TESTING: TElehealth based Synchronous navigation To Improve molecularly-informed care for patients with luNG cancer

Principal Investigator: Charu Aggarwal, MD, MPH
Associate Professor of Medicine
charu.aggarwal@pennmedicine.upenn.edu
(215) 662-6318

Funding Agency: National Institutes of Health

NIH Grant Number: P50CA271338

IRB Protocol Number: 852857

UPCC Protocol Number: 22522

ClinicalTrials.gov Identifier: NCT05790460

Version Date: August 18, 2023 (Version 2)

Protocol Summary

Title	**TESTING: TElehealth based Synchronous navigation To Improve molecularly-informed care for patients with luNG cancer**
Short Title	TESTING
Principal Investigator	Charu Aggarwal, MD, MPH
Co-Investigators	Jeffrey Thompson, MD, MTR Anil Vachani, MD, MS Justin Bekelman, MD Shivan Mehta, MD, MBA Katharine Rendle, PhD, MSW, MPH Marilyn Schapira, MD, MPH Alisa Stephens-Shields, PhD Andy Tan, PhD, MPH, MBA, MBBS Megan Roy MSN, RN, OCN Christoph Hutchinson, MD Kevin Ma, MD David DiBardino, MD Andrew Haas, MD, PhD
Design	Randomized, two-arm clinical trial
Objectives	1. In a randomized pilot trial of patients with suspected locally advanced/metastatic NSCLC, test the effectiveness of enhanced synchronous telehealth nurse navigation, compared to usual care nurse navigation, to increase timely molecularly-informed treatment recommendations through early integration of concurrent molecular testing. 2. Evaluate contextual mechanisms contributing to the effectiveness of synchronous telehealth nurse navigation.
Trial Duration	30 months
Study Sites	University of Pennsylvania Health System (UPHS) sites: Hospital of the University of Pennsylvania Pavilion (HUP) – East Hospital of the University of Pennsylvania (HUP) Pennsylvania Hospital (PAH) Penn Presbyterian Medical Center (PPMC)
Sample Size	Objective 1: 138 patients Objective 2: 20-30 patients and 10-15 clinicians/clinical leaders
Patient Eligibility	Patients will be eligible for the randomized clinical trial if they: a) are aged 18 years or older

	b) based on cross-sectional imaging, are suspected to have locally advanced/metastatic NSCLC (as determined by the evaluating clinician) c) are scheduled for an appointment in the lung cancer evaluation clinic.
Clinician Eligibility	Clinical leaders and clinicians (including physicians, advanced practice providers, and other clinicians) who treat lung cancer at Penn Medicine.
Interventions	Eligible patients will be individually randomized to one of two arms: 1. Usual care – standard nurse navigation. 2. Enhanced nurse navigation – synchronous telehealth nurse navigation visit prior to biopsy.
Outcomes	Objective 1: Receipt of a molecularly-informed treatment recommendation for patients with metastatic NSq NSCLC at the time of the patient's initial oncology visit. Secondary Outcomes: 1. Rate of telehealth visit completion 2. Rate of completion of comprehensive molecular testing (tissue and/or plasma testing) prior to initiation of first line therapy 3. Identification of one or more targetable mutations 4. Timeliness of molecularly-informed treatment recommendation 5. Overall survival 6. Intervention costs 7. Proportion of patients with diagnosis other than metastatic nonsquamous NSCLC (Telehealth arm only) 8. Time to treatment initiation Objective 2: Individual and contextual factors (e.g., treatment knowledge, medical mistrust, clinical beliefs, organizational climate, patient-centered communication, financial toxicity, and knowledge of genetic testing) shaping trial effectiveness and patient experience.
Primary Analysis	Objective 1: Intention-to-treat (ITT) analyses for effectiveness using logistic regression. Objective 2: Mixed methods evaluation of descriptive survey data and thematically coded interview data.
Study Oversight	Dr. Aggarwal (PI) will be responsible for monitoring the trial and ensuring subject safety, as well as the integrity of the interventions and the data collected. Trial oversight will be conducted by the University of Pennsylvania Institutional Review Board.

Contents

1. BACKGROUND AND RATIONALE

The present pilot project is an initiative being conducted by the University of Pennsylvania Telehealth Research Center of Excellence (TRACE). TRACE strives to advance care delivery research through design and testing of innovative telehealth strategies to improve effectiveness and equity across the cancer care continuum.

Precision cancer medicine holds great promise for improving lung cancer outcomes and survival, but its promise will only be realized if patients have broad access to a singular and essential precision component: molecular testing.[1] For non-small cell lung cancer (NSCLC), the past decade has been marked by a steady increase in the number of therapeutically actionable molecular targets used to guide management.[2,3] These therapeutically actionable mutations are present in approximately 30-40% of patients with non-squamous (NSq) NSCLC. At present, over a dozen orally administered targeted therapy regimens for metastatic NSq NSCLC require molecular testing for specific targetable genomic alterations.[4] National guidelines currently recommend that comprehensive molecular testing be performed for all newly diagnosed metastatic NSq NSCLC patients as standard of care.[4,5] Despite the importance of molecular testing in patients with metastatic NSq NSCLC, considerable barriers to timely completion of comprehensive molecular testing prior to initiation of systemic therapy exist, with concerning evidence of disparities by race. In a real-world analysis of 14,768 patients, next-generation sequencing (NGS) was performed among 50.1% of white patients and only 39.8% of Black patients ($p < 0.0001$), even though prevalence of mutations does not vary by race.[6]

Testing of tumor tissue has traditionally been the preferred source of molecular testing, but tumor tissue may be insufficient or unavailable for testing due to factors including location of disease or quality of biopsy.[7,8] Even when feasible, the “turn-around-time” for tumor tissue testing frequently requires 3-4 weeks.[7] These barriers hinder the extent to which patients and clinicians can make guideline-concordant treatment decisions at the time of the initial in-person medical oncology visit, delaying initiation of cancer therapy and diminishing both patient and clinician satisfaction and quality of care. For metastatic NSq NSCLC, treatment initiation without molecular testing or treatment delays of any duration can be consequential, degrading the effectiveness of life-extending therapy, and can weigh heavily on patients and clinicians.[9,10] Our team, and others, have shown that the addition of concurrent plasma-based molecular testing may help address the crucial molecular under-testing gap by offering an approach that is fast and convenient, especially for patients where tissue is unavailable or inaccessible. Plasma-based molecular testing is a complementary mechanism to obtain molecular results upon initial diagnosis, is included in national guidelines, and could be particularly meaningful to address the inequities faced by patients from communities that experience health disparities.[11,12]

The overarching goal of this pilot trial is to design and test a nurse navigation intervention delivered via telehealth for patients with suspected locally advanced/metastatic NSCLC to improve timely molecularly-informed treatment recommendations through early integration of concurrent molecular testing (i.e., tumor tissue and plasma-based molecular testing or plasma only when tumor tissue is insufficient/unavailable). Our central hypothesis is that providing telehealth nurse navigation to support completion of concurrent molecular testing will result in higher rates of comprehensive testing, improved timeliness of molecularly-informed treatment recommendations (primary endpoint), earlier initiation of molecularly-informed treatment, more meaningful patient-clinician communication, and higher levels of overall satisfaction among patients and clinicians. Drawing from systematic evidence on the role of navigation for coordination of cancer care and informed by insights from communication science and behavioral economics, the specific telehealth strategy to be tested is synchronous telehealth nurse navigation in combination with default ordering of plasma-based testing. This trial will allow us to assess multilevel determinants shaping the effectiveness and equity of telehealth strategies for cancer treatment initiation.

2. OBJECTIVES

2.1 Primary Objectives

Objective 1: In a randomized pilot trial of patients with suspected locally advanced/metastatic NSCLC, test the effectiveness of enhanced synchronous telehealth nurse navigation, compared to usual care nurse navigation, to increase timely molecularly-informed treatment recommendations through early integration of concurrent molecular testing.

Objective 2: Evaluate contextual mechanisms contributing to the effectiveness of synchronous telehealth nurse navigation.

2.2 Primary Outcomes

Objective 1: Receipt of a molecularly-informed treatment recommendation for patients with metastatic NSq NSCLC at the time of the patient's initial oncology visit.

Objective 2: Individual and contextual factors (e.g., treatment knowledge, medical mistrust, clinical beliefs, organizational climate, patient-centered communication, financial toxicity, and knowledge of genetic testing) shaping trial effectiveness and patient experience.

2.3 Secondary Outcomes

Objective 1: Secondary outcomes include:

1) Rate of telehealth visit completion
2) Rate of completion of comprehensive molecular testing (tissue and/or plasma testing) prior to initiation of first line therapy
3) Identification of one or more targetable mutations
4) Timeliness of molecularly-informed treatment recommendation
5) Overall survival
6) Intervention costs
7) Proportion of patients with diagnosis other than metastatic NSq NSCLC (telehealth arm only)
8) Time to treatment initiation

3. STUDY POPULATION

3.1 Target Population

Objective 1: The target population is 138 patients with suspected locally advanced/metastatic NSCLC.

Objective 2: The target population is 20-30 patients who participate in the pilot trial and 10-15 clinicians or clinical leaders.

3.2 Inclusion Criteria

Objective 1:

Patients will be eligible for the randomized clinical trial if they:

a) are aged 18 years or older
b) based on cross-sectional imaging, are suspected to have locally advanced/metastatic NSCLC (as determined by the evaluating clinician)
c) are scheduled for an appointment in the lung cancer evaluation clinic.

Objective 2:

Patients will be eligible if they were selected for participation in the pilot trial. Clinicians will be eligible if their area of expertise relates to the protocol topic (e.g., oncologists, nurses, clinical leads).

3.3 Exclusion Criteria

Patients will be ineligible for the pilot randomized clinical trial if they:

a) are not suspected to have locally advanced/metastatic NSCLC
b) have a concurrent active malignancy.

3.4 Vulnerable Populations

Children, fetuses, neonates, or prisoners are not included in this research study.

4. STUDY DESIGN

4.1 Preliminary Studies

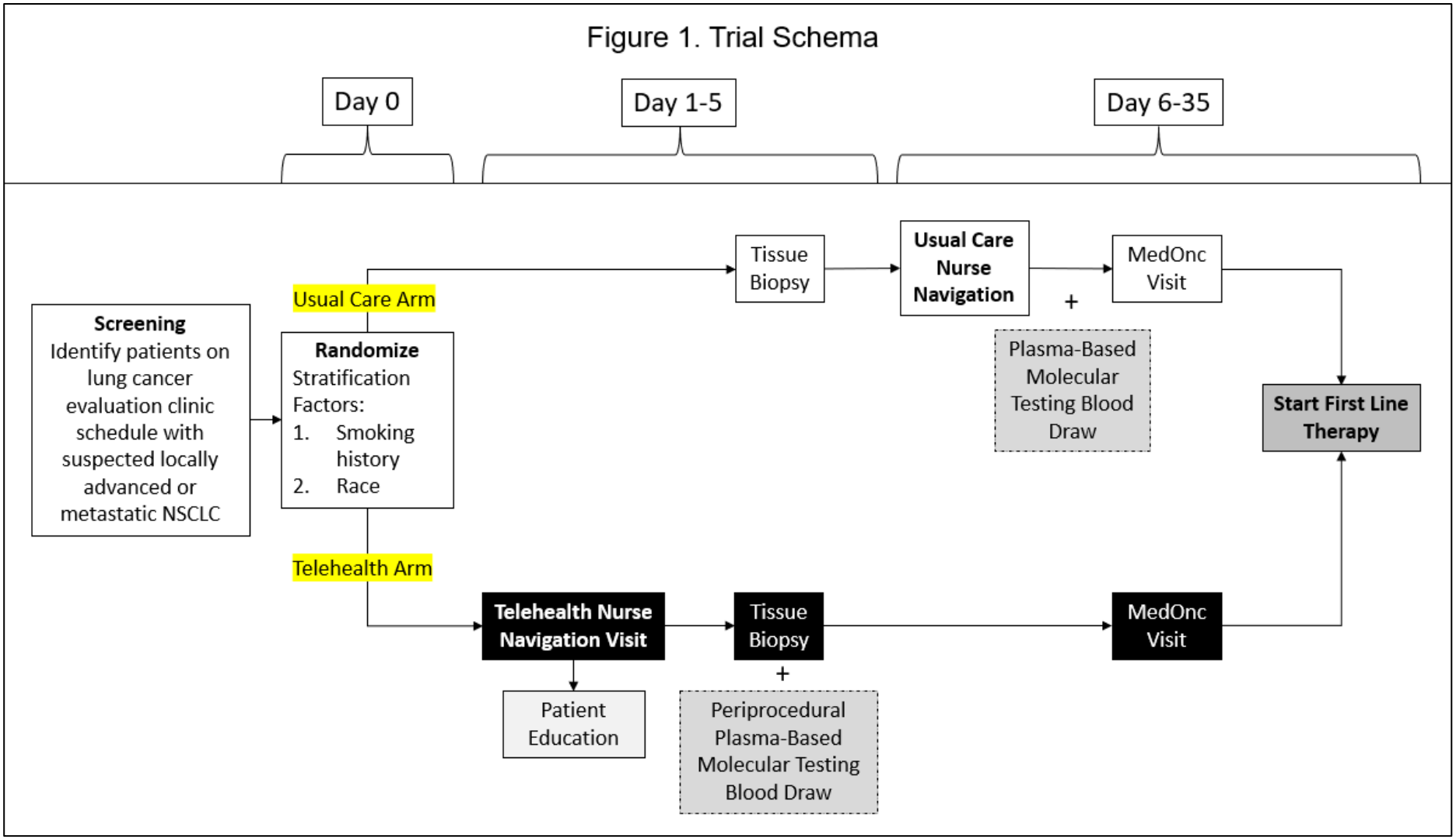
We have conducted two prior studies that inform the design of this trial. In the first, we evaluated the impact of plasma-based molecular testing in addition to tissue testing on the detection of actionable mutations in patients with metastatic NSCLC. In 229 patients who underwent concurrent plasma and tissue molecular testing, tissue alone detected targetable mutations in 21% of patients, whereas addition of plasma testing increased targetable mutation detection to 36%.[13] Thus, plasma-based testing increased the rate of detection of therapeutically targetable alterations in metastatic NSCLC when used concurrently with tissue testing. In a second study, initiation of plasma-based testing performed at time of biopsy resulted in earlier availability of molecular results that translated into treatment recommendations in 75% of patients at initial oncology evaluation, compared to a baseline treatment recommendation rate of 47% in a historical control population.[14] It also decreased time to guideline-concordant treatment initiation. However, implementing this intervention at the time of biopsy also resulted in over-testing of some patients (as tissue confirmation and stage were not yet established). The proposed pilot project will examine effectiveness of telehealth nurse navigation with an early comprehensive molecular testing blood draw during the periprocedural period associated with the patient's diagnostic biopsy in order to reach a larger proportion of patients, reduce disparities in molecular testing, and target testing more optimally.

4.2 Overview

Prior to the trial launch, we will use a rapid-cycle approach (RCA) to optimize delivery of the enhanced synchronous telehealth nurse navigation visit and coordination/default ordering of molecular testing. RCA procedures will involve design meetings with the study team, discussions with administrators and clinicians who are members of our Implementation Lab, as well as contextual inquiry with clinicians and patients to elicit feedback.

Objective 1: As shown in **Figure 1**, this two-arm pilot trial will randomize patients with suspected locally advanced/metastatic NSCLC who are scheduled for an appointment in the lung cancer evaluation clinic. Eligible patients will be identified by screening of clinical schedules by study staff using the EMR. Prior to or soon after completing an appointment in the lung cancer evaluation clinic, eligible patients will be randomized to either enhanced synchronous telehealth nurse navigation or to usual care nurse navigation.

Figure 1. Trial Schema



Usual Care Arm:

Currently, in the standard care pathway at Penn Medicine, a patient who is being evaluated for lung cancer has an appointment within the lung cancer evaluation clinic and is then scheduled for a biopsy (e.g., bronchoscopy, transthoracic needle biopsy). After the biopsy is complete, the patient's clinician contacts the trained lung cancer nurse navigator, who then calls the patient to 1) review the roles of clinicians on the medical oncology care team; 2) provide brief education on lung cancer; and 3) review the patient's diagnostic history and coordinate collection or completion of imaging required for guideline-recommended cancer staging. In the standard care pathway at Penn Medicine this phone call between the patient and the lung cancer nurse navigator usually takes place after the biopsy is complete, though there are some cases in which the clinician asks the lung cancer nurse navigator to reach out to the patient sooner.

For patients randomized to the usual care arm of this study, the researchers will ask the clinicians and the lung cancer nurse navigator not to arrange plasma-based testing earlier than the date of the initial in-person medical oncology visit. Instead, the lung cancer nurse navigator can have the patient complete a blood draw for plasma-based testing on the same day as their initial in-person medical oncology visit.

Intervention (Telehealth) Arm:

Patients in the intervention arm will be scheduled for an enhanced synchronous telehealth visit with a trained lung cancer nurse navigator prior to tissue biopsy. The enhanced synchronous telehealth visit will ideally occur between the initial clinical appointment and diagnostic biopsy (typically a period between two and seven days). In addition to the activities conducted as part of usual care, the nurse navigator will: 1) provide more detailed and individualized education on lung cancer and the rationale for comprehensive molecular testing, including plasma-based tests; and 2) if the patient agrees to testing, pend a default order for plasma-based molecular testing (if not already ordered) for the clinician to sign and arrange for phlebotomy to be performed during the periprocedural window associated with the patient's tissue biopsy.

Objective 2: Using rigorous approaches proven successful in our prior work,[15,16] we will recruit 20-30 patient participants of the primary trial and 10-15 clinicians and clinical leaders to complete semi-structured interviews following the active trial period.

Patients: We will oversample for Black patients to understand effectiveness by race/ethnicity and stratify by trial outcome and study arm to understand factors contributing to both success and failure (e.g., primary endpoint) in either group (5-10 patient in each stratum). Trial participants will be invited in randomly selected batches each month (to enhance capture over time) until we reach our target sample of approximately 20-30 patients. Patients will be invited to participate in interviews via email and/or letter within 6 weeks of their in-person oncology visit.

Clinicians: Recruitment for clinicians will be similar to the procedure for patients, except we will wait until the completion of the full trial to conduct interviews to avoid potential contamination. Clinicians will be purposively sampled by clinical role (e.g., oncologists, nurses, clinical leads) to enhance variation and invited via email. Recruitment will continue until we reach our target sample of 10-15 clinicians.

4.3 Study Duration and Timeline

The study duration will be approximately 30 months. In months 1-3 we will conduct rapid-cycle approaches (RCAs) to optimize the telehealth navigation intervention.

Objective 1: In month 3, we will launch the study and randomize patients by study arm. The active trial enrollment period will be approximately 18 months in length to reach the estimated sample size of 138 patients. Longitudinal data capture to collect secondary outcome information for patients will be completed up to 1-year post-enrollment. Collection and verification of all study endpoints will be completed by 30 months after the study's start date.

Objective 2: Invitations for surveys and qualitative answers for patients will be sent within 6 weeks of the in-person oncology visit and will be completed within 3 months of invitation. Clinician and clinical leader interviews will be completed between months 15 and 21 of funding. Mixed methods analysis for Objective 2 will run from months 18-24.

An overview of the project timeline is below.

Table 1. Trial Timeline

Project Timeline	2023				2024				2025			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Objective 1: Enroll eligible trial participants		•	•	•	•							
Objective1: Deliver intervention		•	•	•	•							
Objective 1: Endpoint ascertainment & analysis		•	•	•	•	•	•					
Objective 2: Recruit & conduct patient interviews			•	•	•	•	•	•				
Objective 2: Recruit & conduct clinician interviews							•	•				
Objective 3: Mixed methods coding & analysis								•	•			
Submit manuscripts & disseminate results									•			

4.4 Study Setting

This study will occur within the University of Pennsylvania Health System (UPHS). Research activities will be conducted at the following UPHS sites:

- Hospital of the University of Pennsylvania Pavilion (HUP) – East
- Hospital of the University of Pennsylvania (HUP)
- Pennsylvania Hospital (PAH)
- Penn Presbyterian Medical Center (PPMC)

5. STUDY PROCEDURES

5.1 Recruitment and Retention

Objective 1: This study will employ a waiver of consent mechanism (see Section 5.2 Informed Consent). Eligible patients will be identified from weekly screening of appointments scheduled at the lung cancer evaluation clinic at Penn Medicine. The process will be optimized to identify all patients with suspected locally advanced/metastatic NSCLC. After eligibility is confirmed based on review of medical records, eligible participants will be randomized to receive an early enhanced synchronous telehealth nurse navigation visit (intervention) or standard nurse navigation (usual care). After completion of the initial clinical appointment, patients in the telehealth arm will be scheduled to receive a synchronous visit (with audio and video capabilities) with a lung cancer trained nurse navigator prior to their tissue biopsy.

Objective 2: This portion of the study will utilize prospective consent with waiver of written documentation (see Section 5.2 Informed Consent). An estimated 20-30 patients and 10-15 clinicians and clinical leaders will be interviewed (sample size dependent upon when data saturation is reached). Interview participants will also complete a survey before or at the time of the interview.

> *Patients:* A sample of patients enrolled in the randomized clinical trial will be invited to participate in the semi-structured interview and survey via email or letter within 6 weeks of in-person visit. Participants will be invited in randomly selected batches (estimate approximately 5 per month to enhance capture over time) until we reach our target sample of approximately 20-30 patients. We will oversample for Black patients to understand effectiveness by race/ethnicity and stratify by trial outcome (treatment recommendation or not) and study arm (telehealth versus usual care) to understand factors contributing to both success and failure of the telehealth strategy (5-10 patients in each stratum).
>
> *Clinicians*: Recruitment of clinicians will be similar to that of patients, except we will wait until the completion of the full trial to conduct interviews to avoid potential contamination. Clinicians will be randomly selected and invited via email. Recruitment will continue until we reach our target sample of 10-15 clinicians, purposively sampled by role (oncologists, nurses and advanced practice providers, practice managers, and health system leaders).

Interviews will be conducted by the qualitative data analyst and other trained research staff supervised by Dr. Rendle, a doctoral-trained qualitative researcher and Co-Investigator on the team. Interviews will be conducted in-person, by phone, or using a HIPAA-compliant video platform.

5.2 Informed Consent

Objective 1: A waiver of informed consent will be used for the randomized pilot trial. A waiver of informed consent is advocated for certain pragmatic trials testing methods for comparing and improving the delivery of established interventions within health care systems. The present study meets criteria for such an alteration of the requirement for informed consent set forth in the Common Rule in the following ways:

- The research involves no more than minimal risk to subjects. The risks to subjects participating in this study and interventions are aimed at improving patient knowledge

and completion of molecular testing. In Sections 7.1 and 7.3, we outline the safeguards we have in place to prevent any breach of confidentiality – the primary risk of study participation.

- The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- To the extent possible, the subjects will be provided with pertinent information after participating in the trial.
- The research cannot be practicably conducted without a waiver or alteration of the requirement for informed consent. This is an explicitly pragmatic approach designed to test the real-world effectiveness of an early telehealth nurse navigation visit to provide patient education and coordinate molecular testing. Key outcomes include assessment of patient centered communication and patient and clinician satisfaction. Requiring traditional (opt-in or opt-out) individual consent would introduce important selection biases (e.g., trial patients would be those willing to be randomized to receipt of a telehealth visit). Knowledge of the trial arms would bias participant opinions on the education and care coordination interventions and influence their views on satisfaction with care received. This would impact the value of the knowledge to be obtained because it would not generalize to the full range of patients diagnosed with lung cancer.

All participants will retain the right to decline patient education or plasma-based molecular testing or other ordered studies, regardless of study assignment.

Objective 2: Potential interview participants will be initially contacted by study team members by email or letter and given the option to decline further contact from the team. If the participant has not opted out within two weeks, they will be contacted by phone to assess their interest in participating in the study. If the participant agrees to participate, they will be scheduled to have an interview in-person, by phone, or using a HIPAA-compliant video platform (based on preference and study procedures at the time). For this portion of the study, a waiver of documentation of written informed consent will be used because the risk to the individual is minimal, a signed informed consent form (ICF) could identify that an individual participated in the study, and obtaining a signed paper form would significantly decrease the likelihood of proceeding towards an interview. Prior to the start of the interview, research staff will review the study purpose, procedures, and the rights of the participant. They will also provide an information statement to participants via email prior to the scheduled interview. Research staff will state that participation is voluntary and ask for the participant's permission to record their interview. They will describe the transcription and de-identification process, and they will ask permission to proceed with the interview. All participants will be free to withdraw participation at any time, and study enrollment will not impact employment or care at Penn Medicine.

5.3 Compensation

Objective 1: Patients who participate in the randomized clinical trial (Objective 1) will not receive compensation.

Objective 2: All patients and clinicians who complete the semi-structured interviews and surveys will receive $50 for their participation. Payments will be made through issuance of GreenPhire ClinCards, which can be used in the same manner as a debit card. The ClinCards will be mailed to participants within 10 days after interview and survey completion.

5.4 Measures and Endpoints

Objective 1: The specific outcomes align with 5 key endpoints (access, quality, outcomes, equity, and efficiency). The primary endpoint is receipt of a molecularly-informed treatment recommendation at the time of the patient's initial in-person oncology visit, measured up to 12 weeks from randomization. This outcome encompasses successful completion of comprehensive molecular testing and the ability of the patient and oncology care team to have all necessary information to collaboratively arrive at the optimal treatment approach. We anticipate that approximately 10% of patients randomized to usual care will be able to receive a molecularly-informed treatment recommendation at initial visit – these include patients in whom tissue was successfully tested and identified a targetable mutation prior to referral. We anticipate this will be substantially improved with enhanced nurse navigation (See Section 6.1 Sample Size). The primary endpoint will be assessed by review of clinician documentation (e.g., progress notes) within the electronic medical record (EMR) on the day of the initial visit.

Secondary outcomes include:

1) Operational endpoints:
    a. Rate of completion of telehealth visit defined as successful completion of a nurse navigator telehealth visit prior to biopsy, measured up to 3 weeks from randomization.
    b. Rate of completion of comprehensive molecular testing (tissue and/or plasma testing) prior to initiation of first line therapy, measured up to 12 weeks from randomization.
2) Clinical endpoints:
    a. Time from randomization to molecularly-informed treatment recommendation, measured up to 12 weeks from randomization.
    b. Proportion of participants with one or more targetable mutations, measured up to 12 weeks from randomization.
    c. Overall survival, measured as 1-year overall survival from time of randomization to death from any cause.
    d. The proportion of enrolled patients with a diagnosis other than metastatic NSq NSCLC (telehealth arm only), measured at 12 weeks from randomization.
    e. Time from randomization to treatment initiation, measured up to 12 weeks from randomization.
3) Cost outcomes:
    a. Intervention costs (measured using a pragmatic method to capture and analyze all system-level resources, such as personnel time and patient outreach costs) that are needed to deploy telehealth strategies in routine care.[19]

Objective 2: We will use structured and validated measures and a semi-structured interview guide based on our Framework for Integrating Telehealth Equity (FITE) to systematically evaluate individual and contextual factors (e.g., treatment knowledge, medical mistrust, clinical beliefs, patient-centered communication, financial toxicity, and knowledge of genetic testing) that will shape the effectiveness of telehealth strategies. Domains that will be assessed as part of the Objective 2 include:

1) Telehealth usability, acceptance, and satisfaction (using the University of Pittsburgh Telehealth Usability Questionnaire)
2) Patient-centered communication (using the University of North Carolina Patient-Centered Communication in Cancer Care Instrument)
3) Medical-related trust and mistrust (using the Group-Based Medical Mistrust Scale [GBMMS])
4) Acceptability, appropriateness, and feasibility of interventions (using the Acceptability of Intervention Measure [AIM] Intervention Appropriateness Measure [IAM] and Feasibility of Intervention Measure ([FIM])
5) Treatment related knowledge and beliefs
6) Other contextual factors (e.g., organizational climate, barriers to using telehealth) that may impact effectiveness of trial

Objective 2 endpoints for the subset of enrolled participants will be assessed up to 1 year from randomization.

5.5 Sources of Materials

Objective 1: Electronic health record (EHR) data will be used to collect the primary endpoint as well as covariates required for statistical analysis. We will use the EHR and survey data collected to assess secondary endpoints.

Objective 2: Semi-structured interviews will be collected and analyzed in conjunction with quantitative measures conducted as part of the RCT.

6. STATISTICAL DESIGN AND POWER

6.1 Sample Size

Objective 1: Sample size is based on estimates of receiving a molecularly-informed treatment recommendation at the initial oncology visit. Based on our prior studies, we anticipate this will occur in 10% of patients in the usual care arm. This pilot study is designed to detect an absolute increase of 20% in our primary outcome for patients in the intervention arm. With a sample size of 124 participants and a two-sided alpha, we will have >80% power to detect an increase of this magnitude. Given the potential for drop-out of patients following randomization, we have increased the estimate by 10%, leading to a final sample size of 138 participants (69 in each arm). Although a difference <20% in our primary outcome rate may be clinically meaningful, this sample size is an optimal balance to allow an assessment of our primary and secondary outcomes and assess for mechanisms of action. Study outcomes will be used to preliminarily assess effectiveness across all outcome domains to inform the design of future studies, including a pragmatic trial, if warranted.

Objective 2: Proposed sample size is based on the estimated number of interviews needed to reach data saturation within each group and by intervention outcome to support mixed methods evaluation; however, interviews will continue until saturation is achieved.[16,21]

6.2 Analysis Plan

6.2.1 Objective 1 Primary Analyses

We will produce data summaries to assess data quality and demographic and clinical characteristics across arms. First, our primary analytic approach will be to conduct ITT analyses

using unadjusted logistic regression to compare the overall effectiveness of the intervention to result in receipt of a treatment recommendation at the initial in-person visit and time to treatment initiation. The ITT analysis provides an unbiased test of the overall effectiveness of the interventions. An additional analysis will adjust for imbalanced covariates, where imbalance is determined by standardized mean differences >0.1. If the number of imbalanced covariates exceeds the number allowed for adjustment based on the number of events, we will prioritize covariates with the largest imbalances.

6.2.2 **Objective 1 Secondary Analyses**

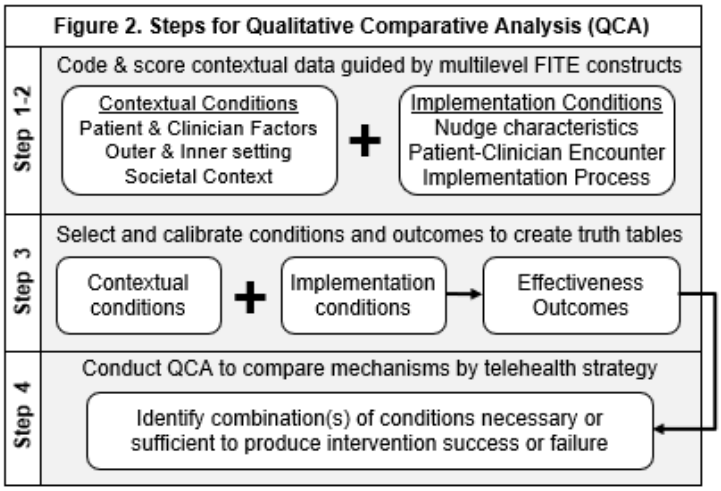
We will use regression methods to assess the impact of the telehealth intervention on secondary outcomes of telehealth visit completion, rate of comprehensive molecular testing, patient satisfaction, clinician acceptability, and intervention costs, with logistic, Cox proportional hazards, and linear regression for binary, time-to-event, and continuous outcomes, respectively. Additional secondary analyses will adjust for factors that exhibit residual imbalance between randomized intervention groups. In addition, secondary as-treated analyses will be conducted.

6.2.3 **Objective 1 Exploratory Analyses**

A difference in effectiveness of the telehealth intervention for Black versus White patients will be conducted by adding a main effect of race and the interaction of race and intervention to the primary unadjusted logistic regression model. Given that hypothesis tests of interaction terms are likely severely underpowered at our pilot study sample size, we will focus statistical inference on the point estimate and 95% confidence intervals for the interaction term. While these intervals may cross the null value consistent with no difference in effectiveness, confidence intervals that largely lie away from the null provide evidence in favor of differential intervention effects that could be detected statistically with a larger sample size in a subsequent study. Patients who do not identify as Black or White will be excluded from this analysis.

6.2.4 **Objective 2 Analyses**

We will descriptively assess survey data and thematically code interview data. These data will be used to conduct qualitative comparative analysis (QCA) to identify how contextual factors shaped both timeliness and quality of care and the effectiveness of nurse navigation. QCA is a multistep analytic method that combines qualitative and quantitative coding and calibration to identify conditions shaping the effectiveness of telehealth strategies. The four-step process will use survey and interview data as inputs or "conditions."



Code Contextual Data (Step 1-2). We will use convergent mixed methods analysis to code contextual conditions (inner setting, outer setting, and individual characteristics) and implementation conditions (characteristics of specific telehealth strategy and process).

Qualitative Data. The constant comparative method, guided by modified grounded theory,[22] will be used to iteratively identify *a priori* domains of interest (guided by FITE) and to inductively explore emergent themes. Two trained coders will first independently read through each transcript to identify themes within each domain. We then will use this list to develop a coding dictionary and apply it to the data. We will measure inter-rater reliability to document and improve coding consistency. Once high reliability is achieved (kappa >0.8), we will apply the full coding dictionary to the interview data using NVivo and produce thematic reports summarizing our findings. We will then use qualitative data to expand upon and triangulate quantitative patterns identified in trial and surveys.[23]

Survey Data. Survey data will be analyzed descriptively and coded dichotomously or categorically as appropriate. Contextual data will serve as QCA inputs to identify necessary and sufficient conditions for telehealth success.

Qualitative Comparative Analysis (QCA) (Steps 3-4). For QCA, our primary endpoint will be receipt of a molecularly-informed treatment recommendation at the time of the patient's initial in-person oncology visit, and success or failure will be determined at the patient level. Each case will be calibrated as having or not having the primary outcome or condition (described above).[24] Thresholds for coding primary outcomes and the presence or absence of each condition (e.g., low quality communication) will be determined based on existing literature or stakeholder consensus. Most outcomes will be dichotomous, but continuous values and fuzzy set QCA will be used as appropriate.[27,28] Data ("truth") tables will be created for analysis, which list all possible configurations of conditions, the number of cases that fall into each configuration, and the consistency of the cases—or the proportion of cases in the specific configuration that have the desired outcome.[28,29] We will conduct QCA analyses using R package *QCApro*.[30–32] Raw and unique coverage will be calculated and consistency will be set at 80% for sufficient and 90% for necessary conditions. This iterative analytic process will identify what conditions—alone or in combination with others—are necessary or sufficient to yield the primary endpoint.

7. DATA MANAGEMENT AND RISK-BENEFIT ASSESSMENT

7.1 Data and Safety Monitoring Plan

A further safeguard to protect research participants is the development of a plan for ongoing data and safety monitoring to anticipate, and protect against, any human subjects research concerns that may arise. The data and safety monitoring plan will have two parts.

1. The study PI (Dr. Aggarwal), biostatistician, and data analyst will develop and implement methods of verifying entered data and of quality control. Individual-level data for participants will be kept confidential and will only be stored on highly secure servers available for patient-level data. Only authorized project personnel will have access to the data and the data will only be stored on servers and not stand-alone PCs or laptops. All data will be reported as units of aggregation which make impossible the identification of individual patients or clinicians.
2. As this is a minimal risk study, monitoring will be performed by Dr. Aggarwal, the principal investigator, who will be directly responsible for identifying and reporting protocol deviations/violations and unanticipated events to the IRBs and funding agency promptly, as appropriate.

A written research protocol will undergo formal institutional scientific and IRB review at the University of Pennsylvania (Penn) to ensure protection of the rights and welfare of human research subjects. Specifically, the PI and the IRB will be responsible for ensuring risks to human subjects are minimized, risks are reasonable, subject selection is equitable, the research team has access to adequate resources to conduct the study, the informed consent process meets regulatory and ethical requirements, adequate provision is made to protect human subjects by monitoring the data collected, and there are adequate provisions to protect subject privacy per HIPAA regulations and confidentiality of data.

All senior/key personnel and research staff who will be involved in the design and conduct of the study must receive education in human research subject protection from a training program that is approved by a properly constituted independent Ethics Committee or Institutional Review Board. The PI will be responsible for ensuring project faculty and staff have the equipment and training required to protect privacy and confidentiality and will monitor and document that these individuals are properly certified. If new senior/key personnel and staff become involved in the research, documentation that they have received the required education will be included in the annual progress reports.

7.2 Potential Risks

Objective 1: For trial participants, the potential risks to human subjects attributable to participating in this trial are minimal. The eligibility processes are designed to identify patients with metastatic NSCLC who are eligible for plasma-based molecular testing according to existing practice guidelines. The main risk of participation is breach of confidentiality; however, we have described the strong data safeguards in place to prevent confidentiality breaches above.

Objective 2: For patient and clinician interviews, potential risks to participating in this study include: potential violation of confidentiality or privacy; possible discomfort in disclosing information on testing knowledge, beliefs, or practices; and possible concern among providers and clinicians that participation will negatively impact job or clinic performance or evaluation. Participation in this pilot project presents minimal risks. There is a potential risk of breach of confidentiality. We will minimize this risk by maintaining confidentiality for individual-level data, storing data on secure servers, and reporting data as units of aggregation. Other risks include possible discomfort in answering interview questions, such as those related to medical distrust or clinical beliefs. Participants are allowed to skip any interview or survey question as needed.

7.3 Protections Against Risk

The primary risk to participants is loss of confidentiality and/or privacy, including of protected health information. To minimize the risk of breach of data and confidentiality, we will use secure, encrypted servers to host the data and conduct the analysis. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project. PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability

and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. All study personnel that will use this data are listed on the IRB application and have completed training in HIPAA standards and CITI human subjects research. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

For Objective 2, all interview and survey data will also be stored on the secure/firewalled servers of the PMACS Data Center, in data files that will be protected by multiple password layers. In addition, we will use the following safeguards: 1) all paper-based data including audio files from interviews, notes from medical record reviews, and qualitative transcripts will be kept in a locked filing cabinet; 2) participant identity will be masked using unique participant IDs and stored on a password-protected master list to which only the PIs will have access; 3) survey data will be collected using a secure, password-protected web-based application (REDCap); 4) surveys will use consent mechanisms that do not require signatures; 5) any protected health information will be housed on secure PMACS servers and only accessible by the PIs and approved research staff; and 6) all statistical or qualitative analytic files will be identified only with participant IDs and not contain any protected health information (all identifiable data will be made de-identifiable prior to including it into the analytic datasets).

For survey and interview participants, a second risk includes possible discomfort of disclosing information on lung cancer knowledge and practices. If experienced, we anticipate this risk will be temporary and minimal.

For survey and interview participants, a third risk for clinicians and patients is that study participation may include possible concern that participation will negatively impact job evaluation or clinical care. In conjunction with efforts to protect confidentiality, we will work to ensure that no individual information regarding lung cancer treatment practices (from clinical record or surveys) is reported to anyone outside the study team, including healthcare management, staff, or providers. The disclosure of lung cancer treatment practices will be communicated only to individual providers. All information regarding beliefs, perspectives, or practices collected in surveys or qualitative activities will be de-identified and reported in aggregate. Lastly, consent language will also clearly state that participation is not required based on employment at UPHS and will not impact employment or clinical care.

7.4 Potential Benefits

There are no direct benefits to patients or clinicians who participate in the interview or survey component of this study. In the trial part of the study, patients may indirectly benefit through improved and more timely communication regarding their cancer diagnosis and the role of molecular testing for treatment planning. For the health of society, the benefits of the study are substantial and include potential improvements in cancer care delivery access, quality, efficiency, equity, and outcomes.

7.5 Importance of the Knowledge to be Gained

Findings from this study will help to advance the field of cancer care delivery and communication science by testing the effectiveness of an early telehealth care coordination visit among patients with advanced lung cancer referred for evaluation and treatment and identifying key conditions that may need to be targeted or adapted to ensure success. By identifying underlying mechanisms supporting or hindering patient-centered care, this project will provide insights into improving lung cancer treatment across the population. This work will also help to advance causal theory in behavioral economics and communication science by evaluating underlying multilevel mechanisms that contribute to the success or failure of care delivery strategies in real-world care.

7.6 Risk-Benefit Ratio

Given the limited risk associated with participation, we anticipate that the benefits of this study will outweigh the risks involved.

8. RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Adequate facilities are available within Penn Medicine's Clinical Practice Network. Members of the research team, listed in HS-ERA, will be overseen by the PI and include appropriate personnel to successfully implement this pilot project. All personnel will complete required training before being granted access to any identifying information. Training includes information on confidentiality through the Collaborative IRB Training Initiative (CITI) courses. All personnel will also be trained in procedures for reporting unintentional breaches in confidentiality to the PI. All personnel will be aware that violations of participant's confidentiality, either unintentional or deliberate, may result in termination of hire.

9. STUDY TEAM

Our team includes investigators with expertise in thoracic medical oncology, pragmatic trials, behavioral economics, and communication science. Dr. Charu Aggarwal will lead this pilot project. Dr. Aggarwal has led multiple prospective studies on the impact of plasma-based molecular testing on clinical outcomes and leads efforts at Penn Medicine and nationally on integration of plasma-based genotyping into the diagnostic algorithm for patients with NSCLC. Dr. Jeffrey Thompson (co-I) also has considerable expertise in NSCLC and plasma-based genotyping. Drs. Justin Bekelman (co-I), Shivan Mehta (co-I) and Anil Vachani (co-I) have considerable experience with leading pragmatic trials with waivers of consent. Other co-investigators include Dr. Alisa Stephens-Shields (biostatistician), Dr. Marilyn Shapiro (decision scientist) as well as Drs. Katharine Rendle and Andy Tan, who bring implementation science and communication science expertise to the team.

10. REFERENCES

1. Politi MC, Yen RW, Elwyn G, et al. Women Who Are Young, Non-White, and with Lower Socioeconomic Status Report Higher Financial Toxicity up to 1 Year After Breast Cancer Surgery: A Mixed-Effects Regression Analysis. *Oncologist*. 2021;26(1):e142-e152. doi:10.1002/onco.13544
2. Carlisle JW, Ramalingam SS. A banner year for immunotherapy and targeted therapy. *Nat Rev Clin Oncol*. 2019;16(2):79-80. doi:10.1038/s41571-018-0138-4
3. Kris MG, Johnson BE, Berry LD, et al. Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *JAMA*. 2014;311(19):1998-2006. doi:10.1001/jama.2014.3741
4. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med*. 2018;142(3):321-346. doi:10.5858/arpa.2017-0388-CP
5. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(9):911-919. doi:10.1200/JCO.2017.76.7293
6. Bruno DS, Hess LM, Li X, Su EW, Zhu YE, Patel M. Racial disparities in biomarker testing and clinical trial enrollment in non-small cell lung cancer (NSCLC). *JCO*. 2021;39(15_suppl):9005-9005. doi:10.1200/JCO.2021.39.15_suppl.9005
7. Gutierrez ME, Choi K, Lanman RB, et al. Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. *Clin Lung Cancer*. 2017;18(6):651-659. doi:10.1016/j.cllc.2017.04.004
8. Bernicker EH, Xiao Y, Abraham A, et al. Adherence to National Comprehensive Cancer Network ALK Testing Guidelines for Patients with Advanced Non-Small Cell Lung Cancer in U.S. Community Medical Centers. *Oncologist*. 2021;26(6):e1050-e1057. doi:10.1002/onco.13779
9. Singal G, Miller PG, Agarwala V, et al. Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. *JAMA*. 2019;321(14):1391-1399. doi:10.1001/jama.2019.3241
10. Schoenfeld AJ, Rizvi H, Bandlamudi C, et al. Clinical and molecular correlates of PD-L1 expression in patients with lung adenocarcinomas. *Ann Oncol*. 2020;31(5):599-608. doi:10.1016/j.annonc.2020.01.065
11. Aggarwal C, Rolfo CD, Oxnard GR, Gray JE, Sholl LM, Gandara DR. Strategies for the successful implementation of plasma-based NSCLC genotyping in clinical practice. *Nat Rev Clin Oncol*. 2021;18(1):56-62. doi:10.1038/s41571-020-0423-x

12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 5.2021. Published online May 2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

13. Aggarwal C, Thompson JC, Black TA, et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. *JAMA Oncol*. 2019;5(2):173-180. doi:10.1001/jamaoncol.2018.4305

14. Thompson J, Aggarwal C, Wong J, et al. Plasma NGS at time of diagnostic tissue biopsy – Impact on time to treatment: results from a pilot prospective study. Presented at: World Conference on Lung Cancer 2021; September 8, 2021; Denver, Colorado.

15. Ogden SN, Glanz K, Schapira MM, Bocage C, Eriksen W, Rendle KA. Patient Perspectives on Primary HPV Testing for Routine Cervical Cancer Screening. *J Gen Intern Med*. Published online July 16, 2019. doi:10.1007/s11606-019-05175-4

16. Rendle KA, Abramson CM, Garrett SB, Halley MC, Dohan D. Beyond exploratory: a tailored framework for designing and assessing qualitative health research. *BMJ Open*. 2019;9(8):e030123. doi:10.1136/bmjopen-2019-030123

17. Parmanto B, Lewis AN, Graham KM, Bertolet MH. Development of the Telehealth Usability Questionnaire (TUQ). *Int J Telerehabil*. 2016;8(1):3-10. doi:10.5195/ijt.2016.6196

18. Thompson HS, Valdimarsdottir HB, Winkel G, Jandorf L, Redd W. The Group-Based Medical Mistrust Scale: psychometric properties and association with breast cancer screening. *Prev Med*. 2004;38(2):209-218. doi:10.1016/j.ypmed.2003.09.041

19. Ritzwoller DP, Sukhanova A, Gaglio B, Glasgow RE. Costing behavioral interventions: a practical guide to enhance translation. *Ann Behav Med*. 2009;37(2):218-227. doi:10.1007/s12160-009-9088-5

20. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. *Implementation Sci*. 2017;12(1):1-12. doi:10.1186/s13012-017-0635-3

21. Morse JM. Critical Analysis of Strategies for Determining Rigor in Qualitative Inquiry. *Qualitative Health Research*. 2015;25(9):1212-1222. doi:10.1177/1049732315588501

22. Glaser BG, Strauss AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. Aldine Pub Co; 1967.

23. Creswell JW, Plano Clark VL. *Designing and Conducting Mixed Methods Research*. 3rd ed. SAGE Publications, Inc; 2018.

24. Rihoux B, Ragin C. *Configurational Comparative Methods*. SAGE Publications; 2008.

25. Kane H, Lewis MA, Williams PA, Kahwati LC. Using qualitative comparative analysis to understand and quantify translation and implementation. *Transl Behav Med*. 2014;4(2):201-208. doi:10.1007/s13142-014-0251-6

26. Weiner BJ, Jacobs SR, Minasian LM, Good MJ. Organizational designs for achieving high treatment trial enrollment: a fuzzy-set analysis of the community clinical oncology program. *J Oncol Pract*. 2012;8(5):287-291. doi:10.1200/JOP.2011.000507

27. Baumgartner M, Ambühl M. Causal modeling with multi-value and fuzzy-set Coincidence Analysis. *Polit Sci Res Methods*. 2020;8(3). doi:10.1017/psrm.2018.45

28. Ragin CC. *Redesigning Social Inquiry: Fuzzy Sets and Beyond*. University of Chicago; 2008.

29. Whitaker RG, Sperber N, Baumgartner M, et al. Coincidence analysis: a new method for causal inference in implementation science. *Implement Sci*. 2020;15(1):108-108. doi:10.1186/s13012-020-01070-3

30. Thiem A. Using Qualitative Comparative Analysis for Identifying Causal Chains in Configurational Data: A Methodological Commentary on Baumgartner and Epple (2014). *Sociol Methods Res*. 2015;44(4):723-736. doi:10.1177/0049124115589032

31. Baumgartner M, Thiem A. Often Trusted but Never (Properly) Tested: Evaluating Qualitative Comparative Analysis. *Sociol Methods Res*. 2020;49(2). doi:10.1177/0049124117701487

32. Baumgartner M, Ambühl M. *Cna: An R Package for Configurational Causal Inference and Modeling*.

11. APPENDICES

1. University of Pittsburgh Telehealth Usability Questionnaire
2. University of North Carolina Patient-Centered Communication in Cancer Care Instrument
3. Group-Based Medical Mistrust Scale (GBMMS)
4. Acceptability of Intervention Measure (AIM) Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM)
5. Patient Recruitment Email/Letter Template
6. Patient Recruitment Telephone Script
7. Patient Interview Verbal Consent
8. Patient Survey and Interview Guide