Genomic Health	**Study Protocol**

A STUDY TO DETERMINE THE CONCORDANCE OF KEY ACTIONABLE GENOMIC ALTERATIONS AS ASSESSED IN TUMOR TISSUE AND PLASMA FROM PATIENTS WITH NON SMALL CELL LUNG CARCINOMA (NSCLC)

Study Protocol Number:	DSP-DE-MS 14-009
Protocol Version:	Version 3.0
Protocol Issue Date:	
Sponsor and Study Laboratory:	Genomic Health, Inc. 301 Penobscot Drive Redwood City, CA 94063 Phone: 650-556-9300
IDE Number:	Not Applicable
Study Sites:	Approximately 25 USA and International centers including centers in France, Germany, Ireland, Spain, United Kingdom, Japan, Chile and Mexico.

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PROTOCOL APPROVAL FORM

Protocol Number:	DSP-DE-MS 14-009
Version Number and Date:	Version 3.0
Study Title:	A study to determine the concordance of key actionable genomic alterations as assessed in tumor tissue and plasma from patients with non small cell lung carcinoma (NSCLC)

This study protocol was subjected to critical review. The information presented in this document is consistent with Genomic Health's current knowledge of the risks and benefits of the developmental genomic sequencing test system/technology, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2002 and clarified in 2004.

Genomic Health approvals:

_____ _____

Steve Shak, MD
Chief Medical Officer
Genomic Health, Inc.

Date

_____ _____

Jim Whitmore, PhD
VP, Biostatistics and Data Management
Genomic Health, Inc.

Date

Genomic Health	**Study Protocol**

Protocol Number: DSP-DE-MS 14-009
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The study protocol has been reviewed and approved by the following Genomic Health Representatives:

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VP, Pathology
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John Bennett, MPH Date
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DOCUMENT HISTORY

Version	Date	Replaces	Description of Change
1.0		N/A	New issue
2.0		1.0	Change in exclusion criterion: 5.2.3 Increase interval between tissue and blood samples from 6 to 8 weeks Added an exclusion criterion 5.2.5 Patients progressing on Osimertinib treatment (clarification) Sample size of the all comer phase increased from 79 to 200 patients Changed the trigger for an interim analysis Other administrative changes throughout
2.5		2.0	Update with corrections made in Letter of Clarification – Exclusion Criteria 5.2.3 dated 08Aug2017.
3.0		2.5	Replace Dr. Christer Svedman with Dr. Rick Baehner as Medical Monitor Remove central CLIA lab / Foundation Medicine study procedures Change follow up data collection procedures to permit outcome analysis of the interim analysis

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DEFINITIONS AND ACRONYMS

ALK	Anaplastic Lymphoma Kinase
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments
CNV	Copy Number Variation
cfDNA	Cell Free DNA
DNA	Deoxyribonucleic Acid
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
FPE	Fixed Paraffin-embedded
HIPAA	Health Insurance Portability and Accountability Act
InDels	Insertion or Deletion
IRB/EC	Institutional Review Board, independent Ethics committee, or equivalent
LBMP	Liquid Biopsy Mutation Panel
LDT	Laboratory Developed Test
NCCN	National Comprehensive Cancer Network
NGS	Next Generation Sequencing
NPA	Negative Percent Agreement
NSCLC	Non-Small Cell Lung Cancer
PCR	Polymerase Chain Reaction
PPA	Positive Percent Agreement
SNV	Single Nucleotide Variant
SOP	Standard Operating Procedure

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1. PROTOCOL SYNOPSIS

Protocol Title	A Study to Determine the Concordance of Key Actionable Genomic Alterations as Assessed in Tumor Tissue and Plasma from patients with non small cell lung carcinoma (NSCLC)
Protocol Number	DSP-DE-MS-14-009
Investigational Product and Intended Use Statement	The Genomic Health Next Generation Sequencing Liquid Biopsy Mutation Panel (LBMP) is currently classified as a Laboratory Developed Test (LDT) System. Genomic Health LBMP has been developed to detect clinically relevant genomic alterations in blood (plasma). The present study aims to characterize the concordance of key actionable alterations in patients with stage IV NSCLC. This clinical concordance study is designed to yield results that support clinical use of the LBMP.
Study Objectives	Primary Objective Assess concordance of genomic alterations of clinical relevance in *EGFR* detected in plasma versus tumor tissue in patients with stage IV non squamous NSCLC who are newly diagnosed or progressing on treatment. Secondary Objectives 1. Assess concordance of genomic alterations in *ALK* (EML4-ALK fusions) detected in plasma versus tumor tissue. 2. Assess concordance of all detected alterations in plasma versus tumor tissue 3. Assess concordance of mutation-specific NCCN guideline-based clinical actions based on alterations found in plasma versus tumor tissue and versus treatment received based on findings in tumor tissue. 4. Assess concordance of detected genomic alterations separately in patients with newly diagnosed metastatic disease and patients progressing on treatment 5. Summarize the overall distribution of genomic alterations present in plasma, tumor tissue or both 6. Characterize the detection of *EGFR* T790M alterations in plasma in patients progressing on EGFR targeting therapy (erlotinib, gefitinib, afatinib).

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	Exploratory Objectives Explore the association of genomic alterations detected in plasma or tumor tissue and time to progression and response to therapy initiated after the liquid biopsy test
Study Design and Study Population	This is a prospective clinical study to characterize the concordance of key clinically relevant genomic alterations in tumor tissue and liquid biopsy (blood) using the Genomic Health LBMP in patients with stage IV non squamous NSCLC that are either newly diagnosed with metastatic disease or progressing on therapy (any line). Tissue biopsy of a metastatic lesion or primary lesion with stage IV presentation at diagnosis and blood collection (liquid biopsy) should be less than eight weeks apart and with no new systemic antitumoral treatment given in the interval between the tissue and liquid biopsies. Tumor tissue material will be assessed at each participating institution as per their clinical standard of care practices. For patients progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib), liquid biopsy will be collected to assess detection of T790M alterations in this population. Participation in the study does not alter clinical care. The only procedure required by the Protocol is collection of a research blood sample by peripheral venipuncture. All other clinical procedures performed and collection of non-study data will be in accordance with each participating institution's standard of care.
Sample Size	The study will enroll approximately 310 patients with stage IV non squamous NSCLC including: • approximately 260 patients with plasma and tissue samples will be enrolled. Initially, approximately 200 patients will be enrolled (First Enrollment Phase) regardless of genomic alteration status in tumor tissue. In order to enroll approximately 69 patients with alterations in *EGFR* and approximately 31 patients with alterations in *ALK* (EML4-ALK fusions) this First Enrollment Phase will be followed by enrollment of patients with genomic alterations in *EGFR* and *ALK* (Second Enrollment Phase) as described in Table 2. • approximately 50 patients with plasma samples (concurrent tumor tissue biopsy not mandatory) who are progressing on EGFR targeted therapy (erlotinib,

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	gefitinib, afatinib) will be enrolled across the enrollment phases. The sample size considerations are based on the probability of observing PPA/NPA estimates in the desired range as well as the size of the confidence intervals around these estimates. The results of the central tissue assessments will be used in analysis where available. In patients without central CLIA laboratory results, local assessments of genomic alterations in tissue will be utilized. We anticipate that ~20% of samples may be excluded from analysis due to insufficient DNA yield and/or pre-specified QC criteria.
Clinical Sites	Approximately 25 USA and International centers including centers in France, Germany, Ireland, Spain, United Kingdom, Japan, Chile and Mexico.
Inclusion/Exclusion Criteria	Initially, approximately 200 patients will be enrolled regardless of genomic alteration status in tumor tissue (First Enrollment Phase). This will be followed by a Second Enrollment Phase including approximately 39 patients with clinically relevant alterations in EGFR and approximately 21 patients with alterations in ALK (EML4-ALK fusions) (as assessed in tumor tissue. In addition, approximately 50 patients progressing on erlotinib, gefitinib, or afatinib will be included across the enrollment phases (see Section 4, Figure 1). **Inclusion Criteria (all of the below)** • Patients must be 18 years or older. • Patients with stage IV non squamous NSCLC who are either newly diagnosed or progressing on any treatment (progression defined as increasing tumor size or new metastatic lesions on clinical or imaging assessment). Patients with available tissue sample from a metastatic site or, if the patient presents with stage IV disease at diagnosis, from the primary tumor or a metastatic site. If a patient is progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib), tumor tissue sample is required only if available. • No new systemic anti-tumor therapy administered in the interval between the tissue biopsy and collection of the blood sample (interval not to exceed eight weeks). Local radiation therapy is permitted.

	• Able and willing to read, understand and sign an informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization where this is applicable, or equivalent in other geographies as required. **Exclusion Criteria:** • Patients who are currently receiving therapy (targeted, immune therapy or chemotherapy) without sign of progression. • Patients with squamous NSCLC. • Patients with more than 8 weeks between collection of tumor specimen and collection of blood sample for analysis. (Not applicable for patients progressing on EGFR targeted therapy with no biopsy at progression) • Patients changing EGFR therapy due to toxicity or preference without documented disease progression. • Patients progressing on Osimertinib. • Patients with brain metastases only. • Patients who are unable to comply with study and/or follow-up procedures. • Patients who are unable or unwilling to provide written informed consent.
Risk versus Benefit Analysis	Participants will undergo a single venous blood draw and they will not receive any diagnostic information or treatment recommendations based on the Genomic Health liquid biopsy mutation panel. Therefore, the risks and discomforts in this study are those associated with a single venous blood draw. These risks include temporary discomfort, bruising, lightheadedness, and in rare occasions infection or fainting. If successful, results of this study may benefit future cancer patients by providing a method to assess genomic alteration status with less discomfort and risk than a tissue biopsy procedure. A liquid biopsy may also overcome heterogeneity issues associated with single biopsies of tumors.

2. INTRODUCTION AND BACKGROUND

Molecular understanding of cancer has enabled personalized treatment of patients with agents targeting cancer specific alterations. For example, in non small cell lung cancer (NSCLC), agents are currently approved for patients with sensitizing *EGFR* mutations (i.e., erlotinib[1], afatinib[2], gefitinib[3]) and *ALK* gene rearrangements (crizotinib[4], ceritinib[5],

alectinib[6] [Japan]) and the recent approval of osimertinib[7] with efficacy in *EGFR* T790M tumors is evidence of the rapidly increasing understanding of the importance of assessing and targeting emerging mutations associated with sensitivity or resistance. In addition, the assessment of alterations associated with agents currently in clinical trials that have demonstrated efficacy is important: *EGFR* T790M (rociletinib[8]), *ROS1* re-arrangements (crizotinib[9]), *MET* amplification (crizotinib[10]), *ERBB2* mutations (trastuzumab[11], afatinib[12]) and *RET* re-arrangements (cabozantinib[13]). There are also genomic alterations associated with either sensitivity or resistance to approved targeted therapies in other solid tumor types: *BRAF* V600 mutations in melanoma (vemurafenib[14,15], dabrafenib/trametenib[16]), *KRAS* mutations in colon cancer (cetuximab[17], panitumumab[18]) and *KIT* (imatinib[19], sunitinib[20]) and *PDGFRA* (imatinib, sunitinib[20]) in Gastrointestinal Stromal Tumors.

To optimize selection of therapy, a clinical need to assess the genomic alterations of a patient's disease not just at diagnosis but at various times over the course of their metastatic disease is leading to repeated tissue sampling becoming a part of the standard of care. Performing biopsies in the metastatic setting is sometimes challenging due to the location of the lesions with risk of procedure related complications such as infection, bleeding and perforation. Even in patients where it is possible to perform biopsy and/or cytology, the amount of material obtained is in some situations scarce and the procedure is not without risk and discomfort for the patient. The representativeness of a biopsy from a single metastatic site is also being questioned due to an increasing body of evidence indicating that substantial tumor heterogeneity exists[21,22]. Thus, alternative, less invasive methods to assess the genomic alterations of patient's tumors are warranted.

It has been demonstrated that circulating cell-free DNA from blood can be used to detect tumor-specific genomic alterations in the metastatic setting in various tumor types and that current sequencing technologies allow for rapid identification of a large number of genomic alterations from a modest volume of blood[23-5]. In addition to causing less discomfort for the patient, assessing the genomic alterations in blood likely reflects the mutational landscape of metastatic lesions at different sites and may overcome molecular heterogeneity between various tumor sites and regions. Recent data also indicate that liquid biopsy may be useful for monitoring the development of alterations associated with acquired resistance[26, 27].

Genomic Health is developing a next generation sequencing LBMP that assesses genomic alterations in plasma including both established alterations where the benefit of treatment with a targeted agent is supported by level I evidence (if present in the tumor). In addition, the LBMP will assess genes that are targets of therapies in late stage clinical trials and genomic alterations that may be relevant for treatment selection but which are supported by only preliminary or preclinical evidence so far.

The reported concordance for assessing genomic alterations in blood versus tumor tissue varies relatively widely due to multiple factors such as methods used, varying tumor burden

(with lower sensitivity in patients with lower tumor burden and earlier stages of disease) and coverage of the regions of interest. It is of clinical importance to characterize the performance of the Genomic Health LBMP in the intended use population by assessing the concordance of key actionable genomic alterations detected in plasma with those found in tissue, the current standard of care (biopsy/cytology/excision).

This study focuses on assessing the concordance between LBMP and tissue biopsy in patients with non squamous NSCLC where the clinical utility of a liquid biopsy based mutation assessment is the highest. In NSCLC, many patients are difficult to biopsy and/or have poor quality tumor material and knowing the status of genomic alterations is necessary to select optimal therapy for patients.

The primary objective of this study is to assess concordance for the detection of clinically relevant genomic alterations in *EGFR*, between tumor tissue and blood in patients with stage IV non squamous NSCLC. In addition, we will perform descriptive analysis of other genomic alterations in tissue and liquid biopsy that may have clinical relevance. An extended number of patients with ALK alterations will also be included in order to generate robust data for this alteration which is difficult to assess in liquid using other technologies.

3. ABOUT THE GENOMIC HEALTH LIQUID MUTATION PANEL

The Genomic Health LBMP is a laboratory developed test that will be performed in a single CLIA-certified laboratory at Genomic Health, Inc. The test assesses selected genomic alterations in cfDNA in plasma and reports whether an alteration is detected or not.

The Genomic Health liquid biopsy test involves a blood collection (2 tubes X 10 mL blood), followed by the isolation of circulating DNA from plasma. Detection of genomic alterations will be performed by an NGS approach following operating procedures specified in a separate laboratory protocol that will be finalized prior to sample processing. The genes/alterations covered in the panel are detailed in Table 1.

Table 1. Genes/alterations covered by the Genomic Health LBMP. The panel includes detection of single nucleotide variants, copy number variation (gain or loss), targeted insertion/deletion and targeted translocations.

Gene	Variant Type(s) Reported
ALK	Targeted and *De Novo* SNVs, Targeted and *De Novo* SVs
AR	Targeted and *De Novo* SNVs
BRAF	Targeted and *De Novo* SNVs, Targeted and *De Novo* InDels

BRCA1	Targeted and *De Novo* SNVs, Targeted and *De Novo* InDels
BRCA2	Targeted and *De Novo* SNVs, Targeted and *De Novo* InDels
EGFR	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
ERBB2	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
ESR1	Targeted and *De Novo* SNVs, CNV gains
KIT	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
KRAS	Targeted and *De Novo* SNVs, Targeted and *De Novo* InDels
MET	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
NRAS	Targeted and *De Novo* SNVs
PDGFRA	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
PIK3CA	Targeted and *De Novo* SNVs, CNV gains, Targeted and *De Novo* InDels
PTEN	Targeted and *De Novo* InDels
RET	Targeted and *De Novo* SNVs, Targeted and *De Novo* InDels, Targeted and *De Novo* SVs
ROS1	Targeted and *De Novo* SNVs, Targeted and *De Novo* SVs

Prior to initiation of the investigational laboratory test procedure, using the Genomic Health LBMP as described in this protocol, the assay will be analytically validated by Genomic Health. The analytical validation study will be documented under other protocols, and will be conducted in accordance with the requirements of CLIA (Clinical Laboratory Improvement Amendments of 1988).

4. STUDY DESIGN

This is a prospective clinical study to characterize the concordance of key clinically relevant genomic alterations in tumor tissue (biopsy/excision/cytology) and liquid biopsy (blood) using the Genomic Health LBMP in patients with stage IV non squamous NSCLC, that are either newly diagnosed with metastatic disease or progressing on therapy (any line). Tissue biopsy and blood collection (liquid biopsy) should be less than eight weeks apart and with no new systemic antitumoral treatment given in the interval between the tissue biopsy and blood collection. Local assessment of tumor tissue samples will be performed at each participating institution as per their clinical standard of care practices and results from the local assessment of genomic alteration status will be used.

Additionally, detection of *EGFR* T790M alterations in plasma samples will be characterized in patients progressing on EGFR targeted therapy (erlotinib, gefinitib, afatinib).

The study will enroll a total of approximately 310 patients (Figure 1):

- approximately 260 patients with plasma and tissue samples will be enrolled. Initially, approximately 200 patients will be enrolled (First Enrollment Phase) regardless of genomic alteration status in tumor tissue. In order to enroll approximately 69 patients with alterations in *EGFR* and 31 patients with alterations in *ALK* this First Enrollment

Phase will be followed by enrollment of patients in a with genomic alterations in *EGFR* and *ALK* (Second Enrollment Phase) as described in Table 2. Patients in both enrollment phases may be either newly diagnosed or progressing on therapy.

- approximately 50 patients with plasma samples (concurrent tumor tissue sample not mandatory) who are progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib) will be enrolled across the enrollment phases. We expect that approximately 25 of these patients will have T790M alteration.

We anticipate that ~20% of samples may be excluded from analysis due to insufficient DNA yield and/or pre-specified QC criteria.

Table 2: Patient enrollment targets for patients with plasma and tissue samples

	All patients	Patients with *EGFR* alterations*	Patients with *ALK* alterations*	Patients without *EGFR* or *ALK* alterations*
First Enrollment Phase: Approximate number of patients enrolled regardless of presence or absence of genomic alterations	200	30	10	160
Second Enrollment Phase: Approximate number of patients enrolled based on known gene alterations of interest	60	39	21	NA
Total	260	69	31	160

*Expected prevalence: 15% for *EGFR* alterations, 5% for *ALK* alterations, 80% without *EGFR* or *ALK* as these alterations are expected to be mutually exclusive.

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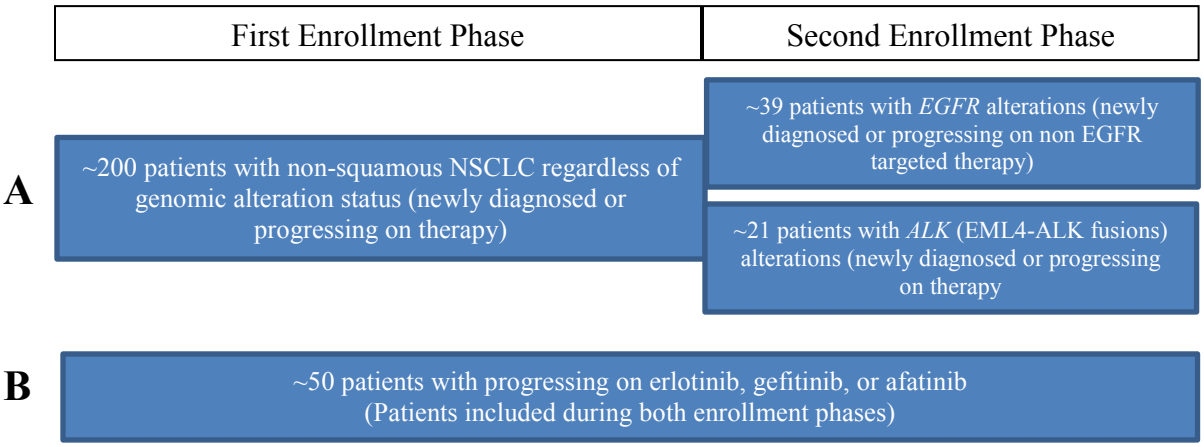
Figure 1. Schematic view of the patient categories to be included in the study



4.1 Required Procedures at Clinical Sites

Participants who are eligible and consent to participate in the study will provide a venous blood sample (2X 10 mL Streck tubes) at a single study related visit. Participants will have no further visits as part of this study. Participants data will be collected at time of progression or at 12 months after blood sample collection, whichever occurs first and in addition, data will be collected to permit outcome analysis of the interim analysis.. Participation in the study will not alter clinical care. All other clinical procedures performed and collection of non-study data will be in accordance with each participating institution's standard of care. Local assessment of tumor tissue samples will be performed at each participating institution as per their clinical standard of care practices and results from the local assessment of genomic alteration status will be used. Each site will need to provide a single H&E slide to Genomic Health for an independent pathology review.

Table 3. Requirements by patient category to help identify correct patients and required materials at the single required patient visit. Detailed overview in Table 6 (page 39).

Requirements	Patient Category (see Figure 1)		
	A: Newly diagnosed with stage IV disease	**A:** Patient progressing on treatment (except if progressing on erlotinib, gefitinib, or afatinib)	**B:** Patient progressing on erlotinib, gefitinib, or afatinib
Biopsy/cytology/excision performed on primary or metastatic lesion	X		
Biopsy/cytology/excision performed on metastatic lesion		X	Only if available
Local pathology report	X	X	X (original diagnosis)
Local mutation report	X	X	X (original diagnosis)
Provide H&E slide from biopsy/cytology/excision to Genomic Health for independent review	X	X	X
Blood sample (2X 10 mL) collected in Streck tubes	X Prior to initiating new systemic anti-tumor treatment AND no more than 8 weeks after tissue biopsy	X Prior to initiating new systemic anti-tumor treatment AND no more than 8 weeks after tissue biopsy	X Prior to initiating new systemic anti-tumor treatment AND no more than 8 weeks after tissue biopsy only in cases where a biopsy was performed

4.2 Processing of Samples and Data Management

The Genomic Health staff involved in the processing of liquid biopsy samples will remain blinded to the central assessment of FPE tissue, Pathology and Clinical data. The laboratory performing central assessment of FPE tissue will be blinded to the results of the liquid biopsy. The liquid biopsy, central FPE tissue assessment, Pathology and Clinical data will be independently processed and reviewed for quality. Once all data QC review and reconciliation are completed and data are locked, Genomic Health Data Management will merge the liquid biopsy, FPE tissue assessment, Pathology and Clinical data and prepare the SAS analysis dataset, following standard Genomic Health procedures. There will be only one, unique Specimen Identifier, and this number will not provide Genomic Health staff a direct link to private patient information. The direct link to private patient information is maintained and secured by study sites and Genomic Health will have no access to this information.

Please see section 8.6 for additional information regarding the planned Interim Analysis.

Sample specimens will not be used to develop genetic lines or nucleic acid banks. Archived samples and/or left over specimens may be used for quality control and/or for exploratory analysis of test result concordance specific to relevant cancer gene alterations that are not currently included in the Genomic Health mutation panel.

5. STUDY POPULATION

Initially, 200 patients will be enrolled regardless of genomic alteration status in tumor tissue (First Enrollment Phase). This will be followed by a Second Enrollment Phase including approximately 39 patients with clinically relevant alterations in EGFR and 21 patients with alterations in ALK (EML4-ALK fusions) (as assessed in tumor tissue). In addition, 50 patients progressing on erlotinib, gefitinib, or afatinib will be included across the enrollment phases (see Table 2 and Figure 1).

Participants may be included in the study only if they meet all the criteria listed below in Section 5.1 and if they are not excluded by any of the criteria listed below in section 5.2.

5.1 Inclusion Criteria

- 5.1.1 Subjects must be 18 years or older.
- 5.1.2 Patients with stage IV non squamous NSCLC who are either newly diagnosed or progressing on any treatment (progression defined as increasing tumor size or new metastatic lesions on clinical or imaging assessment).
- 5.1.3 Patients with available tissue sample from a metastatic site or, if the patient presents with stage IV disease at diagnosis, from the primary tumor or a metastatic site. If a patient is progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib), tumor tissue sample is required only if available.
- 5.1.4 No new systemic anti-tumor therapy administered in the interval between the tissue biopsy and collection of the blood sample. (interval not to exceed eight weeks). Local radiation therapy is permitted.
- 5.1.5 Able and willing to read, understand and sign an informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, or equivalent privacy law, where this is applicable.

5.2 Exclusion Criteria

- 5.2.1 Patients who are currently receiving therapy (targeted, immune- or chemotherapy) without sign of progression.
- 5.2.2 Patients with squamous NSCLC.
- 5.2.3 Patients with more than 8 weeks between collection of tumor specimen and collection of blood sample for analysis. (Not applicable for patients progressing on EGFR targeted therapy with no biopsy at progression)

5.2.4 Patients changing EGFR therapy due to toxicity or preference without documented disease progression.

5.2.5 Patients progressing on Osimertinib treatment.

5.2.6 Patients with brain metastases only.

5.2.7 Inability to comply with study and/or follow-up procedures.

5.2.8 Unable or unwilling to provide written informed consent.

5.3 Study Duration and Withdrawal

Study participation for subjects ends after the research blood sample is drawn. There is no study-related follow-up with the participants but time to progression on therapy given after liquid biopsy or disease status at one year after liquid biopsy will be captured.

Subject participation is voluntary and can be discontinued at any time without loss of benefits or penalty. Should this occur, the reason for withdrawal must be documented in the original source document for the subject and written notification provided to Genomic Health. Participants are notified through the informed consent process that any de-identified research blood and tissue samples will be destroyed upon their request and not used for further analysis. If requested by the Investigator, a participant may be asked to discontinue the study if they are unable to meet the protocol defined study requirements.

Subjects that are screened but who are unable to undergo a successful blood draw or do not meet the protocol requirements will be considered screen failures.

6. STUDY OBJECTIVES

6.1 Primary Objective

Assess concordance of genomic alterations in *EGFR* (see appendix I) detected in plasma versus tumor tissue in stage IV non squamous NSCLC patients who are newly diagnosed or progressing on treatment.

6.2 Secondary Objectives

6.2.1 Assess concordance of genomic alterations in *ALK* (EML4-ALK fusions) detected in plasma versus tumor tissue.

6.2.2 Assess concordance of all detected alterations in plasma versus tumor tissue.

6.2.3 Assess concordance of mutation-specific NCCN guideline-based clinical actions based on alterations found in plasma versus tumor tissue and versus treatment received based on findings in tumor tissue.

6.2.4 Assess concordance of detected genomic alterations separately in patients with newly diagnosed metastatic disease and patients progressing on treatment.

6.2.5 Summarize the distribution of genomic alterations present in plasma, tumor tissue or both overall.

6.2.6 Characterize the detection of *EGFR* T790M alterations in plasma in patients progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib).

6.3 Exploratory Objectives

6.3.1 Explore the association of genomic alterations detected in plasma or tumor tissue and time to progression, defined as first objective sign of progression by clinical examination or imaging, and response to therapy initiated after the liquid biopsy test.

6.4 Measures to Minimize Bias

Genomic Health staff involved in the processing of liquid biopsy samples will remain blinded to the central assessment of FPE tissue, Pathology and Clinical data collected during the study. The Genomic Health staff involved in the central assessment of FPE tissue will be blinded to the results of the liquid biopsy.

7. STUDY PROCEDURES

7.1 Subject Screening

Patients meeting the inclusion and exclusion criteria shall be offered enrollment in the study. Upon enrollment, a unique patient study identifier and unique specimen identifier(s) (for blood samples and tissue specimens), will be issued to each subject. The assigned identification numbers will not provide Genomic Health staff a direct link to private patient information.

7.2 Obtaining Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC approved informed consent. The Informed Consent Form will be reviewed and approved by the Sponsor or its designee prior to submission to the IRB/EC and initiation of enrollment. All appropriate

bills/legislative actions are to be considered and the Informed Consent Form amended, as appropriate. For example, the California Experimental Subject's Bill of Rights will be placed on the forefront of the Informed Consent Form for sites in California. The Informed Consent Form will be administered by the investigator or research staff authorized by the investigator using the most recent version of the informed consent document containing the IRB/EC stamp with dates of approval and or expiration (as required by applicable regulations and IRB/EC standard procedures). All research staff administering informed consent will be trained on Human Participant Protection prior to administering informed consent. Prior to participation in the study, the written Informed Consent Form will be signed and personally dated by the participant, and by the person who conducted the Informed Consent Form discussion. In order to ensure compliance with the HHS HIPAA Administrative Simplification Regulations, participants will be asked to sign a HIPAA authorization form or equivalent privacy law dictated authorization, where this is applicable. The signed HIPAA authorization forms, or equivalent, will allow researchers to use the participants' Protected Health Information in the research study.

7.3 Clinical Assessment and Data Capture

Demographic and clinical data on each participant will be collected at the enrollment visit. All clinical and demographic variables will be obtained from the clinical sites through a validated electronic data capture (EDC) system. The demographic variables will include age and gender. The clinical variables will include diagnosis, stage, histology of the tumor, marker status of primary tumor/metastatic site if available, site(s) of metastatic disease and treatment (prior targeted therapy, last therapy given prior to study enrollment and therapy after liquid biopsy). Additionally, dates of diagnosis, surgery, treatment, metastatic tissue biopsy, liquid biopsy, and of documented disease progression (defined as first objective evidence of progression (increasing tumor size or new lesions) by clinical examination or imaging) after liquid biopsy will be collected, when applicable. The clinical site will provide follow up clinical information including treatment given after liquid biopsy, best response to this treatment (complete response, partial response, stable disease or progressive disease) and date of progression or, at 12 months after liquid biopsy, if still on treatment without progression at that time. Follow up should also be completed upon patient death should that occur prior to first progression or 12 months after liquid biopsy. Genomic Health or its designee will provide the clinical sites with access to a validated EDC system for electronic case report form (eCRF) documentation. The eCRFs will be completed for each study participant through chart abstraction. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's eCRF. Source documentation and/or objective evidence supporting the eCRF data should indicate the participant's inclusion in the study and should document the dates and details of study procedures, adverse events, and participant status. The

investigator, or designated representative, should complete the relevant eCRF pages as soon as possible after information is collected, preferably on the same day that a study participant is seen for enrollment and blood draw. Any outstanding entries must be completed during data monitoring. An explanation should be given for all missing data. Individual subject files should be maintained in addition to the eCRFs. These files constitute "source data" and must be signed and dated by the study site research personnel who recorded the data (electronic signatures are acceptable for electronic medical records). All entries in the eCRFs must be supported by source data. The eCRFs must be kept up-to-date so that they reflect the latest observations on the subjects enrolled in the study. Each subject's file must include the original signed and dated Informed Consent Form and all specimen collection and shipping information.

This study will be registered with and posted on ClinicalTrials.gov (www.clinicaltrials.gov).

7.4 Collection, Shipment and Processing of Blood Samples

A total of 20 mL of venous blood will be collected in two Streck tubes (10 mL each) and shipped to Genomic Health the same day of collection. Blood collection should coincide, when possible, with routine clinical blood draws to minimize discomfort. A *Liquid Collection Form* (LCF) will be filled out, one per participant's blood collection, with the following information:

- Subject ID – unique identifier assigned to each subject, to remain the same number throughout all study collection events. This number will be linked to the clinical data.
- Collection Date and Time and additional administrative variables.
- All samples are to be shipped to Genomic Health on the day of collection via the courier specified for that site. Collections on Fridays may be sent out same day for delivery to Genomic Health on the following Monday, unless otherwise instructed by Genomic Health or its designee.

Genomic Health will perform blood pre-processing (plasma extraction) on the day of sample arrival. The blood samples received at Genomic Health will be handled and processed according to the liquid biopsy Specimen Preparation Instruction (SPI) manual and other Genomic Health related procedures. Genomic Health will notify the study site of all the samples received and their status as acceptable or rejected for further testing (i.e., quality or labeling issues) using the assigned de-identified study subject identifier. If the sample rejected or fails quality control metrics a second blood draw may be requested.

Any samples or remnant specimens (from blood) remaining after the conclusion of the study may be banked for future research. Future use will be explained in the ICF where the subject may elect to not approve banking their left over samples. All remaining samples or specimens will be de-identified and stored in an appropriate storage environment at Genomic Health. De-identified data associated with the banked left over samples will be stored in a secure Genomic Health database and will not be traceable to any identifiable protected health information.

7.5 Collection, and Processing of Pathology Samples

Enrolled subjects will have previously collected pathology tissue samples that will be utilized for the tissue-based sequencing if sufficient tumor material for analysis is available (as defined in section 4.1) and if patient approves of sending the material for analysis.

Local assessment of tumor tissue samples will be performed at each participating institution as per their clinical standard of care practices and results from the local assessment of genomic alteration status will be used. Each site will need to provide a single H&E slide to Genomic Health for an independent pathology review.

Genomic Health will receive and inspect the H&E slides according to approved internal receiving protocols. The received samples will be accessioned and quality inspected. Genomic Health standard histopathology assessments will be made from the single H&E slide of each FPE tumor tissue specimen by a Genomic Health designated pathologist(s) and will include: presence of tumor (adequate quantity).

Additional pathology measures will be obtained from the tissue biopsy pathology and mutation reports and entered into the electronic data capture system by the clinical site personnel.

Any residual DNA remaining after the conclusion of the study may be banked for future research. Tissue blocks or slides not used for analysis will be returned to the ordering physician but residual DNA will be stored by GHI. Future use will be explained in the ICF where the subject may elect to not approve banking their left over samples. All remaining samples or specimens will be de-identified and stored in an appropriate storage environment at Genomic Health. De-identified data associated with the banked left over samples will be stored in a secure Genomic Health database and will not be traceable to any identifiable protected health information.

8. STATISTICAL METHODS

8.1 General Methods

This section provides a general description of the statistical analysis methods. A detailed description of the analysis methods will be provided in the Statistical Analysis Plan, that will be developed blinded to any analytical test results (i.e. from the liquid biopsy tests and tumor tissue assessments) and finalized prior to the data lock for the interim analysis.

This is a descriptive study to characterize the concordance between the results of the Genomic Health LBMP based on plasma and genomic assessment of the tumor tissue. Both the liquid biopsy and the tumor tissue assessments will report the status of the investigated alterations in a binary manner as detected or not detected. No formal hypothesis testing is planned. Unless otherwise stated, two-sided 95% Clopper-Pearson confidence intervals will be reported[28].

The analysis of a single tumor biopsy cannot yield a reference standard for a liquid biopsy assessment due to tumor multifocality and intra- and inter-tumor heterogeneity in stage IV disease. As described in the FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (2007), when a new test is evaluated by comparison to a non-reference standard, it is not possible to directly calculate unbiased estimates of sensitivity and specificity. Therefore, due to lack of reference standard for analysis of liquid biopsies, it would not be appropriate to describe the comparative results of the study in terms of sensitivity and specificity. Instead, we will characterize the concordance in terms of positive percent agreement (PPA) and negative percent agreement (NPA) as presented in section 8.3, Table 4.

8.2 Analysis Populations

Statistical analyses will involve samples from patients with stage IV non squamous NSCLC. Samples that are not collected according to the sample preparation instructions, fail pathology review, fail to meet pre-specified analytical quality control metrics as defined by the Genomic Health LBMP's standard operating procedures, or fail to meet pre-specified quality control specification for the FPE assessment will be considered non-evaluable and will not be included in the analyses described in this section. Approximately 20% of enrolled patients are expected to have non-evaluable samples and thus results from approximately 248 evaluable patients are expected to be included in the analyses.

The primary analysis will be based on patients with non squamous NSCLC with evaluable plasma and tissue samples and reportable results from both the Genomic Health liquid biopsy test and tumor tissue assessments. The results of the central tissue assessments will be used when available. In patients without central CLIA laboratory results, local assessments of genomic alterations in tissue will be utilized. Exploratory analyses will include patients with evaluable samples from the Genomic Health liquid biopsy test and time to progression and available assessment of best response to therapy initiated after the liquid biopsy test.

8.3 Primary Analysis

The primary analysis will characterize the concordance of clinically relevant *EGFR* alterations (see appendix I) detected in plasma versus tumor tissue for patients with stage IV non squamous NSCLC. PPA, NPA and overall concordance will be calculated across all *EGFR* alterations, for all sensitizing alterations and for each individual alteration, separately.

Two tables (Tables 4A and 4B) will be constructed and PPA, NPA, overall agreement and corresponding confidence intervals will be calculated as shown below. Of note, the NPA will be calculated based only on patients enrolled regardless of presence or absence of the genomic alterations (Section 4, Table 2). Patients enrolled after this initial period due to presence of *ALK* alteration in tissue will not be included in this analysis as they are unlikely to have *EGFR* mutations and their inclusion could result in overestimation of NPA.

Table 4. Calculation of PPA and NPA.

4A: Table based on all patients with available tissue biopsy with EGFR alterations detected in tumor tissue

Genomic Health liquid biopsy mutation panel	*EGFR* alteration detected in tumor tissue
EGFR alteration detected	a
EGFR alteration not detected	c
Total	a+c

Positive Percent Agreement (PPA) = a / (a+c) * 100%

4B. Table based on all patients with available tissue biopsy enrolled regardless of presence or absence of genomic alterations as described in Section 4 and Table 2.

Genomic Health liquid biopsy mutation panel	*EGFR* alteration not detected in tumor tissue
EGFR alteration detected	b
EGFR alteration not detected	d
Total	b+d

Negative Percent Agreement (NPA) = d / (b+d) * 100%

If all patients were enrolled regardless of alteration status, the overall agreement would be calculated as (a+d)/(a+b+c+d) * 100%. However, since some patients are enrolled based on known alteration status, the overall agreement will be calculated as a weighted proportion to account for enrichment of the number of patients with marker positive tumors. Details of the calculations will be provided in the Statistical Analysis Plan.

8.4 Secondary Analyses

Secondary analyses will include assessments of PPA, NPA and overall agreement calculated as described in section 8.3 for *ALK* alterations (objective 6.2.1) and all other detected alterations (objective 6.2.2).

In addition, we will report:

1) the total number of all alterations detected in plasma, tumor tissue, or both.
2) the number of patients with at least one alteration with clinical relevance detected in plasma, tumor tissue, or both.
3) the number of hotspot mutations and non-hotspot mutations detected in plasma, tumor tissue, or both.

The results will be presented separately for single nucleotide variant (SNV), copy number variant (CNV) and structural variant (indels, insertions, translocations) alterations.

As described in study objective 6.2.3, mutation-specific NCCN-guideline based clinical actions based on alteration status in plasma will be compared to those based on tissue

and the actual treatment received based on findings in tumor tissue. For each patient, a clinical action will be defined in agreement with NCCN guidelines based on detected key genomic alterations and prior targeted therapies to mimic the clinical context for decision making. A detailed description of each clinical action will be provided in the Statistical Analysis Plan. To assess concordance of clinical actions based on alterations identified in plasma vs those based on tissue as well as concordance of clinical actions based on alterations identified in plasma and the actual treatment received based on tumor tissue findings, PPA, NPA and overall agreement will be calculated.

We will assess PPA, NPA and overall agreement separately for patients with newly diagnosed metastatic disease and patients who progressed on treatment (study objective 6.2.4).

The concordance analyses will also be conducted in the subset of patients with available central CLIA laboratory assessment of tumor tissue.

In addition, we will summarize the distribution of all genomic alterations detected in plasma, tumor tissue, or both using tabulations, histograms and descriptive statistics (study objective 6.2.5). We will provide such summaries for individual alterations, sensitizing vs resistance alterations within a gene (if applicable), all alterations within a given gene and across all genes.

The detection of *EGFR* T790M alterations in plasma samples will be characterized descriptively in patients progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib) (study objective 6.2.6).

8.5 Exploratory Analyses

We will examine the association between the presence of alterations in plasma or tissue and endpoints such as time to progression and response to first therapy initiated after liquid biopsy.

Time to progression is defined as time from first initiated therapy (after liquid biopsy) to progression as documented by imaging or clinical evaluation. Progression identified at the time of death will be considered an event. Patients still on therapy one year after the liquid biopsy assessment will be censored. We will use Cox proportional hazards regression models and Kaplan-Meier analyses and will consider non-linear techniques, including smoothing splines. Subset analyses based on alteration status in tissue and plasma may be conducted.

Response is defined as best response to therapy initiated after liquid biopsy (complete response, partial response, stable disease or progressive disease). We will use logistic regression models and will consider non-linear techniques, including smoothing splines.

8.6 Interim Analysis

An interim analysis will be performed when approximately 30 patients with EGFR mutations in tissue samples are enrolled. Should the laboratory not have finalized analytical validation at that time, enrollment will continue until analytical validation has been performed. The interim analysis will support the documentation of performance of the Genomic Health liquid biopsy test and may be used for submission of an abstract to a scientific conference. The results of this interim analysis will not be used to modify the design or conduct of this study, including the associated Laboratory Protocol and Statistical Analysis Plan. In particular, the sample sizes specified in section 4 will not be modified based on the results of this interim analysis.

8.7 Sample Size

The sample size considerations for this study were based on the probability of observing PPA/NPA estimates in the anticipated range as well as the size of the confidence intervals around these estimates. To account for possible losses (~20%), approximately 260 patients with plasma and tissue samples will be enrolled to obtain approximately 208 patients with evaluable samples for concordance analyses and 50 patients with plasma samples only will be enrolled to obtain 40 evaluable patients to characterize the detection of *EGFR* T790M alterations in plasma. It is expected that the majority of patients with plasma and tissue samples will be newly diagnosed with stage IV non squamous NSCLC since metastatic lesions are not frequently biopsied.

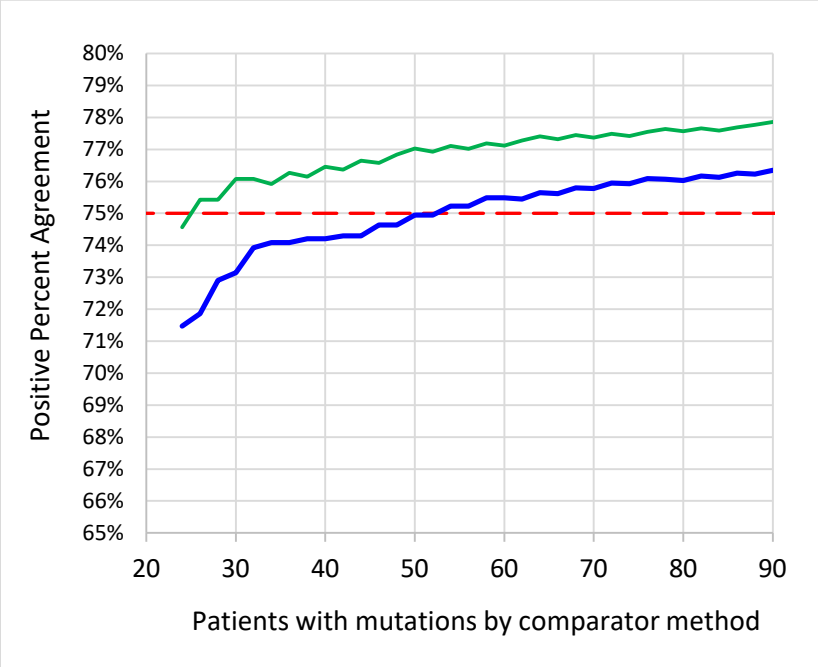
In patients with plasma and tissue samples, two *EGFR* alterations, L858R and exon 19 deletion, are expected to be observed most often: each with ~45% prevalence in patients with EGFR-mutant tumors [29]. The alteration-specific analyses for these alterations are expected to include ~25 evaluable patients each leading to a total of 50 patients with activating *EGFR* alterations. T790M resistance alteration has a low prevalence in untreated NSCLC[30] and hence is expected to be observed relatively rarely.

Figure 2 displays the 20th (blue) and the 30th (green) percentiles of the distribution of positive percent agreement as a function of the sample size using a binomial distribution and assuming a true PPA of 80%. Based on these results, a study with 25 patients with a known alteration will have a 70% probability to observe a PPA estimate

≥75%. A study with 50 patients with a known alteration will have an 80% probability to observe a PPA estimate ≥75%.

Similar calculations for the true PPA of 90% indicate that a study with 25 marker positive patients will have a 75% probability to observe a PPA estimate ≥85% (not shown in figure below). A study with 50 patients with a known alteration will have an 85% probability to observe a PPA estimate ≥85%.

Figure 2. Percentiles of the PPA estimate as a function of sample size assuming true PPA of 80%*



* Moving average smoother was applied to the estimates based on binomial distribution.
Legend: blue line represents 20% percentile and green line – 30% percentile of PPA estimates.

If a PPA of 80% is observed in 50 patients with a known alteration, the 95% exact Clopper-Pearson confidence interval will have a lower bound of 0.66 (Table 5). Similar logic applies to the NPA estimates. These calculations were obtained using PASS version 13.

Table 5. Lower bound of the 95% Clopper-Pearson confidence interval as a function of observed PPA estimate and sample size.

Observed PPA	Number of patients with detected alterations in tissue				
	20	30	40	50	60
0.90	0.68	0.74	0.76	0.78	0.80
0.85	0.62	0.67	0.70	0.72	0.73
0.80	0.56	0.61	0.64	0.66	0.68
0.75	0.51	0.56	0.59	0.61	0.62

In patients with plasma samples only who are progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib where tissue sample is not mandatory) approximately 50% of patients are excepted to have T790M alteration. If the true probability of T790M alteration in this population is 0.50, we will have an 85% chance of detecting these alterations in 40% to 60% of samples from 40 patients progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib). In analysis with 40 patients, the width of the 95% confidence interval around the proportion of detected T790M alterations will be 0.32 if alterations are detected in 50% of plasma samples.

9. DATA MANAGEMENT

Subject demographic and clinical data from the eCRFs will be entered into a password protected database along with the participant's unique and protected study subject ID number. The password protected database will be maintained by Genomic Health Data Management. Results of the Genomic Health liquid biopsy mutation panel and pathology review will be collected and entered into the password protected Genomic Health database.

An independent password protected and validated database will be maintained by the clinical site that includes the subject ID number and results of the pathology report and NGS tissue mutation panel from the independent CLIA laboratory.

A database containing the data collected on the Liquid Collection Form (LCF) will be maintained by Genomic Health BioMaterial Repository (BMR) via accessioning of the received blood samples. This data is associated with the handling and processing of the subject's samples and accompanies all samples that are shipped to Genomic Health for processing and testing.

All databases will be kept separate, and subject samples will be identified only by subject ID number. Databases will be merged only for the planned interim analysis and at the completion of the study.

10. ADVERSE EVENT REPORTING

The investigator, clinical research staff, or a trained phlebotomist will monitor for the occurrence of adverse events for each subject at the time of the study venous blood draw. Adverse events related to the blood draw in subjects will be listed on the AE Form in the EDC. Only events that are clearly attributable to the study blood draw will be considered a study related adverse event and will be reported. Determination should be based on assessment of temporal relationships, biologic plausibility association or lack thereof with other procedures done as standard of care and presence (or adherence) of a more likely cause. All adverse events that occur during the biopsy/resection, clinical therapy, or other invasive diagnostic or treatment procedures, as a result of standard clinical care, and/or distant in time from the study phlebotomy will not be monitored and are not considered a study related adverse event in this study. The investigators will report adverse events to the IRB according to the local or central IRB reporting requirements.

11. RISK VERSUS BENEFIT ANALYSIS

11.1 Risk Analysis

Subjects participating in the study shall be under minimal risk. The only intervention is an additional blood sample that will be de-identified and labeled with a unique study identification number. According to 21 CFR Part 812.3(k), blood sampling that involves simple venipuncture is considered noninvasive. Patients will not receive any diagnostic information or treatment recommendations based on the Genomic Health liquid biopsy mutation panel. Therefore, the risks and discomforts in this study are those associated with venipuncture a single venous blood draw. These risks include temporary discomfort, bruising, lightheadedness, and in rare occasions infection or fainting. Blood samples will be analyzed using the Genomic Health liquid biopsy mutation panel. If the samples are not exhausted at the end of the this study, the samples may be used for quality control purposes and for exploratory analysis of concordance of additional cancer relevant genes not included in the current panel with the approval of the participant. Test results generated from blood samples collected in this study will not be shared with the study participants or their health care providers; therefore, will not impact on their clinical care or outcome.

11.2 Risk Management

The investigators and designated study site staff will be trained in the conduct of the study and patient confidentiality requirements. Only centers with trained phlebotomists will participate in the study. Universal precaution will be utilized for handling blood samples. There will be quality assurance oversight for determining the proper labeling,

identification, shipping/receipt, and processing procedures for handling samples and specimens.

11.3 Study Benefits

There will be no direct benefits to the subject's participation in the study. The advantages of liquid biopsy over tumor biopsy is that it may offer future patients an alternative, less invasive method to assess the genomic alterations of their disease. A liquid biopsy may also overcome issues with tumor heterogeneity associated with single biopsies of tumor tissue.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Study Conduct

The study will be conducted in accordance with all federal, provincial, state, and local laws of pertinent regulatory authorities, and the applicable regulatory requirements. The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki, as applicable, or with the laws and current regulations of the country in which the study is conducted, whichever affords the greater protection to the participant. The study will be conducted in accordance with all country specific privacy rules as applicable. In the US, the study will be conducted in accordance with the HHS Administrative Simplification Regulations (45 CFR Parts 160,162, and 164). If the study includes sites from the European Union, the study will be conducted in accordance with the Data Privacy Directive 95/46/EC. If the study includes sites from Canada, the study will be conducted in accordance with the Therapeutic Products Directorate. After reading the protocol, each investigator will sign a protocol signature page and return the signed page to the Sponsor.

12.2 Subject Confidentiality

Information that would allow identification of the individual, as defined by the HIPAA protected health information (PHI) identifiers (45 CFR § 160.103), includes but is not limited to name, social security number, and any number assigned by the hospital or medical office. PHI collection will be limited to data that are necessary for conducting the study and associated analyses. Patient-related materials (specimen, pathology report) will be identified only by a study-specific unique identifier, and will not be used to directly identify the patient. NGS results from a CLIA registered test service provider from the assessment of the tumor tissue will be reported to the participant's physician but the results will be provided to Genomic Health using only the study-specific identifier. It is the responsibility of the study investigators to ensure de-identification of the specimen and pathology reports. The study investigators are also

responsible for maintaining the link between the participant and the study-specific subject identifier, and Genomic Health will have no access to this information.

12.3 Institutional Review Board / Independent Ethics Committee

The Institutional Review Board / Independent Ethics Committee (IRB/IEC) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the participants. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, investigational plan, informed consent, advertisements (if applicable), written information given to the participants, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator and/or sponsor. Prior to the start of the study the investigator will provide GHI or its designee with documentation that the IRB/IEC has reviewed and approved the protocol and the Informed Consent Form. Additional documentation may be submitted pending applicable local requirements. Each investigator must provide at least the following documentation:

- The IRB/IEC approval of the protocol;
- The IRB/IEC approval of the Informed Consent Form;
- The IRB/IEC composition (membership list),
- The IRB/IEC annual (or any other frequency when applicable - i.e. quarterly, semiannually according to the local/central EC standard operating procedure);
- Renewed approval of the protocol;
- The IRB/IEC approval of any revisions to the Informed Consent Form or amendments to the protocol; and
- The IRB/IEC notification of the study termination.

12.4 Site Monitoring, Audits, Reviews, and Inspections

Genomic Health clinical operations or representative staff will monitor the study according to the study specific monitoring plan. Personnel selected to perform monitoring will be appropriately trained and qualified to perform the required monitoring activities. The study monitor will visit all the sites to ensure that site study staff have the information they need to conduct the study and that the trial is conducted and documented properly through the duration of the study, this includes verifying that:

- The rights and the well-being of the participants are protected.
- The collected data are accurate, complete and verifiable from the source documents.
- The conduct of the trial is in compliance with the current approved protocol.

Prior to study initiation, the study monitor ensures that the investigators:

- Understand the investigational status of the LDT and the requirements for accountability of data and specimens;

- Understand the study protocol;
- Understand the requirements for an adequate and well-controlled study;
- Understand and accepts his or her obligations to obtain informed consent in accordance with 21 CFR Part 50;
- Understand and accepts his or her obligation:
  - to obtain informed consent in accordance with 21 CFR Part 50, GCP and the applicable regulatory requirements;
  - to obtain EC review and approval of a clinical investigation before the investigation may be initiated;
  - to ensure continuing review of the study by the EC in accordance with 21 CFR Part 56, GCP and the applicable regulatory requirements;
  - and to keep the sponsor informed of such EC approval and subsequent EC actions concerning the study;
- Has adequate number of qualified staff and facilities for conducting the study; and
- Has sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations.

The study monitor will visit the study site as defined in the monitoring plan to ensure that the facilities used by the investigator continue to be acceptable for the purposes of the study, has appropriate documentation and supplies (e.g., study protocol, most recently IRB/IEC approved Informed Consent Form, Case Report Forms, specimen collection kits) on site to conduct the study, monitor the informed consent process, adherence to the protocol, and the maintenance of adequate and accurate research records. During these visits, Informed Consent Forms and associated source documents will be reviewed to ensure that the consent process is appropriately documented and that there is an ICF on file for each participant in the study. In addition, electronic Case Report Form (eCRF) fields will be verified to ensure that data collected in the eCRF (EDC system) is consistent with data in the participants' medical records and other primary source documentation (verification of data integrity). The review of the subject records will be performed in a manner to ensure that participant confidentiality is maintained. Study investigators will be required to address any negative findings and submit a written response for corrective measures to be taken to correct and prevent future occurrence of any negative findings.

The FDA, IRBs, and/or the Sponsor’s clinical quality assurance team may request an on-site inspection or Good Clinical Practice audit. Direct access to original source documents will be required for this inspections or audits. The process will be carried out giving due consideration to data protection and medical/patient confidentiality. The investigator agrees to give the auditor/investigator access to all relevant documents for review.

12.5 Financial Disclosure

Financial interest of a clinical investigator is one potential source of bias in the outcome of a clinical study. To ensure the reliability of the data, the financial interests and arrangements of clinical investigators will be disclosed to the IRB/IEC, as required. The investigator is required to provide GHI accurate financial disclosure information. Financial Disclosure applies to investigators and sub-investigators including their spouses and dependent children.

13. MODIFICATIONS TO THE PROTOCOL

Any modification to the protocol which may impact the conduct of the study, affect subject safety or potential benefit of the subjects, including changes of primary study objectives, study design, subject population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Protocol amendments may be initiated by GHI or at the request of an investigator. In either case, research specified in protocol amendments must not be initiated before approval by GHI and, if necessary, review and approval by the central and local IRB/IEC. A protocol amendment, if significant, may also require approval by the FDA and/or Medical Devices Bureau and/or local Regulatory Authorities, where applicable. All protocol amendments that require revisions to the informed consent form must be submitted to the IRB/IEC for approval prior to implementation. It is not expected due to the low-risk nature of the evaluation that emergency protocol deviations or modifications will be initiated without GHI and/or IRB/IEC approval. Administrative changes and/or clarifications that have no effect on the way the study is to be conducted are minor corrections. These administrative changes will be documented in a memorandum. The IRB/IEC will be notified of administrative changes at the discretion of Genomic Health.

14. STUDY DOCUMENTS ACCESS AND AVAILABILITY

The Investigator must ensure the reliability and accuracy of the data provided to Genomic Health and maintaining the confidentiality of the documents and tissue samples. The Investigator(s)/Institution(s) will permit research-related monitoring audits, IRB/IEC review, and regulatory inspections by providing direct access to service data/documents. The investigator must ensure the reliability and availability of the objective evidence including all source documents.

14.1 Record keeping and Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory and clinical site requirement(s). Records will be retained for at least two

years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational procedure. According to applicable regulatory or clinical site requirement(s) if the investigator withdraws from the study, the responsibility of keeping the study records, custody, must be transferred to a person willing to accept the responsibility. Genomic Health must immediately be notified in writing if a custodial change occurs. The records include the following:

- The signed Development Protocol, and amendments;
- Collection, processing, shipping, and receiving records of all specimens and study-related materials;
- Dated and documented IRB approvals;
- Signed informed consent; and
- Financial disclosure.

14.2 Inspection of Records

In the event of an audit and for all monitoring visits, the investigator agrees to allow representatives of Genomic Health, its representative CRO, and other regulatory authorities or government agencies access to all study records.

15. PUBLICATIONS

All information regarding the procedure conducted by Genomic Health is privileged and confidential information. The site investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Genomic Health. The investigators understand that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required. It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific/medical journal. The publication or citation of study results will be managed in accordance with the publication policy of the study agreement.

16. APPENDICES

APPENDIX I

Clinically actionable alterations to be included in the primary analysis:
Exon 19 deletions, L858R, L861Q, G719X and S768I

APPENDIX II

Table 6. Requirements for patients included in category A (See Figure 1)

Patient category:	Enrollment visit requirements	Follow up requirements
Newly diagnosed stage IV patient: 1. Patients regardless of genomic alteration status in tumor (During First Enrollment Phase only) 2. EGFR alterations in tumor 3. ALK alterations in tumor	-Available tumor tissue sample from primary or metastatic lesion. -Pathology report -Mutation report -Clinical data entry in EDC	-Date of progression on first therapy initiated after liquid biopsy, one year after liquid biopsy if still responding, or date of patient death should that occur prior to first progression or 1 year after liquid biopsy. -Clinical and selected treatment data entry in EDC
Patient progressing on therapy (except if progressing on EGFR inhibitors- see below): 1. Patients regardless of genomic alteration status in tumor (During First Enrollment Phase only) 2. EGFR alterations in tumor 3. ALK alterations in tumor	-Available tumor tissue sample from metastatic lesion. -Pathology report -Mutation report -Clinical data entry in EDC	-Date of progression on first therapy initiated after liquid biopsy, one year after liquid biopsy if still responding, or date of patient death should that occur prior to first progression or 1 year after liquid biopsy. -Clinical and selected treatment data entry in EDC

Genomic Health	**Study Protocol**

Requirements for patients included in category B (See Figure 1)

Patient category:	Enrollment visit: requirements	Follow up requirements
Patient progressing on EGFR targeted therapy (erlotinib, gefitinib, afatinib). Note: Patients changing EGFR therapy due to toxicity or preference without documented disease progression will not be included.	-Tumor tissue sample (at progression) preferable but not mandatory. -Pathology report from metastatic lesion at progression if available and from primary tumor if not available -Mutation report from metastatic lesion at progression if available and from primary tumor if not available -Blood sample in Streck tubes (2X 10 mL)	-Date of progression on first therapy initiated after liquid biopsy, one year after liquid biopsy if still responding, or date of patient death should that occur prior to first progression or 1 year after liquid biopsy. -Clinical and selected treatment data entry in EDC

17. REFERENCES

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