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STUDY TITLE: A pilot pragmatic RCT of a hospital-based precision pharmacotherapy smoking cessation program.

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1.0 INTRODUCTION (SIGNIFICANCE, RATIONALE, & HYPOTHESES):

Tobacco use is the leading preventable cause of morbidity and mortality in the United States (US) and Delaware,[1] claiming more than 400,000 US lives each year.[2] Tobacco use disorder (TUD), or the long-term problematic use of tobacco, has been recognized by the American Psychiatric Association as a substance use/behavioral health condition (see [3]). The burdens of TUD disproportionately affect racial minorities and those with low socioeconomic status (SES), thereby contributing to tobacco-related health disparities (TRHDs).[4] Underserved smokers are no less interested in quitting smoking and make just as many quit attempts as more advantaged smokers[5] but are less likely to be advised to quit,[6] have less access to treatment,[7] use evidence-based treatments less frequently, report greater concerns about the safety of these medications, and ultimately experience lower abstinence rates.[5] Hospital-based smoking cessation interventions have the potential to reach large segments of this underserved population. A Cochrane review found that hospital-based interventions significantly increase smoking cessation rates compared to usual care;[8] however, rates rarely exceed 25%. Promising new evidence suggests that applying a *precision pharmacotherapy* approach based on the nicotine metabolite ration (NMR), a commercially available, genetically-informed marker of nicotine metabolism rate can significantly improve cessation outcomes. Evidence from multiple independent studies,[9–12] including a recent randomized clinical trial (RCT),[13] demonstrates that matching slow metabolizers of nicotine with the nicotine patch and fast metabolizers of nicotine with varenicline can maximize treatment response and minimize side effects. While encouraging, a critical gap in knowledge is how to best translate a precision pharmacotherapy approach into a hospital-based smoking cessation intervention and improve cessation rates for underserved smokers. Preliminary data suggest that personalized treatment recommendations may increase TUD medication uptake and effectiveness.[14,15] Thus, the scientific premise of this application is that integrating a precision pharmacotherapy approach into a hospital-based TUD treatment program will increase medication uptake and effectiveness, with particular relevance for smokers from underserved communities.

2.0 STUDY POPULATION:

Approximately 100 adult current smokers (≥ 5 cigarettes/day), who are patients at the Helen F. Graham Cancer Center & Research Institute (Christiana Care) lung/thoracic clinic who are ages 18 and older. Exclusion criteria include: 1) use of non-cigarette tobacco products or current TUD treatment, 2) psychiatric or other medical contraindications to receiving TUD medication (assessed by the study physician), 3) no telephone, 4) medical instability, 7) inability to communicate in English, 8) unable to consent due to mental status, 9) estimated life expectancy of < 6 months, 10) pregnancy.

The duration of study participation will be approximately 6 weeks from the first through the final study visit.

3.0 STUDY PROCEDURES:

3.1 Overview of Proposed Research Design

This investigation employs a randomized controlled trial (RCT) study design. Participants will be randomized into either precision pharmacotherapy, where they will receive a personally-tailored recommendation for a TUD medication based on their NMR plus standard care, or to standard care only. Standard care will adhere to the Ask-Advise-Connect model where participants are asked about tobacco use, advised to quit smoking, offered a choice of FDA-approved TUD medication and offered a referral to the Delaware Quitline for access to counseling services and medications.

Upon enrollment into the study, the research assistant will verify demographic data, administer a baseline survey, and coordinate testing for the NMR at their in-person intake visit. Patients will be randomized to the precision or standard care arms in a 1:1 ratio. Following receipt of the NMR test results and randomization, the research assistant will follow-up with a pre-quit telephonic visit to review procedures with participants. For standard care, the research assistant will provide information on FDA-approved TUD medications and offer to coordinate the process of starting on a medication of the participants' choice (i.e., nicotine patch or varenicline), which participants can decline. Participants randomized to precision pharmacotherapy will be provided with their NMR result, information on how NMR impacts TUD treatment, and a personalized recommendation for medication based on their NMR result (i.e., varenicline for faster metabolizers, nicotine patch for slower metabolizers). Similar to standard care procedures, participants will be offered either the nicotine patch or varenicline and will not be required to choose the medication based on their personalized recommendation, or any medication. For participants in both conditions who opt for medication, per participant preference, medications can be prescribed by the study physician (Dr. Nam) or the patient can be referred to the Delaware Quitline for no-cost medications, a free service available to all Delaware residents. A 1-week follow-up telephonic visit will be conducted to collect data related to medication use, quit date or smoking rate, and side-effects. Finally, a 1-month follow-up in-person visit will be arranged to complete a follow-up survey and to assess smoking status.

3.2 Participant Identification and Recruitment

With the support of Brian Nam, MD, thoracic surgeon, and lead for the "Lung Health Clinic" in the Helen F. Graham Cancer Center & Research Institute and Gretchen Makai, MD, gynecologist and Director of the Division of Minimally Invasive Gynecologic Surgery at ChristianaCare, the research assistant will meet with prospective participants in the clinic or the Center for Advanced GYN & Minimally Invasive Surgery to screen for eligibility, discuss study

procedures, answer questions, and if appropriate review the consent and HIPPA forms. Patients will be clearly informed that not participating in this study will not preclude engaging in other smoking cessation programs, nor will accepting medication be a condition of participation.

Vulnerable Populations: Pregnant women and fetuses, children, neonates, and prisoners are not included in this research study. Women who are pregnant at the time of the baseline assessments will not be eligible for the study. Women will be advised to notify the study staff if they become or intend to become pregnant during the study period.

Populations vulnerable to undo influence or coercion: Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons, including those with poorly managed serious psychiatric conditions, are not included in the current study.

The study consent includes language that informs participants that their care will not be affected if they choose not to participate in the study or withdraw after enrollment. The Principal Investigator may withdraw participants who violate the study plan, to protect the participant for reasons related to safety, or for administrative reasons. Whether or not each participant completes the study will be tracked.

3.3 Study Procedures & Data Collection

The following study procedures will be implemented. A description of the measures used to collect data during these procedures is provided below.

- Intake Session (completed during clinic visit)
  - Participants will complete a self-report survey of demographics, smoking history, and beliefs about the use of smoking cessation aids.
  - [Women only] A pregnancy screen will be administered for women capable of becoming pregnant (55 and under). NOTE: For safety reasons, pregnant women will not be eligible to participate in the research study.
  - The research assistant will complete the blood draw to be used for a nicotine metabolite ratio (NMR) test and arrange for the sample to be transported to the laboratory for processing.

- Randomization: Following completion of the 'intake session' and receipt of NMR testing results, participants will be randomized in a 1:1 ratio to either of the following conditions:
  - Treatment Plan Option 1 (Standard Care): Standard smoking cessation counseling will be offered + participant choice of nicotine patches or varenicline. Participants are also free to decline either medication.
  - Treatment Plan Option 2 (Precision Pharmacotherapy): Standard smoking cessation counseling will be offered + a recommendation to take either the nicotine patch or varenicline based on the results of the NMR test. Regardless of the recommendation, it would still remain the participant's choice to be prescribed either nicotine patches or varenicline. Participants are also free to decline either medication.

- Pre-Quit Telephonic Visit: This visit will take place after the NMR results have been received and randomization is complete, approximately 7-14 days following the intake session (depending on lab processing time).

- Participants will be informed of their treatment condition, including the recommended medication if assigned to 'treatment plan option 2' (i.e., the precision pharmacotherapy arm).
- Participants will be offered their choice of either the nicotine patch or varenicline. Participants will be reminded that taking medication is not a condition of participation in the study. In addition, participants assigned to 'treatment plan option 2' (i.e., the precision pharmacotherapy arm) will not be required to accept only the medication recommended to them based on the results of NMR testing
- For participants who elect to take a medication, the research assistant will communicate with the study physician (Dr. Nam), or the investigators at the Center for Advanced GYN & Minimally Invasive (Dr. Makai or Dr. Ingraham) to arrange for a prescription and/or referral to the Delaware Quitline, per participant preference.
- Even for participants who receive a prescription in the clinic or at the Center for Advanced GYN & Minimally Invasive Surgery, a referral to speak with a smoking cessation counselor, which is made available at no-cost to all Delaware residents through the Delaware Quitline.

- Follow-up Telephonic Visit: This session will occur one week after the pre-quit telephonic/virtual visit.
  - Participants will answer brief questions regarding medication use, quit date or smoking rate if still smoking, and side effects.

- In-Person Assessment: This session will occur four weeks after the pre-quit telephonic/virtual visit. The research assistant will arrange to meet participants at the clinic.
  - Participants will again complete a brief assessment of medication use, quit date or smoking rate if still smoking, and side effects.
  - Participants who self-report smoking cessation will complete a carbon monoxide (CO) reading by breathing into a machine provide a biochemical confirmation of smoking status.

The measures referenced above will be administered accordingly:

Study Measure	**Intake Session Enrollment (in-person)**	**Pre-Quit Visit Week 0 (phone)**	**Follow-Up Visit Week 1 (phone)**	**Final Assessment Week 4 (in-person)**
Demographics	X			
Smoking History	X			
NMR	X			
Medication use, quit date or smoking rate, side-effects			X	X
Carbon Monoxide reading				X

- **Demographics.** The research assistant will confirm demographic data collected from the EHR and collect additional characteristics, including address, phone number, date of birth, race/ethnicity, employment status, education level, and income.
- **Smoking history.** Participants will be asked standard questions about cigarette use, including the number of cigarettes smoked per day, the age of smoking onset, whether the participant ever quit smoking previously and for how long, and whether the participant ever utilized smoking cessation aids previously. In addition, participants will be administered the first item from the Fageström Test for Nicotine Dependence (FTND), a measure of nicotine tolerance and withdrawal.[17]
- **Nicotine Metabolite Ratio (NMR).** NMR testing for cotinine and 3-hydroxycotininie following standard procedures at a commercial laboratory contracted with ChristianaCare (i.e., Quest).[19]
- **Medication use quit date or smoking rate, and side effects.** At the follow-up call and in-person assessment, the research assistant will use the timeline follow-back interview method[20] to ask participants whether they quit smoking (including the quit date). If participants did not successfully quit smoking, current rates of smoking will be assessed. In addition, the research assistant will ask about medication usage and side-effects.
- **Carbon monoxide reading.** For participants self-reporting smoking cessation, biochemical verification of smoking status will be conducted with the use of a breath carbon monoxide monitor manufactured by Vitalograph according to standard procedures.[21]

4.0 RISKS AND BENEFITS TO PARTICIPANTS:

4.1 Potential Risks

Risks include withdrawal symptoms and side effects from the medications, described below.

Nicotine Withdrawal Syndrome

Most individuals who quit smoking experience symptoms of withdrawal. These symptoms can occur almost right away and last for 10-14 days. These symptoms include:

- Sadness and mood changes
- Insomnia or changes in sleep
- Constipation
- Decreased heart rate
- Irritability
- Craving for cigarettes
- Anger
- Difficulty concentrating
- Restlessness or nervousness
- Appetite increase and weight gain

Nicotine Patch

The potential side effects of the nicotine patch are described below:

Most Common Side Effects. Nausea, vomiting, dizziness, weakness, and rapid heartbeat are side effects that occur rarely, but are most often caused by continuing to smoke while using the patch. Difficulty breathing or a notable rash could be the symptoms of an allergic reaction.

Skin Reactions. The most common skin reactions to the patch are skin redness, rash or swelling, itching, bumping or tingling at the patch site. To minimize these reactions, the site of the patch can be changed each day.

Sleep Disturbances. When using the patch, some people also report difficulties sleeping or vivid dreams. However, this is rare and can be minimized by removing the patch at night.

Other Nicotine Patch Risks. These include risks to children and pets if the nicotine patches are not stored or disposed of properly. Unused and used patches have enough nicotine to poison children and pets.

Varenicline (Chantix®)
The potential side effects of taking varenicline are described below:

Most Common Side Effects. Potential side effects of taking varenicline are nausea, sleep disturbance, constipation, flatulence (gas), or vomiting. These can occur in more than 5% of people taking this medication.

Allergic Reactions. There have been rare reports of allergic and skin reactions to varenicline, including swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). These types of allergic reactions are considered serious and may be life-threatening. However, the risk for these reactions is small (about 1 out of 1000 people taking this medication).

Mood-related Side Effects. Rare serious mood-related effects have been reported in a small number of persons taking varenicline. The risk for this type of reaction is about 1 out of 1000 people taking the medication. These include, but are not limited to, depression, agitation, hostility, suicidal thoughts, suicide attempts, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal thoughts, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking varenicline who continued to smoke. When symptoms were reported, most occurred during treatment with varenicline, while some followed discontinuation of varenicline therapy. All patients being treated with varenicline will be assessed for such symptoms. These events have occurred rarely in patients with and without pre-existing psychiatric disease.

Although patients with serious psychiatric illness such as major depressive disorder, schizophrenia, or bipolar disorder did not participate in the pre-marketing studies of varenicline, recent clinical trials that specifically targeted these patient populations have demonstrated safety of varenicline for use in these populations. These studies did not find significant differences in mood-related side effect rates or any exacerbation of psychiatric symptoms between those taking varenicline versus placebo.

Cardiac Side Effects. Varenicline may be associated with an increased risk for certain cardiac (heart) and vascular (blood vessel) side effects, including chest pain, heart attack, stroke, shortness of breath, calf pain when walking or sudden onset of weakness, numbness or difficulty speaking. One study showed that these risks are rare (~1% or 1 out of 100 people using varenicline) but a later study found no difference between placebo and varenicline in terms of these cardiac risks.

Somnambulism. Cases of somnambulism (sleep walking) have been reported in patients taking varenicline.

Brief Cognitive Side Effects. Varenicline may cause noticeable drowsiness, dizziness, headache, loss of consciousness, or difficulty concentrating that may impair one's ability to perform tasks requiring judgment or motor and cognitive skills such as driving a car and operating machinery.

Risk of Seizure. Varenicline may be associated with new or worsening seizures during the first month of treatment. Some patients who reported experiencing a seizure while taking varenicline had no prior history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled.

Potential Interaction with Alcohol. It is possible that varenicline may affect response to alcohol. Some individuals have reported lower alcohol tolerance, aggressive behavior, or impaired memory following consumption of alcohol during varenicline treatment. In these cases, the amount of alcohol consumed was not sufficient to explain the event. It is best to minimize or reduce alcohol intake (no more than 3 drinks per occasion or within a 24-hour time period).

Other Risks

Assessments/Questionnaires and Smoking Cessation Counseling. Some people can experience anxiety and other types of general distress when they complete questionnaires. This is generally related learning about some of the health risks associated with smoking. These reactions are usually very mild and typically diminish with time.

Threats to Privacy/Confidentiality. Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential. However, social harms may result when sensitive and personal information is inappropriately disclosed. Inappropriate disclosure of study data about participants' beliefs, attitudes, behavior (including smoking), and health may result in damage to participants' economic status. These harms can include loss of employment, health insurance, life insurance, housing, and ability to travel.

Reproductive Risks [Females Only]. Because of the effects of varenicline and the nicotine patch, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child.

4.2 Protections Against Risks

The risks associated with the use of study medications will be explained to all participants. This information will also be included in the informed consent forms. We will include a specific measure of side effects associated with study medications that will be administered at two time points during the course of the study. Information will also be provided to participants on how to contact study personnel and other clinical care should a concern arise between assessment time-points. In the event of significant medication side effects, or for any reason, patients can discontinue medication at any point during the study. Accepting medication is not a condition for participation, nor is participating in the study necessary to receive smoking cessation services. Furthermore, during the enrollment phase of the study, when medications will first be initiated, patients will be under the care of an attending physician and will continue to have access to care for the duration of the study.

To protect against the threats to privacy/confidentiality, safeguards will be put into place to minimize the risk of unauthorized access to records (see section 6.0). To minimize the reproductive risks, female participants 55 and under will be screened for pregnancy and advised to use birth control. Pregnant women or women who intend to become pregnant will be excluded from participation. Women will also be advised to inform study personnel in the event they become pregnant.

4.3 Potential Benefits

Smoking remains the leading preventable cause of early mortality in the US. The proposed research is a clinical trial that will evaluate FDA-approved medications for smoking cessation, customized to individual smokers' nicotine metabolism. Prior research has demonstrated that such an approach can significantly increase abstinence rates. Therefore, the potential benefits of the proposed research include a greater likelihood of smoking cessation and the corresponding health benefits, including longer life expectancy. In addition, this research may benefit others by reducing exposure to secondhand smoke and more generally by contributing to the knowledge base on smoking cessation best practices.

4.4 Participant Renumeration

Participants can be remunerated up to $50 for participation in this trial, $25 for each of the two in-person data collection visits.

5.0 DATA SAFETY MONITORING PLAN (DSMP)

For this study, we will use all established ChristianaCare procedures and infrastructure for data and safety monitoring. A Data Safety Monitoring Board will not be used for this study because it is a single center trial that will use FDA-approved drugs with good safety profiles for on-label use. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the PI and research team. Study personnel are responsible for collecting and recording all clinical data using the established operating procedures. This includes ensuring that all source document exist for the data on Case Report Forms, ensuring all fields are completed appropriately, and ensuring that all corrections are done according to Good Clinical Practice. Any inconsistencies or deviations will be documented. The study Key Personnel, which include the study physician (Dr. Nam), will review data on an ongoing basis and will document reviews by initialing and dating reports. Study personnel conduct 100% quality assurance on data, comparing all hard copy to electronic files.

Staff training will consist of an explanation of the protocol and review of the Case Report Forms. In addition, the duties of each staff person will be outline and all applicable regulations will be reviewed by the PI. Mock sessions with critical feedback will be conducted by the PI. The PI will oversee recruitment and data collection and management.

Monitoring will be conducted in accordance with the ChristianaCare Institutional Review Board IRB) procedures (SOP: 402.1) regarding Adverse Events. Study staff will administer a side effects checklist to determine any reporting requirements. Should a report rise to the level of a potential Adverse Event, the decision on the course of action for the participant will be determined by Dr. Nam after review of the review. In addition, both personnel and participants will be given the contact information should they need to reach a member of the study between assessments. The research team will clinically follow all participants who are discontinued due to a Serious Adverse Event until it resolves and becomes stable, unless a referral to another physician (e.g., specialist) is clinical indicated or requested by the participant. All Adverse Events and Serious Adverse Events will be documented on a ChristianaCare IRB Adverse

Event Form. This information will, in turn, be reported immediately to all necessary regulatory committees and maintained in a unique databased to be reviewed monthly by the PI.

6.0 USE OF PHI AND STORAGE OF STUDY RECORDS:
Self-report, blood, and medical data will be collected and stored as part of this study. Therefore, to protect participant privacy and confidentiality, several safeguards will be implemented to prevent unauthorized access to study data. A unique identification number will be generated for each participant to be used in the dataset that contains collected data. A separate table, housed in a unique location, will be created for storing participant name, address, and telephone contact information. Using this method, no identifying participant information will be directly linked to medical information or other study data. Data will be stored on an electronic folder dedicated to research with access limited to only authorized research personnel on the study protocol. Paper documentation will be stored in a badge protected office in the locked drawer of the research coordinator's desk. Data cannot be transferred to personal computers or other memory devices. In the very rare event of a breach of confidentiality, all IRB procedures will be followed, affected participants will be notified, and appropriate corrective measures to secure the data will be taken. In addition, participants will be provided with any reasonable assistance to help mitigate the risk. The results of this study will be presented only in a summary and/or deidentified fashion in peer-reviewed publications and research presentations.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from the participants in the study
- Who will have access to that information and for what purposes
- Who will use or disclose that information
- The rights of the research participant to revoke their authorization for use of their PHI

In the even that a participant revokes authorization to collect or use PHI, the PI, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization.

The following PHI will be collected on study participants:

- Name
- Age
- ICD Codes
- Street Address
- Zip Code
- Medical Record Number
- Sex
- City
- Race
- Insurance
- County
- Birth Date
- Telephone Number

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