Status Page

PROTOCOL **12-249**

MGH

Closed to accrual

Closure Effective Date: 12/12/2014

DFCI

Open to Accrual

No new subjects may be enrolled in the site(s) as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

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

Office for Human Research Studies

Protocol Front Sheet

DFCI Protocol No.: 12-249

1. PROTOCOL TITLE AND VERSION

Title: The Institutional and Professional Impact of Genomic Sequencing in Cancer Care
Protocol Version No./ Date: Version 6 /11/2014 **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:	Stacy W. Gray, MD, AM	**Phone:**	617 632-4939	**Institution(s):**	DFCI
Site Responsible PI:	Elyse Park, PhD	**Phone:**	617 724-6836	**Institution(s):**	MGH

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

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: NHGRI
Grant #: 1U01HG006492-04
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

CTEP Study: [pull down]

Phase: [pull down]

Multi-Center (i.e., non-DF/HCC site participation)**:**
Yes

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: 57 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No

Total DF/HCC Estimated Enrollment Goal: 57 **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 to

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: 12-249

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

Activation Date: 09/21/12 (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	Protocol and Front Sheet replaced due to Amendment #1	09/20/12	n/a
10/18/12	Front Sheet replaced due to Amendment #2	10/09/12	n/a
10/18/12	Front Sheet replaced due to Amendment #3	10/16/12	n/a
01/08/13	Protocol, Consent Form and Front Sheet replaced due to Amendment #4	12/19/12	01/07/13
04/01/13	Interview Guide and New Physician Post-Disclosure Survey added due to Amendment #5	03/29/13	N/A
04/08/13	Physician Post-Disclosure Survey added due to Amendment #6	04/05/13	N/A
07/01/13	Protocol and Front Sheet replaced due to Amendment #7	06/19/13	n/a
08/20/13	Local appendices replaced due to Amendment #8	08/07/13	n/a
08/27/13	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired.	N/A	N/A
08/27/13	Remove Hold. Study renewal/ Consent Form footer replaced due to Continuing Review #1	08/27/13	N/A
09/06/13	Local appendices replaced due to Amendment #9	08/29/13	n/a
01/24/14	Local appendices replaced due to Amendment #10	01/22/14	n/a
03/06/14	Local appendices replaced due to Amendment #11	02/06/14	n/a
03/06/14	Local appendices replaced due to Amendment #12	03/05/14	n/a
04/02/14	Local appendices replaced due to Amendment #13	03/31/14	n/a
08/05/14	Study renewal/ Consent Form footer replaced due to Continuing Review #2	07/22/14	N/A
08/12/14	Local Appendix (New physician post-disclosure survey-informative results) replaced due to Amendment #14	08/07/14	N/A
12/22/14	MGH has been activated as closed to accrual. Protocol and Front Sheet replaced – due to Amendment #15	12/12/14	N/A
02/02/15	MD Non-Responder and Non-Returning Patient Email added to local appendices due to Amendment #16	01/23/15	N/A
05/29/15	Local Appendices added (Non-returning patient MD Survey link, MD PD nonresponder 2 questions, Report to patient- MD opt out email) – due to Amendment #17	05/15/15	N/A
Date Posted	**Revised Sections**	**IRB Approval Date**	**OnCore Version Date**
07/17/15	Study renewal / Consent Form footer replaced due to Continuing Review #3	06/25/15	06/30/15

The Institutional and Professional Impact of Genomic Sequencing in Cancer Care

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1. BACKGROUND AND SIGNIFICANCE

1.1 Overview

The integration of large-scale genomic sequencing into oncology practice promises to revolutionize cancer care by providing clinicians and patients with more accurate prognostic information, genomically tailored treatments that are more effective and less toxic than conventional chemotherapy, and a refined understanding of inherited cancer susceptibility.[1-3] However, evidence-based models for incorporating these transformative technologies into patient care do not currently exist. The imminence of high-throughput sequencing confronts clinicians, genome scientists and health care institutions with profound technical, clinical, organizational, ethical and psychosocial challenges that must be anticipated and addressed in a rigorous and controlled way before the technology is widely adopted for patient care.

One principal challenge of sequencing derives from the vast amounts of complex data that must be interpreted and incorporated into clinical care. In oncology, the need to perform, analyze and interpret somatic and germline sequencing concurrently magnifies this complexity. Sequencing may reveal mutations in the tumor genome with predictive or prognostic significance, germline mutations that imply cancer predisposition, polymorphisms in drug metabolism enzymes, or incidental findings unrelated to cancer.[4-7] While some sequencing data will relate to genetic variants with clear prognostic or treatment implications, most will relate to variants of uncertain significance.[6,7] The heterogeneity and unpredictability of sequencing data presents novel challenges for clinician-patient communication and medical decision-making. Furthermore, the analysis and interpretation of sequencing data is a moving target; as knowledge about cancer biology and pharmacology evolve, so must the process by which genomic data inform care.[6]

Given that clinical decisions will be based on complex, uncertain, and rapidly evolving information, there is a pressing need to understand oncologists' *attitudes* about and *experiences* with sequencing in cancer care. In addition, because integration of sequencing into care requires the development of institutional systems and guidelines, careful study of the *process* by which decisions are made is essential. The overarching goal of this protocol is to study the impact of the clinical integration of whole-exome sequencing (WES) on oncology providers. The resulting lessons will guide development of the institutional structures that will be needed to support large-scale, evidence-based clinical cancer sequencing programs in the future.

This protocol is a companion to Protocol 12-078, "The use of sequencing to guide the care of cancer patients." Protocol 12-078 outlines the procedures for implementation of WES at DFCI and explores the impact of WES on cancer patients. Some of the data gathered through this protocol will be combined with data gathered through 12-078 for paired analysis.

1.2 Background and Rationale

Genetic testing for cancer susceptibility syndromes has been used in oncology for almost two decades.[8] By identifying, testing and prophylactically treating individuals at high risk for cancer, we have seen dramatic improvements in outcomes for patients who carry high-penetrance mutations in genes related to breast, colon, thyroid and other malignancies.[9-13] Although these advances are important, the reduction in overall cancer burden has been limited due to the low frequency of these mutations in the general population.

Over that same time period, we have learned a great deal about how somatic genetic alterations promote carcinogenesis. Because of advances in knowledge about molecular mechanisms, we have made substantial progress in the treatment of selected malignancies. The natural history of cancers such as chronic myelogenous leukemia, Her-2/neu positive breast cancer and EGFR-mutated lung cancer have been dramatically altered by the development and use of molecularly targeted therapies.[14-21]

The introduction of whole-exome sequencing (WES) into oncology has unprecedented potential to transform patient care. In the setting of advanced cancer, WES may identify well-described mutations in "new" tumor types. Some such mutations may be targeted by FDA-approved drugs, offering patients who currently have few treatment options additional therapeutic choices (e.g., c-kit mutations in thymic cancers, leading to treatment with imatinib).[22] WES will also identify many mutations for which there are drugs in development. Such information will facilitate sophisticated decisions about trial participation, speeding the development of novel agents and expanding therapeutic options. Finally, whole-exome tumor and germline sequencing in parallel will undoubtedly reveal novel mutations that may contribute to carcinogenesis through mechanisms yet to be defined. In the aggregate, these data will help genomic scientists and clinical trial investigators prioritize how novel compounds are screened and tested, potentially shortening the time required to move cancer drugs from "bench" to "bedside."

Despite its transformative potential, WES presents patients, clinicians and health care institutions with complex challenges.[23] A principal difficulty arises from the fact that sequencing produces volumes of data that are orders of magnitude greater than those currently used in medical practice.[2,6,7,24] The storage, assessment and analysis of these data necessitate improvements in health information technology and care delivery systems. Second, much information generated by sequencing will be uncertain in nature.[6,7] Areas of uncertainty will include the roles that specific genetic variants play in disease pathogenesis and progression, the magnitude of effect associated with gene alterations, and the appropriateness of applying genomic information to prevention, screening or treatment decisions.[25] Third, WES will result in unanticipated findings, such as carrier status for various medical conditions, predisposition to cancer or to late-onset disorders unrelated to cancer, and pharmacogenetic variants (Table 1).[6,7] Fourth, germline sequencing has implications not just for individual patients but for their family members; furthermore, current forms of genetic counseling, whether performed by primary care physicians, oncologists or genetic specialists, will be inadequate to meet increased demand.[8]#

WES presents clinicians who care for cancer patients with a myriad of challenges. Oncologists will be faced with test results for which there is no clear standard-of-care practice, unexpected results that have implications for patients' family members, and tests that, although not actionable, significantly alter patients' prognoses. The unpredictable and uncertain nature of sequencing data presents particular challenges related to informed consent. Traditionally, consent for genetic testing emphasizes pre-test counseling during which clinicians disclose the range of possible test results and, when appropriate, the actions that can be taken to reduce or modify disease risk.[8,26,27] At present, WES is incompatible with this model because clinicians cannot anticipate test results or prospectively identify potential medical interventions. Cancer care providers will have to make decisions about how they explain WES to patients, the types of information that

Table 1. Categories of somatic and germline genomic observations

Mutation	Result Category	Implications of Alterations	Biological Impact
Somatic	Predictive	Association with drug efficacy or inefficacy	Patient
	Prognostic/ Diagnostic	Association with cancer type or clinical outcome	
	Alterations of uncertain significance	Unknown	
Germline	Cancer-risk	Association with elevated cancer-risk	Patient and family
	Pharmacogenetic	Association with a phenotype or metabolic state that relates to drug efficacy or adverse drug reactions.	
	Non-cancer predisposition or condition	Association with a predisposition, or condition, unrelated to cancer	
	Carrier state	Association with monogenic disorder (autosomal dominant, recessive, or x-linked)	
	Alterations of uncertain significance	Unknown	

they will disclose to patients as well as about how genomic information will inform their treatment recommendations.

The purpose of the proposed studies is to understand the challenges that oncologists face individually and collectively as they integrate WES into cancer care, the solutions that they develop, and the systems and structures they require in order to deliver genomically-guided cancer care.

2. SPECIFIC AIM

Specific Aim: To describe the practical, clinical, ethical and psychosocial *challenges* that cancer physicians identify when considering somatic and germline whole-exome sequencing, the *process* by which they individually and collectively confront these challenges, and the *solutions* that they implement.

Aim 1a: We will describe the challenges that individual oncologists experience as they integrate sequencing information into clinical care. A mixed methods approach will be used to explore challenges and to describe how oncologists resolve them.

Aim 1b: We will critically examine and describe the process by which key decision-makers, working collaboratively, evaluate somatic and germline genomic sequencing data, confront logistical, clinical, psychosocial, ethical and legal challenges and uncertainties, and guide the integration of those data into clinical cancer care. Ethnographic methods will be used to explore and explain the institutional processes that are used to guide the integration of sequencing data into cancer care.

3. STUDY DESIGN AND METHODS

The proposed research involves a longitudinal study of oncologists. We will use a mixed methods approach, conducting both quantitative surveys and qualitative, in-depth interviews at multiple time points. We will also incorporate ethnographic observation of institutional decision-making bodies charged with guiding the integration of sequencing into patient care. Elements include:

Oncologist surveys and interviews: All participating oncologists will be asked to complete brief surveys prior to the initiation of sequencing in their disease programs (in the context of Protocol 12-078) as well as following each patient visit during which sequencing results may or may not have been disclosed. A subset of oncologists will also participate in in-depth interviews prior to sequencing initiation and after using sequencing in their practices for approximately one year.

Ethnographic observation and feedback: To examine the collaborative process by which key decision-makers evaluate sequence data, confront challenges, and develop policies and guidelines, a trained ethnographer will observe regularly scheduled meetings of the Clinical Genomics Evaluation Committee (CGEC, see details in Protocol 12-078), and will interview committee members as needed to achieve greater depth of understanding.

The proposed mixed methods approach will enable us to systematically assess oncologists' beliefs, attitudes, normative framework, practice patterns, behavioral intentions, and behaviors over time (quantitative surveys), as well as more fully explore personal views about the limitations and benefits of genomic testing (qualitative in-depth interviews). Additionally, ethnographic analysis will allow us to identify the advantages and disadvantages of the structures and processes guiding implementation of sequencing, feed information back to committee members to ensure reflective decision-making, and develop evidence-based recommendations to ensure successful integration of large-scale sequencing programs into cancer care.

4. RESEARCH SUBJECT SELECTION

4.1 Eligibility Requirements for the Oncologist Surveys and Interviews

Primary oncologist population

The eligible population for the proposed study consists of all medical oncologists who engage in clinical care in the Thoracic (approximately 13 oncologists) and Gastrointestinal (GI; approximately 14 oncologists) Cancer Treatment Programs at DFCI. Because data from physicians are central to the aims of Protocol 12-078, physician participation in all study-related activities (including interviews and surveys) will be a requirement for physicians who wish to offer enrollment in the WES study (Protocol 12-078) to their patients. Specifically, data from the oncologist post-disclosure survey will report the type(s) of genomic information that were disclosed during the clinic visit. These data will be paired, at the level of the individual patient-physician dyad, with patient reported data gathered on 12-078 in order to assess one of the primary outcomes of 12-078, patient understanding of disclosed information (Aim 3b).

Two of the oncologists who will participate as subjects are themselves co-investigators on this protocol (Janne, Gray). The study investigators have carefully considered the implications of including these co-investigators as subjects, and have decided to include them for two reasons. First, we believe that it would be unacceptable to disadvantage Dr. Gray's and Dr. Janne's patients by precluding their access to participation in this study. Because one of the eligibility criteria for patient-subjects in protocol 12-078 is that their physician is participating in this companion protocol, excluding these physicians from participation would imply the need to exclude their patients from 12-078. Second, our intent is to represent the experience of the entire thoracic and GI oncology programs in these data, and Drs. Janne and Gray are active clinicians within the thoracic program. We will note the inclusion of these co-investigators as study subjects in all relevant study reports, and will discuss any potential implications of their inclusion for interpretation of our findings.

Population of oncologists who participate in cognitive testing of the draft 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 medical oncologists at DFCI who are not participating in Protocol 12-078 (oncologists in disease centers other than Thoracic and GI). We will offer oncologists a $100 gift card upon completion of the cognitive testing as a thank you for their time and effort.

4.2 Eligibility Requirements for the Ethnographic Observation and Feedback

The eligible population for the proposed ethnographic studies consists of all Members of CGEC. There will be approximately 25 members on the CGEC. CGEC members have expertise in the following areas: genomic science, medical oncology, pediatric oncology, medical genetics, genetic counseling, pathology, bioethics, and bioinformatics. CGEC meetings will also be open to the larger DFCI community including physicians and fellows. CGEC discussions will also include non-CanSeq cases (See protocol 12-078 for details). Non-CGEC members will receive an email invitation clearly indicating that meetings will be audio recorded and observed by an ethnographer and that their de-indentified comments may be used for study purposes. Non-CGEC members will have the option to consent to participate as CGEC members if they are interested in doing so.

5. RESEARCH SUBJECT ENTRY

5.1 Study Entry for the Oncologist Surveys and Interviews

Primary oncologist population

The study investigators (Drs. Gray, Joffe, Garber, Garraway, and Janne) will hold an information session for all eligible oncologists in which they will outline the study's purpose and procedures as well as the

requirements for both patient and physician participation. Additionally, potentially eligible oncologists will receive an electronic letter containing study-related details (Appendix 12.1). Physician informed consent will be obtained by the investigators (Drs. Gray and Joffe) as outlined below.

Population of oncologists who participate in the cognitive testing of the survey instrument

Drs. Gray and Joffe will select approximately 5 medical oncologists at DFCI who are in disease centers other than thoracic or GI based on oncologist availability. Drs. Gray and Joffe will explain the purpose of the cognitive testing to potential subjects in person and in an electronic letter (Appendix 12.2). 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 informed consent for the cognitive testing component of the study.

5.2 Study entry for CGEC Members who will Participate in the Ethnographic Activities

The study investigators (Drs. Gray, Joffe, Garber, Garraway, and Janne) will hold an information session for the CGEC Members in which they outline the purpose of the study, study procedures, requirements for patient participation, requirements for physician participation, and details about the ethnographic component of the study. Additionally, all potentially eligible CGEC Members will receive an electronic letter containing study-related details (Appendix 12.3).Informed consent will be obtained by the investigators (Drs. Gray and Joffe) as outlined below. As mentioned previously, non-CGEC members who are interested in becoming voting members of the committee will be given the option to consent to this protocol.

5.3 Documentation of Informed Consent

Because there a few members of CGEC who are also clinically active oncologists in the thoracic or GI oncology programs, we will have one informed consent document that covers all aspects of this protocol (oncologist surveys, oncologist in-depth interviews, ethnographic observation, and interviews of CGEC members). The informed consent document will cover the study purpose, alternative options, study logistics, and the risks and benefits of the study participation. The consent will provide contact numbers for questions regarding the study. The consent document will be signed by the subject and the investigator to document that the consent process took place. The original consent document will be kept in the study's research file, and a copy will be provided to the subject.

Participation in the in-depth interviews, surveys and group observations is a condition of oncologists' participation in the sequencing project, as well as of CGEC members' involvement with the committee. However, oncologists and potential CGEC members have the option to decline involvement with the WES project if they do not wish to participate in the surveys, interviews, and group observations.

There will be a distinct informed consent process for patient participants as outlined in Protocol 12-078.

6. STUDY PROCEDURES

6.1 Oncologist Surveys

We will administer surveys to all oncologists in the thoracic and GI centers at two time points: a) prior to the initiation of WES in the oncologist's clinic (once per physician); and b) following each clinic visit during which sequence-based test result information may or may not have been disclosed to a participating patient.

Individuals who are investigators on this protocol will not participate in the baseline survey.

Survey refinement and data collection: As noted above, the first phase of the project consisted of cognitive testing of the draft survey instruments. The purpose of the cognitive testing was to refine the oncologist surveys based on feedback from clinically active oncologists.

Five DFCI MDs (4 male, 1 female) participated in the cognitive testing of these surveys. Participants completed each survey (baseline, post-disclosure) as they would if they were completing it in the study proper. Time to completion for each survey type was recorded. After completing each of the baseline and follow-up surveys, participants were asked open-ended questions including: their general reaction to the survey, what they thought of the length of the survey, the overall ease of answering questions and their suggestions for improving the items.

All participants completed each survey (baseline, follow-up) in less than 10 minutes. They all noted that the questions were 'fine' and easy to understand and respond to. No one had any difficulties using the response options for any of the questions. No one thought that the surveys were too long although 1 person did note that the post-disclosure informative survey would be burdensome if s/he had to response to these weekly.

Several participants made suggestions about how the survey might be improved. These were analyzed by Martins (survey methodologist) to identify common suggestions. Suggestions were then reviewed by Gray, Joffe and Martins to identify those that were relevant and appropriate. Based on these suggestions, the revised surveys include the following changes:

Baseline:

- Name of the sequencing program specified
- Identify whether the hypothetical patient has children

- Identifying MDs 'philosophical' orientation about the return of sequencing results to patients

Post-Disclosure:

- Streamlined the questions & skip patterns around whether the MD has received results and disclosed. When programmed as a web survey, the new skip patterns will reduce respondent burden.
- Added additional categories to why MDs may not have disclosed
- Streamlined questions and skip patterns around challenges in interpretation of results, actions taken and confidence in actions. When programmed as a web survey, the new skip patterns will reduce respondent burden.

Following the completion of approximately 50 post-disclosure surveys, the investigators will meet again to evaluate possible item reduction.

The baseline oncologist survey (Appendix 12.4) will be offered at the time of consent (on paper) or it can be filled out electronically. If the baseline oncologist survey is not completed at the time of consent, a brief email will be sent to participants that contains a link to the survey instrument (Appendix 12.5). Electronic reminders for the baseline survey will be sent out at one-week intervals until the survey has been completed (Appendix 12.6). After 3 contacts, the investigators will call non-responding physicians to encourage baseline survey completion.

6.1.1 Survey measures

The primary outcome from the oncologist surveys is the physician's report of the challenges that she or he faced in considering the results of WES and in disclosing the information to the patient. This information will be derived from the post-disclosure surveys. Examples of challenges that will be queried specifically will include: clinical challenges (e.g. uncertainty related to treatment recommendations based on genomic data), psychosocial challenges (e.g. difficulty of revealing non-actionable or adverse prognostic information), communication challenges (e.g. lack of patient understanding of test results), ethical and legal challenges (e.g. patients' desire for non-disclosure of germline risk information, disclosure of germline information to patients' family members after patient death), etc. Oncologists will be offered the ability to select from among pre-specified response options; they will also be able to identify other challenges, or to explain their answers to closed-ended questions, using free text. This information will be collected in the post-disclosure oncologist survey (Appendix 12.7). Physicians who receive results that their patient's sequencing contained no informative somatic or germline alternations will also receive a post-disclosure survey (Appendix 12.8). These data will be enriched by findings from the qualitative physician interviews, as described below. To decrease burden, the post-disclosure surveys will be administered electronically. The email notification for the post-disclosure survey will be sent out the day following the patient's clinic appointment where results may or may not have been disclosed (Appendix 12.9). Reminder emails will then be sent every 3 days until completion of the post-disclosure survey (Appendix 12.10). After 4 email contacts, a member of the study team will call physicians to help facilitate post-disclosure survey completion. Even if results were not disclosed at the patient's visit, the oncologist will still be asked to complete the post-disclosure survey. Oncologists will continue to receive subsequent notifications to complete the post-disclosure survey after each clinic visit until results have been disclosed or the physician states that he or she has decided against returning results to the patient.

Table 2

	Baseline	**Post-disclosure**
Predictors and Covariates		
Socio-demographics[28]	X	
Current use of genetic testing[28]	X	
Intentions to disclose genomic information	X	
Confidence in understanding, explaining and managing somatic and germline genetic information	X	
Information-seeking		X
Satisfaction with MD/patient communication		X
Confidence in recommendations		X
Treatment modifications		X
Disclosure of genomic information to patients		X
Outcome Measures		
Challenges confronted during disclosure process		X

Baseline surveys will assess physicians' baseline attitudes and behaviors towards genetic testing and genomic information (Table 2). Specifically, oncologists will be asked to report their current use of genetic testing and their views about disclosing these results. If appropriate, these measures may be used as covariates in the statistical analyses.

We will also physicians an email, when a patient of theirs enrolls, to notify him/her of the enrollment and to ask if s/he has any specific questions that she hopes the sequencing will answer.

6.2 Oncologist Qualitative in-Depth Interviews

Selection of study subjects: A sub-sample of approximately 20 oncologists (thoracic and colorectal) who are participating in the study will be selected to participate in in-depth qualitative interviews prior to the initiation of WES and after 1 year of experience incorporating sequencing into their practices.

Study investigators will not participate as subjects in the oncologist in-depth interviews.

Data collection: All in-depth qualitative interviews will take place in person or, when necessary, by telephone. To decrease physician burden, physicians participating in in-depth interviews at baseline 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. Lara Traeger, a psychologist working under Dr. Park's supervision, and qualitative research staff from the DFCI Survey Core. All interviews will be tape recorded and transcribed for analysis. Invitations will be sent via email for the baseline interview (Appendix 12.11) and for the one-year follow up interview (Appendix 12.12).

In-depth interview guide development and domains of interest: Dr. Park will pilot test the baseline interview guide (Appendix 12.13) and 1 year post-disclosure interview guide with approximately 2-3 oncologists in each disease group to ensure question clarity and comprehensiveness. The guide will be revised as needed. During the interviews, oncologists will respond to a series of open-ended questions and probes related to the following domains:

- **Baseline interview**: Assessment of 1) expectations related to WES, 2) anticipated benefits and challenges of sequencing, and 3) intentions to disclose sequencing results to patients**.**
- **Interview after 1 year of genomic sequencing integration**: Assessment of 1) benefits and challenges encountered with WES, 2) the factors that were most helpful in overcoming sequencing-related challenges, 3) reflections on cases in which predictive, prognostic, cancer susceptibility and incidental genomic test findings were disclosed (or decisions were made not to disclose), and 4) the structures or procedures that would be needed to improve integration of sequencing into care. (Note to IRB: This interview guide will be developed and submitted as an amendment at a later date.)

6.3 Ethnographic Studies

Initially, the CGEC acted as the central institutional body charged with developing the criteria to be used in determining which genomic alterations are potentially medically relevant or actionable. Specifically, CGEC decided which results from sequencing would undergo confirmation in a CLIA-certified laboratory, and would guide which results should be returned to oncologists. CGEC has evolved over time. This evolution was driven by an increasingly consistent committee approach to return somatic results and movement towards the availability of a CLIA exome. Guidelines for return of straightforward findings are based on CGEC practice and the evolving field of genomics and have been developed in collaboration with the CGEC, expert reviewers and study investigators. Going forward CGEC will review annotated lists of somatic and germline genetic alterations identified from sequencing only for unique, complex or otherwise interesting cases. For these cases the committee will make a collective recommendation as to which genomic findings warrant confirmation in a CLIA laboratory (if not already sequenced in a CLIA laboratory) and return to the clinical team (see protocol 12-078 for additional information). The committee's deliberations will also result in the development of policies and institutional practice guidelines over time. Decisions made by this committee will have a profound impact on test validation and test utilization procedures as well as on the questions and decisions that oncologists and patients face. The process of deriving "case law" and of designing and implementing systems that meet the needs of patients, clinicians and the institution will contain innumerable lessons that, if captured, synthesized and disseminated, will inform and smooth the integration of sequencing into cancer care beyond the walls of DFCI. We will extract and share these lessons by conducting extensive ethnographic observation and analysis of CGEC's activities and deliberations to understand the individual, system, and scientific factors that the committee considers when confronting clinical, psychosocial and ethical uncertainty or dilemmas.

6.3.1 In-depth field observation

Dr. McGraw, an expert in ethnographic methods, will observe regularly scheduled CGEC meetings for an average of 6 meetings a year. She will write field notes on each meeting, noting:

members present at the meeting; member interactions; topics covered during the meeting and those tabled for later meetings; agreements and disagreements arising during deliberations; and rationales given for opinions expressed. Meetings will be tape-recorded and transcribed for adequate data capture.

6.3.2 Interviews of key decision-makers on the Cancer Genomics Evaluation Committee

In order to develop a better appreciation for the factors that individual committee members consider when evaluating WES data, Dr. McGraw will supplement observation of CGEC meetings with interviews of CGEC members. We anticipate an average of six interviews per year interviewing each CGEC member approximately once or twice over the course of the 4 year observation period. Dr. McGraw will complete interviews in person at DFCI, or by telephone if necessary. The interviews will be digitally recorded and transcribed. The purpose of the interviews is to explore, in greater depth, individual points of view on committee deliberations and decisions. Questions will elicit information about each respondents own interpretation of key dilemmas encountered during preceding meetings, differences of opinion; the potential benefits and challenges of various policy options and of choices regarding individual patients; and handling of uncertain or difficult-to-interpret information. The interview guide will be submitted to the IRB as an amendment prior to initiation of the interviews of CGEC members.

6.3.3 Domains of interest

Individual CGEC members will bring to the committee process their own perspectives and priorities informed by the norms, values, and belief systems of their disciplines and cultural backgrounds. These varying perspectives will play a role in shaping the quality, content and outcomes of the deliberations. The domains of focus in this ethnographic study of the CGEC will include: 1) types of decisions faced by the committee; 2) the reasoning underlying their recommendations and the principles applied in making their decisions; 3) values emphasized or de-emphasized in the deliberations; 4) procedures employed to reconcile differences in opinion; and 5) members' perceptions about the deliberation process and resulting recommendations.

7. BIOSTATISTICAL ANALYSES

7.1 Analysis Plan

7.1.1 Analysis of oncologist surveys

There are several endpoints including current use of genetic testing, which will be treated as a continuous variable; intentions to disclose genomic information, which will be treated as an ordered categorical or dichotomous variable; confidence in understanding, explaining and managing somatic and germline genetic information, which will be treated as an ordered categorical or dichotomous variable; and challenges oncologists face, which will be treated as an ordered categorical or dichotomous variable. The first analytic task will be to evaluate measurement quality and generate descriptive statistics. Our second analytic task will be to explore the relationships between variables. The third analytic task will be summarization of data. Our general approach to data analyses includes:

- estimating proportions and calculating 95% CIs
- summarizing continuous variables, by physician characteristics (e.g., gender, type of oncology practice) and overall, using descriptive statistics
- determining correlation coefficients and generating cross-tabulations to describe relationships between endpoints.

We will perform additional sensitivity analyses for the challenges endpoint, excluding data from investigators on this protocol, to evaluate potential bias. If results including investigator data differ from those excluding investigator data, these differences will be noted. In addition, all study reports that include data from subjects who are co-investigators will note this fact in the publication and will comment on the issues raised in discussing the limitations of the analysis.

No investigator data will be collected for baseline survey measures, including current use of genetic testing, intentions to disclose genomic information and confidence in understanding, therefore no sensitivity analyses will be performed for these endpoints.

Aim 1a: Oncologists will identify numerous clinical, psychosocial, and ethical challenges as they evaluate and disclose the results of genomic tests to patients. At the post-disclosure time point, we will ask oncologists about the challenges that they faced in evaluating and disclosing sequencing results to their patients. As oncologists will be asked to provide this information for each of their patients, data are expected for each of up to 400 post-disclosure surveys (some patients may not receive disclosure of results, due either to lack of findings that meet the threshold for disclosure or to patient preferences). The frequency and nature of challenges identified may vary by characteristics of the information (e.g., somatic versus germline information) or by characteristics of the patient (e.g., education, clinical status). In addition, oncologists may face multiple challenges in the same setting. To describe the overall experience of oncologists, the frequency of each type of challenge will be summarized using proportions. Proportions will also be reported grouping disclosure visits in several ways such as characteristics of the disclosure (e.g., subtypes of somatic vs. germline information). In exploratory analyses, we will also examine whether the challenges identified vary by disease group (lung, colorectal) or by patient sociodemographic or other characteristics.

7.1.2 Analysis of the oncologist in-depth interviews

Drs. Gray, Joffe, and Park will read all transcripts for completeness. Transcripts will be uploaded into NVivo 9; attributes will be coded for each participant. Analysis of the oncologist data will also be conducted using content analysis to explore the domains outlined above. For each oncologist, baseline and 1-year follow-up comparisons will be conducted. In addition, all oncologist analyses will be conducted by stratifying the two cancer types. 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. 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.

7.1.3 Analysis of the ethnographic study

There are two objectives for the analysis of the ethnographic data: 1) to describe the committee's collective decision making process and the factors which shaped the process and summarize these findings in periodic observation reports that will inform CGEC's evolving processes; and 2) to derive lessons learned from the overall process to inform similar efforts in the future and disseminate these findings through publication of manuscripts. Both inductive and deductive analytic approaches will be employed.[30-33] The field notes and transcripts of interviews and meetings will be imported into Atlas.ti to facilitate analysis.

Periodic Observation Reports: We will produce an annual observation report each year, as well as one final report, that will be provided to CGEC members. We anticipate that this schedule will match the pace and significance of committee decisions, which will be greatest in year 1.

The analysis of the ethnographic data for these reports will proceed in an iterative sequence. Dr. McGraw and a second coder will begin with open-ended readings of the transcripts and field notes gathered in the first quarter. Through this reading, the coders will identify and apply an initial or start list of codes that best captures ideas in the material. This analysis will cover notes about procedural issues (e.g. key committee decisions at each meeting, logistical challenges reported by committee members in

carrying out committee-related work) and conceptual issues (e.g. challenges and uncertainties they report in interpreting and integrating data and making decisions regarding validation).

In a second pass through the transcripts, the coders will use a deductive approach by coding for text relevant to the domains of interest: (1) types of decisions faced by the committee; 2) the reasoning underlying their recommendations and the principles applied in making their decisions; 3) values emphasized or de-emphasized in the deliberations; 4) procedures employed to reconcile differences in opinion; and 5) members' perceptions about the deliberation process and resulting recommendations. The two coders will read and code independently with biweekly meetings to compare coding, reconcile discrepancies, and clarify definitions. In a final round of coding, Dr. McGraw will apply the set of codes identified through the process outlined above to the full set of transcripts and field notes.

The results of these analyses will be summarized in the first observation report. We anticipate that the report will summarize: 1) decisions faced by the committee and recommendations made; 2) differences of opinion among the committee members; 3) the most challenging or controversial decisions; 4) decisions or topics generating limited or no controversy; and 5) emerging concepts not previously identified. Committee members and study co-investigators will be asked to read the report and comment on the accuracy of the interpretations and suggest alternative interpretations and additional domains of interest. In addition, each report will be placed on the agenda for discussion at the next CGEC meeting after it is provided to members for review.

Analyses for subsequent reports will build on the existing code list, which will continually be refined as new themes emerge in later analyses and as CGEC members respond to reports. As new codes are identified, transcripts and field notes gathered in previous quarters will be re-coded as necessary to incorporate the emerging codes.

Review of findings by those who were studied is a form of analytic triangulation and follows in the tradition of collaborative and participatory research.[34] Eliciting respondents' reactions to the themes and interpretation of the findings is one method of assessing the face validity of the findings.

Lessons Learned: In the final year of the project, analyses will focus on lessons learned in the committee process. The analysis employed at this stage will build on the coding and analyses of the preceding years. In addition, we will use axial coding to further develop themes and examine inter-relationships among them.[31] Of particular interest will be themes in the deliberations such as: "clinical action considered," "prognostic implications," "psychosocial concerns," "family implications," "ethical concerns," "legal concerns," "financial concerns" (i.e., for the patient, family, cancer center or third-party payer), and "logistical concerns." In addition, we will explore changes in committee process over time and changes in the principles applied by the committee in making individual-patient and policy decisions.

We will draw on the results of each annual report and the final lessons learned to suggest recommendations for future CGEC deliberations procedures and the organization of similar committees in other settings. These recommendations will build on an understanding of what procedures seemed to optimize or inhibit thorough deliberation of issues among a broad complement of committee membership.

7.2 Sample Size Requirements

We recruited 5 oncologists in disease centers other than GI and thoracic for the cognitive testing of the draft survey instruments. The sample size for cognitive testing was based on standard procedures for survey pre-testing.

For the primary study, all oncologists who are participating in the WES clinical sequencing program outlined under Protocol 12-078 and all CGEC Members will be invited to participate in this study. The estimated sample size for the primary study is 52 (27 physicians in the thoracic and GI programs, 25 CGEC members). The sample size represents all physicians who are eligible to enroll from the two

clinical centers and the entire CGEC committee, so is a census of individuals who can participate, as outlined under Research Subject Selection, Section 4.

8. RISKS AND DISCOMFORTS

Participation in the oncologist surveys, the oncologist in-depth interviews and the ethnographic study involves minimal risk to participants. We anticipate no physical risks to participating in this study. The potential for loss of confidentiality of data collected exists. To minimize the potential for loss of confidentiality, we will employ multiple safeguards. In-depth interviews will be administered by trained interviewers and facilitated by the Survey Core. Each participant will be assigned a unique study identification number that will be stored separately from personal identifiers. All data, including 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.

9. POTENTIAL BENEFITS

Although the surveys, interviews and group observations are not designed to benefit oncologists and CGEC members directly, selected aggregate information derived from the studies outlined in this protocol may be fed back to oncologists and to CGEC throughout the duration of the clinical sequencing program (Protocol 12-078). Thus we anticipate that physicians and CGEC members may derive educational benefit from these activities, and that the information gained may help them improve their practices and activities as clinicians and CGEC members. The information gained from the surveys, interviews and ethnographic observations of the CGEC deliberations will help us to refine our systems for clinical integration of genomic data into oncology care. Only group-level information will be shared with physicians and CGEC; no information that is potentially individually identifying of either patients or providers will be returned.

10. MONITORING AND QUALITY ASSURANCE

Drs. Gray and Joffe will serve as the co-principal investigators for the studies outlined in this protocol and will be responsible for monitoring research data. Drs. Gray and Joffe will work closely with the DFCI Survey & Data Management Core and with Drs. Park, Traeger, Najita and McGraw to ensure adequate monitoring of the study.

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12. APPENDICES

12.1 Email Notification to Oncologists about Study Implementation Information Sessions

Dear Dr. [last name],

We are writing to notify you about an upcoming study, "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care" in the thoracic and gastrointestinal oncology programs and to invite you to a study implementation information session. You are being invited to participate in this study because you are a medical oncologist who engages in clinical care in the Thoracic or Gastrointestinal Cancer Treatment Programs at DFCI.

Participation in this companion study of physicians (including interviews and surveys) is a requirement for physicians who wish to offer enrollment in the whole-exome sequencing study (Protocol 12-078) to their patients.

During the information session the study investigators (Drs. Gray, Joffe, Garber, Garraway, and Janne) will outline the study's purpose and procedures as well as the requirements for both patient and physician participation.

The aim of this study is to describe the practical, clinical, ethical and psychosocial challenges that cancer physicians identify when considering somatic and germline whole-exome sequencing, the process by which they individually and collectively confront these challenges, and the solutions that they implement.

This research involves a longitudinal study of oncologists. It will include both brief quantitative surveys at multiple time points and up to two qualitative interviews. Also, the study will incorporate observation by a trained ethnographer of the institutional committee charged with guiding the integration of sequencing into patient care.

Information sessions will be held on the following dates:

[To IRB: dates and locations to be determined]

You may reply to this email at stacyw_gray@dfci.harvard.edu or steven_joffe@dfci.harvard.edu to let us know about your willingness to attend one of the information sessions noted above. Also, please feel free to contact either of us if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.2 Email Invitation to Oncologists to Participate in Cognitive Testing

Dear Dr. [last name],

We are writing to invite you to participate in an [in-person/telephone] interview regarding our study "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care."

These interviews will help us develop a survey instrument that we will use to administer to all oncologists in the thoracic and GI centers who participate in Protocol 12-078, "The Use of Sequencing to Guide the Care of Cancer Patients."

The interview will take approximately 30 minutes and can be scheduled at your convenience. During the interview we will ask you to complete the draft survey instrument. Afterward, we will ask how you understood and interpreted the instructions and questions. We may ask you how you arrived at your answers and if you have any suggestions for how we might improve the survey questions. By doing this interview, you will help us to assess the clarity of the survey and to identify any problems.

The interviews will be conducted by Dr. Yolanda Martins or Mr. Josh Gagne of the DFCI Survey and Data Management Core. We expect approximately five oncologists to participate in this phase of the study.

To thank you for your time and effort, we will offer you a $100 gift card upon completion of the interview.

You may reply to this email at stacyw_gray@dfci.harvard.edu or steven_joffe@dfci.harvard.edu to let us know about your willingness to participate in the interview. Also, please feel free to contact either of us if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.3 Email Invitation to Attend an Initial Clinical Genomics Evaluation Committee Meeting

Dear Dr. [last name],

You were recently asked to become a member of the Clinical Genomics Evaluation Committee at the Dana-Farber Cancer Institute for "The Use of Sequencing to Guide the Care of Cancer Patients" (Protocol 12-078). In order to participate in the Clinical Genomics Evaluation Committee (CGEC), we are asking you to enroll in the study, "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care."

The components of the study for CGEC members will include up to two qualitative interviews and observations of CGEC meetings by a trained ethnographer.

During one of the initial CGEC meetings the study investigators (Drs. Gray, Joffe, Garber, Garraway, and Janne) will outline the study's purpose and procedures as well as the requirements for both patient and physician participation.

The aim of this study is to describe the practical, clinical, ethical and psychosocial challenges that cancer physicians identify when considering somatic and germline whole-exome sequencing, the process by which they individually and collectively confront these challenges, and the solutions that they implement.

CGEC meetings will be held on the following dates:

[To IRB: dates and locations to be determined]

You may reply to this email at stacyw_gray@dfci.harvard.edu or steven_joffe@dfci.harvard.edu to let us know about your willingness to attend one of the initial CGEC meetings noted above. Also, please feel free to contact either of us if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.4 Physician Baseline Survey

Physician Baseline Survey

Thank you for agreeing to participate in our study on the use of whole-exome sequencing in cancer care. To begin, we would appreciate it if you would complete this short questionnaire about your current use of genomic testing and about how you expect to use sequencing in your clinical practice.

Please indicate the extent to which you agree or disagree with the following statements about the return of genomic sequencing information to patients:

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
Patients should *only* be offered their genomic sequence results if evidence demonstrates that actions based on the results can change patient management decisions and improve net health outcomes					
Patients should be offered genomic sequence results for which there is an *established relationship between genotype and phenotype* (e.g., results can be used to diagnose a disorder or to assess risk for a disease), even if the results do not alter management decisions or improve net health outcomes.					
Patients should be *offered as many of their genomic sequence results as they want*, up to and including their raw genomic sequence data					

Through the use of whole-exome sequencing of **tumor DNA**, oncologists may find somatic alterations with various implications. Somatic alterations may…

- Provide **information that may be relevant to cancer treatment**. For example, somatic alterations may help to inform decisions about:
    - FDA approved targeted therapies (e.g., EGFR mutations in a patient with advanced lung cancer; KRAS mutations in a patient with advanced colorectal cancer),

      and/or

    - Clinical trials of targeted therapies (e.g., BRAF mutations in patients with advanced lung cancer, PIK3CA mutations in advanced colorectal cancer)
- Provide **information relevant to the patient's prognosis** (e.g., IDH1 mutations in glioblastoma multiforme)

Below are scenarios describing a particular type of genomic alteration derived from sequencing the patient's tumor DNA. **Assume:**

- the tumor DNA belongs to YOUR adult patient with a metastatic solid tumor
- the sequencing was performed in a clinically certified (i.e., CLIA) lab
- the patient is currently receiving a first-line standard chemotherapy regimen
- the patient has an ECOG performance status of 0 or 1
- the patient has indicated that s/he would like to be told about all clinically valid genomic results

Please check the box that reflects how likely you would be to disclose the information described in each scenario to your patient. *Please read each scenario carefully.*

Sequencing of tumor DNA identifies a somatic alteration that…	**In this situation, I would…**				
	Definitely disclose	**Probably disclose**	**Probably not disclose**	**Definitely not disclose**	**Unsure**
1. Is in a pathway that is *not* targeted by any FDA-approved agent. However, an agent that targets this pathway is currently being studied in a phase II clinical trial that's open at your institution. Your patient may be eligible for this trial.	☐	☐	☐	☐	☐
2. Is in a pathway that is targeted by a commercially available agent that is FDA-approved *for a different cancer*. There are no reports in the literature of agents that target this pathway being used in your patient's type of cancer.	☐	☐	☐	☐	☐
3. Is known to confer a *favorable* prognosis, compared with the average for patients with this condition. There are no available agents, either commercially or through a clinical trial, that target the relevant pathway.	☐	☐	☐	☐	☐
4. Is known to confer an *unfavorable* prognosis, compared with the average for patients with this condition. There are no available agents, either commercially or through a clinical trial, that target the relevant pathway.	☐	☐	☐	☐	☐

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Whole-exome sequencing to identify somatic mutations is enhanced by sequencing patients' germline DNA in parallel. Sequencing of patients' **germline DNA** may incidentally identify information about hereditary genetic alterations with varying implications for the patient and/or the patient's family.

Below are scenarios describing types of hereditary genetic alterations that might be identified during the process of whole-exome sequencing in the patient with a metastatic solid tumor described above. *Please read each scenario carefully and think about the implications of the information for both your patient and the patient's family.*

For each scenario, please check the box that reflects how likely you would be to disclose the information described to your patient and/or family. In answering these questions, please assume your patient has biological children.

Sequencing of germline DNA identifies…	**In this situation, I would…**				
	Definitely disclose	**Probably disclose**	**Probably not disclose**	**Definitely not disclose**	**Unsure**
5. An alteration in a cancer risk gene for which risk reduction strategies *are* available.	☐	☐	☐	☐	☐
6. An alteration in a cancer risk gene for which risk reduction strategies *are not* available.	☐	☐	☐	☐	☐
7. A pharmacogenetic polymorphism that impacts the metabolism of *anti-cancer* medications that may be relevant to your patient's care.	☐	☐	☐	☐	☐
8. A pharmacogenetic polymorphism that impacts the metabolism of *non-cancer-related* medications that may be relevant to your patient's care.	☐	☐	☐	☐	☐
9. An alteration that confers an increased risk of developing a condition, other than cancer, for which risk reduction strategies *are* available.	☐	☐	☐	☐	☐
10. An alteration that confers an increased risk for developing a condition, other than cancer, for which risk reduction strategies *are not* available.	☐	☐	☐	☐	☐
11. An alteration that identifies your patient as a carrier of a non-cancer-related condition that might be passed on to a child.	☐	☐	☐	☐	☐

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The next set of questions is about you and your experience with genomic information.

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Please indicate how confident you are in your…	**Very confident**	**Moderately confident**	**A little confident**	**Not Confident at All**
12. Ability to interpret somatic (tumor) genomic results in your disease area.	☐	☐#	☐#	☐#
13. Ability to explain somatic genomic concepts to patients.	☐#	☐#	☐#	☐#
14. Ability to make treatment recommendations based on somatic genomic information.	☐#	☐#	☐#	☐#
15. Ability to identify consultants who have special expertise in integrating somatic genomic information into patients' care.	☐#	☐#	☐#	☐#
16. Ability to provide psychosocial support related to coping with a somatic alteration that has adverse prognostic implications.	☐#	☐#	☐#	☐#

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Please indicate how confident you are in your ability to carry out each of the following tasks related to germline genetic conditions:	**Very confident**	**Moderately confident**	**A little confident**	**Not confident at all**
17. Take a family history.	☐	☐#	☐#	☐#
18. Identify a family history of a potentially inherited condition.	☐#	☐#	☐#	☐#
19. Identify an autosomal dominant family pattern.	☐#	☐#	☐#	☐#
20. Explain an autosomal dominant family pattern to a patient.	☐#	☐#	☐#	☐#
21. Counsel an individual with a family history of an inherited cancer risk syndrome to decide whether or not to have presymptomatic genetic testing.	☐#	☐#	☐#	☐#
22. Provide psychosocial support related to coping with a genetic test result that confirms the presence of an inherited cancer risk syndrome.	☐#	☐#	☐#	☐#
23. Identify specialist genetic services in your local area.	☐#	☐#	☐#	☐#
24. Obtain informed consent before taking blood for DNA testing to evaluate for an inherited cancer risk syndrome.	☐#	☐#	☐#	☐#

#
#
#
#

#
The next set of questions is about your use of genomics in practice.

On average, how many times a year do you *order or interpret* the following types of genetic or genomic tests in your clinical practice?

Include both cases in which you order the test yourself and cases in which you use or interpret the results of tests ordered by others.
#
#

		Approximate Number of Times Per Year
25.	Somatic tests to evaluate for alterations in tumor DNA.	___
26.	Germline tests to evaluate for inherited cancer predisposition syndromes.	___
27.	Germline tests to evaluate for pharmacogenetic polymorphisms (i.e., that affect drug metabolism or toxicity) related to *cancer drugs*.	___
28.	Germline tests to evaluate for pharmacogenetic polymorphisms related to *non-cancer drugs*.	___
29.	Germline tests to evaluate for inherited conditions *unrelated to cancer.*	___
30.	Germline tests to evaluate whether a patient is a carrier of a non-cancer-related condition that might be passed on to a child.	___

#
The final set of questions is about you:

31. Do you consider yourself Hispanic or Latino/a?

- ☐ Yes, Hispanic or Latino/a
- ☐ No

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

- ☐ American Indian or Native American
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or other Pacific Islander
- ☐ White

33. In what year did you complete fellowship training?

_____ (year)

34. What is your gender?

- ☐ Male
- ☐ Female

35. On average, how many unique patients do you see for treatment or evaluation each month? Please include both new and established patients. Your best estimate is fine.

_____ number

36. Are you a principal investigator for research in any of in the following areas? (response options no/yes)

a. Clinical trials research
b. Translational science research
c. Basic science research
d. Outcomes or health services research

e. Other research (specify)

37. During a typical month, approximately what percent of your professional time do you spend in the following activities?

a. Providing patient care _____percent of time
b. Research _____percent of time
c. Teaching _____percent of time
d. Administration _____percent of time

Do you have any additional thoughts that you wish to share about the issues raised in this survey? Please feel free to write in the space below as we welcome your feedback.

(Provide text entry box)

Thank you very much for completing this survey! Your participation is greatly appreciated. #

12.5 Email Notification to Oncologists to Complete the Baseline Survey

Dear Dr. [last name],

You recently attended an information session regarding our study, "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care." During this session we outlined the study purpose and procedures.

We are now writing to request that you complete the baseline survey for this study. Participation in this study (including interviews and surveys) is a requirement for physicians who wish to offer enrollment in the whole-exome sequencing study (Protocol 12-078) to their patients.

The baseline survey can be accessed at:

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

You will also receive an email notification to complete a brief survey after each clinic visit with a patient for whom you received whole-exome sequencing results.

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

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.6 Follow up Email Notification to Oncologists to Complete the Baseline Survey

Dear Dr. [last name],

We recently sent you an email requesting that you complete the baseline survey for our study "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care." According to our records, you have not completed the baseline survey. We are now writing to request that you complete the survey at your earliest convenience.

The baseline survey can be accessed at:

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

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

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-529

12.7 Email Notification to Oncologists to Complete the Post-disclosure Survey

Dear Dr. [last name],

We are writing because you may recently have received results from whole-exome sequencing for your patient named below, as part of the "The Use of Sequencing to Guide the Care of Cancer Patients" (Protocol 12-078) study. According to our records your most recent visit with this patient occurred recently. Regardless of whether results were returned at this visit we ask you to complete a brief survey for our study.

Patient Name: [PATIENT NAME] Date of Visit: [DATE OF PATIENT VIST]

MRN: [PATIENT MRN]

The survey can be accessed at:

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

If results were not returned at this visit, you may receive another request to complete a survey after subsequent clinic visits or interactions.

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

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.8 Reminder Email Notification to Oncologists to Complete the Post-disclosure Survey

Dear Dr. [last name],

We recently sent you an email requesting that you complete a brief survey for your patient named below. According to our records, you have not yet completed the survey. We are now writing to request that you complete the survey at your earliest convenience.

Patient Name: [PATIENT NAME] Date of Visit: [DATE OF PATIENT VIST]

MRN: [PATIENT MRN]

The survey can be accessed at:

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

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

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.9 Email Invitation for the Baseline Qualitative Interview

Dear Dr. [last name],

We are writing to invite you to participate in an [in-person/telephone] interview. This interview is a component of our study "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care" in which you are enrolled.

Interviews will be conducted prior to the initiation of whole-exome sequencing in your practice. We expect a sub-sample of approximately 20 oncologists (thoracic and GI) to participate.

We hope that these baseline interviews will help us to understand your expectations for WES, what you think might be the benefits and challenges of WES, and your intentions related to test result disclosure.

Interviews will take about 45 minutes and will be conducted by Drs. Yolanda Martins, Elyse Park, Lara Traeger, or Mr. Josh Gagne. Interviews will be recorded and later transcribed.

You may reply to this email at stacyw_gray@dfci.harvard.edu or steven_joffe@dfci.harvard.edu to let us know about your willingness to participate in the interview. Also, please feel free to contact either of us if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.10 Email Invitation for the One-Year Follow up Qualitative Interview

Dear Dr. [last name],

We are writing to invite you to participate in an [in-person/telephone] interview. This interview is a component of our study "The Institutional and Professional Impact of Genomic Sequencing in Cancer Care" in which you are enrolled.

Interviews are being conducted about one year after you have used whole-exome sequencing in your practice. We expect a sub-sample of approximately 20 oncologists (thoracic and GI) to participate.

We hope that you will be able to provide us with an assessment of the benefits and challenges you have encountered with WES, the factors that were helpful in overcoming sequencing related challenges, reflections on different types of WES cases, and how we might improve the use of WES going forward.

Interviews will take about 45 minutes and will be conducted by Drs. Yolanda Martins, Elyse Park, Lara Traeger, or Mr. Josh Gagne. Interviews will be recorded and later transcribed.

You may reply to this email at stacyw_gray@dfci.harvard.edu or steven_joffe@dfci.harvard.edu to let us know about your willingness to participate in the interview. Also, please feel free to contact either of us if you have any questions.

Thank you for your consideration,

Stacy Gray, MD, AM
617 632-6049

Steven Joffe, MD, MPH
617 632-5295

12.11 Patient Enrollment Confirmation Email

Dear Dr. _____:

We are writing to notify you that your patient, [NAME, DFCI MRN #], has consented to enroll on the CanSeq study (protocol 12-078). As you know, this protocol involves whole-exome sequencing of tumor and matched germline DNA. Findings from this sequencing that are judged by the Cancer Genomics Evaluation Committee (CGEC) to be clinically informative, and that are consistent with the patient's preferences, will be returned to you once they are confirmed.

In interpreting the genomic data, it would help us to know if there are any specific clinical questions you are hoping will be answered or informed by the results of tumor or germline sequencing. If so, please respond to this email with a brief description of your question(s).

Thanks,

The CanSeq Team

Qualitative Baseline Interview Guide

U01 MD Baseline In-Depth Interview Questions

You recently agreed to participate in a study that aims to explore the use of whole exome sequencing (WES) in the care of lung/colon cancer patients. WES is different from the current PROFILE study in a couple of ways. First, whereas PROFILE focuses on a defined set of alterations in a limited set of cancer-related genes, WES can detect alterations in the coding regions of any gene. Second, PROFILE currently only looks at the somatic, or tumor, genome. In contrast, for this study, we will be conducting WES of both the tumor and the germline genomes. In this interview, we will be asking about your expectations regarding sequencing of both tumor DNA and germline DNA.

All alterations will be reviewed by the newly formed Cancer Genomics Evaluation Committee at the Dana-Farber Cancer Institute and confirmed in a CLIA lab before they are returned to the treating oncologist.

I am going to ask you some questions today about your impressions and expectations related to the use of WES in your patients' care. I understand that we are asking you questions that might be difficult to answer. I also understand that it may be hard to anticipate what WES use will be like for you, as you have not routinely used WES in your clinical practice. However, it's very helpful for us to get a sense of what you anticipate might happen; in one year we'll talk again, and I'll ask what your actual experiences were like.

1) **Anticipated benefits, risks and challenges of whole exome sequencing <u>of tumor DNA</u>**:

Next, I would like to ask you what you anticipate will be the benefits, risk and challenges as whole exome sequencing of tumor DNA becomes incorporated into clinical practice.

- What do you anticipate will be the benefits **for your patients** as you incorporate whole exome sequencing **of tumor DNA** into their care?

- What do you anticipate will be the risks **for your patients** as you incorporate whole exome sequencing **of tumor DNA** into your practice?

    - Probes
        - Data volume
        - Inaccuracy/misinterpretations
        - Sequencing results for which there is no targeted therapy
        - Patients overwhelmed by too much information
        - Cost to patient
        - Repeated testing/biopsies
        - Delay treatment
        - Anything else?

- What do you anticipate will be the challenges **for you** as you incorporate whole exome sequencing **of tumor DNA** into your patients' care?

    - Probes:
        - Interpreting test results
        - Deciding what to disclose
        - Explaining test results
        - Addressing psychosocial concerns

        - Fitting discussions into oncology visits
        - Anything else?

- What do you think will be the biggest challenge (for your patients or you?)? Why?

2) Intentions related to test result disclosure <u>from tumor DNA</u>

Whole exome sequencing of tumor DNA can yield a variety of different types of test results. For example, results may reveal predictive information- which can help inform treatment selection- as well as prognostic information.

Now I'm going to ask you about 4 different types of results from tumor DNA that you might anticipate disclosing or consider **not** disclosing to your patients.

- 1. Do you think you will disclose sequencing results that suggest a patient may benefit from a **targeted therapy that is FDA-approved for a *different* cancer**? Why/why not?
    - What factors will make you more likely to disclose a result? Less likely to disclose a result?
        - Probes (*reflect on answer*):
        - Anything about the patient?
        - Disease?
        - Potential treatment?

- 2. Do you think you will disclose sequencing results that suggest a patient may be eligible for a **clinical trial of a targeted therapy**? Why/why not?
    - What factors will make you more likely to disclose a result? Less likely to disclose a result?
        - Probes (*reflect on answer*):
        - Anything about the patient?
        - Disease?
        - Potential treatment?

- 3. Do you think you will disclose sequencing results that have **positive prognostic implications** for your patient, but don't inform decisions about treatment? Why/why not?
    - What would influence your decision?

- 4. Do you think you will disclose sequencing results that have **negative prognostic implications** for your patient, but don't inform decisions about treatment? Why/why not?
    - What would influence your decision?

3) **Informed consent for whole-exome sequencing of tumor DNA**

- When thinking about the use of whole-exome sequencing of tumor DNA in your practice (in the future), do you anticipate having informed consent conversations with your patients before ordering sequencing of their tumor DNA?/
    - Why/why not?
    - *If yes*: What are the main issues you expect to discuss during those informed consent conversations?

      Probes:

      What risks do you expect to discuss during the IC process?

      What benefits do you expect to discuss during the IC process?
    - *If no*: Are there any risks of whole-exome sequencing of tumor DNA that you think patients should consider before sequencing is performed?

4) **Anticipated benefits, risks and challenges of whole exome sequencing <u>of germline DNA</u>**:

As I noted previously, performing whole-exome sequencing of tumor DNA requires that whole-exome sequencing of germline DNA be performed in parallel. This sequencing of germline DNA may lead to findings of relevance to your patients. Next, I would like to ask you what you anticipate will be the benefits, risk and challenges as whole exome sequencing of **germline DNA** becomes incorporated into clinical practice.

- What do you anticipate will be the main benefits **for your patients** as you incorporate whole exome sequencing **of germline DNA** into your practice?

- What do you anticipate will be the main risks **for your patients** as you incorporate whole exome sequencing **of germline DNA** into your practice?
    - Probes (concerns that have been found in prior research)
        - Data volume
        - Uncertain nature of results
        - Unanticipated/unintended findings
        - Family member implications
        - Emotional risk of patients learning information that they might not be ready to hear.
        - Unnecessary info for the patient to have
        - Potential for discrimination (e.g., health insurance) due to genetic predispositions

- What do you anticipate will be the main challenges **for you** as you incorporate whole exome sequencing **of germline DNA** into your practice?

- Probes:
  - Interpreting test results
  - Deciding what to disclose
  - Explaining test results
  - Patient and family member responses to the test results.

- What do you think will be the biggest challenge (for your patients or you)? Why?

5) Intentions related to test result disclosure

Whole exome sequencing of **germline DNA** can yield a variety of different types of test results. For example, results can reveal information about cancer risk, risk of non-cancer disease, and pharmacogenetic information.

Now I'm going to ask you about 5 different types of results from **germline DNA** that you might anticipate disclosing or consider **not** disclosing to your patients.

- 1. Do you think you will disclose germline results suggesting that your patient has an inherited predisposition to *cancer*? Why/why not?
  - What would influence your decision?

- 2. Do you think you will disclose germline results suggesting that your patient has an inherited predisposition to *a disease other than cancer*? Why/why not?
  - What would influence your decision?

- 3. Do you think you will disclose pharmacogenetic results that might influence your use of cancer drugs? Why/why not?
  - What would influence your decision?

- 4. Do you think you will disclose pharmacogenetic results that might influence your use of non-cancer drugs? Why/why not?
  - What would influence your decision?

- 5. Do you think you will disclose germline results suggesting that your patient is a carrier of an autosomal recessive mutation that is associated with serious manifestations in individuals who inherit two copies of the abnormal gene? Why/why not?
  - What would influence your decision?

6) **Informed consent for whole-exome sequencing of germline DNA**

- When thinking about the use of whole-exome sequencing of tumor DNA in your practice, do you anticipate having informed consent conversations with your patients before ordering sequencing of their germline DNA?
  - Why/why not?
  - *If yes:* What are the main issues you expect to discuss during those informed consent conversations?

- *If no risks mentioned*: Any risks?
- *If no benefits mentioned*: Any benefits?

o *If no*: Are there any risks of whole-exome sequencing of germline DNA that you think patients should consider before sequencing is performed?

6) Closing

Is there anything else that you would like to say about using whole exome sequencing in your practice?

What types of resources would be helpful to you, in integrating WES into your practice?

Thank you very much for participating in this interview. We greatly appreciate all of your time and effort.

If you have any questions or concerns, please contact Drs. Steven Joffe or Stacy Gray.

NOTE TO IRB: The interview guide below should not be viewed as a fixed, structured interview instrument. Rather, it is a guide for ethnographic interviews. As is typical for ethnographic research, it may prove necessary to modify questions as the interview process proceeds to follow new areas that arise over the course of the study.

Open-ended interviews with CGEC members:

My name is Sarah McGraw and I am calling from The Hastings Center as part of the ethnography which evaluates the U01 CanSeq Cancer Genome Evaluation Committee, or CGEC process. Last [DAY], we scheduled this time for the interview. Is this still a good time for you?

Before we get started I want to remind you that the interview will take approximately 45 minutes and I will be recording the interview. It will cover 15 questions on your thoughts about the CGEC review process.

As you know the interview is completely voluntary. If at any time during the interview you would like to stop, please tell me. Also, you may choose not to answer any question for any reason.

The only people who will see the raw data are me and a research assistant at The Hastings Center who will assist with coding. No one else will see anything that is identifiable. No one at DFCI, the Broad Institute or Brigham and Women's Hospital will know who made which comments. None of the reports will include names, titles or any demographic information that would reveal the identity of the respondent.

In answering these questions, please think not only about your reviews of patient cases and the discussions that occur during committee meetings, but also about the process of annotation and curation of genomic data that occurs prior to CGEC review.

Do you have any questions before we begin?

1. Have you reviewed germline alterations, somatic alterations, or both types of genomic information?

2. What are your overall impressions of the CGEC process?
   PROBE: Efficiency of process? Validity of decisions?

3. What challenges, if any, have you encountered in reviewing genomic alterations prior to the meeting?

4. In general, when you assigned to review a case, about how long does it take for you to conduct your review in preparation for a meeting? What elements of your review are the most time-consuming?

5. As you conduct your reviews, how important is the information you receive from the curation team? PROBE: Can you please explain why?

6. Thinking about the work required to conduct the reviews, were there any new areas of knowledge you had to learn, or skills you had to develop, in order to do the review? Would you describe them to me?

7. Do you recall any decisions from a previous CGEC meeting that struck you as particularly difficult or controversial?
    a. Can you describe the situation to me?
    b. In your view, what was the source of this difficulty or controversy?
    c. What are your thoughts about the quality of the discussion about this topic? To what extent were the issues or concerns you thought were the most important taken into account?
    d. What were your thoughts about the resolution?

8. To what extent do you think the CGEC appropriately weighs information available for each patient?

    PROBE: Are some members placing too much or too little emphasis on certain types of information? For example, are they placing too much or too little emphasis on information such as such as availability of treatment or validity of the genotype-phenotype association?

    PROBE: To what extent are members appropriately accounting for the quality or certainty of the information available?

    PROBE: To what extent are members appropriately considering the medical implications of these results for the

    - patient?
    - family?

    PROBE: To what extent are members appropriately considering the psychosocial implications of these results for the patient and family?

9. Thinking about your experience with CGEC so far, is there anything about the committee or the committee process that you did not anticipate? Is there anything that has surprised you?

10. In your opinion, what are the most important goals of CGEC?

    PROBE: What do you think about these goals?

    PROBE: Should CGEC have different goals?

11. What impact, if any, is your work on CGEC having on your work outside the committee?

12. What impact, if any, is CGEC having on your institution more broadly?

13. Do you think a mechanism like CGEC will be of value to cancer centers as they integrate genomic analysis into cancer care.

14. What barriers, if any, might make it difficult to implement a mechanism like CGEC as a component of genomically based cancer care?

15. Finally, thinking about your experience with CGEC to date, what, if anything would you recommend be changed:
    a. in the committee procedures?
    b. in the nature or focus of the committee deliberations?
    c. to help members feel prepared for their role on CGEC including the review of cases and participation in the CGEC discussions and decisions.

1.1 New Physician Post-disclosure Survey – Informative Results

New Physician Post-Disclosure Survey – Informative Results
CanSeq U01 MD Informative Results Received from Cancer Genomics Evaluation Committee (CGEC)

Did you receive a report from the Cancer Genomics Evaluation Committee (CGEC) outlining the whole-exome sequencing results for your patient, NAME OF PATIENT HERE? **This report was prepared because your patient is participating in the U01 CanSeq Protocol.**

- ☐ Yes
- ☐ No -- go to "We will confirm that a report was sent to you and contact you again shortly. "

Did you review the report from CGEC?

- □ Yes
- □ No – go to "Thank you for your answers. We will contact you again after your next visit with this patient."

The report you received includes ***at least*** 1 somatic or germline genomic alteration for your patient.
What type(s) of results did you receive:

- ☐ Somatic – only
- ☐ Germline - only
- ☐ Both

Have you discussed any somatic or germline results ***from the CanSeq whole-exome sequencing report*** with your patient or his/her family? *Please choose the one response that best describes what you have disclosed to the patient.*

- yes, I have discussed one or more **specific** somatic or germline alterations with this patient/family-->*continue with MD informative survey-->patient gets informative survey*
- no, I have not discussed any **specific** alterations with this patient. However, I have told the patient/family that the results of the CanSeq whole-exome sequencing do not currently have implications for his/her health or treatment-->*continue with MD informative survey-->patient gets uninformative survey*
- no, but I plan to discuss results from the CanSeq whole-exome sequencing with this patient/family at a future visit-->*"Thank you. We will contact you again after your next visit with this patient"*
- no, and I do not plan to discuss any results from the CanSeq whole-exome sequencing with this patient/family at any point in the future-->*continue with informative survey-->patient does not get a post disclosure survey*

Physician Post-Disclosure Survey – Informative Results

The questions that follow ask about what types of results, if any, you have received, and which you have discussed with this patient.

Section 1. Questions about *Somatic Results*

1.1 Please write the name of the most important **somatic** genomic alteration identified through whole-exome sequencing (WES) of this patient's **tumor DNA**:

(open text box)

1.1.1 Did you know that this patient's tumor had this somatic genomic alteration before you received the results from the CanSeq whole-exome sequencing study?

- ☐ Yes, this alteration was previously identified through **standard clinical testing** (e.g., KRAS /BRAF for colorectal cancer or EGFR/KRAS/ALK for lung cancer)
- ☐ Yes, this alteration was previously identified through cancer genome **panel testing,** but it is not a standard clinical test.
- ☐ Yes, this alteration was previously identified through **testing for another research study**
- ☐ Yes, but I don't recall how this alteration was identified
- ☐ No

1.2 What are the clinical implications of this result?

(check all that apply)

- ☐ The result may be used to help select FDA approved cancer-directed therapies
- ☐ The result may be used to help identify appropriate clinical trials of targeted agents
- ☐ The result has positive prognostic implications
- ☐ The result has negative prognostic implications
- ☐ The result does not have any clinical implications at this time
- ☐ Other (please describe):

If the patient has at least one somatic genomic result ask (and then follow flow sequence as appropriate):

1.3 Did the results of whole-exome sequencing identify any additional somatic genomic alterations for this patient?

- ☐ Yes
- ☐ No

If yes:
Please write the name of the next most important somatic genomic alteration identified through WES of this patient's **tumor DNA**:
(go through sequence 1.1 – 1.2, changing wording as appropriate)
continue as appropriate until:

Please write the name of the next most important somatic genomic alteration identified through WES of this patient's **tumor DNA**:
Please write the names of any additional somatic genomic alterations identified through WES of this patient's **tumor DNA**:
--open text box

Are there important clinical implications for any of these somatic WES results? (if yes, please describe)

Section 2. Disclosure Question

2.1 Have you discussed this result with this patient or the patient's family since receiving the CanSeq report?

- ☐ Yes → ***Follow flow & ask remaining questions.***
- ☐ No, but I plan to at a future visit
- ☐ No, and I do not plan to discuss this result with the patient/family.

Section 3. Questions Assessing Why Will Not Disclose

(ASKED ONLY IF THEY ANSWERED "NO, AND I DO NOT PLAN TO…" TO THE PREVIOUS QUESTION.)

3.1 Please indicate why you decided not to discuss this **specific** result with this patient (*please check all that apply*)

- ☐ This genomic result was already known and had previously been disclosed to the patient
- ☐ Patient is too sick
- ☐ I was concerned that patient/family would not understand the result
- ☐ I was concerned about the psychosocial impact of the result
- ☐ I did not think that this was essential information for the patient/family to have
- ☐ The patient/family did not want to discuss the result
- ☐ Would not have influenced therapy at this time
- ☐ Lack of evidence demonstrating an effective intervention for this alteration
- ☐ Too much effort would be required to implement possible intervention
- ☐ It would have taken too much time to explain the result
- ☐ Outside the scope of my responsibilities
- ☐ Other_____

Section 4. Questions about *Germline Results*

4.1 Please write the name of the most important **germline** genomic alteration identified through whole-exome sequencing (WES) of this patient's **non-tumor DNA**:

(open text box)

4.1.1 Did you know that this patient carried this germline genomic alteration before you received the results from the CanSeq whole-exome sequencing study?

- ☐ Yes, this alteration was previously identified through **standard clinical testing** (e.g., MLH1/MSH2 testing for Lynch Syndrome or BRCA1/BRCA2 for Hereditary Breast and Ovarian Cancer)
- ☐ Yes, this alteration was previously identified through cancer genome **panel testing** but it is not a standard clinical test.
- ☐ Yes, this alteration was previously identified through **testing for another research study**
- ☐ Yes, but I don't recall how this alteration was identified
- ☐ No

4.2 What are the clinical implications of this result?

(check all that apply)

A ☐ Confer(s) an increased risk of developing cancer

B ☐ Impacts the metabolism of an **anti-cancer medication** (i.e., pharmacogenetic polymorphism)

C ☐ Impacts the metabolism of a **non-cancer-related medication** (i.e., pharmacogenetic polymorphism)

D ☐ Confers an increased risk for developing a condition, other than cancer, that **can** be treated

E ☐ Confers an increased risk for developing a condition, other than cancer, that **cannot** be treated

F ☐ Identifies your patient as a carrier of a non-cancer-related condition that might be passed on to a child

G ☐ This result does not have any clinical implications at this time

If they have at least one germline genomic result ask (and follow flow sequence):

4.3 Did the results of WES identify any additional germline genomic alterations for this patient?

- ☐ Yes
- ☐ No

If yes:

4.4 Please write the name of the next most important genomic alteration identified through WES of this patient's **germline DNA**:

(go through sequence 4.1 – 4.2, changing wording as appropriate)
continue as appropriate until:

Please write the name of the next most important genomic alteration identified through WES of this patient's **germline DNA**:

Please write the names of any additional genomic alterations identified through WES of this patient's **germline DNA**:
--open text box

Are there important clinical implications for any of these germline WES results? (if yes, please describe)

Section 5. Questions about Interpretation Challenges

How challenging was each of the following?	Not Challenging at All	A Little Challenging	Moderately Challenging	Very Challenging	Not Applicable
5.1 Interpreting this test result.	☐	☐	☐	☐	☐
5.2 Formulating treatment recommendations based on this test result.	☐	☐	☐	☐	☐
5.3 Deciding whether this test result should be disclosed to the patient or family.	☐	☐	☐	☐	☐
5.4 Identifying appropriate referrals related to this test result.	☐	☐	☐	☐	☐

Section 6. Questions about Communication Challenges

How challenging was each of the following?	Not Challenging at All	A Little Challenging	Moderately Challenging	Very Challenging	Not Applicable
6.1 Explaining this test result to the patient or family.	☐	☐	☐	☐	☐
6.2 Answering the patient's or family's questions about this test result.	☐	☐	☐	☐	☐
6.3 Addressing the patient's or family's psychosocial concerns in response to this test result.	☐	☐	☐	☐	☐

Section 7. Cancer-Specific *Action(s) Taken*

Have you taken any of the following actions **because of this alteration**?

Action	Yes	No, but plan to do so	No	N/A
7.1 Made changes to the patient's cancer treatment.	☐	☐	☐	☐
7.2 Offered the patient enrollment in a clinical trial of a specific targeted agent.	☐	☐	☐	☐

Section 8. Non-Cancer Specific *Action(s) Taken*

Action	Yes	No, but plan to do so	No	N/A
8.1 Made changes to any non-cancer-related medications.	☐	☐	☐	☐
8.2 Referred the patient to another clinician (e.g., physician, genetic counselor).	☐	☐	☐	☐

Section 9. Family *Action(s) Taken*

Action	Yes	No, but plan to do so	No	N/A
9.1 Recommended that family members be tested for this alteration	☐	☐	☐	☐

Section 10. Question about *Confidence in Recommendation(s)*

10.1 Please indicate how confident you are in the actions you took in response to this test result:

- ☐ Very confident
- ☐ Moderately confident
- ☐ A little confident
- ☐ Not confident at all

Section 11. Question about *Overall Satisfaction*

11.1 Overall, how satisfied were you with your communication with the patient or family about this test result?

- ☐ Very satisfied
- ☐ Somewhat satisfied
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied

Section 12. Disclosure to Family or Proxy Questions

SKIP PATTERN: If the physician answers “yes” s/he disclosed *any* test result (whether somatic or germline), then ask the following questions about family.

12.1 Did you discuss any information about the results of somatic or germline genomic sequencing with the patient’s family members or with another proxy, rather than discussing the information with the patient her/himself?

- ☐ Yes
- ☐ No

If yes:

12.2 Please describe what information you discussed with the family/proxy:

(open text box)

12.3 Please describe why you discussed this information with the family/proxy rather than with the patient:

(open text box)

Section 13. Additional Information Questions

If: no, I have not discussed any **specific** alterations with this patient. However, I have told the patient/family that the results of the CanSeq whole-exome sequencing do not currently have implications for his/her health or treatment -->

13.01 Please describe why you decided to tell the patient or his/her family that the results of the whole-exome sequencing do not currently have implications for the patient's health or treatment?

13.02 Overall, how satisfied were you with your communication with the patient or family about the fact that the results of the whole-exome sequencing do not currently have implications for the patient's health or treatment?

- ☐ Very satisfied
- ☐ Somewhat satisfied
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied

13.1 Did you use any of the following sources of information to learn more about this patient's somatic or germline sequencing results?

- ☐ Colleagues within your disease center
- ☐ Colleagues at DFCI/BWH outside your disease center
- ☐ National/international experts outside DFCI/BWH
- ☐ Peer-reviewed medical literature
- ☐ Professional society or government websites (e.g., ASCO or NIH)
- ☐ Evidence-based, synthesized websites (e.g.,UpToDate)
- ☐ Genomic databases (e.g.,Cancer Gene Census)
- ☐ Other (please specify) _____
- ☐ I did not use any additional sources of information to learn more about this patient's sequencing results

13.2 Do you have any additional thoughts that you wish to share about the issues raised in this survey? Please feel free to write in the space below as we welcome your feedback.

(Provide text entry box)

Thank you very much for completing this survey! Your participation is greatly appreciated.

Physician Post-Disclosure Survey – Uninformative Results

Physician Post-Disclosure Survey – Uninformative Results

Q1. Did you receive a report from the Cancer Genomics Evaluation Committee (CGEC) describing the results of whole-exome sequencing for your patient, NAME OF PATIENT HERE? This report describes the fact that the sequencing did not identify any genomic alterations with current implications for his/her health or treatment? We refer to these below as "uninformative results." **This report was prepared because your patient is participating in the U01 CanSeq Protocol.**

- ☐ Yes
- ☐ No -- go to "We will confirm that a report was sent to you and contact you again shortly. "

Q2. Did you review the report from CGEC?

- □ Yes
- □ No – go to "Thank you for your answers. We will contact you again after your next visit with this patient."

Q3. Did you tell the patient or his/her family that whole-exome sequencing did not identify any informative genomic alterations?

- ☐ Yes
- ☐ **No but I plan to disclose the uninformative sequencing result at a future visit-** *Go to Screen that says "Thank you for your answers. We will contact you again after your next visit with this patient"*
- ☐ No, **and I do not plan to disclose any results from whole-exome sequencing at any point in the future** - ***continue with survey***

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If the physician answers "no, and I do not plan to disclose any results from whole exome sequencing at any point in the future" to the previous question, ask the following:

Q4.. Please describe why you decided not to disclose this result to this patient/family :

(*check all that apply*)

- ☐ Patient is too sick

☐ Patient is deceased
☐ I was concerned that patient/family would not understand the result
☐ I was concerned about the psychosocial impact of the result
☐ I did not think that this was essential information for the patient/family to have
☐ The patient/family did not want to discuss the result
☐ Would not have influenced therapy at this time
☐ It would have taken too much time to explain the result
☐ Other_(specify):_____

If the physician answers “yes” to Q1 question, ask **5a –5d**

If the physician answers “no, **and I do not plan to disclose any results from whole-exome sequencing at any point in the future**” ask 2a only

How challenging was each of the following?	Not Challenging at All	A Little Challenging	Moderately Challenging	Very Challenging	Not Applicable
5a. Deciding whether the uninformative sequencing result should be disclosed to the patient or family.	☐#	☐#	☐#	☐#	☐#
5b. Explaining the uninformative sequencing result to the patient or family.	☐#	☐#	☐#	☐#	☐#
5c. Answering the patient’s or family’s questions about the uninformative sequencing result.	☐#	☐#	☐#	☐#	☐#
5d. Addressing the patient’s or family’s psychosocial concerns in response to the uninformative sequencing result.	☐#	☐#	☐#	☐#	☐#

If physician answers yes to Q1 ask:

.

6. Overall, how satisfied were you with your communication with the patient or family about the fact that the results of the whole-exome sequencing do not currently have implications for the patient's health or treatment?

- ☐ Very satisfied
- ☐ Somewhat satisfied
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied

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7. Do you have any additional thoughts that you wish to share about the issues raised in this survey? Please feel free to write in the space below as we welcome your feedback.

(Provide text entry box)

Thank you very much for completing this survey! Your participation is greatly appreciated.

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Dear Dr. [insert Name]:

Your patient [insert patient first name] [insert patient last name] is enrolled in our study "The Use of Sequencing to Guide the Care of Cancer Patients" (CanSeq). This patient's sequencing results are now available for your review. You may have already received an email with instructions for how to access the results report for this patient (MRN #: [insert MRN#]).

During the consent process, this patient answered a series of questions regarding his/her preferences for return of sequencing results. Results have been filtered according to patient preference. S/he expressed the following preferences:

- Somatic - Predictive for use of an agent within a clinical trial
  - [Insert Survey Response]
- Somatic – Positive Prognostic
  - [Insert Survey Response]
- Somatic – Negative Prognostic
  - [Insert Survey Response]
- Germline – Cancer Risk
  - [Insert Survey Response]
- Germline - Cancer Pharmacogenomic
  - [Insert Survey Response]
- Germline - Non-cancer Risk, Treatable
  - [Insert Survey Response]
- Germline - Non-cancer Risk, Untreatable
  - [Insert Survey Response]
- Germline - Non-cancer Pharmacogenomic
  - [Insert Survey Response]
- Germline - Carrier State
  - [Insert Survey Response]

As part of your participation in the CanSeq study, you will be asked to complete a short survey about your experience interpreting, making decisions about and communicating these results after your next clinic visit with this patient. We greatly appreciate your completing this survey as soon as possible after you've had a chance to discuss the results with the patient.

Please do not hesitate to contact our study team at CanSeq@DFCI.HARVARD.EDU with any questions about this patient's results or about the CanSeq study.

Thank you,
Pasi Janne, M.D., Ph.D.
Levi Garraway, M.D., Ph.D.
Stacy W. Gray, M.D., A.M.

PATIENT NAME: _____

DFCI MRN: _____ DATE: _____ Protocol #: 12-078

U01 STUDY REMINDER:

This patient is enrolled in our study "**The Use of Sequencing to Guide the Care of Cancer Patients" (CanSeq).** His/her sequencing results are enclosed in the attached envelope.

During the consent process, this patient answered a series of questions regarding his/her preferences for return of sequencing results. Results have been filtered according to patient preference and are provided in the attached report. The patient's preferences are also noted on the report.

As part of your participation in the CanSeq study, we will ask you to complete a short survey after your clinic visit with this patient about your experience interpreting, making decisions about and communicating these results. We greatly appreciate your completing this survey as soon as possible after you've had a chance to discuss the results with the patient. Your input will help us to better understand your experiences with whole-exome sequencing and improve our process for integrating sequencing results into patient care.

We have also created a template that you may wish to use when writing your notes on the clinic visit in which the disclosure occurred. This template will be sent via email.

Please do not hesitate to contact our study team at CanSeq@DFCI.HARVARD.EDU with any questions about this patient's results or about the CanSeq study.

Sequencing Results for your patient enrolled on protocol 12-078 (CanSeq)

Dear Dr. [insert Name]:

Your patient [insert patient first name] [insert patient last name] was enrolled in our study "The Use of Sequencing to Guide the Care of Cancer Patients" (CanSeq). This patient's sequencing results are attached for your review. We recognize that this patient has passed away and are sorry that the results were not available sooner.

During the consent process, this patient answered a series of questions regarding his/her preferences for return of sequencing results. Results have been filtered according to patient preference and are included in the attached report. Because it is critical to our study to understand your experiences receiving and interpreting this information, even if the patient has passed away, you will be asked to complete a short survey about your experience interpreting and making decisions about these results. We greatly appreciate your completing this survey as soon as possible after you receive the invitation.

If there are any germline findings in the report that have implications for the patient's family members, please let us know if we can help identify genetics or genetic counseling resources that may be helpful to you or to the family.

Please do not hesitate to contact our study team at *DFCI_CanSeqU01@DFCI.HARVARD.EDU* with any questions about this patient's results or about the CanSeq study.

Thank you,
Pasi Janne, M.D., Ph.D.
Levi Garraway, M.D., Ph.D.
Stacy W. Gray, M.D., A.M.

Invitation

We are writing because you may recently have received results from whole-exome sequencing for your patient named below, as part of the "The Use of Sequencing to Guide the Care of Cancer Patients" (Protocol 12-078) study. We recognize that this patient has passed away and are sorry that the results were not available sooner.

Because it is critical to our study to understand your experiences receiving and interpreting this information, even if the patient has passed away, we ask you to complete a brief survey for our study. We greatly appreciate your completing this survey as soon as possible after you receive this invitation.

Patient Name: **XXXXX**

MRN: XXXXX

Study ID: XXXXXX

The survey can be accessed at: Click here to begin Survey

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

Thank you for your consideration,

Stacy Gray, MD, AM

Reminder

We recently sent you an email requesting that you complete a brief survey for your patient named below. We recognize that this patient has passed away and are sorry that the results were not available sooner.

Because it is critical to our study to understand your experiences receiving and interpreting this information, even if the patient has passed away, we ask you to complete a brief survey for our study.

According to our records, you have not yet completed the survey. We would greatly appreciate it if you would complete the survey at your earliest convenience.

Patient Name: **XXXXX**

MRN: XXX

Study ID: XXXX

The survey can be accessed at: Click here to begin Survey

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

Thank you for your consideration,

Stacy Gray, MD, AM

Living patients

Hi **Dr. (Insert Last Name)**,

I wanted to check in with you quickly to find out if you have disclosed the results of whole-exome sequencing from the CanSeq study to **PATIENT NAME (MRN)**?

I believe that we sent you the WES report on **DATE** (we apologize for the long delay). From our review of the records, it does not seem as though you have returned the results to the patient.

Because we are interested in your experiences with interpreting WES results, and in your patient's experience receiving the results, we are conducting patient and physician surveys after the reports have been delivered. We would like for you to complete the survey after you see the patient in clinic. The survey takes, on average, about 5-7 minutes to complete and it should be filled out even if you do not plan on returning the WES results.

If you haven't received the report, please let us know and we will deliver another one to you immediately.

If you need us to re-send the survey link to you, please let us know and we will send it.

In addition, if you have returned the results to **PATIENT NAME**, please let us know so that we can send the patient the post-disclosure survey.

Please let me know if you have any questions or concerns.

Thanks so much for your time,

Stacy

Stacy Gray, MD, AM
Pasi Janne, MD, PhD
Levi Garraway, MD, PhD

Deceased Patients

Hi **Dr. (Insert Last Name)**,

I wanted to check in with you quickly to find out if you have disclosed **PATIENT NAME'S (MRN)** whole-exome sequencing results from the CanSeq study on to anyone? We realize that the patient has passed away and we are sorry that we did not get the WES results to you sooner. We are interested in knowing if you were able to return the results to the patient before he/she passed away or if you have disclosed any germline (or somatic) information to the patient's family members.

In order to understand your experiences with interpreting and disclosing WES results we would like for you to complete a survey. The survey takes, on average, about 5-7 minutes to complete and it should be filled out even if the patient has died or if you do not plan on returning the WES results to anyone.

If you haven't received the report, please let us know and we will deliver another one to you immediately.

If you need us to re-send the survey link to you, please let us know and we will send it.

In addition, if you have returned this patient's results to anyone, please let us know.

Please let me know if you have any questions or concerns.

Thanks so much for your time,

Stacy

Stacy Gray, MD, AM
Pasi Janne, MD, PhD
Levi Garraway, MD, PhD

Hi (MD NAME),

I wanted to check in with you quickly to see if there is anything that we can do to help you complete the surveys for your patients in the CanSeq study?

You recently received an informative/uninformative report on (PATIENT NAME). If you need the survey link, I have attached it below. *(repeat if multiple patients)*

Even if you have not disclosed the results, or plan never to disclose the results, to this/these patients we are asking you to fill out the surveys so that we know whether or not there has been a disclosure and how we should follow-up with the patients.

The surveys have generally been taking less than 4-7 minutes to complete, even when there has been a disclosure, and we hope that you find them to be quick.

If I can do anything to help or if you have any other questions, please let me know.

Thanks!
Stacy

PATIENT NAME (MRN), Alive. Report Informative, delivered 11/28. Survey link for PATIENT NAME (MRN) here – enter the study ID number XXXXXXX to access survey.

PATIENT NAME (MRN), Alive. Report Uninformative, delivered 5/12, Survey link PATIENT NAME (MRN) here – enter the study ID number XXXXXXX to access survey.

Dear Dr. (MD NAME):

You recently received a CanSeq Report for your patient **(PATIENT NAME)** who is enrolled in our study "The Use of Sequencing to Guide the Care of Cancer Patients" on (DATE OF REPORT DELIVERY).

According to the electronic medical record, this patient will no longer be receiving his/her care at DFCI. Given this, will you please let us know which category you fall into: you have already disclosed CanSeq results to the patient, you are planning to disclose CanSeq results to this patient in the near future or you plan NOT to disclose CanSeq results to this patient.

If you have already disclosed to the patient or plan never to disclose to the patient we are asking you to fill out a short survey regarding the interpretation and communication of the results, and will send you the survey link immediately.

If you do plan to disclose, we would appreciate you letting us know once disclosure has occurred so we can send you the correct survey link and follow-up appropriately with the patients.

The surveys have generally been taking less than 4-7 minutes to complete, even when there has been a disclosure, and we hope that you find them to be quick.

If we can do anything to help or if you have any other questions please let us know.

Thanks!

Stacy W. Gray, M.D., A.M.

Dear Dr. [LAST NAME],

We are planning to send a copy of your patient [PATIENT NAME]'s ([MRN]) CanSeq results to them.

If you would prefer we do not send the report, please notify us by [DATE].

If you have any questions please feel free to call me, 617-632-4939.

Thank you!

Stacy Gray

[DATE]

Dear Dr. [MD LAST NAME],

In order to contact patients for post-disclosure research activities in the CanSeq study, we need to know whether you have disclosed their CanSeq results to them. Please let us know the following:

1. Have you discussed [PATIENT NAME]'s ([PATIENT MRN]) CanSeq results with him/her at a recent appointment?

☐ Yes (Please respond to Question 2)

☐ No, but I plan to discuss results from the CanSeq whole-exome sequencing with this patient/family at a future visit.

☐ No, and I do not plan to discuss any results from the CanSeq whole-exome sequencing with this patient/family at any point in the future.

2. **If yes**, please choose the response that best describes what you have disclosed to the patient.

☐ I have discussed one or more **specific** somatic or germline alterations with this patient/family.

☐ I have not discussed any **specific** alterations with this patient. However, I have told the patient/family that the results of the CanSeq whole-exome sequencing do not currently have implications for his/her health or treatment.

If you have the time to fill out your post-disclosure survey, we would still appreciate if you could do so. Please check below and we will send you another copy of the link to the survey.

☐ Yes, please send me the link for the post-disclosure survey.

If you have any questions, please contact Nelly Oliver at nelly_oliver@dfci.harvard.edu.

Thank you for your assistance!

The CanSeq Team

Hi (MD NAME),

You recently received an informative/uninformative report on (PATIENT NAME, MRN) (see attached). We recognize that your patient is no longer receiving care at DFCI. Even if you plan never to disclose results to this patient we are asking you to fill out the survey regarding the interpretation of the results as these are important outcomes for our study.

The survey generally takes 4-7 minutes to complete.

SURVEY LINK HERE

If I can do anything to help or if you have any other questions, please let me know.

Thanks!
Stacy Gray