iNUDGE: INtegration of liqUiD biopsy based next generation Gene sEquencing in newly diagnosed NSCLC – A stepped wedge cluster randomized clinical trial

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1. BACKGROUND AND RATIONALE

The development of targeted therapies has changed the treatment paradigm for non–small cell lung cancer (NSCLC). With the growing number of FDA approved targeted therapies, current NCCN guidelines recommend comprehensive molecular genotyping, defined as detection of mutations in seven genes (*EGFR, ALK, BRAF, ROS1, MET, RET*, and *NTRK*) prior to first line (1L) therapy for all newly diagnosed patients with metastatic non-squamous (mNSq) NSCLC to enable the delivery of personalized therapy.[1, 2] Furthermore, the emergence of immune-checkpoint inhibitors has amplified the importance of molecular genotyping in the care of these patients because patients with actionable genomic alterations rarely respond to immunotherapy, even in the presence of high PD-L1 expression and should be preferentially treated with targeted therapy.[3] In addition, there is a growing body of evidence that introduction of targeted tyrosine kinase inhibitors after immunotherapy may be associated with higher rates of immune related adverse events, even after discontinuation of immunotherapy.[4] Additionally, in previous studies, amongst patients with a mutation in a NCCN-listed gene, exposure to targeted therapy has been shown to be associated with improved overall survival.[5] Given these considerations, upfront tumor genotyping is now considered an essential step in guiding treatment decisions for all patients with mNSq NSCLC, prior to 1L therapy.

Despite the critical importance of molecular testing in patients with advanced NSCLC, numerous barriers impede timely completion of testing prior to initiation of 1L systemic therapy.[6-8] Common issues include insufficient tissue for testing, lack of infrastructure for obtaining and sending biopsy samples for testing, and unacceptably long turnaround times for results.[9] These issues have created a critical need for additional convenient, and minimally invasive options for tumor genotyping.[10, 11] We and others have previously demonstrated that the incorporation of concurrent plasma based next-generation gene sequencing (NGS), ordered at the same time as tissue NGS, improves detection of clinically actionable mutations in patients with advanced NSCLC.[11]

At our institution, we piloted a behavioral economics (BE) informed “nudge” strategy to guide physicians’ clinical practice to include concurrent use of plasma and tissue-based NGS at initial diagnosis. This real-world cohort study was conducted at the Abramson Cancer Center and 2 community sites within UPHS. Across the 3 practice sites, a provider team-focused Electronic Health Record (EHR) -based “nudge intervention” was designed to order plasma-based NGS at the time of new patient consultation. Eligible patients for the nudge were identified using an EHR based checklist, that included 3 criteria: i. new diagnosis, ii. treatment naïve, iii. mNSq NSCLC. Results from the intervention period (4/2021-12/2021) were compared to baseline data from similar patients treated at our institution between 01/2019 and 03/2021. Of the 526 patients with mNSq NSCLC that were included in the analysis: 381 were included in the pre-intervention cohort and 145 in the post-intervention cohort. After implementation of the EHR-based nudge, we observed that a higher proportion of patients underwent concurrent tissue + plasma testing in the post intervention cohort compared to pre-intervention 90.3% (131/145) vs. 68.8% (262/381), $p<0.00001$. Additionally, by virtue of having robust tissue + plasma testing performed, there were improved rates of comprehensive molecular genotyping in the post-intervention cohort compared to pre-intervention, 98.6% (143/145) vs. 87.1% (332/381), $p=0.00007$. A greater proportion of patients had comprehensive genotyping available prior to 1st-line therapy in the post-intervention vs. pre-intervention cohort (86.2% vs. 76.3%, $p=0.013$).

These findings demonstrated that behavioral, EHR-based nudges are feasible and can promote guideline concordant diagnostic testing at both community and academic sites. The overarching goal of this current trial is to expand the application of this BE informed nudge approach, which has been operationalized within Epic, the EHR used at UPHS, to six satellite hospitals. Our

central hypothesis is that this approach will dramatically increase adoption of comprehensive molecular testing and enhance the delivery of molecularly informed first-line therapy in patients with newly diagnosed metastatic non-squamous NSCLC. Molecular testing will be defined as i) comprehensive: *EGFR, ALK, BRAF, ROS1, MET, RET,* and *NTRK* testing, ii) incomplete: <6 genes tested, and iii) no testing performed. Clinically actionable mutations will be defined as an alteration in one of the seven genes on the comprehensive gene list with an FDA approved targeted therapy in the 1L setting, plus *KRAS* G12C, *EGFR* exon 20 insertion, and *ErbB2* mutations. Molecularly informed first line therapy will be defined as one that is informed by results of NGS, obtained by plasma, tissue or both.

2. OBJECTIVES

2.1 Primary Objectives

Objective 1: In a stepped wedge cluster randomized trial of patients with newly diagnosed metastatic NSCLC, test the effectiveness of a BE informed EHR nudge intervention to increase timely receipt of comprehensive molecular test results before 1L therapy by incorporating concurrent tissue and plasma-based molecular testing into the workup of newly diagnosed patients.

Objective 2: Evaluate contextual mechanisms contributing to the adoption, reach, and effectiveness of EHR nudge interventions with a lens for health equity.

2.2 Primary Outcomes

Objective 1: Availability of comprehensive molecular test results (as defined above) prior to first line therapy for patients with mNSq NSCLC.

2.3 Secondary Outcomes

Objective 1: 1) successful EHR based nudge delivery, 2) turnaround time of delivery of provider focused alerts after receipt of plasma genotyping results, 3) completion of comprehensive molecular testing (tissue and/or plasma testing), 4) reasons for failure to complete comprehensive molecular testing (QNS or other), 5) time to molecularly-informed treatment initiation, 6) type of therapy received (targeted therapy, chemo-immunotherapy, immunotherapy, clinical trial or none) and 7) overall survival.

Objective 2: Individual and contextual factors shaping adoption (provider-level ordering of molecular testing), reach (patient-level completion of molecular testing), and effectiveness (receipt of molecular testing), of interventions, guided by RE-AIM with Equity Extension Framework[12].

3. STUDY POPULATION

3.1 Target Population

This stepped wedge cluster randomized trial will be conducted across newly diagnosed patients with mNSq NSCLC treated at Penn Medicine that comprise 3 clusters (sites): 1) Lancaster General Hospital (LGH), 2) Penn – New Jersey (Princeton Medical Center (PMC), Penn Medicine at Cherry Hill (PMCH), Penn Medicine at Washington Township (PMWT), and Penn Medicine Voorhees (PMV)), and 3) Penn Presbyterian Medical Center (PPMC).

3.2 Inclusion Criteria

a) Patients with histological, or cytological diagnosis of mNSq NSCLC who have not yet received systemic treatment for metastatic disease.
b) Patients must be seen at LGH, PMC, PPMC, PMCH, PMWT, or PMV for mNSq NSCLC.

3.3 Exclusion Criteria

a) Incomplete staging information.

3.4 Vulnerable Populations

a) Children, pregnant women, 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%.[11] 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, based on a BE informed EHR based nudge at time of new patient evaluation increased the proportion of patients undergoing concurrent tissue + plasma NGS testing to 90.3% (131/145) vs. 68.8% (262/381), $p<0.00001$(Aggarwal C et al, ASCO Quality Care Symposium, 2022). Thus, the proposed stepped wedge cluster randomized trial will examine effectiveness of this approach in a larger proportion of patients, reduce disparities in molecular testing, and target testing more optimally.

4.2 Overview

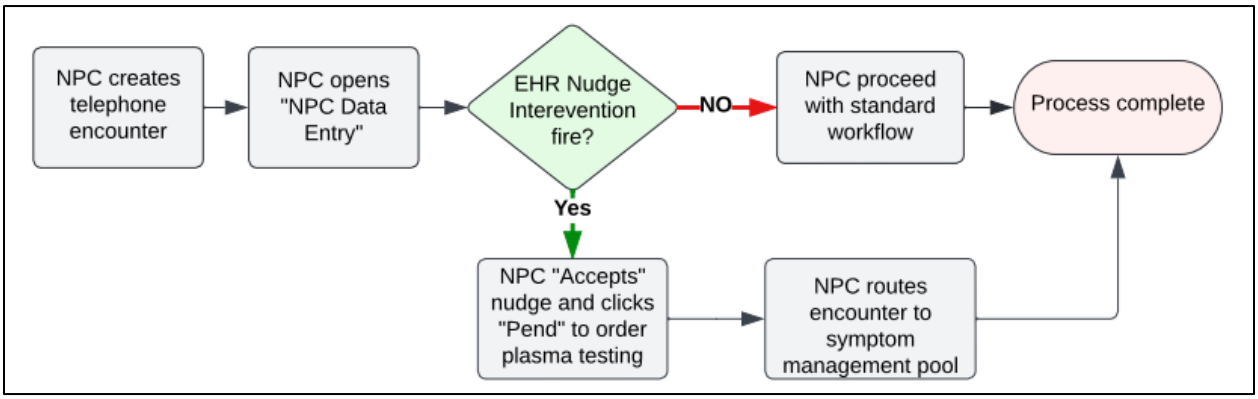
Objective 1: In a stepped wedge cluster randomized trial of patients with newly diagnosed mNSq NSCLC, test the effectiveness of BE informed EHR nudge intervention to increase timely receipt of comprehensive molecular test results before 1L therapy by integration of concurrent tissue and plasma molecular testing.

The design of this trial will include 3 clusters, representing the 6 community hospitals. There will be an initial period in which no clusters are exposed to the intervention. Subsequently, at regular intervals (the “steps”) one cluster (or a group of clusters) will be randomized to cross from the control to the intervention under evaluation. This process will continue until all clusters have crossed over to be exposed to the intervention. At the end of the study there will be a period when all clusters are exposed. Data collection will continue throughout the study, so that each cluster will contribute observations under both control and intervention observation periods.

Intervention:

An EHR-based nudge intervention that allows for default placement of a plasma based molecular genotyping order at time of the first new patient visit will be implemented **(Figure 1).** Subsequently, results detected on the default plasma NGS order will be conveyed to providers in the form of an electronic clinical decision support notification (**Figure 3**). The intervention will be tailored to the organizational needs of each cluster.

Figure 1. EHR based nudge intervention workflow.

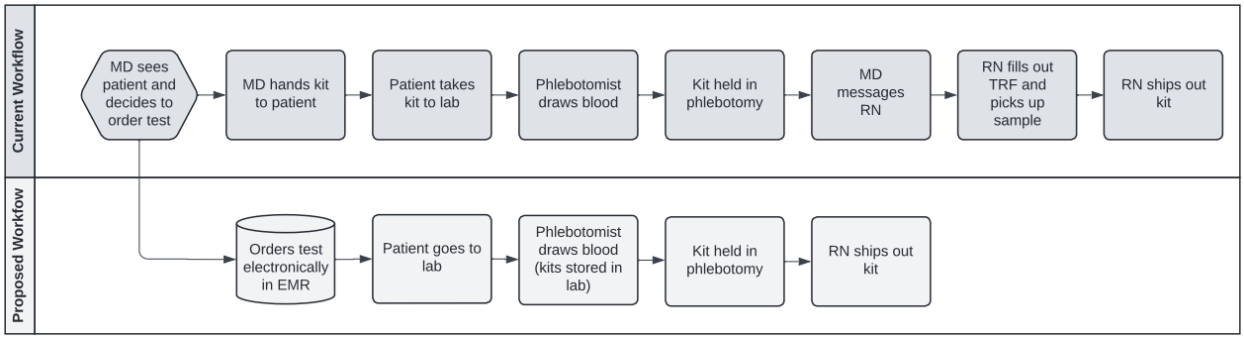


1. The EHR-based nudge intervention will fire at the time of the first telephone encounter with a new patient coordinator (NPC) based on a set of pre-populated molecular questions (**Supplemental eFigure 1**) for all patients with a new diagnosis of mNSq NSCLC.

2. The EHR-based nudge intervention will appear when the visit is opened within the electronic medical record by a provider and will allow default placement of a plasma-based NGS order. Thoracic oncology providers can opt out of this order if they feel it is not appropriate for the patient or because other molecular testing has already been initiated/completed. Large gene panel (>50 genes) based plasma will be used, and be based on site preference.

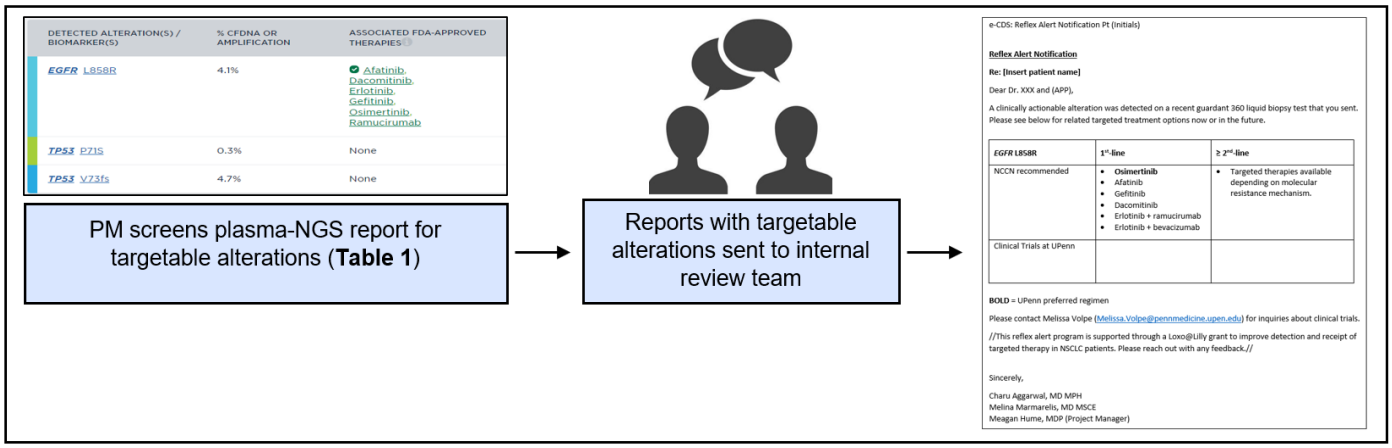
Standardization of the process will include availability of plasma kits at each of the sites (LGH, PMC, PPMC, PMCH, PMWT, and PMV) and clinical labs, and communication of the ordering process will be conveyed with the respective medical support teams (APP, RN) (**Figure 2)**. Sites will be encouraged to choose one plasma-based assay to be used at their site in order to streamline order design.

Figure 2. Current and proposed future workflow for plasma-NGS ordering.



As part of the downstream EHR-based nudge intervention workflow, an electronic clinical decision support (e-CDS) system for alterations detected on plasma genotyping will be created and implemented into the EHR as a “Research (non-chargeable) Encounter” to alert the provider team caring for the patient (**Supplemental eFigure 2**). This support program will be created to notify clinicians of targetable mutations, as well as absence of mutations detected on plasma testing as a means of improving the timely delivery of molecularly informed therapy.

Figure 3: Screening of plasma NGS reports and creation of e-CDS.



1. The study team will review plasma NGS reports for therapeutically targetable alterations (based on NCCN recommended biomarkers including *EGFR, ALK, ROS1, RET, MET*, *BRAF*, *KRAS*, ErbB2 and *NTRK*) (**Table 1**). When identified, the project manager (PM) will alert the internal review team (Drs. Aggarwal and Marmarelis).
2. If deemed appropriate the PM will assemble and send an EHR-based reflex alert with the information included in **Figure 3** to the patient's oncologist and associated APP. This alert will be created by the internal review team and will include information about the possible therapeutic options for this alteration including available clinical trials.
3. To ensure that providers are reaching the most appropriate molecularly informed treatment decision, e-CDS alerts will be sent to providers even for mutations deemed not "therapeutically targetable" (i.e., *STK11, TP53*, etc.).
4. Provider response to the e-CDS program, plan to prescribe targeted therapy as well as prescription of targeted therapy in response to a molecular alteration will be monitored to determine provider engagement. Reasons for not prescribing targeted therapy will also be recorded.

Table 1.

Gene	Mutations	Targeted Therapies
EGFR	**Exon 19 del/ Exon 21 L858R**	Osimertinib
EGFR	**Exon 18del/ins, E709A, G719A, G719C, G719R, G719S**, **Exon19del**, *Exon20Ins*, **T790M**, **S768I**, C797S, **L858R**, **L861Q**	Afatinib, Erlotinib, Gefitinib, Osimertinib, Dacomitinib, Amivantamab
ALK	**EML-ALK fusion**, F1174L, G1123S, G1202R, I1171S, I1171T, L1196Q	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib
ROS1	**Fusions**	Brigatinib, Ceritinib, Crizotinib, Entrectinib, Lorlatinib
RET	**RET-KIF5B Fusion**	Pralsetinib, Selpercatinib

	RET fusions with CCDC6, NCOA, TRIM33, CUX1, KIAA1217, FRMD4A, KIAA1468	
MET	Exon 14 skipping mutation	Crizotinib, Capmatinib, Cabozantinib
BRAF	**V600E**, V600	Dabrafenib, Dabrafenib/Trametinib, Vemurafenib
KRAS	**G12C**	Clinical Trials
ErbB2	Exon20Ins	Trastuzumab-deruxtecan, Ado-trastuzumab, emtansine, Afatinib, Lapatinib, Neratinib
NTRK	NTRK 1,2,3 fusions	Larotrectinib, Entrectinib

Objective 2: Evaluate contextual mechanisms contributing to the adoption, reach, and effectiveness of EHR nudge interventions, with a lens for health equity.

Using rigorous approaches proven successful in our prior work[13], we will recruit 10-15 patient and clinician participants from each site (estimated 40-60 participants total) to complete semi-structured interviews (**Supplemental eFigure 3**) following the active trial period. The goal of this objective is to understand contextual mechanisms (e.g., patient, clinician, clinic, structural factors) shaping adoption, reach, and effectiveness of each intervention and identify how response may differ by race and ethnicity, socioeconomic status, and other key social determinants of health. These data will be analyzed using qualitative comparative analysis, a mixed method approach well suited to identify mechanisms in pragmatic trials with smaller sample sizes.

Patients: We will oversample (at least 50% of the sample at each site) for Black patients and patients living in impoverished neighborhoods to understand effectiveness by race/ethnicity and socioeconomic status and stratify by reach (completion of comprehensive testing) and site to understand factors contributing to both success and failure (e.g., primary outcome). Trial participants will be invited in randomly selected batches following active trial engagement (to enhance capture over time) until we reach our target sample of approximately 30-40 patients. Patients will be invited to participate in interviews via email and/or letter within 6 weeks of their return oncology visit.

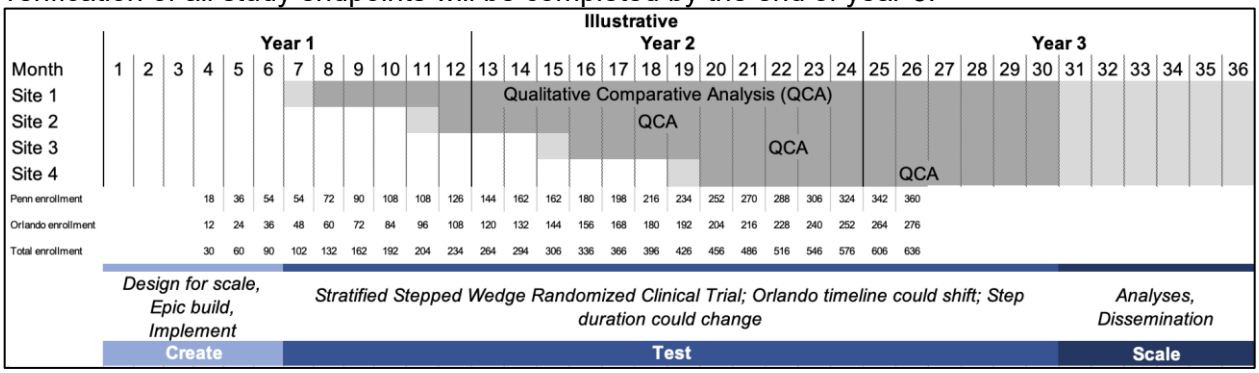
Clinicians: Recruitment for clinicians will be similar to the procedure for patients, except we will wait until the completion of the full trial to conduct interviews to avoid potential contamination. Clinicians will be purposively sampled by adoption (low or high levels of ordering for molecular testing) and 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 10-20 clinicians.

4.3 Study Duration and Timeline

The study duration will be approximately 36 months.

Trial Timeline												
Project Timeline	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Protocol Development, IRB	•											
Objective1: Deliver intervention		•	•	•	•	•	•	•	•	•		
Objective 1: Endpoint ascertainment		•	•	•	•	•	•	•	•	•		
Objective 1: Endpoint analysis									•	•	•	
Objective 2: Recruit & conduct patient interviews		•	•	•	•	•	•	•	•	•		
Objective 2: Recruit & conduct clinician interviews					•	•	•	•	•	•	•	•
Objective 2: Mixed methods coding & analysis					•	•	•	•	•	•	•	•
Baseline Analysis and disseminate results			•		•		•		•			
Submit manuscripts & disseminate overall results									•	•	•	•

Objective 1: Following an observation period, in month 6, we will initiate the stepped wedge cluster randomized trial. Each cluster will include a 5-month observation period, and a 1-month washout. The active enrollment period will be 24 months, with a 6-month lookback for baseline period observation. Longitudinal data capture to collect secondary outcome information for patients will be completed up to 90 days post-initial oncology visit Thus, collection and verification of all study endpoints will be completed by the end of year 3.



Objective 2: For patient interviews, we will use rolling enrollment to capture variation in processes and effectiveness overtime. Patient interview recruitment and data collection will begin during the first month of intervention observation (i.e., second month of after implementation to account for washout period and continue until saturation if reached. Clinician recruitment and data collection will start after active trial observation is completed at the specific site. Mixed methods analysis (including transcription and coding) will run throughout Years 2-3.

4.4 Study Setting

This study will occur within the University of Pennsylvania Health System.

5. STUDY PROCEDURES

5.1 Recruitment and Retention

Objective 1: A waiver of informed consent is requested for the stepped wedge cluster randomized trial. The study evaluates molecular testing rates before and after intervention at each site. Molecular testing at the initial diagnosis of mNSq NSCLC is standard, therefore, physicians and their patients will not be consented as this is the standard of practice.

Objective 2: This portion of the study will utilize prospective consent with waiver of written documentation. An estimated 30-40 patients and 10-20 clinicians will be interviewed (sample size dependent upon when data saturation is reached). Interview participants will also complete a structured questionnaire at the time of the interview. The final interview guide and questionnaire will be submitted for review prior to commencement of Objective 2.

Patients: A sample of patients will be invited to participate in the semi-structured interview and survey via email and/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 30 patients. We will oversample for Black patients and patients living in low-income neighborhoods (at least 50% of the sample at each site) to understand effectiveness by key social determinants of health and by reach (patient completion of testing) and site to understand factors contributing to both success and failure the interventions (5-10 patients at each site).

Clinicians: Recruitment of clinicians will be similar to that of patients, except we will wait until end of active observation at each site to avoid potential contamination. Clinicians will be purposively sampled by adoption (low or high levels of ordering for molecular testing) and 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 5-10 clinician (per site) or until data saturation is reached.

Data Collection: Email and/or letter invitations will be followed by a phone call from research staff to assess interest and schedule interviews with all interested participants. Interviews will be conducted by the qualitative data analyst or trained staff at Penn's Mixed Methods Research Lab (MMRL), a service center that provides expertise and support in qualitative and mixed methods data collection, data management, and data analysis. Interviews will be conducted in-person, by phone or using a HIPAA-compliant video platform, depending on participant preference. Structured questionnaire data will be collected via REDCap, a HIPAA compliant survey platform, or verbally administered if the participant cannot access this platform.

5.2 Informed Consent

Objective 1: This study will employ a waiver of consent mechanism.

Objective 2: Potential interview participants will be initially contacted by study team members by patient portal, email, and/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 interest in participating in the study. If the participant agrees to participate, they will be scheduled to have an interview via telephone or in person (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 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 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. Prior to commencement of interviews, we will submit all relevant recruitment materials (e.g., telephone script and recruitment letter), the interview guide, and the information statement for IRB review and approval. Objective 2 (interviews) activities will not commence prior to approval of these documents.

5.3 Measures and Outcomes

Objective 1: The primary endpoint is receipt of comprehensive molecular test results prior to 1L therapy for patients with mNSq NSCLC. This outcome encompasses successful completion of concurrent tissue and plasma based 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 80% of patients in the interventional arm will have molecular test results available prior to initiation of first line therapy. The primary outcome will be assessed by review of clinician documentation (e.g., progress notes) within the electronic medical record (EHR). Baseline data will be collected from all 4 sites. Molecular testing rates will be assessed, proportion of patients that undergo complete molecular genotyping prior to start of 1L therapy for mNSq NSCLC will be tabulated (Comprehensive testing will be defined as testing of all NCCN recommended biomarkers). Proportion of patients receiving targeted therapies when therapeutically targetable alterations are detected (**Table 1**) will be tabulated on a quarterly basis.

Secondary outcomes include: 1) successful EHR based nudge delivery, 2) turnaround time of delivery of provider focused alerts after receipt of plasma genotyping results, 3) completion of comprehensive molecular testing (tissue and/or plasma testing), 4) reasons for failure to complete comprehensive molecular testing (QNS or other), 5) time to molecularly-informed treatment initiation, 6) type of therapy received (targeted therapy, chemo-immunotherapy, immunotherapy, clinical trial or none) and 7) overall survival at 1 year, and 2 years.

Objective 2: We will use structured and validated measures and develop a semi-structured interview guide. The interview guide will be developed using RE-AIM with Equity Extension Framework, a widely used implementation science framework that measures key implementation outcomes (reach, effectiveness, adoption, implementation, and maintenance) and monitors how these outcomes vary by key determinants of health (equity). We will also draw upon the Consolidated Framework for Implementation Research to assess multilevel determinants that may shape implementation success. For patients, we will also assess factors that we hypothesize will impact completion of patient testing (e.g., patient knowledge of molecular testing, perceived importance of molecular testing, barriers to testing) and sociodemographics (e.g., self-reported race/ethnicity, health literacy, insurance, medical mistrust) using structured and validated items when available. A full interview guide and questionnaire will be submitted for IRB review prior to commencement of interviews.

5.4 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.

Objective 2: Semi-structured interviews and structured questionnaire data will be collected and analyzed in conjunction with quantitative measures conducted.

6. STATISTICAL DESIGN AND POWER

6.1 Sample Size

Objective 1: We have calculated sample size based on estimates of completion of comprehensive molecular testing prior to initiation of first line therapy. Based on our prior studies, we anticipate that the baseline rate of comprehensive molecular testing prior to first line therapy is 60%. In this stepped wedge cluster randomized trial, we wish to detect an absolute increase of 20% in our primary outcome for patients in the intervention arm.

A sample of 3 clusters in a complete stepped-wedge cluster-randomized design with 4 time periods (including the baseline), 3 steps, 1 cluster(s) switching from control to treatment at each step, and an average of 120 subjects per cluster with an average of 30 subjects per cluster per time period (for a total sample size of 360 subjects) achieves 80% power to detect a difference between proportions of 0.21701. The treatment proportion is assumed to be 0.81701 under the alternative hypothesis. The control proportion is 0.6. The test statistic used is the two-sided Wald Z-Test. The ICC is 0, and the significance level of the test is 0.05.

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.

6.2 Analysis Plan

Objective 1 Primary Analyses Outcome Measures: Relative and absolute change in availability of molecular testing prior to IL therapy. The change will be calculated from baseline pre-intervention period to intervention periods in all the intervention arms. Comprehensive molecular testing will be defined as comprehensive if results for EGFR*, ALK, BRAF, ROS1, MET, RET,* and *NTRK* testing are available from plasma, tissue, or both.

Primary Analyses Statistical Plan

The primary outcome is binary and will be analyzed using logistic regression, fitted using Generalized Estimating Equations (GEE). The model will include a time varying covariate to represent pre-treatment, washout, and treatment, within each randomized cluster, and an ordinal categorical variable to represent time. The GEE model will adjust variances for correlation within institution (cluster). The primary hypothesis will be tested using the z-score corresponding to the difference between treatment and pretreatment proportions (after adjustment for time effects).

Objective 1 Secondary Analyses Outcome Measures:

1. Successful EHR based nudge delivery:
    a. Amongst eligible patients (see eligibility above), calculate the proportion of patients for whom the EHR nudge fired successfully (yes/no). Applicable for the patients enrolled in the time periods following randomization.

2. Turnaround time of delivery of provider focused alerts:
    a. Reported as number of days, median. Applicable for the patients enrolled in the time periods following randomization.

3. Completion of comprehensive molecular testing:

a. Amongst eligible patients, relative and absolute change in completion of comprehensive molecular testing will be tabulated, regardless of timing of 1L therapy.
b. Relative and absolute change in completion of comprehensive testing by tissue and plasma, plasma alone, or tissue alone will be tabulated.

4. Reasons for failure to complete comprehensive molecular testing:
    a. Summarize reasons for failure of completion of testing
        i. Tissue related (QNS)
        ii. Patient related factors (unable to biopsy, patient declined biopsy etc)
        iii. Assay related factors (plasma assay does not detect mutations)
        iv. Other
5. Time to molecularly informed treatment initiation:
    a. Amongst eligible patients, relative and absolute change in time to start 1L therapy.
        i. Calculated as time to therapy from the date of diagnosis of Stage IV disease (date of biopsy)
        ii. Calculated as time to therapy from the date of first new patient visit with medical oncology

6. Type of therapy received:
    a. Targeted therapy
    b. Chemo-immunotherapy
    c. Immunotherapy
    d. Clinical trial or n
    e. None

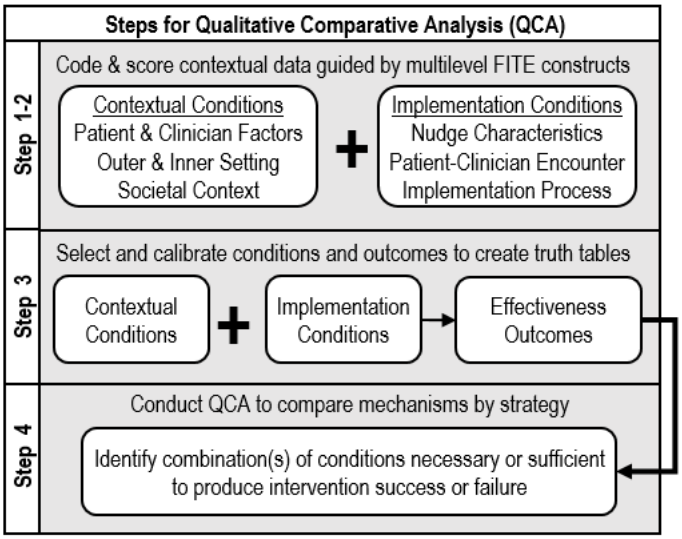
7. Overall Survival:
    a. Time from initial diagnosis to date of death or last follow up.
    b. 1 year and 2-year overall survival rates will be calculated for the intervention group, and compared to baseline.

Secondary Analyses Statistical Plan

Secondary outcomes will be summarized by time and treatment condition, as proportions, means, medians, as appropriate with two-sided 95% CIs. Successful nudge delivery, completion of testing, reasons for failure to complete testing, and type of therapy received will be tabulated and summarized as proportions. Turnaround time of delivery for provider focused alerts will be treated as time to event and summarized as median time with 95% CI. Time to treatment initiation and Overall Survival will be summarized as time to event using Kaplan Meier methods, with the effect of intervention estimated as the hazard ratio (with two-sided 95% CI).

For a complete list of clinical and interventional related variables that will be collected throughout the course of this study please refer to **Supplemental eTable 1** below.

Objective 2 Analyses Plan



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 timelines and quality of care and the effectiveness of nudge intervention. QCA is a multistep analytic method that combines qualitative and quantitative coding and calibration to identify conditions shaping the effectiveness of EHR based nudge intervention 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 EHR strategy and process).

Qualitative Data. The constant comparative method, guided by modified grounded theory,[14] will be used to iteratively identify *a priori* domains of interest (guided by RE-AIM and CFIR) 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 subset of 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 qualitative software, 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.[15]

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 completion of comprehensive molecular testing prior to initiation of first line therapy, 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).[16] 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.[17,18] Most outcomes will be dichotomous, but continuous values and fuzzy set QCA will be used as appropriate.[19,20] 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.[20, 21] We will conduct QCA analyses using R package *QCApro*.[22–24] 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. RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Adequate facilities are available within Penn Medicine's Clinical Practice Network. Members of the research team, listed in HSERA, 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.

Protection of Human Subjects

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are already in place to ensure the data are secure by using passwords and HIPAA-compliant encryption. Data on physicians and patients will be obtained from EHR and Penn Data Store. Any information that is obtained will be used only for research purposes and to inform the interventions described above. Information on individual patients will only be disclosed within the study team. All study staff will be reminded of the confidential nature of the data collected and contained in these databases. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

8. STUDY TEAM

Our interdisciplinary team includes investigators with world known experts in thoracic oncology, and clinical implementation of molecular testing, implementation science, behavioral economics, EHR-based strategies, and mixed-methods research. At the University of Pennsylvania, the work will be led by **Charu Aggarwal, MD, MPH**, Leslye M. Heisler Associate Professor of Lung Cancer Excellence and Associate Director, Penn Center for Precision Medicine and **Justin Bekelman**, **MD**, Professor of Radiation Oncology, Medicine, and Health Policy and Director of PC3I and an international leader in cancer care innovation. Other key investigators include **Melina E. Marmarelis, MD,** a medical oncologist with clinical and research expertise in lung cancer. Other co-investigators include **E. Paul Wilyeto, PhD** (biostatistician), and **Katharine Rendle, PhD, MSW, MPH** who bring statistical and implementation science expertise to the team. Local team leaders will be **Chris D. Avella, MD** at Penn Presbyterian Medical Center, **Ramy Sedhom, MD** at Penn-Princeton, **Shayma Kazmi, MD** at Penn-Cherry Hill and Penn-Washington Township, and **Samuel Kerr, MD** at Penn-LGH. The study team will include **Peter Gabriel, MD**, Chief Oncology Informatics Officer at the Abramson Cancer Center, **Meagan Hume**, **MDP**, Innovation Manager at PC3I, **Anthony Martella**, **BA**, Clinical Research Coordinator B, PC3I, and **Dylan Scholes, BS**, Clinical Research Coordinator B, Clinical Research Unit.

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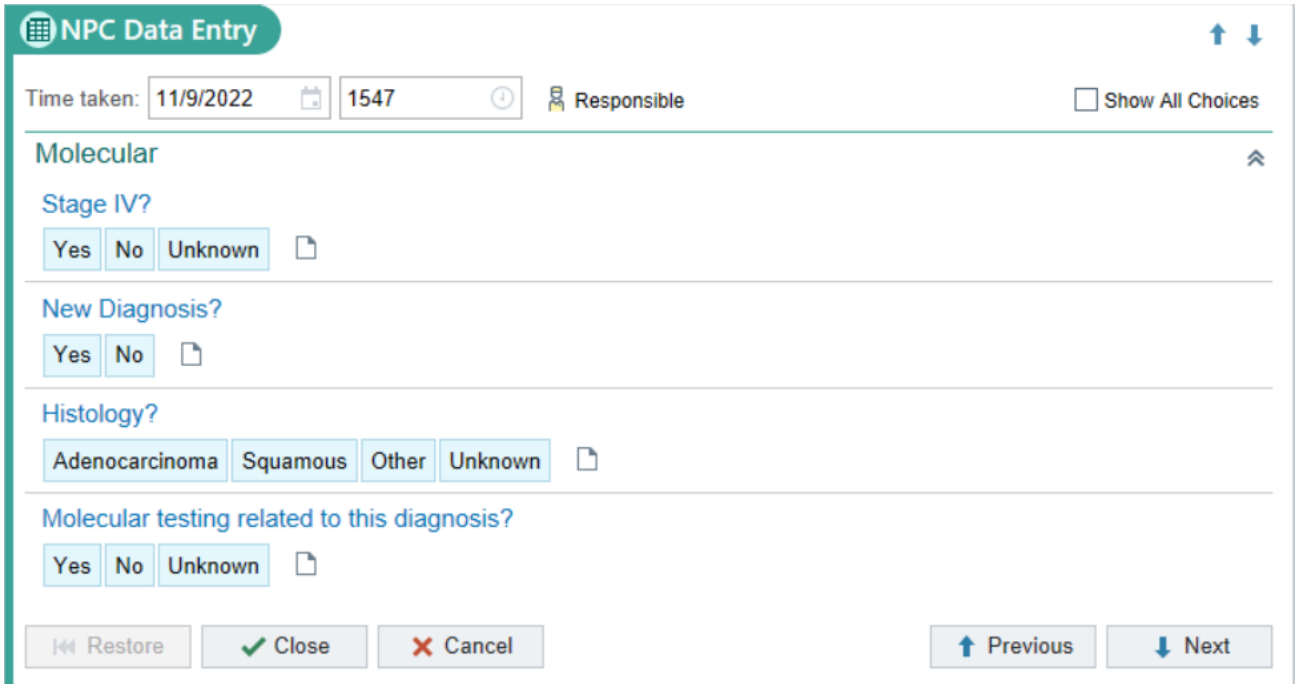
10. APPENDICES

Supplemental eTable 1: Clinical variables and tumor characteristics

Variable	Description
Demographics	
Study Patient ID	Unique identifier generated by study team
Name	First Last
MRN	Medical record number
DOB	date of birth, MM/DD/YYYY
DOD	date of death, MM/DD/YYYY
Vital status	Alive, deceased
ECOG date (@ time of 1st MedOnc visit)	MM/DD/YYYY
ECOG value	0-1, >2
Days difference (ECOG date – Dx date)	# (days)
Race	American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Declined, Unknown
Ethnic group	Hispanic or Latino, Non-Hispanic or Latino, Declined
Sex	Female, male, other (if available)
Date of Diagnosis	date of clinical or pathologic diagnosis, MM/DD/YYYY
Age at Diagnosis	# (year)
Histology	i.e. adenocarcinoma, poorly differentiated etc.
TNM Stage	Stage IV (T4, N0, M0 or any T, N1, M0 or any T, any N, M1)
Primary site of treatment	PPMC, PMC, LGH, PMCH, PMWT, OHCI
Medical Oncologist	MD name (First Last)
Date of 1st MedOnc encounter	MM/DD/YYYY
Smoking status	Current, former, never
Molecular testing	
Date of Tissue Testing	MM/DD/YYYY
Type of Tissue Testing	Spot, NGS, FISH, IHC, etc.
Tissue testing successful?	yes/no (QNS – quality/quantity not sufficient, cancelled, etc.)
Tissue Testing Platform	CPD NGS/FTP, CARIS, GenPath OnkoSight, etc.
Gene panel size	>50 vs. <50 genes
Tissue NCCN markers*	*EGFR, ALK, BRAF, ROS1, MET, RET, ErbB2, NTRK*.
Tissue additional markers	*KRAS, ErbB2, BRCA1* (yes/no and specific alteration)
Date of Plasma Testing	MM/DD/YYYY
Plasma Testing Platform	Guardant360®, Foundation etc.
Type of Plasma Testing	Spot, NGS, FISH, IHC, etc.

Plasma testing successful?	yes/no (QNS – quality/quantity not sufficient, cancelled, etc.)
Plasma NCCN markers*	*EGFR, ALK, BRAF, ROS1, MET, RET, ErbB2, NTRK*.
Plasma additional markers	*KRAS, ErbB2, BRCA1* (yes/no and specific alteration)
Gene panel size	>50 vs. <50 genes
Testing modality	T, P, or T+P
Treatment	
First line start date	MM/DD/YYYY
First line treatment regimen	systemic therapy regimen (IO, chemo-IO, TKI, etc.)
First line last treatment date	MM/DD/YYYY
Second line treatment start date	MM/DD/YYYY
Second line treatment regimen	systemic therapy regimen (IO, chemo-IO, TKI, etc.)
Second line last treatment date	MM/DD/YYYY
Radiation prior to first line?	yes/no
Type of radiation prior to first line	curative, palliative etc.
Date of completion of radiation	MM/DD/YYYY
Assessment	
NCCN markers tested prior to 1L start?	yes/no
Targeted Tx prescribed if targetable mutation detected? (If no, will record reasons why)	yes/no
Line of targeted TX prescribed?	1L, 2L, subsequent lines
Response to Reflex Alert Notification	
Alteration detected	yes/no
Alteration gene	*EGFR* L858R, *KRAS* G12C, *KIF5B-RET* Fusion, etc.
Date of plasma report	MM/DD/YYYY
Date reflex alert sent	MM/DD/YYYY
Turnaround time (TAT) of alert	# (days)
Name of MD receiving alert	First Last
Tx naïve at time of alert?	yes/no
Tx pre-reflex alert	systemic therapy regimen (IO, chemo-IO, TKI, etc.)
Tx post-reflex alert	systemic therapy regimen (IO, chemo-IO, TKI, etc.)
Change in Tx pre-vs. post reflex alert?	yes/no
Plan to prescribe a targeted Tx?	yes/no
Receipt of targeted Tx?	yes/no
Clinical team review requested	yes/no

Supplemental eFigure 1: Pre-populated molecular questions



Supplemental eFigure 2: e-CDS alert template

Research (Non-Chargeable)

11/8/2022
Division of Hematology/Oncology

Scholes, Dylan

Progress Notes

Scholes, Dylan (Research Coordinator) • Encounter Date: 11/8/2022 • Signed

EMR-based Clinical Decision Support (e-CDS) Notification

A clinically actionable alteration was detected on a recent liquid biopsy test that you sent. Please see below for related targeted treatment options now or in the future.

EGFR p.E746_A750del (Exon 19 deletion)	**1st-line**	**≥ 2nd-line**
NCCN recommended	• **Osimertinib** • Afatinib • Gefitinib • Dacomitinib • Erlotinib + ramucirumab • Erlotinib + bevacizumab	• Targeted therapies available depending on molecular resistance mechanism.
Clinical Trials at UPenn		

BOLD = UPenn preferred regimen

Please contact Melissa Volpe (Melissa.Volpe@pennmedicine.upenn.edu) for inquiries about clinical trials.

//This patient is enrolled in the study: *iNUDGE: Liquid biopsy based NGS in newly diagnosed NSCLC* (**UPCC: XXXX**) funded through Loxo Oncology. Plasma DNA analysis for molecular profiling was sent at the time of new patient consultation with medical oncology. The full results are now available in Epic//

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Supplemental eFigure 3: Patient Interview Semi-Structured Questions

iNUDGE Patient Interview Guide (Version Date: 11/8/2022): Semi-Structured Questions

As part of cancer care, some patients are recommended to undergo molecular testing to identify which treatments might be best for your specific cancer. Sometimes this is done even before you know you have cancer for sure. It often involves giving your blood or another type of sample at a lab or in the clinic when you seek your care team.

1. At any point in your care, did you complete molecular testing to help guide your treatment decisions or options for lung cancer?
2. [IF YES]: Can you tell me a bit more about <u>when</u> and <u>where</u> you completed molecular testing? Did you complete the testing before your first visit with your oncologist?
3. [IF NO]: Did you care team ever recommend that you complete molecular testing? If so, can you tell me a bit more about why you did not complete molecular testing?
4. How, if at all, did your cancer care team discuss why you might need molecular testing?
5. How, if at all, did your care team discuss how molecular testing might change what treatment options might be best for you?
6. How comfortable did you feel asking questions about molecular testing with your care team?
7. What things made it easier for you to complete molecular testing?
   Probe: patient, clinic, societal
8. What things made it harder for you to complete molecular testing?
   Probe: patient, clinic, societal
9. How important, if at all, do you think molecular testing is for your cancer care?
10. How much, if at all, do you understand what molecular testing is looking for and why it might change your treatment options?
11. How, if at all, did your oncologist discuss molecular testing during your first visit?
    PROBE: Can you describe the conversation a bit more for me?
12. How comfortable did you feel asking questions about molecular testing during your first visit?
13. [If TESTED]: How, if at all, did your oncologist discuss molecular testing results?
14. [If TESTED]: How, if at all, did your molecular testing results impact your treatment options? Your treatment decisions?
15. [If TESTED]: How comfortable did you feel asking questions about molecular testing results with your cancer care team?
16. How satisfied are you with your decision to complete (or not) molecular testing?
    a. Probe: Do you have any regrets with your decision?
17. Prior to meeting with your oncologist for the first time in person, did you complete an in-person or telehealth visit with the lung cancer nurse navigator? [IF yes, was it in in-person or using telehealth]?
    a. [IF NO]: Have you ever completed a telehealth or in-person visit with a lung cancer nurse navigator?
    b. [IF COMPLETED BEFORE]: How comfortable did you feel discussing necessary testing or other items related to lung cancer <u>prior to</u> meeting with your oncologist?

c. [IF COMPLETED EVER]: Did you discuss molecular testing with the lung cancer nurse navigator? Please describe the conversation a bit for me if yes.
d. [IF COMPLETED BEFORE]: How, if at all, did your appointment with the lung cancer nurse navigator make it easier or harder for you to prepare for your initial in-person oncology visit? Why?
e. [IF COMPLETED EVER]: How, if at all, did your appointment with the lung cancer nurse navigator make it easier or harder for you to prepare for treatment? Why?
   PROBE: Molecular testing in particular
f. [IF COMPLETED EVER]: How, if at all, did your appointment with the lung cancer nurse navigator make it easier or harder for you to communicate with your cancer care team? Why?
g. [ALL]: Do you think it was (or would be) appropriate to meet with a lung cancer nurse navigator before meeting with your oncologist? Why or why not? Would you prefer in-person or telehealth?

18. Do you have any additional thoughts on any of the items we discussed?