# Personalizing Smoking Cessation Pharmacotherapy Based on the Nicotine Metabolite Ratio (NMR): A Systematic Review

Okoli, CTC., PhD, MSN, MPH, RN1,3; Anand, V., M.D2.

<sup>1</sup>University of Kentucky College of Nursing <sup>2</sup> Brody School of Medicine, East Carolina University <sup>3</sup>Eastern State Hospital, Lexington, KY



### OBJECTIVES

- The ratio of nicotine metabolites, 3' Hydroxicotinine (3HC)/cotinine (COT), commonly referred to as the nicotine metabolite ratio (NMR) is an important biomarker for CYP2A6 activity, which has high correlation to nicotine dependence.
- Moreover, the NMR may be a crucial biomarker to predict the efficacy of smoking cessation pharmacotherapy and guide personalized treatment.
- The purpose of this study was to review the extant literature for interventions that incorporate the use of NMR in determining the efficacy of smoking cessation pharmacotherapy.
- Specifically, we describe:
- a) Characteristics (i.e., sample, intervention components, NMR values) of each study and
- b) Smoking cessation outcomes by NMR status

## Methods

- A comprehensive search of the PubMED database was conducted
- Key words for the search included combinations of Smoking cessation and Nicotine Metabolite Ratio and Quitting smoking and NMR
- The search was limited to:
- a) Studies that assessed interventions addressing smoking cessation NMR,
- b) Were quantitative
- c) Were not literature reviews or Meta-analyses
- d) In the English language
- e) Were published before March 2016 (references of selected articles were also examined for potentially relevant articles)
- f) Studies that were secondary analyses of a parent study were excluded. In such a case, only the parent study was included
- Of 429 studies initially retrieved, after removing duplicates and employing a histrionic search of relevant articles, 9 studies remained pertinent for our study (see Figure 1).

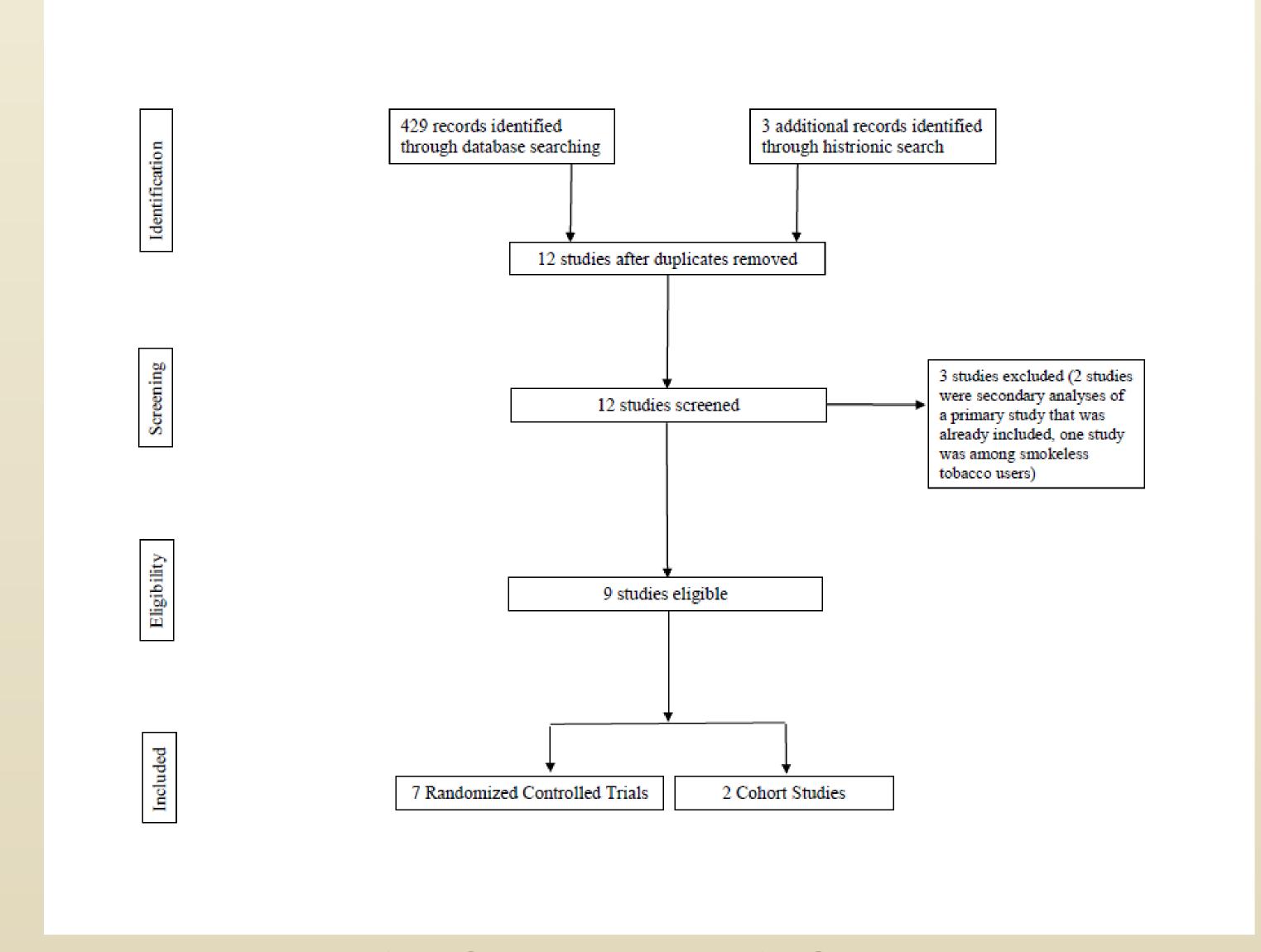


Figure 1. Flow Diagram of the Selection Process for Studies Included in the Review

#### Table 1. Sample Characteristics, Intervention Components, and Outcomes

Lerman et al. (2006)   65% Caucasian, >10 cigs/day   6-month	Author	Population	Design, Time	Treatment	Outcomes (significant p<.05, unless otherwise specified)
al. (2006) 65% Caucasian, >10 cigs/day   6-month   either NP vs. Nasal spray   (29.6% vs 0.8%). No difference in SC by NMR in Nasal Spray group   Greater SC among FM between BUP group and placebo gro (27% vs. 8%). No difference in SC by NMR in Nasal Spray group   Greater SC among FM between BUP group and placebo group (25% vs. 16%)   No difference in SC among SM between BUP group and placebo group (25% vs. 16%)   No difference in SC among SM between BUP group and placebo group (25% vs. 16%)   No difference in SC among SM between BUP group and placebo group (25% vs. 16%)   Self-help guide and behavioral counseling plus   Self-help guide and behavioral counseling plus   Nicotine gum vs. Placebo   Self-help guide and	(Year)	NI_480	point	Robaviaral counceling plus	Greater SC among SM as compared to EM in NP group
Patterson et al. (2008) Patterson et al. (2008) Patterson et al. (2008) Patterson et al. (2008) Patterson et al. (2009) Patterson et al. (2010) Patterson et al. (2010) Patterson et al. (2015) Patterson et al. (2015) Patterson et al. (2015) Patterson et al. (2015) Patterson et al. (2016) Patterson et al. (2017) Patterson et al. (2018) Patte					
Patterson et al. (2008)  N=414  RCT 6-month  RCT 82% European, cigs/day=21.5  RCT 82% European, cigs/day=21.5  RCT 826	ai. (2000)	05% Caucasian, >10 cigs/day	0-111011111	eilliei ivr vs. ivasai spray	· ·
al. (2008) 82% European, cigs/day=21.5 6-month (27% vs. 8%). No difference in SC among SM between BUP group and placebo group (25% vs. 16%)  Schnoll et al. (2009) 84% Caucasian, >10 cigs/day EOT (8wks) 21mg NP  Ho et al. (2009) African American, ≤10 cigs/day  Lerman et al. (2010) Caucasian, cigs/day=22.1 6-, 12-months  Chen et al. (2014) European, ≥10 cigs/day  Lerman et al. (2015) RCT Support	Dottorson of	NI111	DCT	PLID vs. Placebo	
Schnoll et al. (2009)   Robert African American,				BUP VS. Placebo	
Schnoll et al. (2009) 84% Caucasian, >10 cigs/day EOT (8wks) 21mg NP Ho et al. N=646 RCT Self-help guide and behavioral counseling plus NP (standard-8 wks)  Lerman et al. (2010) Caucasian, cigs/day=22.1 6-, 12-months Paronnom P	ai. (2008)	82% European, cigs/day=21.5	6-month		
Schnoll et al. (2009)  N=568 (2009)  Ho et al. (2009)  African American, ≤10 cigs/day  Lerman et al. (2010)  Chen et al. (2014)  Lerman et al. (2015)  A=10 cigs/day  N=568  RCT  Self-help guide and behavioral counseling plus likely to achieve cessation as compared to placebo.  RCT  Self-help guide and behavioral counseling plus behavioral counseling plus likely to achieve cessation as compared to placebo.  Greater SC among SM group as compared to IMs/NMs (27% vs. 19%).  Among females, SM group receiving NRT not significantly melikely to achieve cessation as compared to placebo.  Greater SC among SM with extended therapy at 6- and 12-months months  Greater SC among SM with extended therapy at 6- and 12-months months  MP (extended-6 months) vs. Greater SC among SM with extended therapy at 6- and 12-months  NP (standard-8 wks)  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  Greater SC among SM group as compared to IMs/NMs (27% vs. 19**).  Greater SC among SM with extended therapy at 6- and 12-months  NP (standard-8 wks)  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  Greater SC among SM as compared to placebo.  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  Greater SC among SM as compared to Placebo.  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR (22.0% vs. 13.6%) & 12-(16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6-(19.1% vs. 21.6%) & 12-(14.1% vs. 19.4%) month.  NMR was negatively associated with the odds of SC at delive (OR=0.79; 95%Cl=.066-0.95; p =0.010).  Associat					
al. (2009) 84% Caucasian, >10 cigs/day EOT (8wks) 21mg NP Ho et al. N=646 (2009) African American, ≤10 cigs/day Lerman et al. (2010) Caucasian, cigs/day=22.1 6-, 12-months Cren et al. (2014) European, ≥10 cigs/day Lerman et al. (2015) RCT  Al. (2015) RCT  African American, ≤10 cigs/day  EOT (8wks) 21mg NP RCT  African American, 6-months behavioral counseling plus behavioral counseling plus helavioral counseling plus helavioral counseling plus helavioral counseling plus likely to achieve cessation as compared to placebo.  NP (extended-6 months) vs. Greater SC among SM group receiving NRT not significantly months likely to achieve cessation as compared to placebo.  NP (extended-6 months) vs. Greater SC among SM with extended therapy at 6- and 12- months  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  No effect of Bupropion on relapse delay by NMR  RCT  Al. (2015) Racially diverse, ≥10cigs/day  VAR vs. NP vs. Placebo  VAR vs. NP vs. Placebo  VAR vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  VAR vs. 19%).  Among females, SM group receiving NRT not significantly months ikiely to achieve cessation as compared to placebo.  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  NP more effective in delaying relapse among FM as compared to SM.  No effect of Bupropion on relapse delay by NMR  (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR vs. 19-%).  Among females, SM group receiving NRT vs. 19%.	O alama all a t	NI ECO	O a la a ut	Dalas danal assumable a subse	
Ho et al. (2009)  African American, ≤10 cigs/day  Lerman et al. (2010)  Caucasian, cigs/day=22.1  Cautagian, ≥10cigs/day  RCT (2014)  European, ≥10cigs/day  RCT (2015)  RCT (2015)  RCT (2016)  RCT (2016)  RCT (2017)  Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge (2018)  RCT (2018)  RCT (2019)  RCT (2019					Greater SC among SM as compared to NM (42% vs. 28%)
African American,   Significantly months	,		,	8	
Lerman et al. (2010) Chen et al. (2014)  Lerman et al. (2015)  RCT Arcially diverse, ≥10cigs/day  Vaz et al. (2015)  RCT Arcially diverse, ≥10cigs/day  RCCT Arcially diverse, ≥10cigs/day  RCCC Arcially diverse, ≥10cigs/				•	· · · · · · · · · · · · · · · · · · ·
Lerman et al. (2010) Chen et al. (2014) European, ≥10cigs/day Lerman et al. (2015)  RCT Behavioral counseling plus BUP vs. NP os. Placebo VAR vs. NP vs. Placebo  RCT Racially diverse, ≥10cigs/day  Vaz et al. (2015)  RCT Racially diverse, ≥10cigs/day  Vaz et al. (2015)  RCT Racially diverse, ≥10cigs/day  Vare et al. (2015)  RCT Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge VAR vs. NP vs. Placebo  RCT Racially diverse, ≥10cigs/day  RCT Raciall	(2009)		6-months	<b>.</b>	<b>,</b>
Lerman et al. (2010) Caucasian, cigs/day=22.1 6-, 12-months NP (standard-8 wks)  Chen et al. (2014) Suropean, ≥10cigs/day  Chen et al. (2015) RCT al. (2015) RCT Al. (2015) RCT Al. (2016) RCT Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge  VAR vs. NP vs. Placebo  RCT Al. (2015) RCT Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge VAR vs. NP vs. Placebo  RCT Al. (2015) Rectare SC among SM with extended therapy at 6- and 12-months  NP more effective in delaying relapse among FM as compared to SM. No effect of Bupropion on relapse delay by NMR  Greater SC with VAR as compared to NP among NM at 6- (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  Vaz et al. N=662  Women, ≥10cigs/day  RCT Behavioral counseling plus NMR was negatively associated with the odds of SC at delivery  NRT vs. placebo  NP more effective in delaying relapse among FM as compared to SM. No effect of Bupropion on relapse delay by NMR  Greater SC among SM with extended therapy at 6- and 12-months  NP more effective in delaying relapse among FM as compared to SM. No effect of Bupropion on relapse delay by NMR  Greater SC among SM with extended therapy at 6- and 12-months		≤10 cigs/day			
al. (2010) Caucasian, cigs/day=22.1 6-, 12-months NP (standard-8 wks) months  Chen et al. N=709 European, ≥10cigs/day  Lerman et al. (2015) N=1246 Racially diverse, ≥10cigs/day  N=1246 Racially diverse, ≥10cigs/day  RCT Behavioral counseling plus BUP vs. NP and/or Lozenge vs. BUP + Lozenge VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  N=1246 Racially diverse, ≥10cigs/day  RCT G- & 12-month VAR vs. NP vs. Placebo  RCT G- & 12-month VAR vs. NP vs. Placebo  N=1246 RCT Greater SC with VAR as compared to NP among NM at 6-(22.0% vs. 13.6%) & 12-(16.0% vs. 13.1%) month. VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12-(14.1% vs. 19.4%) month.  Vaz et al. N=662 Women, ≥10cigs/day  RCT At delivery NRT vs. placebo NP more effective in delaying relapse among FM as compared to SM. No effect of Bupropion on relapse delay by NMR Greater SC with VAR as compared to NP among NM at 6-(22.0% vs. 13.6%) & 12-(16.0% vs. 13.1%) month. VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12-(14.1% vs. 19.4%) month.  Vaz et al. (2015) Women, ≥10cigs/day  RCT At delivery NRT vs. placebo NRT vs. placebo OR=0.79; 95%CI=.066-0.95; p =0.010). Association unaffected by treatment assignment.					
Chen et al. (2014)				*	Greater SC among SM with extended therapy at 6- and 12-
European, ≥10cigs/day   3-month   BUP vs. NP and/or Lozenge vs. BUP + Lozenge   to SM. No effect of Bupropion on relapse delay by NMR	al. (2010)	Caucasian, cigs/day=22.1	6-, 12-months	NP (standard-8 wks)	months
Lerman et al. (2015)N=1246RCTVAR vs. NP vs. PlaceboGreater SC with VAR as compared to NP among NM at 6- (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.Vaz et al. (2015)N=662RCTBehavioral counseling plus (2015)NMR was negatively associated with the odds of SC at delivery (10.79; 95%Cl=.066-0.95; p =0.010).Vaz et al. (2015)Women, ≥10cigs/dayAt deliveryNRT vs. placebo(OR=0.79; 95%Cl=.066-0.95; p =0.010).	Chen et al.	N=709	RCT	Behavioral counseling plus	NP more effective in delaying relapse among FM as compared
Lerman et al. (2015)N=1246 Racially diverse, ≥10cigs/dayRCT 6- & 12-monthVAR vs. NP vs. PlaceboGreater SC with VAR as compared to NP among NM at 6- (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month. VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.Vaz et al. (2015)N=662 Women, ≥10cigs/dayRCT At deliveryBehavioral counseling plus NRT vs. placeboNMR was negatively associated with the odds of SC at delivery (OR=0.79; 95%Cl=.066-0.95; p =0.010). Association unaffected by treatment assignment.	(2014)	European, ≥10cigs/day	3-month	BUP vs. NP and/or Lozenge	to SM.
al. (2015) Racially diverse, ≥10cigs/day 6- & 12-month VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  Vaz et al. (2015) Women, ≥10cigs/day  RCT At delivery NRT vs. placebo NRT vs. placebo (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  (22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (16.0% vs. 13.1%) month.  Association unaffected by treatment assignment.				vs. BUP + Lozenge	No effect of Bupropion on relapse delay by NMR
VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  Vaz et al. N=662 (2015) Women, ≥10cigs/day  At delivery NRT vs. placebo  VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12- (14.1% vs. 19.4%) month.  Vaz et al. (0R=0.79; 95%Cl=.066-0.95; p =0.010).  Association unaffected by treatment assignment.	Lerman et	N=1246	RCT	VAR vs. NP vs. Placebo	Greater SC with VAR as compared to NP among NM at 6-
Vaz et al. (2015)N=662 Women, ≥10cigs/dayRCT At deliveryBehavioral counseling plus NRT vs. placeboNMR was negatively associated with the odds of SC at delivery (OR=0.79; 95%CI=.066-0.95; p =0.010). Association unaffected by treatment assignment.	al. (2015)	Racially diverse, ≥10cigs/day	6- & 12-month		(22.0% vs. 13.6%) & 12- (16.0% vs. 13.1%) month.
Vaz et al.N=662RCTBehavioral counseling plus NRT vs. placeboNMR was negatively associated with the odds of SC at delivery (OR=0.79; 95%Cl=.066-0.95; p =0.010). Association unaffected by treatment assignment.					VAR as effective as NP in SM at 6- (19.1% vs. 21.6%) & 12-
(2015) Women, ≥10cigs/day At delivery NRT vs. placebo (OR=0.79; 95%Cl=.066-0.95; p =0.010).  Association unaffected by treatment assignment.					(14.1% vs. 19.4%) month.
(2015) Women, ≥10cigs/day At delivery NRT vs. placebo (OR=0.79; 95%Cl=.066-0.95; p =0.010).  Association unaffected by treatment assignment.	Vaz et al.	N=662	RCT		NMR was negatively associated with the odds of SC at delivery
Association unaffected by treatment assignment.	(2015)	Women, ≥10cigs/day	At delivery		
					Association unaffected by treatment assignment.
Traditianity plus o Toleatel 30 among 311 as compared to rivi (35% vs. 24%).	Kaufmann	N=499	Cohort	Behavioral counseling plus 8	Greater SC among SM as compared to FM (33% vs. 24%).
et al. (2015) Racially diverse, >10cigs/day EOT (8wks) weeks of 21 mg NP	et al. (2015)	Racially diverse, >10cigs/day	EOT (8wks)		

#### Results

- Five RCTs (Lerman et al., 2006; Patterson et al., 2008; Lerman et al., 2010; Chen et al., 2014; Lerman et al., 2015) and two Cohort studies (Schnoll et al., 2009; Kaufmann et al., 2015) found that NMR was significantly associated with the efficacy/effectiveness of smoking cessation pharmacotherapy (see Table 1).
- Studies which found no association between NMR and smoking cessation pharmacotherapy were among low African American Female cigarettes smokers (Ho et al., 2009) and pregnant and post partum women (Vaz et al., 2015)(see Table 1).
- In general, there was greater efficacy of nicotine replacement products in smoking cessation among slow metabolizers (lower NMR), whereas there was greater efficacy of smoking cessation with oral products (i.e., bupropion or varenicline) among fast metabolizers (see series of studies in Figure 2).

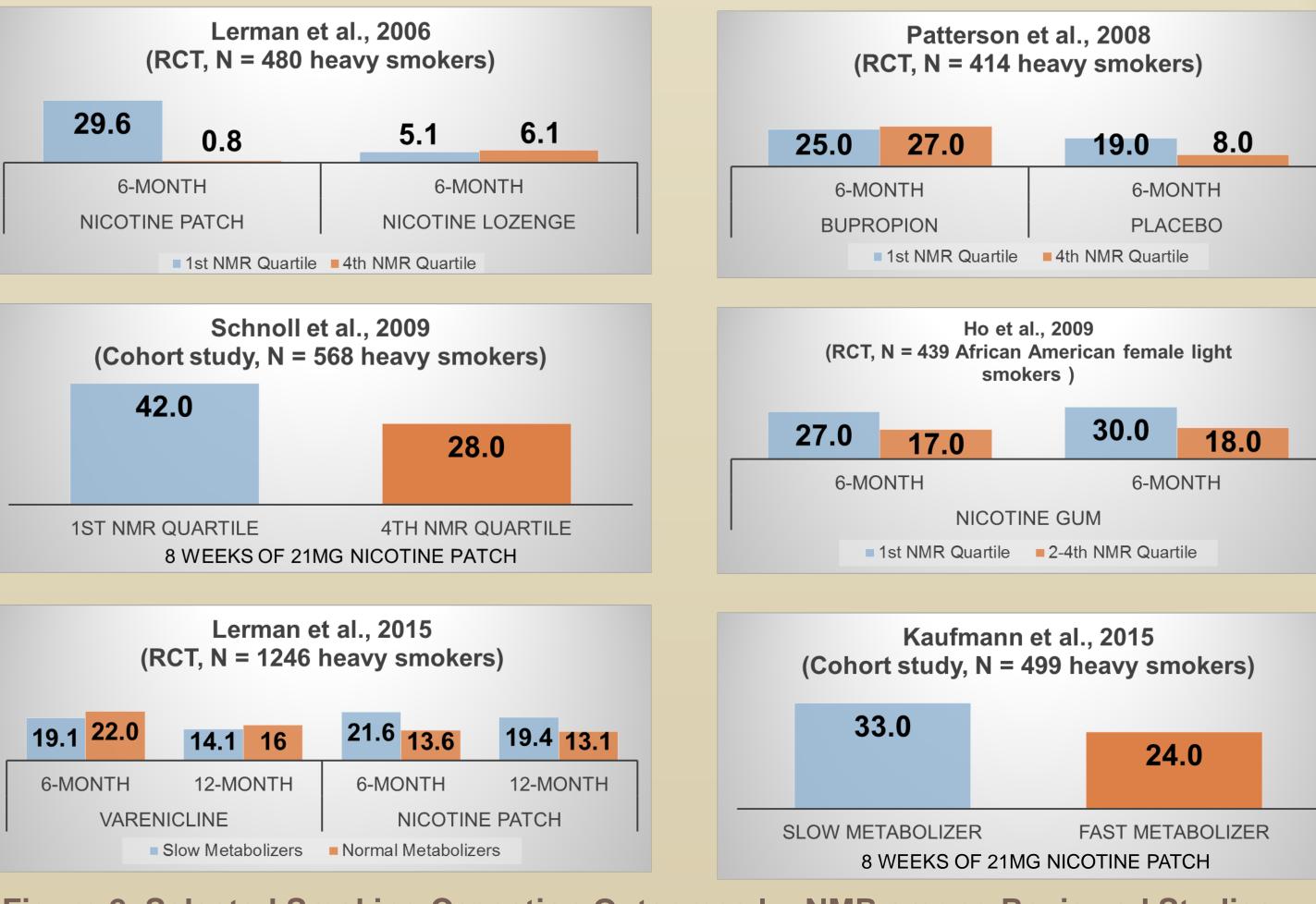


Figure 2. Selected Smoking Cessation Outcomes by NMR among Reviewed Studies

#### Conclusions

- The findings of this review suggest that the NMR is an important biomarker that can be used to personalize and optimize smoking cessation treatment.
- Future studies are needed to examine the outcomes of smoking cessation pharmacotherapy that is tailored to smokers based on NMR.
- Such studies will be instrumental in reducing the current disease burden associated with tobacco addiction.

Cessation, RCT = Randomized Controlled Trial, EOT = End of treatment