Short Communication

A pilot pragmatic randomized controlled trial of a nicotine metabolite ratio-guided smoking cessation intervention in a lung health and screening program

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ABSTRACT

Introduction: Patients with pulmonary nodules detected through lung cancer screening or as incidental findings are often followed in lung health and screening programs. The use of personalized pharmacotherapy for smoking cessation informed by the nicotine metabolite ratio (NMR), a measure of nicotine metabolism, has not yet been evaluated in this setting. This pilot randomized controlled trial (RCT) evaluated the feasibility of conducting a larger trial.

Methods: Through a pragmatic RCT design, participants were recruited from a Mid-Atlantic lung health and screening program. Eligible participants smoked >5 cigarettes per day and completed a blood draw to determine NMR before being randomized to standard or NMR-guided care treatment arms. Standard care participants were offered nicotine replacement therapy (NRT) or varenicline and a referral to phone-based smoking cessation counseling. NMR-guided participants received standard care except they were provided a personalized medication recommendation based on their NMR. Study outcomes included measures of feasibility, medication uptake, and treatment matching (i.e., uptake of the optimal medication).

Results: More than 80 % of 205 screened patients were eligible. However, only 37 (22 %) of these patients enrolled in the study, with a mean age of 65 years, 43 % female, and 25 % Black. Nearly all patients who declined cited a disinterest in smoking cessation. Participants in both treatment arms had high rates of medication uptake (68 %), with NMR-guided participants showing a trend towards greater treatment matching (55 % vs. 29 %).

Conclusions: The results of this pilot study provide support for conducting a larger RCT of an NMR-guided smoking cessation intervention in a lung health and screening setting. Consideration should be given to augmenting the intervention to address barriers to study entry.

1. Introduction

The US Preventive Services Task Force (USPSTF) recommends annual lung cancer screening with low-dose computed tomography (LDCT) for adults aged 50–80 years who have a 20 pack-year smoking history (Krist et al., 2021). A pulmonary nodule is identified in 30 % of individuals who undergo LDCT (Results of Initial, 2013), or approximately 400,000 cases annually based on screening rates in the US (Fedewa et al., 2021). An additional 1.6 million people per year in the US are estimated to have pulmonary nodules identified as an incidental finding on chest CT for indications other than lung cancer screening

(Gould et al., 2015). While more than 95 % of pulmonary nodules are benign (Gould et al., 2015), patients with positive findings should be clinically evaluated (Mazzone and Lam, 2022), which is increasingly provided in multidisciplinary lung health and screening programs (Lemense et al., 2020). In contrast to the USPSTF recommendations that clearly state smoking cessation interventions should be offered to patients who continue to smoke at the time of screening, less attention has been paid to offering tobacco treatment to patients found to have pulmonary nodules (Gould et al., 2015). This is concerning because the detection of pulmonary nodules is often not sufficient for patients to alter their smoking behavior (Clark et al., 2019). When patients do

abstain from smoking, they often experience a reduction in nodule size and improved lung function (Maci et al., 2014). These findings underscore the importance of systematically providing smoking cessation services in lung health and screening programs.

Recent advances in the use of biomarkers to guide the pharmacological treatment of tobacco use offer the potential to improve smoking cessation outcomes and further advance lung cancer prevention (Siegel et al., 2023). As reviewed elsewhere, the most promising biomarker-based approach has been the nicotine metabolite ratio (NMR) (Siegel et al., 2023). Briefly, nicotine is metabolized in the liver by the CYP2A6 enzyme into cotinine, which is then metabolized again by CYP2A6 into trans-3'-hydroxycontinine (3HC). The NMR is the ratio of 3HC to cotinine and quantifies rates of nicotine metabolism. A prospective NMR-stratified multicenter randomized placebo-controlled clinical trial found that fast metabolizers of nicotine responded better to varenicline vs. the nicotine patch while slow metabolizers of nicotine showed the same quit rates from the two treatments but significantly worse side effects from varenicline (Lerman et al., 2015). However, few high-quality studies have investigated the use of NMR in "real world" clinical settings, including in lung health and screening programs (Siegel et al., 2023).

The objective of this study was to conduct a pilot pragmatic randomized controlled trial (RCT) of an NMR-guided smoking cessation intervention in a lung health and screening program. This study was designed to primarily evaluate the feasibility of conducting a larger RCT and secondarily whether providing a personalized smoking cessation medication recommendation increased medication uptake and treatment matching. The results of this study can inform the development of larger trials that can determine whether NMR-guided approaches improve smoking cessation outcomes in lung health and screening programs.

2. Methods

2.1. Enrollment and randomization

This study protocol was approved by the health system Institutional Review Board (CCC# 41042) and enrollment was conducted between March 16, 2022, and November 15, 2022.[1] This study was registered with ClinicalTrials.gov (NCT04897607). Participants were recruited from a lung health and screening program in a Mid-Atlantic community cancer center, which provides follow-up care for patients with pulmonary nodules identified through LDCT or as an incidental finding. Eligible participants were adult (>18 years) state residents (to be eligible for quitline services) who currently smoked (> 5 cigarettes/day) and were medically appropriate to receive either NRT or varenicline, two Food and Drug Administration (FDA)-approved smoking cessation medications. Consistent with a pragmatic approach, exclusion criteria were limited to the use of non-cigarette tobacco products or smoking cessation treatment, unstable serious psychiatric illness, inability to reliably communicate by telephone or to read and/or speak English, current pregnancy or actively breast feeding, or a limited life expectancy (<6 months). The research coordinator reviewed patient charts and potentially eligible participants were approached during their clinic visit to discuss the study, confirm eligibility, and obtain written informed consent. Enrolled participants completed an intake self-report survey (demographics and smoking history) and a blood draw for the NMR. Testing for cotinine and 3HC values followed standard procedures at a commercial laboratory that were used to calculate the NMR ratio (3HC/

cotinine) (Tanner et al., 2015). Participants were categorized as "slower" (NMR <0.31) or "faster" (NMR >0.31) metabolizers,[2] consistent with prior approaches (Lerman et al., 2015). Participants were then randomized to standard care or NMR-guided care treatment arms in a 1:1 ratio.

2.2. Treatment arms

Approximately 7 days following the intake visit, when NMR results were available, the research coordinator notified participants about their randomization by phone. Participants randomized to standard care were advised to quit smoking and offered a choice of NRT patches or varenicline, which participants were free to decline. Participants in this arm were not made aware of their NMR status or provided a specific medication recommendation. For participants who wanted to take a medication, the study physician (BN) wrote a prescription and NRT or varenicline pills were made available directly from the clinic at no cost. Participants were also provided with information for the state quitline to receive counseling if that was something they chose to initiate. Participants randomized to NMR-guided care received standard care with the exception that they were made aware of their NMR status and provided with a medication recommendation based on their NMR (i.e., NRT for slower metabolizers and varenicline for faster metabolizers). Regardless of their NMR status or medication recommendation, participants were free to choose either medication or decline all medication.

2.3. Follow-up study visit

Four weeks after the telephone visit where participants were made aware of their randomization and provided medication (if applicable), the research coordinator conducted another phone visit to ask participants about their usage of cessation medication. Given COVID-19 restrictions, we were not able to request that participants return to the clinic to biochemically confirm smoking status at the four-week follow-up.

2.4. Statistical analyses

Feasibility measures included number of eligible participants and proportion of eligible participants who enrolled. Descriptive statistics were used to characterize participant demographics, smoking history, and clinical reason for being followed by the clinic. Odds ratios were used to compare the rates of medication uptake and treatment matching for the treatment arms. Testing was done with a two-sided 5 % type 1 error.

3. Results

As shown in the Consort Diagram (Supplemental Figure), 205 patients were screened in clinic. Of these patients, 167 (81 %) were deemed eligible and approached, with 37 participants (22 %) enrolling in the study. Participants were randomized to standard care (N=17) or NMR-guided care (N=20). Of the 130 patients who declined (78 %), 128 gave the reason of not being interested in smoking cessation. A total of 6 participants were lost to follow-up (16 %; 4 from standard care and 2 from NMR-guided care), including 1 participant who died for reasons unrelated to the study and 5 participants who did not participate after randomization. These participants were classified as not taking medication.

Table 1 provides the characteristics of the study sample. Participants were, on average, 61.8 years old (SD=8.9), 43 % were women, 60 % were White and 25 % were Black, and 3 % were Hispanic. Most

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[1] The recruitment period was originally supposed to be a year but was truncated because of delays imposed by COVID-19 and a recall of the study medication.

[2] The terms 'normal' and 'fast' are used interchangeably in the literature to refer to NMR values ≥0.31.

Table 1
Characteristics of enrolled patients by randomized study arm.

	Standard Care (N=17)	NMR-Guided Care (N =20)	Total (N=37)
Age, *mean (SD)*	65.00 (7.06)	59.08 (9.65)*	61.80 (8.96)
Race, *n (%)*			
White	11 (64.7 %)	11 (55.0 %)	22 (59.5 %)
Black	5 (29.4 %)	8 (40.0 %)	13 (25.1 %)
Other	1 (5.9 %)	1 (5.0 %)	2 (5.4 %)
Ethnicity, *n (%)*			
Hispanic/Latino	0 (0.0 %)	1 (5.0 %)	1 (2.7 %)
Non-Hispanic/Latino	17 (100 %)	19 (95 %)	36 (97.3 %)
Gender, *n (%)*			
Male	7 (41.2 %)	9 (45.0 %)	16 (43.2 %)
Female	10 (58.8 %)	11 (55.0 %)	21 (56.8 %)
Relationship Status, *n (%)*			
Never married	1 (5.9 %)	6 (30.0 %)	7 (18.9 %)
Married/Partnered	10 (58.8 %)	11 (55.0 %)	21 (56.8 %)
Divorced or separated	6 (35.3 %)	3 (15.0 %)	9 (24.3 %)
Education, *n (%)*			
Some high school	1 (5.9 %)	3 (15.0 %)	4 (10.8 %)
High school/GED	5 (29.4 %)	8 (40.0 %)	13 (35.1 %)
Some college	8 (47.1 %)	6 (30.0 %)	14 (37.8 %)
College graduate or beyond	3 (17.6 %)	3 (15.0 %)	6 (16.2 %)
Employment Status, *n (%)*			
Employed Part-or Full-Time	4 (23.5 %)	10 (50.0 %)	14 (37.8 %)
Retired or not currently employed	13 (76.5 %)	10 (50.0 %)	23 (62.2 %)
Annual Household Income[a], *n (%)*			
Less than $20,000	4 (23.5 %)	3 (15.0 %)	7 (18.9 %)
$20,001 - $35,000	1 (5.9 %)	4 (20.0 %)	5 (15.5 %)
$35,001 – $50,000	5 (29.4 %)	2 (10.0 %)	7 (18.9 %)
$50,001 – $75,000	3 (17.6 %)	4 (20.0 %)	7 (18.9 %)
Greater than $75,000	4 (23.5 %)	5 (25.0 %)	9 (24.3 %)
Missing	0 (0 %)	2 (10.0 %)	2 (5.4 %)
Plans for a new quitting attempt, *n (%)*			
Within the next 30 days	12 (70.6 %)	13 (65.0 %)	25 (67.6 %)
Within the next 6 months	5 (29.4 %)	5 (25.0 %)	10 (27.0 %)
Unsure/Don't know	0 (0.0 %)	2 (10.0 %)	2 (5.4 %)
Current cigarettes per day, *mean (SD)*	15.71 (10.83)	15.00 (5.80)	15.32 (8.37)
Number of pack years, *mean (SD)*	44.88 (11.21)	39.60 (11.10)	43.03 (11.31)
Previously advised to quit, *n (%)*	14 (82.4 %)	16 (80.0 %)	30 (81.1 %)
Made prior quit attempt, *n (%)*	14 (82.4 %)	19 (95.0 %)	33 (89.2 %)
Previous cessation medication use, *n (%)*	9 (52.9 %)	15 (75.0 %)	24 (64.9 %)
Reason for being in clinic/visit, *n (%)*			
LDCT screening follow-up	10 (58.8 %)	11 (55.0 %)	21 (56.76 %)
Incidental pulmonary nodule follow-up	3 (17.6 %)	4 (20.0 %)	7 (18.92 %)
Lung cancer treatment follow-up	3 (17.6 %)	3 (15.0 %)	6 (16.22 %)
Self-referral	1 (5.9 %)	2 (10.0 %)	3 (8.11 %)
NMR category, *n (%)*			
Slower metabolizers	7 (41.2 %)	3 (15 %)	10 (27.0 %)
Faster metabolizers	10 (58.8 %)	17 (85.5 %)	27 (73.0 %)

* Represents a significance level of *p* < 0.05
[a] Percentage does not equal 100 % because two participants from the NMR-Guided arm declined to answer.

participants were married/partnered, had at least a high school education, and were retired or not employed. Participants smoked on average 15 cigarettes/day with a more than 40 pack-year history. More than 80 % of participants had been previously advised, and attempted, to quit

smoking, with about 65 % doing so with medication, and the majority were considering a new quit attempt within the next 30 days. Most patients in the clinic were being followed for positive findings on LDCT screening or incidental pulmonary nodules. Slower metabolizers represented 41 % of the standard care and 15 % of the NMR-guided treatment arms; faster metabolizers represented 59 % of the standard care and 85 % of the NMR-guided treatment arm. Apart from a higher average age for standard care participants, no significant baseline differences were found between treatment arms.

As shown in Table 2, the rate of medication uptake between study arms was similar, with 65 % (24 % NRT, 41 % varenicline) of standard care and 70 % (15 % NRT, 55 % varenicline) of NMR-guided care participants reporting study drug use. However, there was a difference approaching significance in treatment matching such that 29 % of the standard care and 55 % of the NMR-guided care participants reported taking the optimal medication based on their NMR status (OR 2.93, 95 % CI [0.75, 11.49; *p* = 0.122])). Among only those participants who took either medication, 45 % of the standard and 79 % of the NMR-guided arms achieved treatment matching (OR 4.40, 95 % CI [0.77, 25.15; *p* = 0.096]).

4. Discussion

Findings from this pilot RCT of an NMR-guided smoking cessation intervention provides support for the feasibility of conducting a larger trial in a lung health and screening clinic setting. More than 80 % of the screened patients in this setting were eligible, highlighting the opportunity to efficiently reach individuals who smoke. However, only 22 % of the eligible participants enrolled in the study. For comparison, in the one other published pilot of an NMR-guided RCT in a "real world" specialty medical setting, Wells and colleagues (Wells et al., 2017) reported an enrollment rate of over 60 %.[3] In this study, approximately

Table 2
Medication uptake and treatment matching.

Category, *n (%)*	Standard Care (N=17)	NMR-Guided Care (N=20)	Total[c] (N=37)
Slower Metabolizers[a]	7 (41.2 %)	3 (15.0 %)	10 (27.0 %)
NRT[b]	**1 (14.3 %)**	**1 (33.3 %)**	**2 (20.0 %)**
Varenicline[b]	3 (42.9 %)	1 (33.3 %)	4 (40.0 %)
No medication	3 (42.9 %)	1 (33.3 %)	4 (40.0 %)
Faster Metabolizers[a]	10 (58.8 %)	17 (85.0 %)	27 (73.0 %)
NRT[b]	3 (30.0 %)	2 (11.7 %)	5 (18.5 %)
Varenicline[b]	**4 (40.0 %)**	**10 (58.9 %)**	**14 (63.0 %)**
No medication	3 (30.0 %)	5 (29.4 %)	8 (29.6 %)
Medication uptake[d], *n (%)*	11 (64.7 %)	14 (70.0 %)	25 (67.6 %)
Treatment matching[e], *n (%)* (percentages reported by arm; among those taking medication)	5 (29.4 %; 45.5 %)	11 (55 %; 78.6 %)	16 (43.2 %; 64.0 %)

Bolded statistics denote treatment matching.
[a] Percentage of participants in this metabolism category for the treatment arm.
[b] Percentage of participants who reported using this medication within this metabolism category and treatment arm.
[c] Percentage of total participants who were within each group/study arm.
[d] Percentage of participants who used medication from each arm.
[e] Percentage of participants who were matched to the appropriate treatment and used the medication.

[3] This enrollment rate was calculated by including the following patients as eligible: 1) those deemed preliminarily eligible but declined to participate for unknown reasons and 2) those who were excluded but would have been eligible for this study (e.g., unwilling to take medication).

77 % of eligible patients declined because of a lack of interest in smoking cessation. Despite the relatively low enrollment rates, 4.6 participants/month were enrolled with a research coordinator funded at 50 % effort. Even without improving upon the enrollment rate, extrapolating to a 100 % effort for a 3-year recruitment period could result in over 330 participants. Including multiple sites at this rate would be on par with previously conducted, sufficiently powered RCTs of NMR-guided care (Lerman et al., 2015).

It is unclear why the enrollment rate for this study was relatively low, but two non-mutually exclusive explanations may apply. First, prior qualitative research unexpectedly found that the identification of a pulmonary nodule following lung cancer screening can lead some patients to feel overly reassured (Zeliadt et al., 2015). They perceived that the harms of smoking were "caught early" and that ongoing imaging would manage the risk, thereby removing any sense of urgency to make a quit attempt. Second, while participation in this study came with referrals to the State Quitline for smoking cessation counseling, eligible patients may not have perceived that this would have adequately addressed their barriers to making a quit attempt (e.g., smoking as a coping strategy for life stressors) (Smith et al., 2023). New research is needed to evaluate these and alternate hypotheses to help inform whether additional intervention components could improve enrollment. Nevertheless, even at low enrollment rates, providing smoking cessation services to individuals not ready to quit smoking are clinically- and cost-effective (Ali et al., 2018).

The secondary finding of this study was that providing NMR-guided care did not increase the uptake of medication over the already high rate in the standard care group but may have increased treatment matching. The high rates of uptake were likely due to a self-selection bias such that participants were inclined to take medication in support of a quit attempt. Participants in the NMR-guided care treatment arm showed a trend towards a higher treatment matching than participants in standard care overall (55 % vs. 29 %) and among participants who reported taking medication (79 % vs. 45 %). Much of this difference was driven by a higher uptake of varenicline among faster metabolizers in the NMR-guided group, an encouraging finding. While these differences were not significant, this study lacked power given the truncated recruitment period. The findings do suggest that a true benefit of NMR-guided care on treatment matching could be readily detected in a larger RCT. Furthermore, major commercial labs offer this assay for a reasonable cost with a 3–7 day turnaround, making this potentially feasible and cost effective at scale.

This pilot RCT was limited by its single-site design, small sample size, limited staffing, reliance on self-report measures, and imbalances across treatment arms (age, NMR). Strengths include a representative sample along demographic, socioeconomic, and smoking characteristics. The enrollment rates and preliminary treatment matching findings provide support for developing a larger, multisite RCT of NMR-guided care that evaluates the impact on smoking cessation and stratifies participants by age and NMR status to ensure balanced treatment arms. Further consideration should be given to augmenting the intervention to improve enrollment, which may include addressing misperceptions about the significance of detecting pulmonary nodules and non-pharmacological barriers to smoking cessation.

Role of the Funding Source

CRediT authorship contribution statement

Robert Schnoll: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Essie Layton:** Writing – review & editing, Project administration, Investigation. **Brian Nam:** Writing – review & editing, Resources, Project administration. **Scott D Siegel:** Writing – original draft, Resources, Methodology, Funding acquisition, Conceptualization. **Ross Budziszewski:** Writing – review & editing, Software, Project administration, Formal analysis.

Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2024.100275.

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