks that you may or may not be able to change
- Give you information about family health risks that they may or may not be able to change
- Not be completed because of technical issues

YOU CAN DECIDE which kind(s) of results you want to get. That's why it's important to think it through ahead of time.

COMMON QUESTIONS

WHAT DO GENES HAVE TO DO WITH CANCER?

Cancer is a disease of genes. Cancers occur when the molecules that control normal cell growth (genes and proteins) are altered.

WHY ARE GENE ALTERATIONS IMPORTANT FOR CANCER?

Identifying alterations in cancers has led to new drugs that "target" those alterations. Finding more alterations will help develop more new drugs.

WILL GENE SEQUENCING ONLY LOOK AT MY CANCER CELLS?

Gene sequencing is performed on cancer cells and normal tissues. You can decide which types of results you want to get.

HOW MIGHT I FEEL ABOUT GENE SEQUENCING AFTER I'VE HAD IT?

Some people may be excited or relieved. The information may help them feel more empowered. Other people may become anxious, disappointed, or worried about their family, and wish they didn't have the burden of more information.

MAKING THE RIGHT DECISIONS

GENE SEQUENCING RESULTS MAY PROVIDE INFORMATION ABOUT YOUR CANCER AND/OR OTHER HEALTH ISSUES.

CONSIDER HOW IT MIGHT AFFECT YOU OR YOUR FAMILY TO LEARN:

GENETIC RESULTS RELATED TO CANCER

- Your type of cancer may benefit from an available treatment or current research study.
- Your cancer may progress faster or more slowly than average.
- You may be at risk for other kinds of cancer.
- Your family members may be at risk for certain kinds of cancer.
- Your body may respond well or poorly to specific cancer drugs.

GENETIC RESULTS NOT RELATED TO CANCER

- You might be at increased risk for a health problem that can be treated or prevented, like heart disease, or for one that can't be, like Alzheimer's disease.
- Some of your family members may be more likely to develop a health problem that can be treated or prevented, or to develop one that can't be.
- You may pass on a health risk to your child, even if you don't have the condition yourself.
- Your body may or may not respond well to noncancer drugs.

LET YOUR DOCTOR KNOW if you have questions about gene sequencing.

Consider talking to one of our genetic counselors for information and support while you consider your options. Your doctor can refer you.

A genetic counselor can help you understand the medical, emotional, and family implications of sequencing results, and help you come to your own "right" decisions.

You can also talk to one of our genetic counselors after you receive sequencing results, whether or not you talked to one before.

Dear [First Name] [Last Name],

You may remember that, some time ago, you agreed to participate in a study at Dana-Farber called the CanSeq study. This study involves sequencing of the genes in your tumor cells as well as your normal cells. The goal of the sequencing is to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. According to our records, you discussed your genetic sequencing results from the CanSeq study with your physician at a recent appointment.

After patients have received their results we're asking them to complete a final study survey. The survey takes about 15 minutes. It asks questions about the conversation you had with your physician regarding your results, and about your impressions of the study overall. Even if you do not remember the conversation with your physician you can still complete the survey.

If you are interested in participating, please reply to DFCI_CanSeqU01@dfci.harvard.edu, and indicate whether you would prefer to complete the survey online, or have a paper copy mailed to you. If you have questions regarding the survey feel free to email or call us at 617-632-3458.

This survey is voluntary, but your input is extremely valuable to us as we work to bring this genetic sequencing technology to all our patients.

Thank you for your consideration,

Stacy Gray, MD, AM

TABLE

Phenotype	MIM - Disorder	PMID -GeneReviews Entry	Age of Onset	Gene	MIM - Gene	Inheritance*	Variants to Report#
Hereditary Breast and Ovarian Cancer	604370, 612555	20301425	Adult	*BRCA1*	113705	AD	KP & EP
				BRCA2	600185		
Li-Fraumeni Syndrome	151623	20301488	Child/adult	*TP53*	191170	AD	KP & EP
Peutz-Jeghers Syndrome	175200	20301443	Child/adult	*STK11*	602216	AD	KP & EP
Lynch Syndrome	120435	20301390	Adult	*MLH1*	120436	AD	KP & EP
				MSH2	609309		
				MSH6	600678		
				PMS2	600259		
Familial adenomatous polyposis	175100	20301519	Child	*APC*	611731	AD	KP & EP
MYH-Associated Polyposis; Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456, 132600	23035301	Adult	*MUTYH*	604933	AR**	KP & EP
Von Hippel Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537	AD	KP & EP
Multiple Endocrine Neoplasia Type 1	131100	20301710	Child/adult	*MEN1*	613733	AD	KP & EP
Multiple Endocrine Neoplasia Type 2	171400, 162300	20301434	Child/adult	*RET*	164761	AD	KP
Familial Medullary Thyroid Cancer (FMTC)	1552401	20301434	Child/adult	*RET*	164761	AD	KP
				NTRK1	191315	Suspected AD	
PTEN Hamartoma Tumor Syndrome	153480	20301661	Child	*PTEN*	601728	AD	KP & EP
Retinoblastoma	180200	20301625	Child	*RB1*	614041	AD	KP & EP
Hereditary Paraganglioma-Pheochromocytoma Syndrome	168000 (PGL1)	20301715	Child/adult	*SDHD*	602690	AD	KP & EP
	601650 (PGL2)			*SDHAF2*	613019		KP
	605373 (PGL3)			*SDHC*	602413		KP & EP
	115310 (PGL4)			*SDHB*	185470		
Tuberous Sclerosis Complex	191100, 613254	20301399	Child	*TSC1*	605284	AD	KP & EP
				TSC2	191092		
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP & EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP & EP
EDS - vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP & EP

Phenotype	MIM - Disorder	PMID -GeneReviews Entry	Age of Onset	Gene	MIM - Gene	Inheritance*	Variants to Report#
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections	154700, 609192, 608967, 610168, 610380, 613795, 611788	20301510, 20301312, 20301299	Child/adult	*FBN1*	134797	AD	KP & EP
				TGFBR1	190181		
				TGFBR2	190182		
				SMAD3	603109		
				ACTA2	102620		
				MYLK	600922		
				MYH11	160745		
Hypertrophic cardiomyopathy, Dilated cardiomyopathy	115197, 192600, 601494, 613690, 115196, 608751, 612098, 600858, 301500, 608758, 115200	20301725	Child/adult	*MYBPC3*	600958	AD	KP & EP
				MYH7	160760		KP
				TNNT2	191045		KP & EP
				TNNI3	191044		KP
				TPM1	191010		
				MYL3	160790		
				ACTC1	102540		
				PRKAG2	602743		
				GLA	300644	XL	KP & EP (hemi, het, hom)
				MYL2	160781	AD	KP
				LMNA	150330		KP & EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP
Arrhythmogenic right ventricular cardiomyopathy	609040, 604400, 610476, 607450, 610193	20301310	Child/adult	*PKP2*	602861	AD	KP & EP
				DSP	125647		
				DSC2	125645		
				TMEM43	612048		KP
				DSG2	125671		KP & EP
Romano-Ward Long QT Syndromes Types 1, 2, and 3, Brugada Syndrome	192500, 613688, 603830, 601144	20301308	Child/adult	*KCNQ1*	607542	AD	KP & EP
				KCNH2	152427		
				SCN5A	600163		
Familial hypercholesterolemia	143890, 603776	No GeneReviews entry	Child	*LDLR*	606945	SD	KP & EP

Phenotype	MIM - Disorder	PMID -GeneReviews Entry	Age of Onset	Gene	MIM - Gene	Inheritance*	Variants to Report#
				APOB	107730	SD	KP
				PCSK9	607786	AD	
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	*RYR1*	180901	AD	KP
				CACNA1S	114208		

• Some conditions that may demonstrate semi-dominant inheritance have been indicated as autosomal dominant (AD) for the sake of simplicity.

** Although carriers may have modestly increased risk, we recommend only searching for individuals with bi-allelic mutations.

KP = known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP = expected pathogenic, sequence variation is previously unreported and is of the type which is expected to cause the disorder.

Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list.

Patient Preferences Post-Consent Interview Email Communication

Dear [Patient Name],

You recently spoke with us on the phone about participating in a telephone interview for the CanSeq research study on [DAY, DATE]. Attached to this email, you will find a copy of the decisions that you made for the return of gene sequencing results when you agreed to take part in the CanSeq study. During your telephone interview on [DAY, DATE], you will be asked to refer to these decisions while answering some questions, in order to refresh your memory.

As a reminder, the main goal of the CanSeq research study is to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists will use a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

You may reply to this email at CanSeq@dfci.harvard.edu if you have any questions.

Thank you for your consideration, and for your participation in this important study,

Stacy Gray, MD, AM
617-632-6049

Patient Preferences Post-Consent Interview Mail Communication

Dear [Patient Name],

You recently spoke with us on the phone about participating in a telephone interview for the CanSeq research study on [DAY, DATE]. In this mailing, you will find a copy of the decisions that you made for the return of gene sequencing results when you agreed to take part in the CanSeq study. During your telephone interview on [DAY, DATE], you will be asked to refer to these decisions while answering some questions, in order to refresh your memory.

As a reminder, the main goal of the CanSeq research study is to help doctors and scientists better understand why cancers occur and to develop ways to better treat and prevent them. As part of the study, doctors and scientists will use a method called gene sequencing to identify changes in the genes of your cancer cells as well as in the genes of your normal cells.

You may send an email to CanSeq@dfci.harvard.edu if you have any questions.

Thank you for your consideration, and for your participation in this important study,

Stacy Gray, MD, AM
617-632-6049

Stacy Gray, MD, AM
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215

Dear [PATIENT NAME],

You recently participated in a telephone interview for the CanSeq research study on [DAY, DATE]. We are pleased to provide you with a $25 gift card to show our appreciation for your participation. We greatly appreciate you taking the time to speak with us.

You may send an email to CanSeq@dfci.harvard.edu or contact me at 617-632-6049 if you have any questions.

Thank you again for your participation in this important study,

Stacy Gray, MD, AM

My name is _____ and I am working with the researchers and doctors on the "CanSeq study."
To briefly summarize, in the CanSeq study, we are sequencing the genes in your cancer cells. The purpose of this sequencing is to see if there are gene changes in your cancer cells that your doctors can use to help select your cancer treatments.

We are also sequencing the genes in your normal cells. When we sequence the genes in your normal cells, we might also find changes related to health problems other than cancer.

In this interview, I will ask you about your <u>experiences with getting your gene sequencing results back from the CanSeq study</u>.

Do you remember your cancer doctor telling you about your gene sequencing results from the CanSeq study?

--*If yes- continue the interview.*

--*If no*- I understand that you don't remember getting the results from the CanSeq study. If you are interested in learning about your CanSeq results, you might want to ask your cancer doctor about them. If it would be helpful, we can also let your doctor know that you don't remember getting your gene sequencing results from the CanSeq study. Unfortunately, we are only interviewing patients who remember learning about their CanSeq results and therefore I cannot interview you at this point in time. I want to thank you very much for talking the time to talk with us today, and for your participation in the CanSeq study. *End interview*

The interview will take about 45 minutes. Is this a good time to do the interview? (*If not, try to reschedule with patient*)

Please let me remind you that the interview is completely voluntary. If at any time during this interview you would like to stop, please tell me. Also, you can choose not to answer any question.

We will keep your name confidential, and we won't share your name or other identifying information with anyone outside our research team.

To thank you for your time, we will send you a $25 gift card after you have completed your interview.

Do you have any questions?

Before we start, I would like to remind you that we are recording these interviews so that we can make sure that we capture what patients are telling us. Is it okay with you that I record the interview?

--*if yes:* Thank you. After I turn on the recorder, I will ask you to tell me again that you agree that I can record the interview.

--*If no:* I understand. Because it's important for our research that we have recordings of our interviews, we won't be able to continue with the interview today. Thank you for your time, and for your participation in the CanSeq study.

Turn on recorder

Now that I have turned on the recorder, can you confirm whether you agree that I can record this interview?

Thank you.

In this interview, I would like to ask you about your CanSeq gene sequencing results.

First, I'd like to know what it was like for you to get gene sequencing results back from the CanSeq study.

1. Did your cancer doctor tell you about one result from gene sequencing, or about more than one result from gene sequencing?

2. Please tell me what you were told about…

   --*if one result*: the gene sequencing result your doctor told you about
   Probe: Anything else?

   -- *if more than one result:* the gene sequencing result that you remember best from the CanSeq study?

   a. Did the results provide you with information that is related to your cancer? *If yes*: Please describe.

      i. Has this result affected your cancer treatment? *If yes*: Please tell me about this.

      ii. Has this result told you anything about the prognosis (outlook) for your cancer? *If yes*: Please describe

      iii. Has this result told you anything about your risk of developing cancer in the first place? *If yes*: Please describe

   b. Did this result tell you anything about how your body handles medications? *If yes*: Please describe

i. Prompt: what kinds of medications?

c. Did this result have any implications for your health other than your cancer? *If yes*: please describe.

d. Did this result have any implications for the health of your family members? *If yes*: Please describe.

e. *If not already covered in (d):* Did this result tell you anything about a condition you might pass down to a child? *If yes:* Please describe.

f. Have you or your doctor taken any action in response to this result that we haven't already talked about?

i. Prompt: Changed chemotherapy or cancer treatments?

ii. Prompt: Changed other medications?

iii. Prompt: Seen another health care provider?

iv. Prompt: Had any tests or procedures?

v. Prompt: Other actions?

3. Did your doctor tell you about any other results from your CanSeq gene sequencing, besides the one(s) that we just talked about? *(Instruction to interviewer: repeat this question, and the follow-on questions, until the patient can't identify any further results, or until in your judgment it's best to move on)*

If yes:

4. Please tell me what you were told about another gene sequencing result from the CanSeq study that your doctor told you about?

a. Did the results provide you with information that is related to your cancer? *If yes*: Please describe.

i. Has this result affected your cancer treatment? *If yes*: Please tell me about this.

ii. Has this result told you anything about the prognosis (outlook) for your cancer? *If yes*: Please describe

iii. Has this result told you anything about your risk of developing cancer in the first place? *If yes*: Please describe

b. Did this result tell you anything about how your body handles medications? *If yes*: Please describe

    i. Prompt: what kinds of medications?

c. Did this result have any implications for your health other than your cancer? *If yes*: please describe.

d. Did this result have any implications for the health of your family members? *If yes*: Please describe.

e. *If not already covered in (d):* Did this result tell you anything about a condition you might pass down to a child? *If yes:* Please describe.

f. Have you or your doctor taken any action in response to this result that we haven't already talked about?

    i. Prompt: Changed chemotherapy or cancer treatments?

    ii. Prompt: Changed other medications?

    iii. Prompt: Seen another health care provider?

    iv. Prompt: Had any tests or procedures

    v. Prompt: Other actions?

Thank you for sharing so much about what you were told about your test results. Now I'd like to ask about what it was like for you to receive these results and how you've responded to these results.

5. How easy or difficult was it for you to understand what your CanSeq gene sequencing [result/results] mean?
    a. *Prompt*: Please explain more.

    b. *Prompt*: What made the result(s) easy to understand? /What was difficult to understand? Why?

6. How [has this result/have these results] affected you emotionally?

    a. *Prompt:* Which result(s) most affected you emotionally? Can you explain why?

    b. *Prompt*: Any positive effects?

    c. *Prompt*: Any negative effects?

7. How do you feel about the way in which your cancer doctor communicated your CanSeq gene sequencing results?

a. Prompt: Is there anything your cancer doctor did when sharing the results with you that seemed really good?

b. Prompt: Is there anything your cancer doctor did when sharing the results with you that they could have done better?

8. Have you shared [this result/any of these results] with anyone in your family?

    a. *If yes*: which result or results did you share with someone in your family?

        i. With whom did you share [it/them]?

        ii. *If yes*: What did you tell them? How did they respond?

        iii. *If yes*: How has learning [this result/these results] affected your family members?

    b. *If no*: Why haven't you shared [the result/these results] with anyone in your family?

9. Have you shared [this result/any of these results] with anyone else?

    a. *If yes*: With whom did you share [it/them]?

        i. Prompt: Have you shared [it/them] with any health care providers outside your oncology team?

    b. *If yes*: What did you tell them? How did they respond?

10. Now that you've had gene sequencing done, and received your results, how do you feel about your decision to undergo gene sequencing in the CanSeq study?

11. Is there anything that you wish that you had known before you decided to have gene sequencing in the CanSeq study?

12. Do you have any additional thoughts about how we can help patients decide whether or not to have the kind of gene sequencing that we offer in the CanSeq study?

13. Would you recommend the kind of gene sequencing that we offer in the CanSeq study to other patients?

14. Before I close, I'd like to check in to see if any of the questions that I asked during the interview were upsetting?

    a. Prompt: Can you explain what made the question(s) upsetting?

15. Before we finish, do you have any questions or additional comments for me?

Thank you for taking the time to do this interview with me today! We really appreciate your willingness to help us learn from your experiences in the CanSeq study.