# Changes in Biomarkers of Exposure Associated with Switching for 5 Days from Combusted Cigarettes to Nicotine Salt Pod System

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## Introduction:

The JUUL ENDS (JUUL Labs, San Francisco, CA) is a closed nicotine-salt pod system (NSPS) which aerosolizes an e-liquid solution through vaporization. A temperature control system integrated into the breath-actuated inhalation pathway is designed to maintain an operating temperature that is independent of puff intensity and to minimize the generation of combustionrelated byproducts. The objective of the following clinical study was to determine whether exposure to key toxicants is reduced when adult smokers switch from their usual cigarette brand to exclusive use of the NSPS. With that goal in mind, we examined the effect of a 5-day obligatory, controlled, absolute switch from combusted cigarettes to the NSPS on the levels of biomarkers of exposure (BOE's) in urine and blood, compared to usual brand of combustible cigarette or complete abstinence. The primary endpoint was reduction in NNN compared to baseline.

## Methods:

Ninety subjects were randomized into one of six cohorts: use of NSPS (n=15 for each of four flavors - Virginia Tobacco, Mint, Mango, Creme; all flavors 5% nicotine by weight), use of usual cigarette (n=15), or abstinence (n=15). Total nicotine equivalents, and the following biomarkers were measured in 24-hour urine collections at baseline (Day -1) and at Day 5: NNN, NNAL, 3-HPMA, MHBMA, S-PMA, HMPMA, CEMA, and 1-OHP. COHb was measured in blood.

The study population consisted of healthy smokers, age 22 to 62 inclusive, with a minimum 12-month history of smoking 10 or more king-size (or 100s) manufactured, combusted cigarettes per day. Participants were naïve to use of ENDS products and willing to be confined at the clinic for up to 7 days. The study was carried out in accordance with FDA and ICH guidelines regarding Good Clinical Practice and the ethical principles set forth in the Declaration of Helsinki. The study protocol and informed consent form were reviewed and approved by the Chesapeake Institutional Review Board (Columbia, Maryland, USA). Participants received monetary incentives for completing specific milestones related to the study.

## Results:

Subjects on average were 39 years old, and smoked 16 cigarettes per day; 38% were female. All subjects randomized to the use of NSPS (n=60) and usual cigarettes (n=15) completed the study; four subjects from the abstinence arm terminated early (n=11;73%completion rate in-arm)

Table 1: Baseline demographics and characteristics (safety population)a

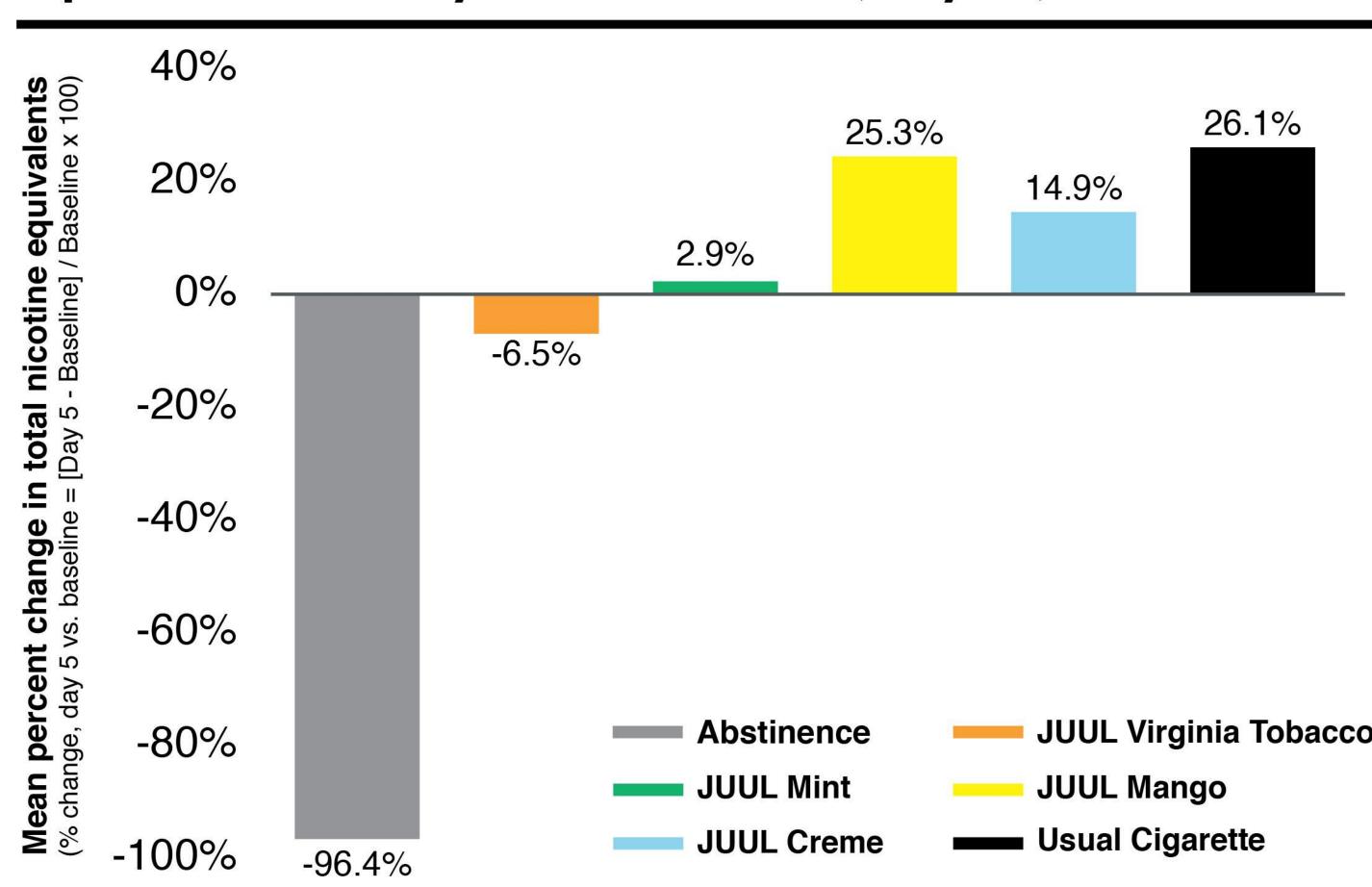
	NSPS Pooled	Usual Cigarettes	Abstinence	Overall
N	60	15	15	90
Age, y	39.0±10.59	40.3 ± 11.13	38.6 ± 14.26	39.1 ±11.40
Sex, male	37 (62%)	9 (60%)	10 (67%)	56 (62%)
Race				
Black or African American	9 (15%)	1 (7%)	3 (20%)	13 (14%)
White	49 (82%)	13 (87%)	10 (67%)	72 (80%)
Ethnicity				
Hispanic or Latino	2 (3%)	2 (13%)	0 (0%)	4 (4%)
Not Hispanic or Latino	58 (97%)	13 (87%)	15 (100%)	86 (96%)
BMI[JM2] , kg/m2	28.2 ± 5.31	27.8 ± 4.28	27.5 ± 5.67	28.0 ± 5.19
Fagerstrom Dependency Score	5.50 ± 1.55	4.87 ± 1.72	5.20 ± 1.42	5.34 ± 1.55
Cigarettes per day	16.5 ± 3.75	15.1 ± 3.66	16.2 ± 2.58	16.2 ± 3.64

<sup>&</sup>lt;sup>a</sup>Data are presented as n (%) or mean  $\pm$  standard deviation

#### Nicotine Consumption and Excretion:

Over the course of 5 days, mean total nicotine equivalents increased by 9% in the pooled NSPS group vs. 26% in the usual cigarette group (p-value for difference >0.05). Total nicotine equivalents were reduced by 96.4% in the abstinence group, consistent with compliance with no smoking or nicotine consumption for 5 days in that arm.

Figure 1: Mean percent change in total nicotine equivalents at Day 5 vs. Baseline (Day -1) in urineb



Mean total nicotine equivalents excreted on day 5 was similar between the usual cigarette arm (19.0 mg/24h) and the NSPS pooled arms (18.3 mg/24h). The usual cigarette cohort consumed a mean of 19.3 cigarettes per day, and the NSPS cohorts consumed a mean of 0.79 grams per day. In this experimental setting with this population, this suggests that an NSPS pod, if completely consumed, would result in the mean total nicotine equivalents excreted associated with consuming 91% of a pack of cigarettes.

Table 2: Relative mean product consumption and mean total nicotine excreted<sup>c</sup>

Measure	Units	NSPS Pooled Groups	Usual Cigarettes
Num participants	ITT participants	n = 60	n = 15
Mean e-liquid consumed / day (days 4-5)	Grams (actual)	0.79 ± 0.39	
Mean cigarettes consumed / day (days 4-5)	Num cigarettes (actual)		19.3 ± 4.87
Mean pod equivalents consumed / day	Pod content equivalents (estimated; assuming 0.77 g per pod)*	1.03 ± 0.50	
Mean pack equivalents consumed / day	Pack equivalents (actual; assuming 20 cigarettes per pack)		0.97 ± 0.23
Mean total nicotine equiv excreted (day 5)	mg / 24h (actual)	18.3 ± 10.2	19.0 ± 4.53
Relative total nicotine equivalents excreted per pod or cigarette pack consumed	(estimated)	~91%	100%

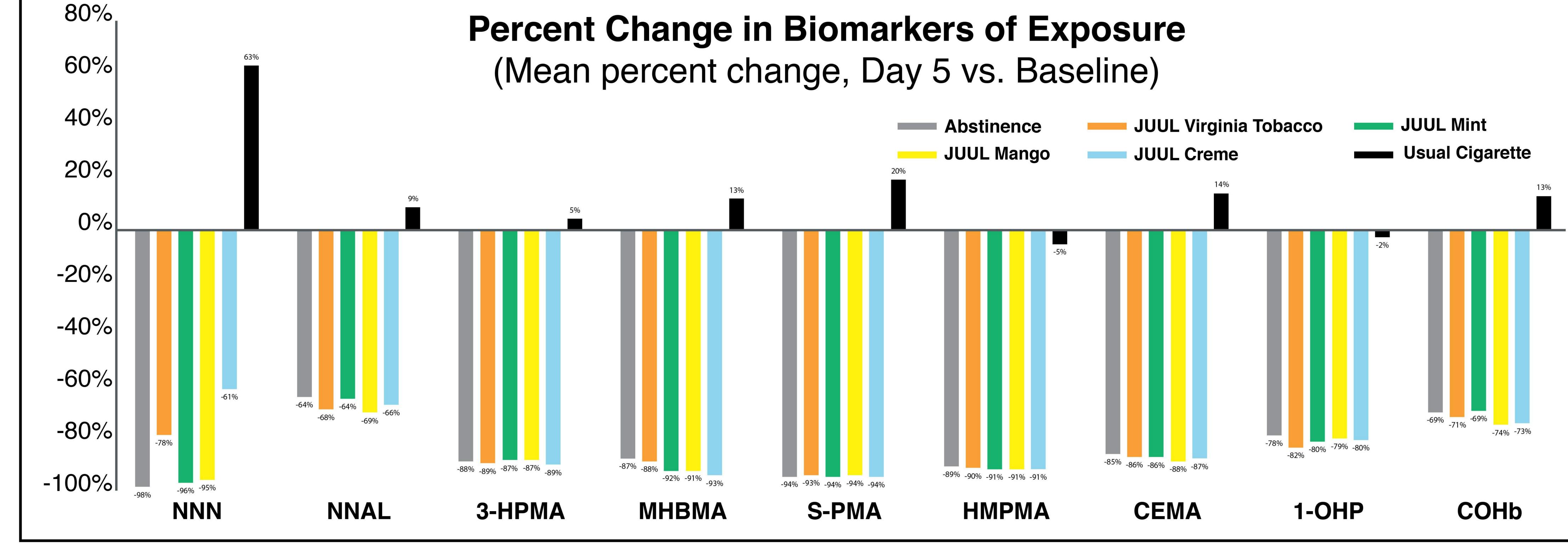
#### Changes in Biomarkers of Exposure (Non-Nicotine):

Decreases in the mean levels of all non-nicotine BOEs were observed in the abstinence group and four NSPS groups at Day 5 compared to baseline (Day -1); the cigarette group demonstrated increases in all BOEs except for 1-OHP and HPMA. The eight non-nicotine urine BOEs were reduced by an average of 85.3% in the abstinence group and 85.0% in the pooled NSPS group (99.6% relative reduction in aggregate biomarkers; p-value for difference >0.05). Similar reductions were seen in the pooled NSPS and abstinence groups for each individual BOE (p>0.05 for each analyte). In the usual cigarette group, these BOEs increased by an average of 14.4% (pooled NSPS vs. usual cigarette; p<0.001 for each analyte). COHb was likewise reduced by 71.8% in the pooled switching group vs. 69.1% in the abstinence group (p-value for the difference >0.05), while increasing by 13.3% in the usual cigarette group (p<0.001).

In contrast to combusted cigarettes, NNAL, 3-HPMA, MHBMA, S-PMA, HMPMA, CEMA, 1-OHP, and COHb were significantly reduced in the blood and urine of smokers who switched to any of the NSPS flavors, and the mean percent reduction was similar to the percent reduction seen in the abstinence arm. For NNN, the mean percent reduction was not statistically different from abstinence for all flavors. However, within two cohorts, a subject showed increase in NNN, which impacted our primary hypothesis (median reduction similar to NNN, but mean reduction not statistically different from mean). Furthermore, an increase of 63% was seen in NNN in the cohort which continued smoking their usual cigarette. This will be further evaluated in future studies.

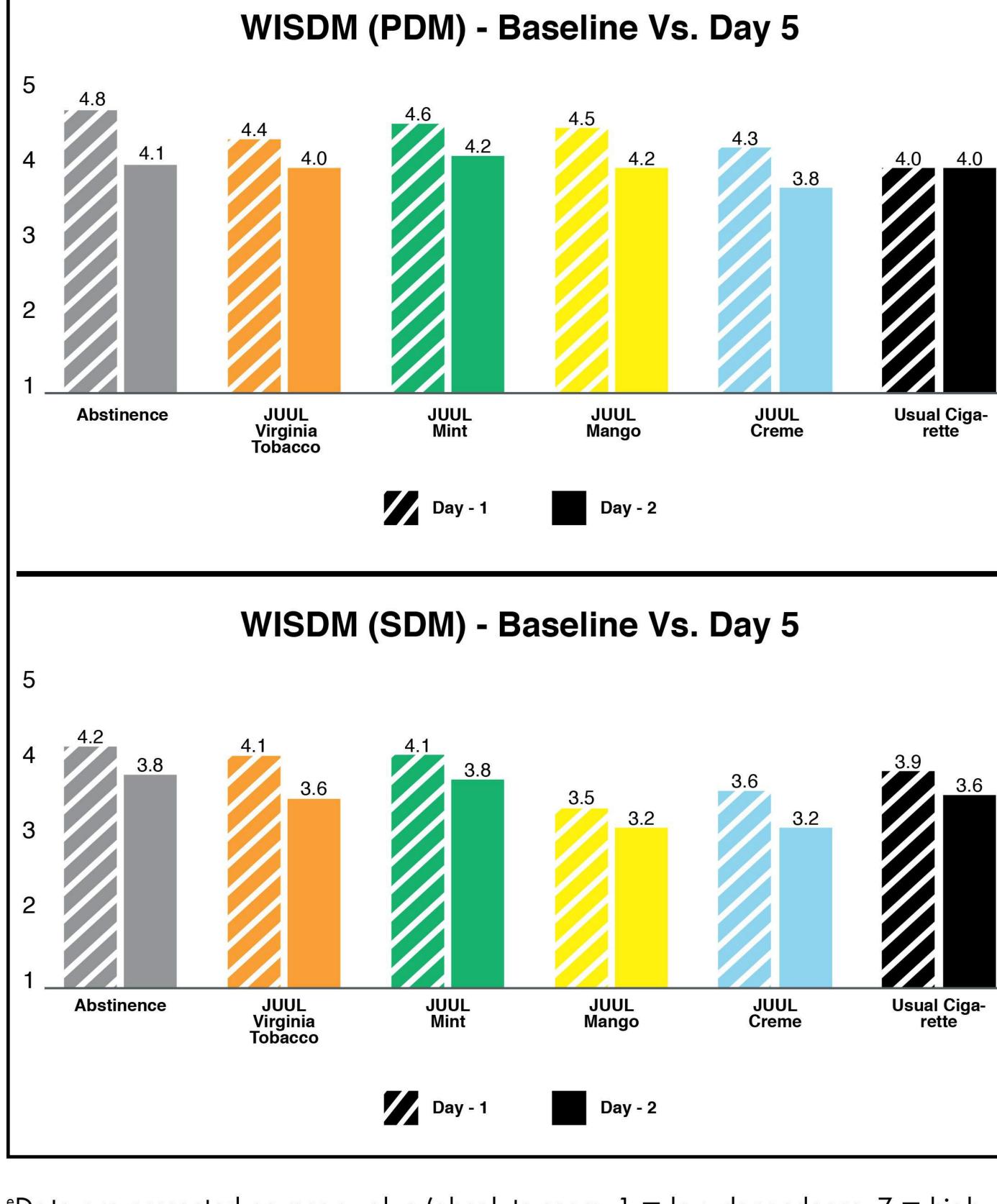


Figure 2: Mean change in biomarkers of exposure (BOE's)d



dData are presented as percent change (%, Day 5 vs. Baseline)

#### Figure 3: WISDM (Primary Dependence Motives, PDM); WISDM (Secondary Dependence Motives, SDM)<sup>e</sup>

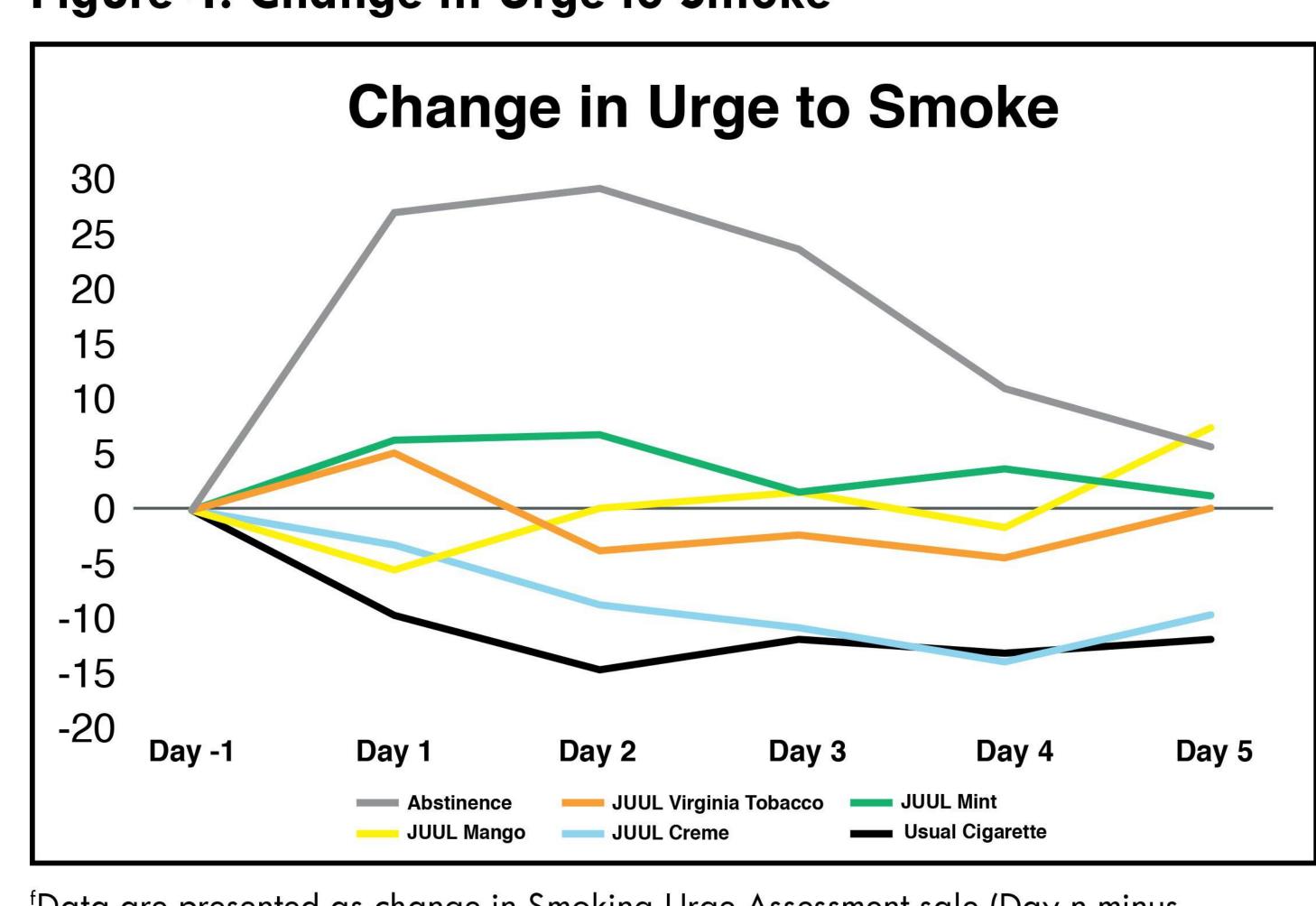


Data are presented as mean value (absolute score, 1 = low dependence, 7 = high

#### Changes in Psychometric Measures:

Mean primary dependency motives (WISDM-PDM) were reduced for the abstinence arm and for all four flavors of NSPS, but not for the usual cigarette arm. Secondary dependence motives (WISDM-SDM) were reduced for all products (Figure 3). Urge to smoke increased in subjects in the abstinence arm and this moderated over time. For NSPS and usual cigarettes, mean urge to smoke did not similarly increase during the first 4 days, or decreased (Figure 4). Note that a limitation of the scale used is it does not clearly specify whether urge to smoke refers to cigarettes or urge to use any tobacco product, including e-cigarettes, and this will be further explored in future studies.

#### Figure 4: Change in Urge to Smoke<sup>f</sup>



fData are presented as change in Smoking Urge Assessment sale (Day n minus Baseline). Scale ranges from 1 (no urge to smoke) to 100 (extreme urge to smoke)

## Conclusion:

For the non-nicotine urinary biomarkers studied, for adult smokers who switched to NSPS, an aggregate mean reduction of 99.6% was observed relative to the reduction associated with five days of abstention. Likewise, blood COHb was similarly reduced in the NSPS and abstention arms. These results support the objective that complete switching from cigarettes to the NSPS may lead to meaningful reductions in multiple key, short-term biomarkers of exposure observed with combustible use. Nicotine delivery and subjective measures are consistent with acceptability of JUUL as substitute for combusted cigarette for adult smokers.

#### Limitation:

Incomplete switching from cigarettes to NSPS (dual-use) was not studied.

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# U.S. Adolescents' Perceptions of the Harmfulness and Addictiveness of Using a JUUL E-Cigarette Compared to Smoking Conventional Cigarettes



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## Background

In 2017, the proportions of 8th, 10th and 12th graders who believed regular e-cigarette use poses a 'great risk of harm' were 20%, 19% and 16%, respectively (Monitoring the Future, 2017).

The U.S. FDA has expressed concern that these data indicate the majority of youth are either unaware of the potential health risks of e-cigarette use, or underestimate their likelihood of experiencing harm from using e-cigarettes.

Harm perceptions provide a strong empirical basis for explaining why adolescents initiate and continue to use tobacco products. Previous research suggests that youth who perceive vaping as posing little to no risk of harm or addiction will be more open to try using, or continuing to use, e-cigarettes.

In 2018, JUUL became the fastest growing and highest selling brand of e-cigarette/vapor products in the United States.

This study assessed adolescents' perceptions of the absolute and relative harmfulness and addictiveness of using a JUUL e-cigarette and smoking regular cigarettes.

## Methods

A non-probabilistic sample of U.S. adolescents aged 13-17 years (n = 9,872) was recruited from an internet research panel to complete an online survey between 23 November and 13 December 2018. Individuals were excluded if they had not seen or heard of JUUL e-cigarettes before this study. Parental consent and youth assent were obtained.

Perceived harm of occasional and daily use of a JUUL e-cigarette and combustible cigarettes was assessed by four questions: How much do you think people harm themselves when they:

- 1. Use a JUUL e-cigarette on some days?
- 2. Use a JUUL e-cigarette every day?
- 3. Smoke cigarettes on some days?
- 4. Smoke cigarettes every day? ((1) No harm; (2) A little harm; (3) Some harm; (4) A lot of harm).

Perceived length of time till harm is caused by using a JUUL e-cigarette and smoking cigarettes was assessed by the question: How long do you think someone has to use a JUUL e-cigarette/ smoke cigarettes before it harms their health? ((1) It will never harm their health; (2) Less than a year; (3) 1 year; (4) 5 years; (5) 10 years; (6) More than 20 years; (7) Don't know).

Perceived likelihood of becoming addicted to JUUL e-cigarettes and combustible cigarettes was assessed by the question: How likely is someone to become addicted to using a JUUL e-cigarette/ smoking cigarettes? ((1) Very unlikely; (2) Somewhat unlikely; (3) Neither likely nor unlikely; (4) Somewhat likely; (5) Very likely).

## Email: russell@csures.org A little harm Some harm A lot of harm Some Days "How much do you think people harm themselves when they\_\_\_\_\_" Figure 1. Perceived harm from occasional and daily use of a JUUL e-cigarette and combustible cigarettes. It will never harm their health < 1 year</p> ■ 1 year ■ 5 years ■ 10 years ≥ 20 years Don't Know Use a JUUL E-Cigarette "How long do you think someone has to \_\_\_\_\_\_ before it harms their health?" Figure 2. Perceived length of time till harm is caused by using the JUUL e-cigarette and smoking cigarettes. Very unlikely Somewhat unlikely Neither likely Nor unlikely 60% Somewhat likely 50% Very likely 34.8% 35.3% ■ Missing Using a JUUL E-cigarette Smoking Cigarettes "How likely is someone to become addicted to \_\_\_\_\_?" Figure 3. Perceived likelihood of becoming addicted to JUUL e-cigarettes and combustible cigarettes. Less addictive Less harmful Equally addictive Equally harmful ■ More addictive ■ More harmful ■ I don't know ■ I don't know enough about these enough about products these products ■ Missing ■ Missing Perceived Harmfulness Perceived Addictiveness

"Do you believe using a JUUL e-cigarette is less harmful, about the same, or more harmful "Do you believe using a JUUL e-cigarette is less addictive, about the same, or more

Figure 4. Adolescents' perceived harmfulness and addictiveness of using a JUUL e-cigarette compared to smoking combustible cigarettes.

than smoking cigarettes?"

addictive than smoking cigarettes?"

## Results

#### Daily Use

Around 6 out of 100 U.S. adolescents (6.1%) think using a JUUL e-cigarette every day would be harmless. Around 46 out of 100 U.S. adolescents (45.9%) think using a JUUL e-cigarette every day would cause 'a lot of harm'.

#### Occasional Use

Around 9 out of 100 U.S. adolescents (9.3%) think using a JUUL e-cigarette on some days would be harmless. Around 29 out of 100 U.S. adolescents (28.9%) think using a JUUL e-cigarette on some days would cause 'a lot of harm'.

#### Duration of use before experiencing harm

Around 11 in 100 U.S. adolescents either believed they would never experience any harm from using a JUUL e-cigarette or that they could use a JUUL e-cigarette for at least 20 years before they would experience any health harms.

#### Likelihood of addiction

17.3% of U.S. adolescents believed people are somewhat/very unlikely to become addicted to using a JUUL e-cigarette.

#### Relative harmfulness and addictiveness

39.3% and 29.3% of adolescents believed using a JUUL e-cigarette is less harmful and less addictive than smoking cigarettes, respectively.

## Conclusions

The majority of U.S. adolescents believe using a JUUL e-cigarette poses fewer risks to health than smoking regular cigarettes, but also that using a JUUL e-cigarette would put them at some risk for experiencing health problems and addiction.

However, a small but significant proportion of adolescents hold the erroneous belief that using a JUUL e-cigarette would be risk-free.

Several theories of health behavior change and previous research on tobacco harm perceptions would predict this smaller group of adolescents is at higher risk for initiating or continuing to use JUUL e-cigarettes.

#### Ethics Approval

This study was approved by Advarra Institutional Review Board (Approval no. 00030080, 2 October 2018).

#### Declaration of Funding

Funding for this study was provided by JUUL Labs Inc. JUUL Labs Inc. had no input to or control over the study design, contents of the survey instrument, sample recruitment, data analysis, interpretation, or reporting of findings. The authors alone are responsible for the contents, production and decision to report this study. Availability of data and materials

The datasets analysed in the current study are available from the corresponding author on reasonable request. The raw data collected in this study and the survey instrument will be submitted by the authors to FDA Center for Tobacco Products. The raw data collected in this study has not and will not be shared with JUUL Labs

Data were weighted to be nationally representative of the U.S. adolescent population on age, gender and census region.

# Identifying Predictive Attributes of Adult Smokers Who Cease Combustible Smoking using the JUUL Electronic Nicotine Delivery System (ENDS) via Logistic Regression and CART

1113 (16.4%) < 0.001

661 (9.8%)

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## Background:

- Prior research has shown that JUUL products may assist adult smokers in switching from combustible cigarettes<sup>1</sup>, however little is known about characteristics of smokers who successfully switch from cigarettes after initiating use.
- Using the classification and regression tree (CART) methodology of Breiman et al<sup>2</sup> and recursive feature elimination with logistic regression, we sought to identify attributes of similar cohorts of adult smokers no longer smoking 90 days after purchasing a JUUL starter kit, and the subset of features that were most related to switching.

## Methods:

- Sample: Data from 15,116 current adult smokers
- Smoked in past 30 days prior to JUUL purchase
- ♦ Purchased a JUUL starter kit in the retail or ecommerce setting between June - September 2018
- Completed baseline data and 90-day followup data
- Data on 36 individual-level attribute covariates that related to smoking status, demographics, smoking history, previous ENDS-use and other characteristics were assessed at baseline.
- Use of combustible cigarettes and JUUL products was reassessed at 90 days post baseline.
   Participants were defined as non-smokers if they reported having smoked no cigarettes, not even a puff, in the last 30 days.
- The sample was randomly divided into independent training (67% of sample) and validation (33% of sample) data sets for CART and logistic regression modeling. The training sample was used to derive the model, while the remaining data were used to evaluate the predictive ability of the final model.
- CART analysis was performed on the training data with cross-validation to produce a tree. The maximum tree with the minimum misclassification error was examined, and the tree was then pruned to remove insignificant nodes based on the misclassification error graph. The minimum node size was set to be 10% of the training sample size.
- Recursive feature elimination was performed on the full sample to identify the subset of covariates that maximized accuracy and Area Under the Receiver Operating Curve (AUC) in the overall sample, with 5-fold cross-validation.
- The parsimonious subset of features that was identified was used to fit a logistic regression model on the training data.

## Results:

- Table 1 presents data from the univariate analyses of switchers vs. non-switchers.
- ♦ Overall, 49% of smokers who were assessed at baseline and 90 days had switched away from cigarettes in the month prior to the 90-day assessment.
- Baseline variables identified by the parsimonious CART model included smoking >10 days in month prior to JUUL purchase, smoking >10 years in lifetime, previous use of an ENDS, physical health, Cigarettes smoked Per Day (CPD), and whether their stated reason for purchasing a JUUL product was to help with quitting (Figure 1 and Table 2).
- ♦ The CART tree performed well in both the training and validation samples (Table 2).
- Number of days smoked seemed to be particularly relevant in classifying smokers based on switching status, as smoking >10 days per month was identified as the first significant split among switchers and nonswitchers, and smoking >20 days per month was relevant for further classifying switchers in the sample (Figure 1).
- Baseline variables predictive of switching that were identified by recursive feature elimination and utilized in the logistic regression model included covariates such as CPD, number of days smoked in month prior to baseline, years smoked, previous use of an ENDS, gender, whether the respondent was currently attempting to quit smoking, and whether respondents were planning to quit smoking with JUUL (Table 3).
- ♦ The logistic regression model performed well in both the training and validation samples, yielding similar accuracy as the CART model (Figures 2 and 3).
- ♦ Features in the subset identified in recursive feature elimination were significantly associated with increased odds of switching included: smoking 0-10 CPD, smoking for <= 1 year, smoking <20 days in month prior to JUUL purchase, planning on quitting smoking with JUUL and currently trying to quit smoking. Conversely, having previously used an ENDS was associated with lower odds of switching. (Table 3)

Table 1: Examples of univariate differences between smokers who switch at 90 days as compared to those who continue to smoke in efficacy sample

	Did not Switch at 90 Days	Switched at 90 Days	p value
	(n=7,444)	(n=7,672)	
Demographics/Potential Predictors	Overall Switching	Rate: 49% of Res	spondents
Age			
21-24	2165 (29.1%)	3228 (42.1%)	<0.001
<u>25-34</u>	2636 (35.4%)	2662 (34.7%)	
35-44	1486 (20.0%)	1107 (14.4%)	
45-64	1083 (14.5%)	645 (8.4%)	
65+	74 (1.0%)	30 (0.4%)	
Male	3916 (53.3%)	4464 (59.0%)	<0.001
Motive for Buying: To Quit Smoking	6220 (83.6%)	6158 (80.3%)	<0.001
Baseline Cigarette Levels			
0-5 CPD	1869 (29.9%)	2417 (48.3%)	< 0.001
6-10 CPD	1674 (26.8%)	1202 (24.0%)	
11-15 CPD	1030 (16.5%)	553 (11.1%)	
16-20 CPD	1273 (20.4%)	647 (12.9%)	
20+ CPD	401 (6.4%)	184 (3.8%)	
Days Smoked Per Month at Baseline			
1-9 Days	730 (11.5%)	1371 (27.1%)	< 0.001
10-19 Days	614 (9.7%)	698 (13.8%)	
20-29 Days	1310 (20.7%)	1071 (21.2%)	
All 30 Days	3686 (58%)	1919 (38%)	
Years Smoked			
<= 1 Year	563 (8.8%)	899 (17.7%)	<0.001
1-5 years	1389 (21.7%)	1510 (29.8%)	
5-10 years	1455 (22.8%)	1123 (22.1%)	
10- 20 years	1275 (20.0%)	792 (15.6%)	
20+ years	1708 (26.7%)	746 (14.7%)	
Mean Age First Smoked (±SD)	16.1 (3.5)	16.6 (3.4)	<0.001
Number of Minutes Smoked after Wa	aking		
0-30 minutes	4521 (60.7%)	4763 (62.1%)	<0.001
30-60 minutes	1140 (15.3%)	897 (11.7%)	
60+ minutes	1783 (24.0%)	2012 (26.2%)	
Smoked >100 cigarettes in lifetime	6604 (88.8%)	5876 (76.6%)	< 0.001
Smoke Menthol cigarattes	2169 (29.3%)	1725 (22.7%)	<0.001
Planning to Quit Smoking with Juul	5499 (86.2%)	4470 (87.8%)	0.01
Previous Juul Use at Baseline	3976 (53.6%)	4476 (58.5%)	<0.001
Currently Trying to Quit Smoking	3031 (82.9%)	2802 (85.6%)	0.002
Physical Health			
Poor	275 (3.8%)	185 (2.5%)	< 0.001
Fair/Good	4552 (62.1%)	4045 (53.8%)	
Very Good/Excellent	2505 (34.2%)	3292 (43.8%)	
Currently Have Mental Health Condition	3120 (43.8%)	2664 (36.8%)	<0.001
Mean Alcohol Days in Past Month (±SD)	7.4 (8.4)	6.6 (7.8)	<0.001
Experienced Money Shortage in Past Year	1323 (20 0%)	1112 (16 /10/6)	<b>∠</b> 0.001

1323 (20.0%)

829 (12.6%)

Experienced Money Shortage in Past Year

Receive Some Form of Economic Assistance

Figure 1. Classification and Regression Tree model for predicting switchers

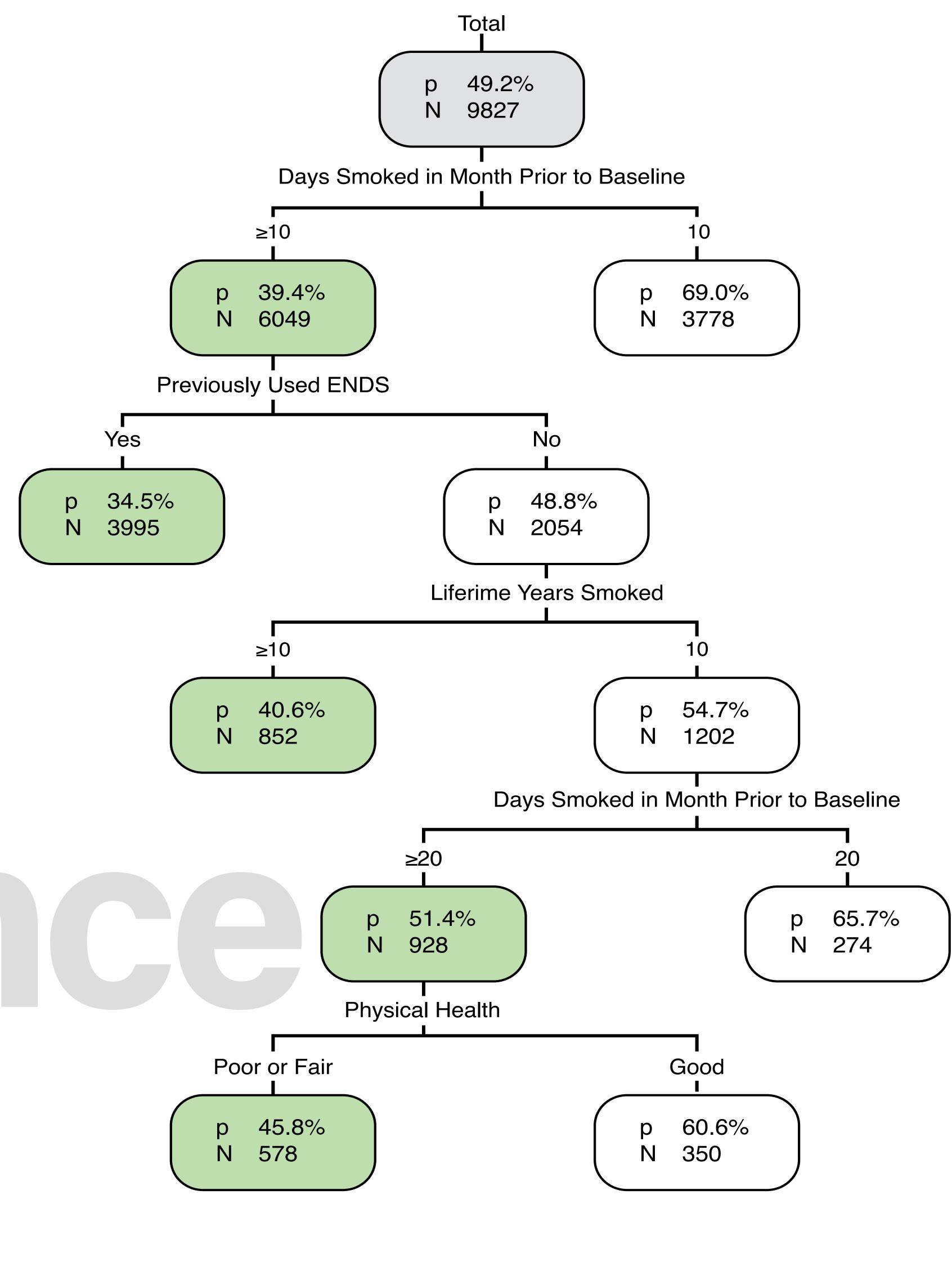


Table 2. Variables of Importance and Measures of Fit for CART

Variables with Greatest	mportance in Pruned Tree
Days Smoked in Month	at Baseline
Lifetime Number of Yea	s Smoked
Physical Health	
Previous ENDS Use bet	ore Juul purchase
Cigarettes Per Day Smo	ked at Baseline
Bought JUUL with moti	e to quit smoking
Smoked >100 cigarette	in Lifetime

<b>CART Tree Measure of Fit</b>	Training Sample	Validation Sample
ACCURACY:	65%	65%
MISCLASSIFICATION RATE:	35%	35%
Sensitivity (True Positive Rate)	60%	72%
Precision	68%	63%
F1 Score:	64%	67%

Table 3. Results from logistic regression with recursive feature elimination on the training cohort: parameter estimates and odds ratios for most important features

Parameter

Odds ratio 95% CL for OR P-value

Intercept	0.14	[0.04-0.46]	0.001	
Baseline Cigarette Levels	(reference	= 20+ CPD)		
0-5 CPD	1.83	[1.26-2.66]	0.001	
6-10 CPD	1.40	[0.98-1.99]	0.065	
11-15 CPD	1.14	[0.79-1.64]	0.494	
16-20 CPD	1.07	[0.75-1.53]	0.692	
Years Smoked (reference	= >20 years	s)		
<= 1 Year	1.45	[0.99-2.13]	0.058	
1-5 years	1.35	[0.97-1.87]	0.071	
5-10 years	1.08	[0.81-1.46]	0.591	
10- 20 years	1.02	[0.78-1.35]	0.871	
Age (reference: 65+ years				
21-24	2.28	[0.8-6.5]	0.122	
25-34	2.24	[0.8-6.29]	0.126	
35-44	1.98	[0.72-5.44]	0.187	
45-64	1.34	[0.49-3.71]	0.569	
Days Smoked Per Month	at Baseline	(reference = all 30	days)	
1-9 Days	1.99	[1.55-2.56]	0.000	
10-19 Days	1.30	[1.01-1.68]	0.041	
20-29 Days	1.11	[0.92-1.34]	0.284	
Marital Status (reference:	not current	ly married)		
Married	0.88	[0.69-1.12]	0.289	
Never Married	1.26	[0.99-1.59]	0.06	
AIAN	1.01	[0.66-1.53]	0.978	
Currently Trying to Quit Smoking	1.27	[1.03-1.56]	0.026	
Receive Some Form of Economic Assistance	0.97	[0.77-1.21]	0.771	
Currently Have Heart Condition	1.08	[0.9-1.29]	0.415	
Smoked >100 cigarettes in lifetime	0.70	[0.55-0.91]	0.007	
Currently Have Mental Health Condition	0.88	[0.76-1.03]	0.108	
Asian	1.15	[0.82-1.61]	0.425	
Male	1.21	[1.04-1.41]	0.014	
White	1.11	[0.86-1.42]	0.422	
Currently Have Respiratory Condition	0.95	[0.78-1.15]	0.579	
Previous ENDS Use at Baseline	0.63	[0.54-0.74]	0.000	
Planning to Quit Smoking with JUUL	2.03	[1.35-3.06]	0.001	
Physical Health	1.08	[0.94-1.24]	0.279	
		[0 00 4 50]	0.000	
NHPI	0.6	[0.23-1.53]	0.283	

Figure 2. ROC Curve from Logistic Regression Model on Training Sample

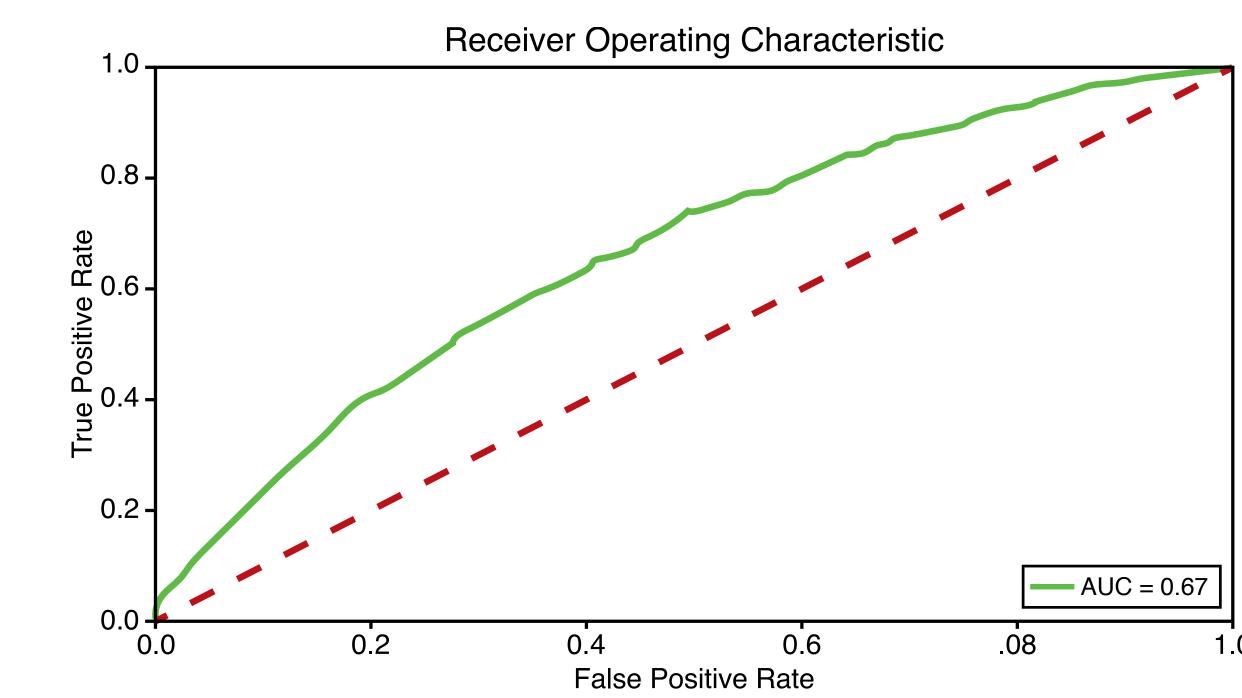
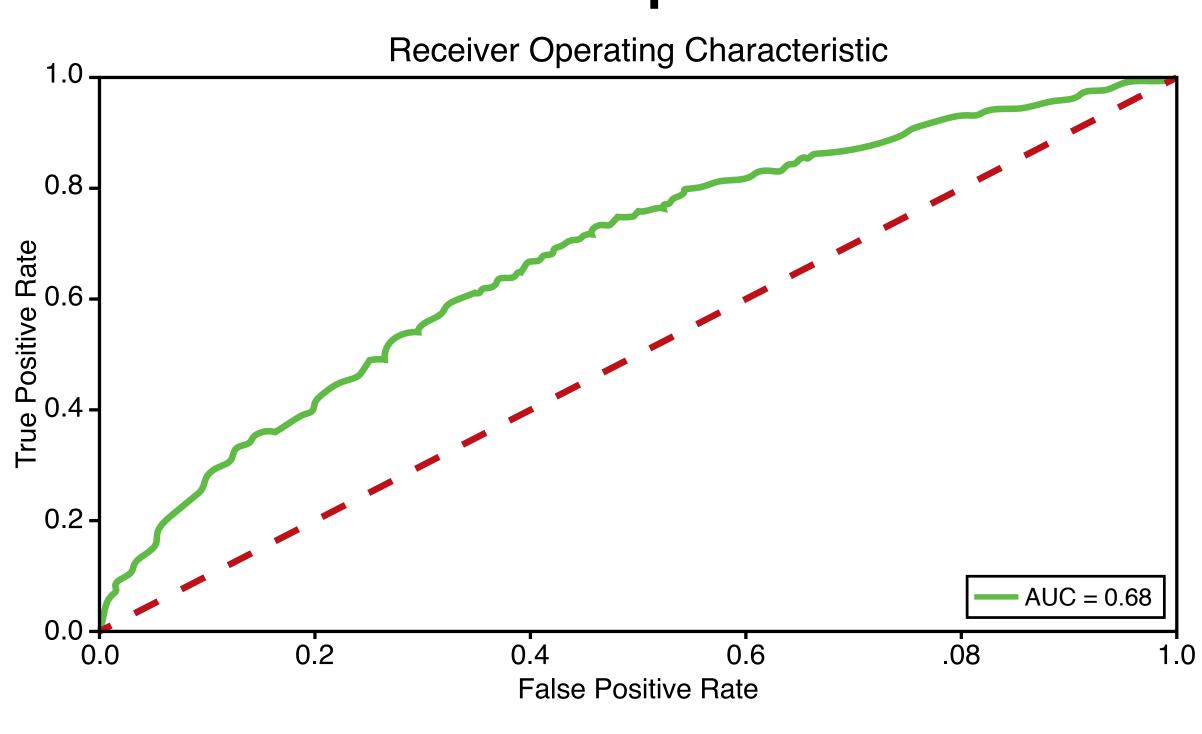


Figure 3. ROC Curve from Logistic Regression Model on Validation Sample



## Conclusions:

- This study provides preliminary information on attribute predictors of adult smokers who switch successfully from combustible cigarette use, and of those at high risk of continued smoking after initiating JUUL use.
- In general, both the CART and logistic regression analyses suggested that lighter smokers with less smoking history were more likely to successfully switch from combustible tobacco.
- ♦ This finding is consistent with the broader smoking intervention literature and supports considerations that heavier smokers may benefit from additional resources (e.g., behavioral support) to improve switching rates.
- The results also indicated that smokers who were actively attempting to quit smoking and those who stated they had purchased a JUUL product to help them quit smoking were more likely to successfully switch than those who purchased the product for other reasons.
- This finding has implications for interpreting population-level data regarding the potential success of vapor products to switch adult smokers from combustible tobacco.
- Additional research is needed to further understand switching patterns among subgroups and the possible role additional health behavior change assistance may serve to more effectively support switching.

Russell et al. (2019). Factors associated with past 30-day abstinence from cigarette smoking in a non- probabilistic sample of 15,456 adult established current smokers in the United States who used JUUL vapor products for three months. Harm Reduction Journal. Forthcoming.
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# Differences among Subgroups of Adult Smokers using JUUL in Switching from Smoking after 90 Days

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## Background:

- Previous studies have shown that JUUL products may be useful in assisting adult smokers in switching from combustible cigarettes.<sup>1</sup> Switching behavior may be informed by different characteristics that vary by age and intensity of smoking status.
- We conducted recursive feature elimination with logistic regression on four distinct cohorts of adult smokers, identified based on age and cigarettes per day (CPD) smoked at baseline, to classify those who were no longer smoking 90 days after purchasing a JUUL starter kit.

## Methods:

- Sample: Data from 11,520 current adult smokers
- Smoked in past 30 days prior to JUUL purchase
- ♦ Purchased a JUUL starter kit in the retail or ecommerce setting between June -September 2018
- ♦ Completed baseline data and 90-day follow-up data
- Provided information on cigarettes smoked per day
- Data on 36 individual-level attribute covariates that related to smoking status, demographics, smoking history, previous ENDS-use and other characteristics were assessed at baseline.
- Use of combustible cigarettes and JUUL products was reassessed at 90 days post baseline. Participants were defined as non-smokers if they reported having smoked no cigarettes, not even a puff, in the last 30 days.
- Respondents were divided into four cohorts based on smoking intensity (smoking more or less than 10 cigarettes per day at baseline) and age (those aged 21-25 vs. above 25)
- The sample was randomly divided into independent training (67% of sample) and validation (33% of sample) data sets per cohort for logistic regression modeling. The training sample was used to derive the model, while the remaining data were used to evaluate the predictive ability of the final model.
- Recursive feature elimination was performed separately on each cohort to identify the subset of baseline covariates that maximized accuracy and Area Under the Receiver Operating Curve (AUC) in the sample, with 5-fold cross-validation.

 The parsimonious subset of features that was identified for each separate cohort was used to fit a logistic regression model on the training data.

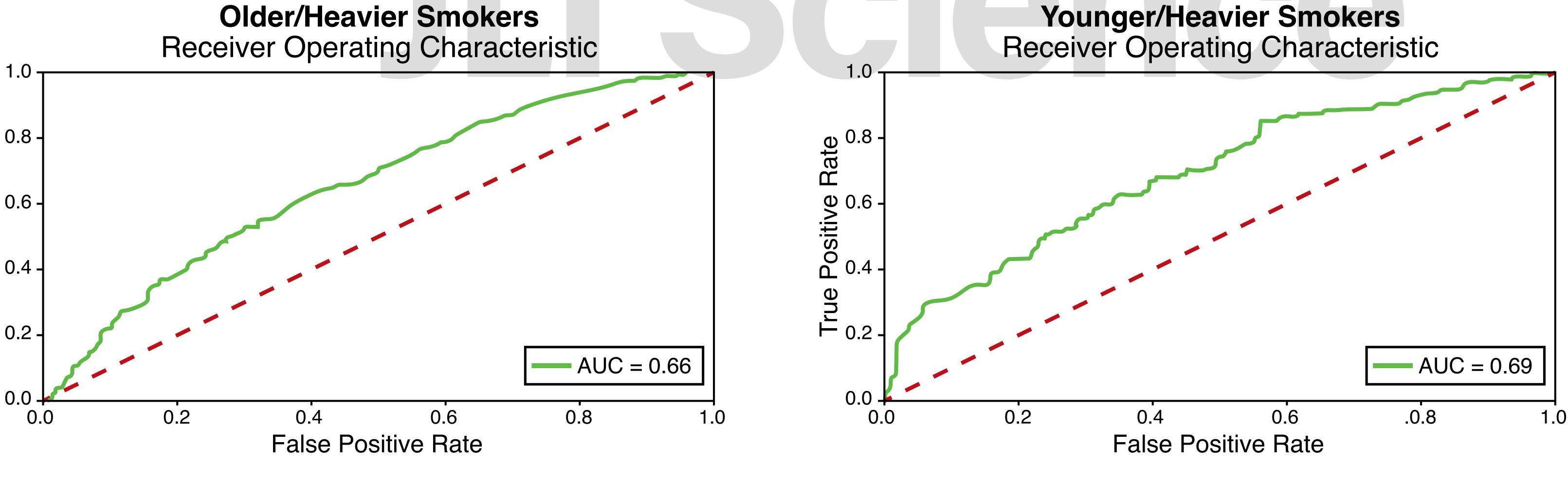
## Results:

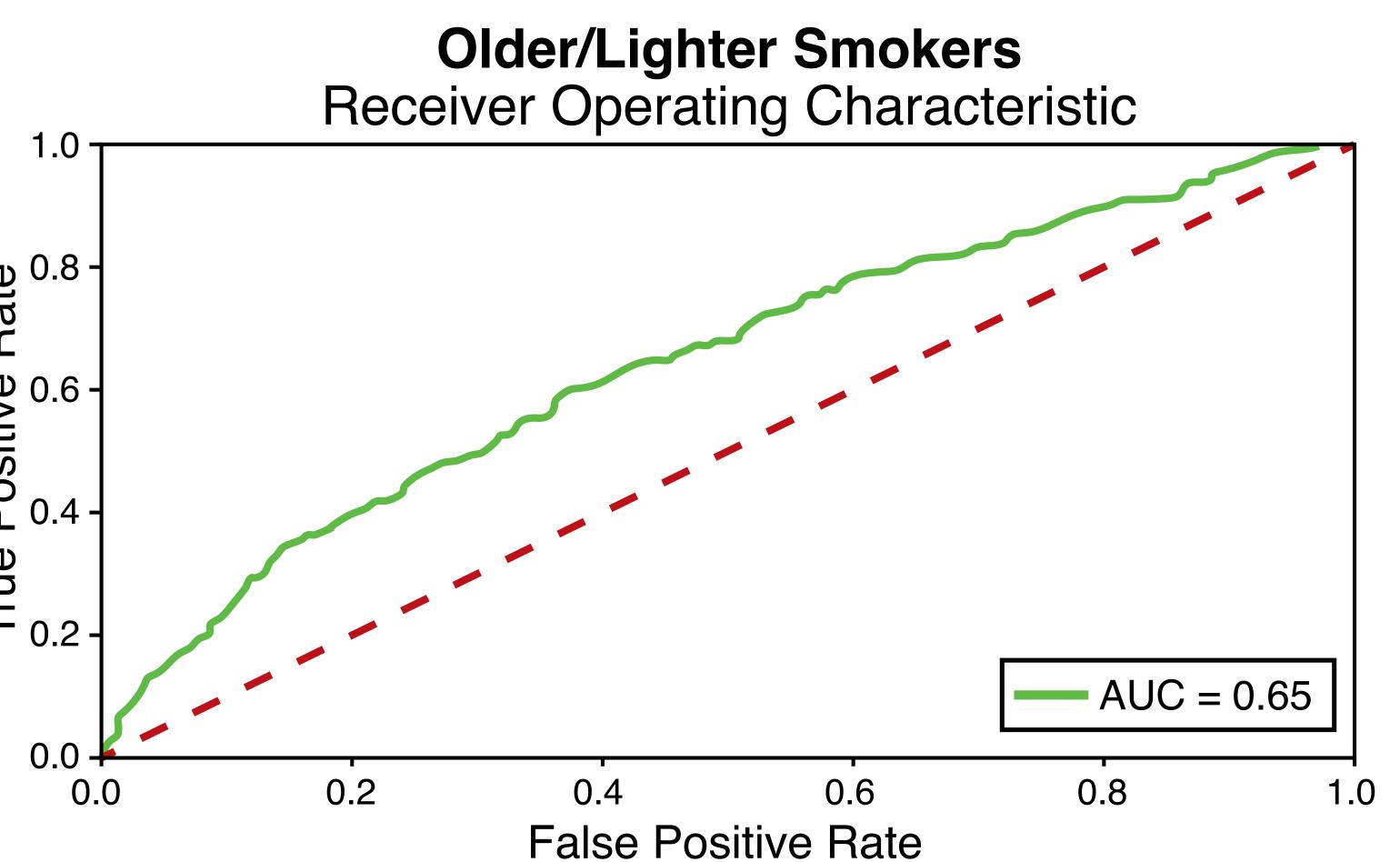
- Univariate analyses of differences across cohorts (Data not shown).
- A large majority of younger smokers were male. Smokers in both younger cohorts were also less likely to have been ever married and to have experienced emotional stress in the past week prior to JUUL purchase.
- A larger percentage of smokers in both heavier smoker cohorts smoked >20 days in the month prior to JUUL purchase, had their first cigarette within 0-30 minutes of waking up, had bought JUUL with the motive of wanting to quit smoking, were planning on using the JUUL to quit smoking, and reported having a respiratory or mental health condition, as compared to lighter smokers.
- While the majority of smokers were currently trying to quit smoking, younger/heavier smokers in particular were currently trying to quit smoking.
- The subset of baseline variables that were collectively predictive of switching and maximized AUC as identified by recursive feature elimination varied significantly by cohort (Table 1).
- ♦ For both cohorts of heavier smokers, the optimal number of features identified by recursive feature elimination was 26, indicating a great deal of variation and need for additional explanatory variables to maximize AUC and classify switching behavior within these cohorts. The identified feature subset was the same across both heavy smoker cohorts.
- The optimal number of features for the older/lighter cohort was 11, and for the younger/lighter smoker cohort, the optimal number was 4. Switching behavior in these cohorts seemed to vary less as switchers could be classified similarly accurately by a smaller group of covariates.
- Overall, 49% of smokers who were assessed at baseline and 90 days had switched away from cigarettes in the month prior to the 90-day assessment. Switching rates ranged from 34% to 56% across cohorts, with higher switching rates in cohorts of lighter smokers (Table 2).
- Russell et al. (2019). Factors associated with past 30-day abstinence from cigarette smoking in a non-probabilistic sample of 15,456 adult established current smokers in the United States who used JUUL vapor products for three months. Harm Reduction Journal. Forthcoming

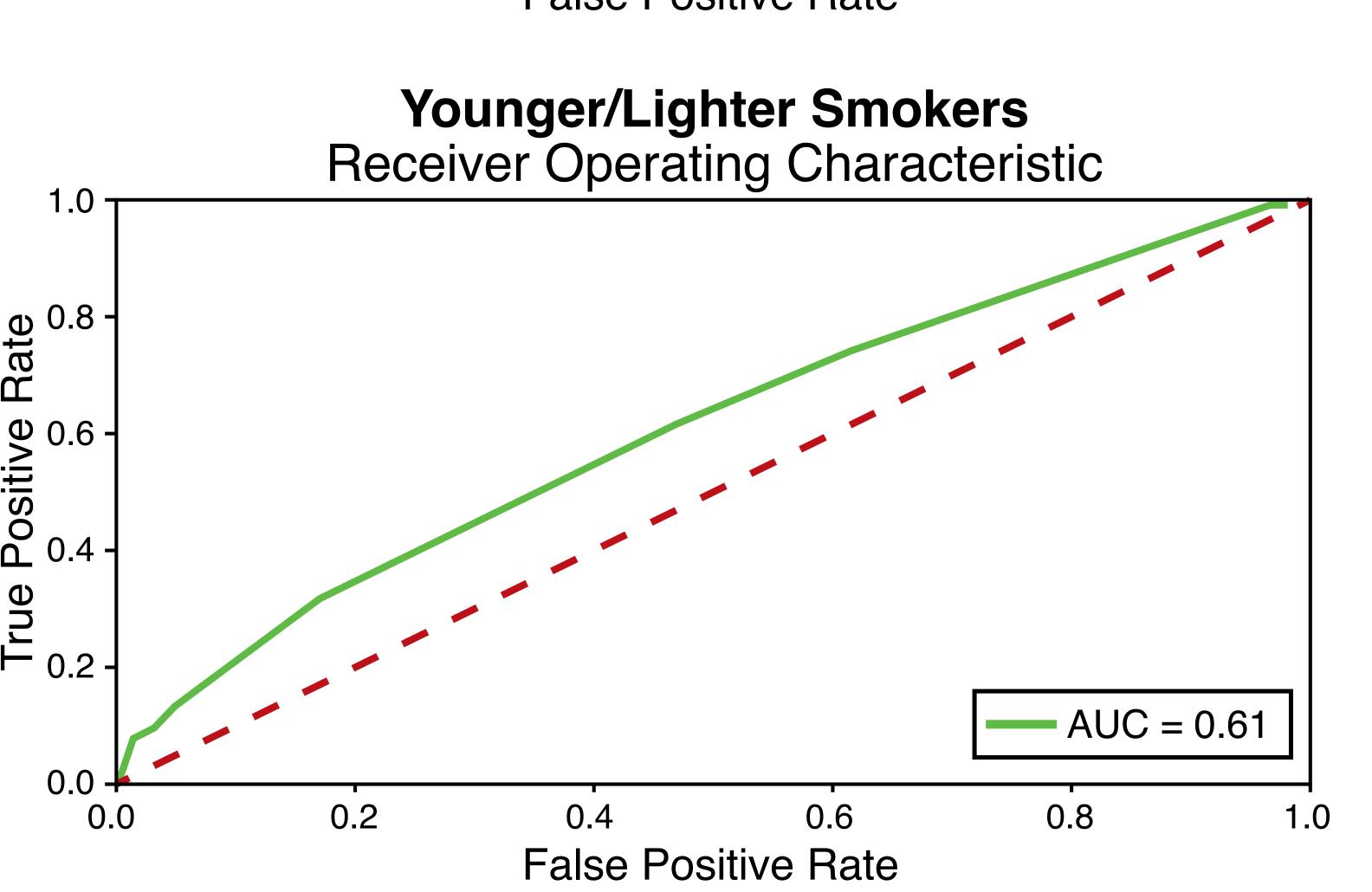
Table 1. Top Variables of Importance in each Cohort as Identified by Recursive Feature Elimination with Cross-Validation

Variables with Greatest Importance for Older/Heavier Smokers	Variables with Greatest Importance for Younger/Heavier Smokers	Variables with Greatest Importance for Older/Lighter Smokers	Variables with Greatest Importance for Younger/Lighter Smokers
Planning to Quit with Juul	Planning to Quit with Juul	Planning to Quit with Juul	Planning to Quit with Juul
Previous ENDS Use at Baseline	Previous ENDS Use at Baseline	Previous ENDS Use at Baseline	Previous ENDS Use at Baseline
Male	Male	Male	Male
Smoked >100 cigarettes in Lifetime	Smoked >100 cigarettes in Lifetime		Smoked >100 cigarettes in Lifetime
Days Smoked Per Month at Baseline	Days Smoked Per Month at Baseline	Days Smoked Per Month at Baseline	
Lifetime Number of Years Smoked	Lifetime Number of Years Smoked	Lifetime Number of Years Smoked	
Currently Trying to Quit Smoking	Currently Trying to Quit Smoking	Currently Trying to Quit Smoking	
Physical Health	Physical Health	Physical Health	
Overall Health	Overall Health	Overall Health	
White	White	White	
Asian	Asian	Asian	
Marital Status	Marital Status	Marital Status	
Motive for buying JUUL: To Quit Smoking	Motive for buying JUUL: To Quit Smoking		
Number of Minutes Smoked after Waking	Number of Minutes Smoked after Waking		
Age First Smoked Regularly	Age First Smoked Regularly		
Level of Cigarette Dependence	Level of Cigarette Dependence		
Interest in Quitting Smoking	Interest in Quitting Smoking		
Smoke Menthol cigarattes	Smoke Menthol cigarattes		
Number of Days Alcohol Consumed in Month	Number of Days Alcohol Consumed in Month		
Currently Have Heart Condition	Currently Have Heart Condition		
Currently Have Mental Health Condition	Currently Have Mental Health Condition		
Currently Have Respiratory Condition	Currently Have Respiratory Condition		
Black	Black		
Hispanic	Hispanic		
Receive Some Form of Economic Assistance	Receive Some Form of Economic Assistance		

Figure 3: ROC Curves and Measures of Fit for Cohort-Specific Logistic Regression Models







Overall Switching Rat								
Older/Heavier Smokers Overall Switching Rate in Cohort: 34%								
Parameter	Odds ratio	95% CL for OR	P-value					
Intercept	0.43	[0.03-6.45]	0.541					
Years Smoked (reference = >20 years)								
<= 1 Year	1.7	[0.25-11.35]	0.585					
1-5 years	2.32	[1.04-5.19]	0.040					
5-10 years	1.24	[0.8-1.92]	0.340					
10- 20 years	1.1	[0.76-1.59]	0.610					
Marital Status (reference: not currently married)								
Married	1.04	[0.68-1.58]	0.860					
Never Married	1.43	[0.97-2.11]	0.072					
Days Smoked Per Month at Baseline (reference = all 30 days)								
1-9 Days	2.07	[0.79-5.43]	0.139					
10-19 Days	1.72	[0.65-4.55]	0.275					
20-29 Days	1.66	[1.09-2.52]	0.018					
Number of Minutes Smoked after Waking (reference = 60+ minutes)								
0-30 minutes	0.98	[0.55-1.74]	0.936					
30-60 minutes	1.24	[0.65-2.36]	0.516					
Age First Smoked Regularly	0.97	[0.92-1.02]	0.218					
Alcohol Days in Past Month	0.98	[0.96-1]	0.049					
 Asian	1.18	[0.38-3.67]	0.770					
Black	1.37	[0.46-4.09]	0.573					
Level of Cigarette Dependence	1.1	[0.97-1.25]	0.141					
Currently Trying to Quit Smoking	1.15	[0.74-1.77]	0.533					
Receive Some Form of Economic Assistance	0.84	[0.53-1.33]	0.452					
Currently Have Heart Condition	0.97	[0.71-1.34]	0.870					
Interest in Quitting Smoking	0.96	[0.83-1.1]	0.552					
Smoked >100 cigarettes in lifetime	0.76	[0.4-1.43]	0.396					
Hispanic	0.52	[0.24-1.12]	0.096					
Currently Have Mental Health Condition	0.78	[0.56-1.09]	0.146					
Male	1.31	[0.96-1.79]	0.093					
Smoke Menthol cigarattes	0.97	[0.71-1.33]	0.872					
Motive for buying JUUL: To Quit Smoking	1.37	[0.5-3.77]	0.542					
Overall Health	1.34	[0.85-2.12]	0.209					
Physical Health	0.84	[0.55-1.28]	0.421					
Planning to Quit with Juul	1.99	[0.5-7.96]	0.331					
Previous ENDS Use at Baseline	0.57	[0.41-0.79]	0.001					
Currently Have Respiratory Condition	0.78	[0.53-1.15]	0.213					
	1.19	[0.38-3.69]	0.762					

vvnite	1.19	[0.38-3.69]	0.762				
Older/Lighter Smokers Overall Switching Rate in Cohort: 47%							
Parameter	Odds ratio	95% CL for OR	P-value				
Intercept	0.22	[0.08-0.66]	0.007				
Currently Trying to Quit Smoking	1.37	[0.97-1.93]	0.075				
Male	1.17	[0.9-1.53]	0.243				
Planning to Quit with Juul	2.47	[1.13-5.41]	0.024				
Previous ENDS Use at Baseline	0.71	[0.53-0.93]	0.015				
Overall Health	0.82	[0.56-1.18]	0.280				
Physical Health	1.33	[0.92-1.92]	0.133				
Asian	1.46	[0.78-2.72]	0.240				
White	1.04	[0.61-1.74]	0.896				
Years Smoked (reference = >20 years)							
<= 1 Year	2.55	[1.3-5.02]	0.007				
1-5 years	2.42	[1.55-3.78]	0.000				
5-10 years	1.57	[1.07-2.3]	0.022				
10- 20 years	1.28	[0.88-1.88]	0.201				
Marital Status (reference: not currently married)							
Married	0.72	[0.49-1.06]	0.099				
Never Married	1.1	[0.74-1.62]	0.651				
Days Smoked Per Month at Baseline (reference = all 30 days)							
1-9 Days	2.69	[1.81-3.99]	0.000				
10-19 Days	1.17	[0.8-1.71]	0.422				
20-29 Days	0.97	[0.7-1.33]	0.842				

able 2. Results from logistic regression with recursive feature elimination or	1 the
aining cohorts: parameter estimates and odds ratios	

Older/Heavier Smokers Overall Switching Rate in Cohort: 34% Overall Switching Rate in Cohort: 43%							
neter	Odds ratio	95% CL for OR	P-value	Parameter	Odds ratio	95% CL for OR	P-v
ept	0.43	[0.03-6.45]	0.541	Intercept	7.25	[0.11-478]	0.
Smoked (reference = >20 years)				Years Smoked (reference = >10 years)			
ear	1.7	[0.25-11.35]	0.585	<= 1 Year	0.68	[0.11-4.14]	0.
ars	2.32	[1.04-5.19]	0.040	1-5 years	0.59	[0.13-2.59]	0.
ears	1.24	[0.8-1.92]	0.340	5-10 years	0.66	[0.16-2.61]	0.
years	1.1	[0.76-1.59]	0.610	10- 20 years	N/A	N/A	N
Status (reference: not currently d)				Marital Status (reference: not currently married)			
d	1.04	[0.68-1.58]	0.860	Married	0.70	[0.13-3.93]	0.0
Married	1.43	[0.97-2.11]	0.072	Never Married	0.70	[0.11-4.48]	0.
Smoked Per Month at Baseline nce = all 30 days)				Days Smoked Per Month at Baseline (reference = all 30 days)			
ıys	2.07	[0.79-5.43]	0.139	1-9 Days	2.03	[0.6-6.82]	0.
Days	1.72	[0.65-4.55]	0.275	10-19 Days	2.55	[0.89-7.26]	0.0
Days	1.66	[1.09-2.52]	0.018	20-29 Days	1.73	[0.97-3.07]	0.
er of Minutes Smoked after g (reference = 60+ minutes)				Number of Minutes Smoked after Waking (reference = 60+ minutes)			
ninutes	0.98	[0.55-1.74]	0.936	0-30 minutes	1.41	[0.58-3.44]	0.
minutes	1.24	[0.65-2.36]	0.516	30-60 minutes	1.15	[0.44-3.01]	0.
rst Smoked Regularly	0.97	[0.92-1.02]	0.218	Age First Smoked Regularly	0.93	[0.77-1.13]	0.
ol Days in Past Month	0.98	[0.96-1]	0.049	Alcohol Days in Past Month	0.99	[0.96-1.02]	0.4
	1.18	[0.38-3.67]	0.770	Asian	1.17	[0.33-4.12]	0.
	1.37	[0.46-4.09]	0.573	Black	2.00	[0.57-7.04]	0.
of Cigarette Dependence	1.1	[0.97-1.25]	0.141	Level of Cigarette Dependence	0.83	[0.69-1.01]	0.0
tly Trying to Quit Smoking	1.15	[0.74-1.77]	0.533	Currently Trying to Quit Smoking	1.03	[0.31-3.37]	0.9
re Some Form of Economic ance	0.84	[0.53-1.33]	0.452	Receive Some Form of Economic Assistance	0.47	[0.21-1.02]	0.
itly Have Heart Condition	0.97	[0.71-1.34]	0.870	Currently Have Heart Condition	1.75	[0.89-3.44]	0.
t in Quitting Smoking	0.96	[0.83-1.1]	0.552	Interest in Quitting Smoking	1.08	[0.89-1.31]	0.
ed >100 cigarettes in lifetime	0.76	[0.4-1.43]	0.396	Smoked >100 cigarettes in lifetime	0.7	[0.26-1.88]	0.
nic	0.52	[0.24-1.12]	0.096	Hispanic	1.08	[0.4-2.94]	0.
tly Have Mental Health ion	0.78	[0.56-1.09]	0.146	Currently Have Mental Health Condition	1.1	[0.62-1.94]	0.
	1.31	[0.96-1.79]	0.093	Male	0.99	[0.57-1.71]	0.9
Menthol cigarattes	0.97	[0.71-1.33]	0.872	Smoke Menthol cigarattes	1.19	[0.74-1.92]	0.
for buying JUUL: To Quit	1.37	[0.5-3.77]	0.542	Motive for buying JUUL: To Quit Smoking	1.62	[0.39-6.78]	0.
I Health	1.34	[0.85-2.12]	0.209	Overall Health	1.27	[0.66-2.48]	0.
al Health	0.84	[0.55-1.28]	0.421	Physical Health	0.85	[0.48-1.5]	0.
ng to Quit with Juul	1.99	[0.5-7.96]	0.331	Planning to Quit with Juul	0.32	[0.05-2.13]	0.2
us ENDS Use at Baseline	0.57	[0.41-0.79]	0.001	Previous ENDS Use at Baseline	0.56	[0.33-0.96]	0.
tly Have Respiratory Condition	0.78	[0.53-1.15]	0.213	Currently Have Respiratory Condition	0.78	[0.43-1.41]	0.
	1.19	[0.38-3.69]	0.762	White	1.36	[0.43-4.25]	0.9

Younger/Lighter Smokers Overall Switching Rate in Cohort: 56%							
Parameter	Odds ratio	95% CL for OR	P-value				
Intercept	0.84	[0.22-3.16]	0.798				
Smoked >100 cigarettes in lifetime	0.32	[0.17-0.62]	0.001				
Male	1.63	[1.15-2.3]	0.005				
Planning to Quit with Juul	3.48	[1.04-11.62]	0.043				
Previous ENDS Use at Baseline	0.79	[0.55-1.14]	0.205				

- Across all four cohorts, previous use of an ENDS device decreased odds of switching by 20-40%. In three of the four cohorts, planning to quit smoking with JUUL and smoking < 10 days in the month prior to JUUL purchase increased odds of switching (Table 2).
- ♦ In both cohorts of heavy smokers, those who bought a JUUL starter kit with the motive of quitting smoking demonstrated 35-50% higher odds of switching.
- ♦ Several characteristics within each subset of features, such as previous ENDS use at baseline and planning to quit with JUUL, also had a statistically significant association with the outcome (p<0.05), suggesting that these predictors might specifically predict individual switching once other covariates in the optimal feature set were controlled for in the model.
- The cohort-specific logistic regression models for the subset of features identified by recursive feature elimination performed well in both training and validation samples, demonstrating similar discriminatory capability across both (Figure 3).

### Conclusions:

- Although a growing body of evidence suggests ENDS devices may have potential in helping smokers switch away from combustible tobacco, little is known about drivers of the variation in switching among different subgroups of smokers.
- More variation was seen among heavier smoker cohorts, as a greater subset of optimal features was needed to maximize the accuracy of the model. These cohorts also had lower switching rates.
- These preliminary findings begin to expand our understanding of the variables associated with variation in switching success within and between groups. This in turn may inform the development of targeted intervention programs, including those which provide behavioral support, to maximize the likelihood of switching success.