Developing precision smoking treatment in the Southern Community Cohort Study

Brief title: Precision Interventions for Smoking in the Southern Community Cohort Study (PRISM-SCCS)

NCT03521141

[*]Hilary Tindle, MD, MPH Co-PI
[#]Maureen Sanderson, PhD, RD, MPH Co-PI
[+]Rebecca Selove, PhD, MPH Co-PI
[*]Department of Medicine, Vanderbilt University
[#]Department of Medicine, Meharry Medical College
[+]Center for Prevention Research, Tennessee State University
Dr. Tindle Phone: [redacted]
Dr. Tindle Email: [redacted]

Table of Contents:

1.0 Background

Cigarette smoking significantly increases the risk of multiple cancers, accounting for more than 30% of all cancer deaths and 80% of deaths from lung cancer [1]. Compared to whites, African Americans have lower cessation rates and are disproportionately burdened by lung cancer[2,3], underscoring the urgent need for improved smoking cessation strategies in these underserved groups. Personalizing standard care [4] with biological data to enhance accuracy of lung cancer risk [5] or measure speed of nicotine metabolism to inform pharmacotherapy choice [6] is a promising, yet understudied, approach in low income minority smokers.

The Southern Community Cohort Study (SCCS) is comprised of adults who were ages 40-79 at cohort entry and who reside in twelve states throughout the southeastern US. The majority (86%) were enrolled at 71 CHCs, which continue to serve as study partners, with recruitment completed in 2009. In addition to annual passive follow up of the SCCS from 2008 to 2012 via linkage with national and state mortality and cancer registries, the entire surviving cohort was re-contacted to participate in a follow-up self or telephone administered survey, with a nearly 70% response rate. The follow-up survey elicited information on new health outcomes and updated information on exposures and lifestyle factors, including smoking. Smoking-related questions were added to the 3rd follow up in order to probe participants' motivation, use of quit aids, receipt of provider advice, quit attempts, and cessation.

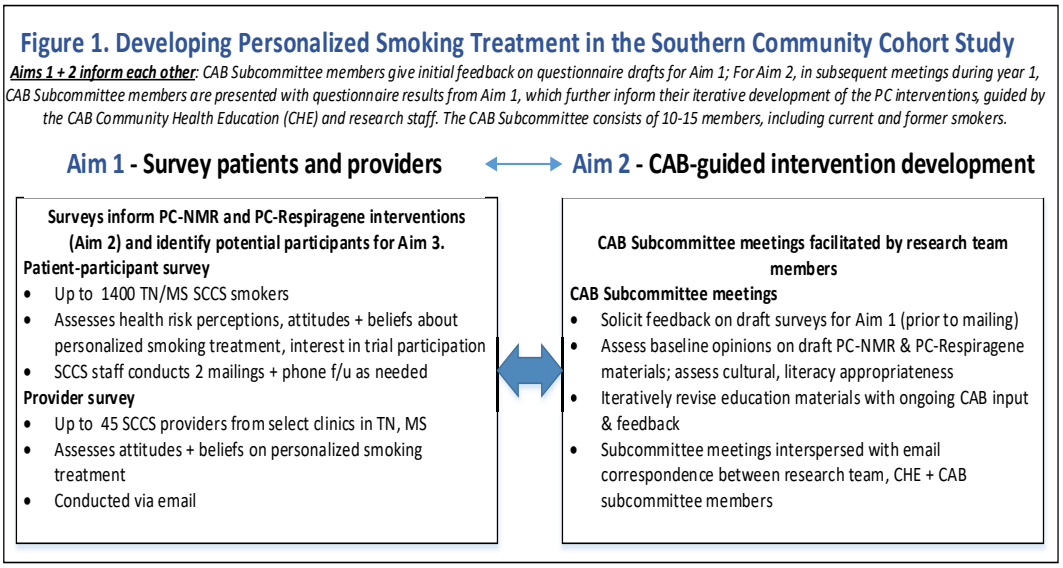
Through the SCCS, genetic polymorphisms in cytochrome P450 2A6 (CYP2A6), a primary driver of metabolism of nicotine and carcinogenic tobacco-specific nitrosamines, have been found to predict lung cancer risk in African-American male smokers[7]. Additionally, it has been found that individuals who metabolize nicotine and nitrosamine more quickly, termed "fast/normal" metabolizers, have a 45% higher risk of lung cancer compared to so-called "slow" metabolizers[8].

2.0 Rationale and Specific Aims

Biologically informed precision treatment could benefit smokers in several ways. Biological tailoring may increase the salience of messaging about smoking-related disease and advice to quit. This in turn could reduce the optimistic bias, a tendency to underestimate one's own health risk, which hinders cessation efforts[9], thereby increasing motivation to quit. Data has demonstrated that the nicotine metabolite ratio (NMR), a biomarker reflecting CYP2A6 activity, can inform choice of smoking cessation pharmacotherapy, such that "fast/normal" metabolizers are twice as likely to quit smoking on varenicline compared to "slow" metabolizers[6]. Additionally, smokers who are presented results from a commercially available, gene-based lung cancer risk assessment, Respiragene, are more likely to undergo lung cancer screening[10-13]. Respiragene recipients were also more likely to use nicotine replacement therapy (NRT) and quit smoking[5,14-16].Though promising tools to help engage smokers in cessation treatment, these individual, biologically informed feedback interventions have not yet been studied in community smokers in the US.

Our overarching aim is to leverage the SCCS and the U54 Community Outreach Core Community Advisory Board (CAB) to guide the development of two precision care (PC) interventions for smoking cessation: PC-NMR and PC-Respiragene. Both will be tailored to attitudes and beliefs of low socioeconomic status (SES) community smokers in the southeastern US, where tobacco use prevalence is one of the highest in the country. PC is rooted in the PRIME Model of behavior change[17-19], which reflects a multi-faceted view of motivation for tobacco cessation. We will assess feasibility of PC in SCCS participants who smoke and conduct a 3-arm randomized controlled trial (RCT) to determine preliminary estimates of PC interventions vs. standard guideline-based care (GBC) on engagement[4,20], smoking cessation, and likelihood of undergoing recommended lung cancer screening if eligible[21]. Our hypothesis is that, compared to GBC, PC participants will exhibit higher smoking cessation and lung cancer screening rates. These effects will be explained by lower optimistic bias, higher self-efficacy and motivation to quit, and use of proven quit aids (medication, behavior therapy via state quit line).

To accomplish our aim, daily smokers who are SCCS participants and providers at SCCS Community Health Centers (CHC), in Mississippi or Tennessee will be surveyed to assess their attitudes and beliefs about precision smoking treatment. Survey results will inform CAB-guided development of the PC study interventions. PC interventions will then be piloted in a RCT of up to 100 SCCS daily smokers willing to make a quit attempt with medication and be randomized 1:1:1 to PC-NMR, PC-Respiragene, or GBC and followed for 6 months. All RCT participants are referred to the shared TN/MS state quitline and provided the NCI "Clearing the Air" standard intervention.



An overview of Aims 1 and 2, which are now completed, is shown to the left.

Aim 1: Survey up to 1400 TN and MS SCCS smokers and up to 45 selected CHC providers to assess attitudes and beliefs on smoking-related health risk perceptions, precision smoking treatment, and willingness to engage in a smoking cessation trial of PC.

Aim 2: With continuous input from the CAB, develop two PC interventions, PC-NMR and PC-Respiragene, for use among diverse, low-socioeconomic status community smokers in the SCCS.

Aim 3: Conduct a 3-arm RCT to pilot PC interventions for feasibility and to determine preliminary estimates of biochemically-validated smoking cessation at 6 months vs. GBC. We hypothesize that, compared to GBC, PC participants will exhibit higher smoking cessation and lung cancer screening rates. (Illustration of Aim 3 is shown below on p. 8).

3.0 Animal Studies and Previous Human Studies

Our group has not performed prior animal or human studies related to the proposed PC interventions.

4.0 Inclusion/Exclusion Criteria

AIM 1:

Patient Inclusion Criteria: Eligible participants include adult (18 years of age or older) self-identified current smokers who are SCCS Participants.

Provider Inclusion Criteria: Eligible participants include independent providers at selected CHCs as provided by CHC CEOs.

AIM 3:

Inclusion Criteria: Eligible participants include adult (18 years of age or older) daily smokers (i.e., indicated they were smoking ≥ 5 cigarettes per day on most recent survey) who are SCCS participants and agreed to be contacted in the Aim 1 survey. Participants must have a stored blood sample with the

SCCS and an established PCP. Participants must agree to participate and be willing to accept a medication prescription for tobacco cessation. Participants must be eligible (i.e., no medical contraindications) to receive at least 1 non-nicotine FDA-approved smoking cessation medication (i.e., varenicline) and NRT. Smokers across the motivational spectrum (all levels of readiness to quit) are eligible.

Exclusion Criteria: Inability to give informed consent or participate due to serious psychiatric (e.g., psychosis, schizophrenia, hospitalization for psychiatric condition in the past 6 months) or cognitive disorder (e.g., dementia,that prevents them from completing study procedures); enrolled or scheduled to be enrolled in another smoking cessation program; no access to a telephone or inability to communicate by telephone; unable to speak and read English; history of seizures; pregnant or breastfeeding.

5.0 Enrollment/Randomization

For AIM 1 provider participants, we will first obtain name and contact information for CHC CEOs from the SCCS. CEOs for selected CHCs will be mailed an introductory letter directing them to an emailed REDCap survey, the purpose of which is to obtain, at the discretion of the CEO, CHC providers' names, credentials, and email addresses. This email will be re-sent 2 times at 2 week intervals in order to ensure maximum response rates. Using the obtained email addresses, we will email the AIM 1 provider REDCap survey, which assesses providers' current tobacco treatment practices as well as attitudes toward personalizing smoking cessation treatment. This email will be sent to non-responding providers 2 times at 2 week intervals in order to ensure maximum response rates.

For AIM 1 patient participants, we will use the well-established SCCS procedures for entry into, and follow-up within, the SCCS. Mailed packets will include a pre-addressed and postage-paid return envelope, with only the SCCS participant number for identification. The packets will also contain an introductory letter describing the research, and an AIM 1 questionnaire to complete. . To ensure maximum response rate, participants will be mailed up to three times;. Participants will mail back the questionnaire and, upon receipt of these items, will be considered potentially eligible for the AIM 3 pilot RCT.

Respondents to the AIM 1 survey who report that they have a PCP and who have an SCCS stored blood sample will be mailed an AIM 3 invitation letter and informed consent with a pre-paid return envelope. These patients will be screened for eligibility by phone and, for those providing verbal consent, given the AIM 3 baseline questionnaire by phone. Upon return of the signed written consent form, the participant's labs will be run using their stored blood. When these results are available, participants will be called and informed of their randomization assignment (PC-NMR, PC-Respiragene, GBC). The baseline questionnaire for the RCT will contain questions on lifestyle factors, readiness to quit, and smoking patterns as described below. Computer-assisted telephone interviewing will also be used for completion of study questionnaires by phone using the study call line; study staff will contact non-responders by mail or phone.

Eligible patients will be randomized according to a stratified permuted block randomization scheme. Stratification will be based on cigarettes per day. Randomization will be proceeded within strata according to a permuted block scheme with a block size, or balancing interval, varying randomly between 3 or 6 according to the outcome of a computer generated random number. This will ensure that the cumulative number of assignments to each treatment is in balance after making each block of assignments.

6.0 Study Procedures

Baseline Data Collection

For Aim 1, participants will be mailed a questionnaire and a postage-paid return envelope. The survey will assess current smoking behavior as well as attitudes toward smoking cessation, precision medical care, and participants' perceptions of health risk. This survey will be mailed up to 3 times.

Aim 1 and Aim 2 inform each other as outlined in Figure 1 below. Aim 3 is an RCT piloting the use of the behavioral and educational interventions developed in AIM 2 within a low-income population, a subset of our Aim 1 participants as described above.

Respiragene measurement

For Aim 3, participants will undergo Respiragene testing, a genetic test that assesses lung cancer risk. Respiragene can be run on stored blood samples from the SCCS. If blood is not available, saliva could be used as a back-up. Risk level is stratified as high, higher and highest risk based on genetic markers. The VUMC lab that has performed most of the SCCS analyses to date will perform the Resiragene analysis. Those in the Respiragene arm of the study will receive the results of their Respiragene lab test during their first quit attempt. All others will receive their results at the end of the study. This final results call will be offered to all participants around the Month 6 follow up..

Nicotine metabolite ratio (NMR) measurement

For Aim 3, participants will also undergo nicotine metabolite ratio (NMR) testing of stored biological samples (blood will be used when possible and is preferred; saliva can be used as a substitute). NMR testing helps to determine how quickly a participant's body breaks down nicotine, which will inform his or her provider about whether nicotine replacement therapy (NRT) or varenicline is more effective to help the participant quit smoking. Samples will be securely shipped to Canada for testing. Slow metabolizers will be defined by an NMR <0.31 and fast metabolizers will be defined by an NMR ≥ 0.31[6]. Those in the NMR arm of the study will receive the results of their NMR lab test and their medication will be selected based on their NMR status. At the end of the study, those who were not in the NMR arm will receive their NMR results. This final results call will be offered to all participants around the Month 6 follow up.

Medication provision and blinding

Guideline Based Care Group

All participants assigned to guideline based care (GBC) will be referred to the state quitline and will receive a smoking cessation intervention through the National Cancer Institute's (NCI) "Clearing the Air" program. Additionally, as part of clinical care, the primary care provider (PCP) will document guideline-based treatment recommendations and provide participants with prescriptions sufficient for a 3-month course of pharmacotherapy chosen at the clinical discretion of the provider. Written and verbal instructions will be provided to participants given medication to contact their primary provider and the research study staff (during regular business hours) to address any questions about medication. Participants will be instructed to call 911 if they believe they are having a medical emergency. GBC participants will also receive Respiragene and nicotine metabolite ratio (NMR) testing on their SCCS stored blood sample and will be informed of these results at the end of the study.

Respiragene Precision Care Group (PC-Respiragene)

All participants assigned to Respiragene precision care will receive guideline-based care, including a referral to the state quitline, as described above. Additionally, the PCP will have clinical decision support regarding the interpretation of the Respiragene test. Study staff will discuss results of the Respiragene test with the participant and the PCP will provide participants with prescriptions sufficient for a 3-month course of pharmacotherapy chosen at the clinical discretion of the provider based on guidelines relevant to differential health risks.

NMR Precision Care Group (PC-NMR)

All participants assigned to NMR precision care will receive guideline-based care, including a referral to the state quitline, as described above. Additionally, the PCP will have clinical decision support regarding the interpretation of NMR from the study team. Using the NMR data, the PCP will discuss

results with the participant and provide participants with prescriptions sufficient for a 3-month course of pharmacotherapy based on NMR results (NRT for "slow" metabolizers and non-nicotine smoking cessation medication (varenicline) for "fast/normal" metabolizers). Participants who do not wish to receive varenicline, may have the option of a higher nicotine patch dose that has been studied previously. In this previous study, there were no significant differences between treatment arms in the frequency of severe side effects and serious adverse events or blood pressure during treatment ($p > .10$).[22]

Participants may receive prescriptions through their own pharmacies or through a mail order pharmacy.

Check-in phone calls

Study staff will call participants at approximately 2 weeks after the study results call, and again approximately 1- 2 months following the results call, to encourage medication adherence and assess self-reported tolerance. If additional communication is needed, a tobacco counselor can be available for extra calls.

Table 1: RCT Data Collection Table for Aim 3

Follow up Assessments	BL	1 mo f/u	Informal Check-in (2)	3 mo f/u	6 mo f/u
Smoking status	X	X		X	X
Cigarettes per day	X	X		X	X
Health risk perceptions	X	X		X	X
Lung cancer screening	X	X		X	X
Notify of PC results*		X			X
Calls to support med		X	X	X	

adherence, tolerance					
CO-validated abstinence					**X**
*Participants in PC arms (Respiragene, NMR) notified of results; GBC participants are contacted to match for time					

Outcome assessment
Subject outcomes will be assessed via phone calls at approximately 1, 3, and 6 months, as shown in Table 1. At follow up, an RA who is separate from intervention staff will complete interviews assessing smoking behavior, medication use and self-reported side effects, patient health risk perceptions and attitudes toward the PC interventions, and whether the patient received a lung cancer screening. Participants reporting abstinence at six months will be mailed a standard salivary cotinine kit for biochemical validation of smoking abstinence, defined as ≤ 10 ng/ml.

7.0 Risks

Nicotine Metabolite Ratio (NMR), Respiragene, & Salivary Cotinine Test: There are no known serious adverse effects from these tests.

Breach of confidentiality: All efforts, within reason, will be made to keep personal information in the research records confidential. Total confidentiality cannot be guaranteed. To prevent a breach of confidentiality, participant data will be collected using password protected and encrypted computers, and electronic participant tracking spreadsheets stored on a secure server. All paper records will be locked in secure areas and accessible to study staff only. To prevent the loss of data, all electronic information is password protected on anti-virus software enabled computer systems. Only study staff will have access to the study data on Shared File Areas. Participants will be identified on study forms and in the database by a participant number. Participant names and contact information will be stored in a separate file.

Adverse drugs reactions: Participants in this study may receive one of two FDA-approved smoking cessation therapies (NRT or varenicline) and will have the potential to experience drug-related side effects. Nicotine replacement therapy is generally very safe and several preparations of it have been sold over the counter for decades). However, possible side effects include, but are not limited to, skin irritation or itching (patch), dizziness, headache, nausea, mouth/throat irritation (inhaler/nasal spray), and rapid heartbeat. Common side effects of varenicline include nausea, sleep disturbance and vivid dreams, gastrointestinal symptoms, and vomiting. Very rarely, patients, particularly those with unstable psychiatric conditions, may experience symptoms such as behavioral changes, agitation, depressed mood, and suicidal behavior during varenicline treatment. In a large FDA-mandated trial (EAGLES, Lancet 2016) all three of these medications were found to be safe and effective in patients with and without pre-existing psychiatric conditions.[23] To protect against risk from pharmacotherapy usage, this study will only use FDA-approved smoking cessation medications and tobacco treatment providers will screen patients to identify contraindications to NRT or varenicline. Written and verbal instructions will be provided to patients given medication to contact their primary physician and the research PI, Hilary Tindle, in case of adverse effects of a medication. Additionally, study staff will call participants during active treatment to monitor for medication side effects. Ultimately, the PI (Dr. Tindle) will review any serious adverse events and report them appropriately to the IRB.

8.0 Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

Any serious adverse events will be reported to the IRB and NIH according to appropriate policies and procedures. Serious adverse events are defined as untoward or undesirable medical events, related to study procedures, that 1) are of at least moderate severity as reported by participants at follow-up; 2) require hospitalization or ER visit; 3) are life-threatening or cause death or permanent impairment/disability; or 4) require intervention to prevent death or permanent impairment/disability.

9.0 Study Withdrawal/Discontinuation

Individuals who wish to withdraw from the study may do so at any time by contacting the Principal Investigator (Dr. Tindle) in writing without penalization or change to their medical care. Any data collected prior to withdrawing from the study will be analyzed as enrolled unless requested for full withdrawal by the participant. The PI and study personnel withhold the right to withdraw participants from the study if they are non-compliant with study procedures or if there is a perceived imminent medical threat to the participant.

10.0 Statistical Considerations

This pilot project is intended to create infrastructure, establish feasibility, and provide necessary preliminary data to design and conduct a prospective pilot RCT comparing precision smoking cessation treatment to usual care. As such, the primary outcome is feasibility and the study is not powered to detect differences between treatment groups for smoking cessation. However, we will conduct descriptive and exploratory analyses of collected data as well as assess for between-group differences in this clinical outcome.

Aim 1: Survey up to 1400 TN and MS SCCS smokers to assess attitudes and beliefs on smoking-related health risk perceptions, precision smoking treatment, and willingness to engage in a smoking cessation trial of PC. We anticipate a response rate of up to 70% of contacted participants.

Primary Analysis: Analysis of survey data will utilize the following general strategies: to test statistical differences in the frequency distributions of variables of interest, we will calculate t-tests for continuous parameters of interest, and chi-square tests for categorical parameters of interest. Participants will be categorized according to objective and subjective classifications of smoking-related disease risks. The objective measurement of lung cancer risk will be calculated using the validated $PLCO_{M2012}$ model (Tammemagi NEJM 2013). Subjective measures of disease risks will be obtained via participant response to the study survey, as to whether the participant believes their risks for heart attack, cancer or lung cancer are lower, about the same, or higher than other smokers their age. Pearson correlation coefficients will be calculated to evaluate the relation between objective and subjective lung cancer risk estimates. Regression analyses will be used to calculate risk ratios and 95% confidence intervals for the associations between objective lung cancer risk, subjective disease risks, and use of smoking cessation aids or interest in precision smoking treatment. Regression statistical models will include variables for potential confounders such as age, race, sex, education, alcohol intake, and family history of lung cancer diagnosis in a first degree relative. P-values for trend tests will be calculated by treating ordinal variables as continuous in statistical models. Potential interactions will be evaluated by completing likelihood ratio tests comparing statistical models with and without the addition of cross-product terms.

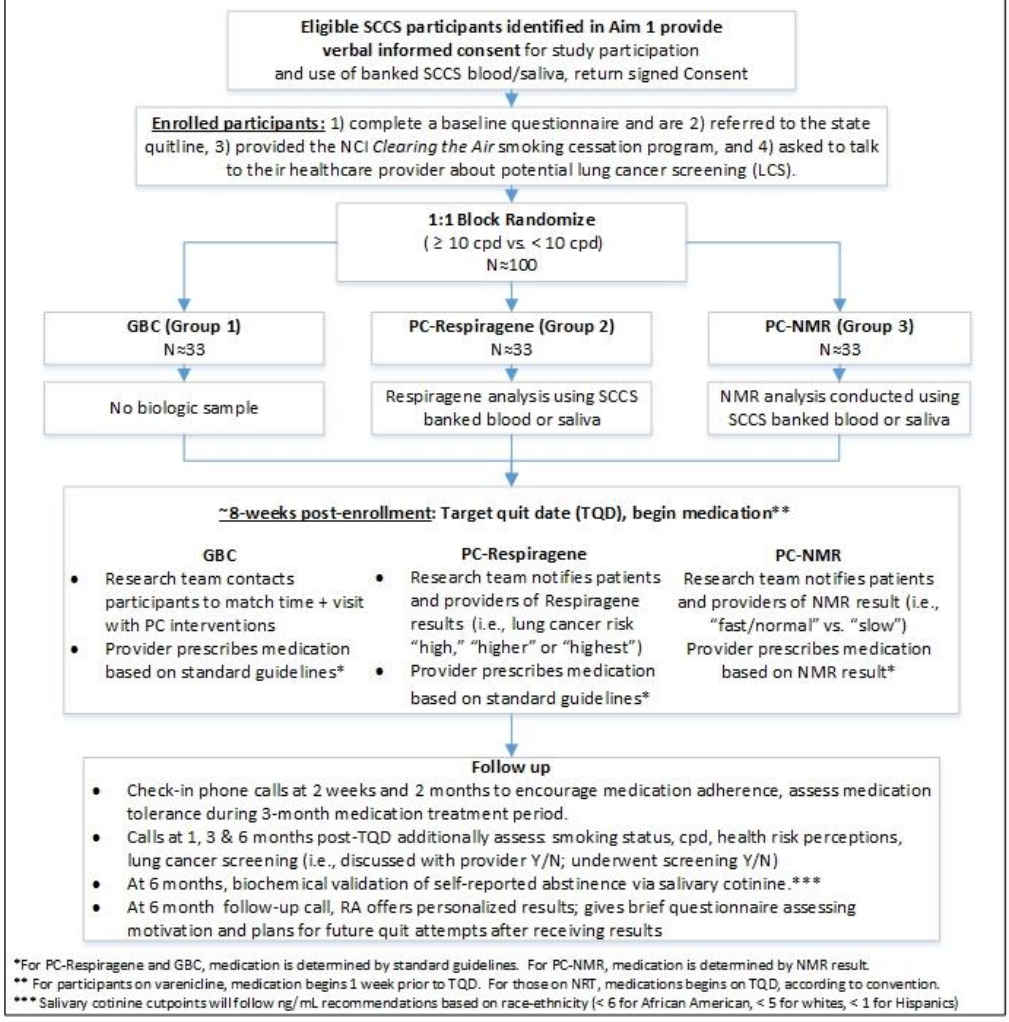
Aim 3: Conduct a 3-arm RCT (Figure 2) to pilot PC interventions for feasibility and to determine preliminary estimates of biochemically-validated smoking cessation at 6 months vs. GBC.

Hypothesis: PC interventions will be acceptable to participants and feasible to administer.

Secondary hypotheses (exploratory): Compared to GBC, PC participants will exhibit higher smoking cessation and lung cancer screening rates.

Primary Analysis: We will assess engagement in smoking cessation treatment as measured by: (1) connection with the study tobacco treatment counselor, (2) connection with the state quitline and (3) use of study-provided medication. We will also obtain preliminary estimates of behavior change at 6 months, including: 1) biochemically-validated smoking cessation and 2) rates of lung cancer screening for individuals who meet screening criteria. We will also collect information on process measures such as enrollment, educational material format, and costs per patient treated. Note, the current pilot RCT will not be powered to demonstrate significant differences in cessation rates by study group.

Figure 2: Aim 3 - Pilot RCT: PC-Respiragene vs. PC-NMR vs. Guideline-based Care (GBC)



Privacy/Confidentiality Issues

Participant data will be collected using password protected and encrypted computers, and electronic participant tracking spreadsheets stored on a secure server. All paper records will be locked in secure areas and accessible to study staff only. To prevent the loss of data, all electronic information is password protected on anti-virus software enabled computer systems. Only study staff will have access to the study data on Shared File Areas. A participant number will identify all participants on study forms and in the database. Participant names and contact information will be stored in a separate file.

Protected Health Information (PHI) will be used in this study. The investigators will comply with the patient privacy guidelines of Vanderbilt University Medical Center and the rules outlined by the Health Insurance Portability and Accountability Act (HIPAA). Surveys will be associated with a participant number and all patient identified information will be managed by the SCCS offices in Jacksonville, FL, where they will be stored. The

Survey Research Shared Resource will receive identified information in order to make necessary phone calls; study staff associated with Vanderbilt, Meharry, and TSU will receive only de-identified data files.

11.0 Follow-up and Record Retention

Participants will be followed up through approximately 12-months after enrollment (as outlined above in Study Procedure). Records will be kept indefinitely but will be destroyed if no longer needed.

12.0 References

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