Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** Trustees of the University of Pennsylvania

2. **Reporting Period (start and end date of grant award period):** 1/1/2011 – 12/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Gearline Robinson-Hall, BSF

4. **Grant Contact Person's Telephone Number:** 215-746-6821

5. **Grant SAP Number:** 4100054874

6. **Project Number and Title of Research Project:** 5-Pharmacogenetics of Nicotine Addiction

7. **Start and End Date of Research Project:** 7/1/2011-12/31/2014

8. **Name of Principal Investigator for the Research Project:** Caryn E. Lerman, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $191,377.79

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Dubroff, Jacob	Co-Principal Investigator	1% YR1; 4% YR2; 6% YR3; 4% YR4	$27,334.95
Schnoll, Robert	Co-Investigator	6% YR1	$9,568.01
Falcone, Mary	Research Fellow; Research Investigator	18% YR1; 28% YR2; 7% YR3; 8% YR4	$21,856.04
Baldwin, Donald	Co-Investigator	1% YR2	$16,829.40
Goelz, Patricia	Research Coordinator	6% YR1	$2,289.39
Hou, Catherine	Lab Tech	12% YR3	$7,457.13

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Lerman, Caryn	Co-Principal Investigator	1%
Ray, Riju	Co-Investigator	1%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes____X_____ No_____

If yes, please indicate the source and amount of other funds:

Pfizer GRAND pilot grant ($200,000) to Riju Ray was used to supplement the Commonwealth funds due to the high cost of recruitment, PET screening and data processing.

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you

able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____X____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
The influence of nicotinic hepatic metabolism on neuroreceptor substrates of nicotine addiction 1-K23-DA-038726-01A1	★NIH ☐ Other federal (specify:__) ☐ Nonfederal source (specify:_)	11/2014	$1,240,300	$ PENDING

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No_____X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

Dr. Dubroff plans to continue this line of research, including analyses to use PET imaging to predict response to therapy. Due to the high cost of recruitment, PET scanning and analyses, we were not able to enroll a sufficient number of participants to study smoking cessation as part of the current project. Therefore, Dr. Dubroff will apply for NIH funds to continue this line of research in the future.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes____X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				1
Black				
Asian				
Other				
Unknown				
Total				**1**

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X

15. Impact on Researh Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This project was vital to enhance our capacity in the area of neuroimaging, including data acquisition, neurobehavioral probe task development, and data analytic procedures for fMRI.

16. Collaboration, business and community involvement

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes___X_____ No_____

If yes, please describe involvement with community groups that resulted from the research project:

Through involvement in this research project, smokers in the community were provided with free smoking cessation counseling and medication.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the

progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Original Aims

Aim 1) To conduct a prospective stratified pharmacogenetic (PGx) trial of alternative therapies for smoking cessation. Smokers will be randomized prospectively to treatment within two NMR strata: slow metabolizers (SMs) versus normal metabolizers (NMs). Treatment arms within each stratum will include: placebo (PLA), transdermal nicotine 21mg (TN; the most widely used treatment/low cost and low risk option), and varenicline 1mg bid (VAR; the most efficacious treatment/higher cost and increased risk option). Note: this aim was supported by an NIH grant. The current project was an add-on to this clinical trial (i.e., Aim 2 below).

Aim 2) To examine whether pretreatment neuronal nicotinic acetylcholine receptor availability predicts smoking cessation and treatment response. Within the prospective stratified clinical trial, we will perform pretreatment positron emission tomography (PET) to assess α4β2* neuronal nicotinic receptor availability during abstinence in slow and normal metabolizers. We will determine whether binding potential predicts response to different smoking cessation treatment, testing for both additive and interacting effects of the NMR.

Methods and Findings:

Aim 1: Aim 1 is an NIH funded pharmacogenomics trial of nicotine dependence treatment. Tobacco settlement funds were not used for this trial, but rather for Aim 2, the PET imaging study that was an add-on to the trial. However, because the Commonwealth grant supported an add-on to this trial, we report the findings of the primary trial below and acknowledge the Commonwealth in the publication.

Methods and Results: We completed a nicotine metabolite ratio (NMR)-stratified multi-center randomized placebo-controlled clinical trial including 1,246 smokers. Smokers seeking treatment were randomly assigned to 11 weeks of placebo (placebo patch plus placebo pill), nicotine patch (active patch plus placebo pill), or varenicline (placebo patch plus active pill).

Slow and normal metabolizers were characterized at pre-treatment based on the NMR (ratio of 3'hydroxycotinine/cotinine). Varenicline was more efficacious than nicotine patch in normal metabolizers, but not in slow metabolizers. Slow, but not normal metabolizers, also reported greater overall side effect severity with varenicline (vs. placebo). These findings suggest that treating normal metabolizers with varenicline and slow metabolizers with nicotine patch could optimize quit rates while minimizing side effects. Results are published in *The Lancet Respiratory Medicine*, January, 2015.

Aim 2: This PET imaging study is an add-on to the NIH funded pharmacogenomics trial of nicotine dependence treatment described above.

Methods and Results:

Participants

This study was conducted in accordance with the Declaration of Helsinki and the University of Pennsylvania Institutional Review Board approved all procedures. Individuals who had expressed interest in participating in smoking cessation research at the University of Pennsylvania completed an in-person intake session where they provided written informed consent and were screened for eligibility. Eligible participants were smokers between the ages of 18-65 who reported smoking at least 10 cigarettes per day (CPD) for the past 6 months, provided a baseline exhaled carbon monoxide (CO) reading greater than 10 parts per million (ppm), and were fluent English speakers. Persons with a history of DSM-IV Axis I psychiatric or substance disorders (except nicotine dependence), assessed using the Mini International Neuropsychiatric Interview, and those taking psychotropic medications were excluded. Other exclusion criteria included: current use of chewing tobacco, snuff, or smoking cessation products; pregnancy, planned pregnancy or breastfeeding; history of brain injury; or magnetic resonance imaging (MRI)-contraindicated material in the body.

Details on Recruitment and Explanation for Not Meeting Recruitment Goals. A total of 71 participants were screened for this substudy; 64 were screened prior to the clinical trial to obtain consent for a PET scan for this substudy. All participants eligible for the clinical trial at the UPenn site (one of 4 sites) were offered participation in this PET study, and those who expressed interest were screened. An additional 7 participants were recruited from prior study participants after recruitment for the primary clinical trial ended. Of the 71 interested potential PET study participants, only 35 met all eligibility criteria and scheduled a PET Scan Session. Five participants withdrew prior to the PET scan session and five were ineligible at the start of the session, resulting in 25 completed PET scans. Of these 25, one participant acquired an MRI contraindication prior to completing the MRI scan session, resulting in 24 participants with complete data. Of these, 13 were female; 17 were African American; and 12 were slow metabolizers. Due to the completion of the primary clinical trial ahead of schedule, our final sample for the PET imaging substudy includes only 24 participants.

Procedures and Results

The nicotine metabolite ratio was determined from a plasma sample provided at intake. Participants were classified as slow metabolizers (SMs, NMR < 0.26) or normal metabolizers

(NMs, NMR ≥ 0.26) based on prior clinical data which show differences in smoking cessation outcomes using this cutoff. Because slow metabolizers typically comprise one-quarter of the general population of smokers, we oversampled this group to obtain equal numbers of slow and normal metabolizers. Participants and research staff involved with the PET scans were blind to NMR.

After overnight nicotine abstinence, participants underwent PET brain imaging of 2-[^{18}F]FA delivered by bolus plus infusion to shorten the required duration of the PET imaging session due to the relatively slow receptor uptake of 2-[^{18}F]FA. The time period of overnight abstinence was chosen because most smokers relapse in the first 24 hours of a quit attempt, and because our primary hypothesis concerned differences in receptor availability in early abstinence due to differences in rates of nicotine metabolism. At the start of the session, participants provided a urine sample for a drug screen, a breath alcohol sample (BrAC > 0.01 exclusionary), and a breath carbon monoxide (CO) sample for biochemical confirmation of abstinence (CO <15ppm, or at least a 50% reduction from the intake session). During the PET scan session, 2-[^{18}F]FA (3.08-5.88 mCi) was administered as a 50% bolus initially with an additional 2-[^{18}F]FA (3.11-6.0 mCi) administered as a continuous infusion over 8 hours (50%). Participants completed two hours of brain scanning beginning six hours (±30 min) post-injection to allow for the radiotracer to achieve steady state. PET scanning was performed on a Gemini TruFlight (TF) Big Bore PET/CT scanner (Philips Healthcare, Eindhoven, The Netherlands). A low dose (120 kVp, 50 mAs), unenhanced CT scan of the head was performed before the emission acquisition in order to perform attenuation correction. The PET/CT images were reconstructed via an iterative LOR-RAMLA algorithm using 2 iterations and 4 subsets and the Sharp filter setting. Just prior to and immediately following the 2-hour PET scan, participants completed the Brief Questionnaire on Smoking Urges (QSU).

To facilitate automatic generation of brain volumes of interest (VOIs), all participants received a T_1-weighted anatomic scan on a Siemens MR scanner (Siemens Medical Solutions USA, Knoxville, TN with 3 participants on a 3T Magnetom Sonata Syngo and 21 participants on a 1.5T Magnetom Trio A Tim System) acquired using magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MP RAGE) sampling. Subjects underwent MRI scanning at a different session than PET imaging.

Baseline venous blood samples were obtained prior to injection for assessment of 2-[^{18}F]FA binding to plasma proteins, and for preparation of standards for the solid phase extraction process. Average non-metabolized concentration of free 2-[^{18}F]FA in plasma during the scan period was determined from an average of 5.8 blood samples for each participant from 5-7.5 h after bolus injection 2-[^{18}F]FA binding to plasma proteins was evaluated by ultrafiltration using YM-10 filtration devices (Millipore Corporation, Bedford, MA). Additional venous blood samples (~3 mL each) were drawn at predetermined intervals during the infusion period for measurement of unbound, non-metabolized 2-[^{18}F]FA. Samples were centrifuged at 4000 x g for 15 min and plasma radioactivity was measured using an automated gamma counter. Radioactivity attributable to non-metabolized 2-[^{18}F]FA was determined using solid phase extraction with Clean Screen extraction columns (200 mg/10 ml, United Chemical Technologies, Inc., Bristol, PA)(*32*).

In order to standardize the PET imaging acquisition times following radiotracer administration across all subjects, we used only the 90 minutes of PET scanning that was contemporaneous for all participants acquired between 6.25 to 7.75 hours after bolus injection using six 15 min time bins (mean midpoint of scans was 7.0 hours +/- 0.1 hours after bolus injection). Each participant's PET image was co-registered to his or her T_1-weighted MR scan and brain VOIs were automatically defined using the T1-MRI parcellation PNEURO tool in PMOD software (Pmod Technologies LTD, version 3.5, Zurich, Switzerland). Mean regional time activity curves (TAC) were output by Pmod software with partial volume correction based on a variant of the Rousset correction method whereby only 15% of the pixels in the inner VOI were used for calculating the VOI average. Average activity concentrations for the 90-minute time period were decay corrected to the time of bolus injection for use in subsequent calculations.

Participant total distribution volumes (designated as V_T/f_P based on standard nomenclature) were calculated as the ratio of average partial volume corrected 2-[^{18}F]FA concentration in brain to unbound, non-metabolized 2-[^{18}F]FA concentration in plasma.

Mean images of participant total distribution volumes (V_T/f_P) were created by dividing each participant's PET images by the participant's mean activity concentration of non-metabolized 2-[^{18}F]FA in plasma, with both PET image and plasma activity concentrations decay corrected to the time of 2-[^{18}F]FA bolus injection. All participants' V_T/f_P images were spatially normalized to the same template followed by averaging the resulting V_T/f_P images for all participants with normal hepatic nicotine metabolism (n = 12) and averaging the resulting V_T/f_P images for all participants with slower rates of hepatic nicotine metabolism (n = 12).

Descriptive statistics were generated for demographic and smoking variables, with differences between NMR groups being tested using t-tests and χ^2 tests. Group differences in V_T/f_P in the *a priori* VOIs were estimated by ANOVA including age, sex, and average cigarettes per day (CPD) as covariates; non-significant covariates were allowed to drop from the models at $p > 0.1$. Associations between V_T/f_P and craving were tested using regression models including mean QSU total score as the outcome and V_T/f_P in the *a priori* regions as the primary predictor. Alpha was adjusted on the basis of 4 VOIs with an average correlation of 0.95, resulting in an adjusted *p* value of 0.047. Twenty four smokers provided 80% power to detect an NMR group effect size of 1.2. There were no significant differences in age, sex, race, CPD, or FTND score between NMR groups (all $p > .05$).

There was significantly greater receptor availability (as measured by 2-[^{18}F]FA V_T/f_P) in NMs compared to SMs in the thalamus bilaterally ($F = 4.92$, $p = 0.037$, Figure 1). Significant associations (those surviving correction for multiple testing) were not observed in other tested regions: whole brain, temporal lobes and frontal lobes.

There were no significant associations between V_T/f_P in the 4 VOIs and self-reported urges to smoke. Urges to smoke did not differ between slow and normal nicotine metabolizers prior to scanning; however, the groups differed with respect to changes in urges from pre- to post-scan, with slow metabolizers exhibiting a decrease (mean change in slow metabolizers -8.1 (SE=2.9) and normal metabolizers showing a slight increase (mean change of +1.8 (SE=2.2).

Given the costs of screening, conducting the PET scans, and processing the imaging data, we were not able to enroll the projected sample of 48 participants. Moreover, because the primary clinical trial ended before the substudy was completed, about 25% of the sample were enrolled from the community and not from the cessation trial. Therefore, we were unable to test whether V_T/f_P predicted smoking cessation (in response to placebo, patch or varenicline).

Figure 1. 2-[18F]FA volume of distribution by region

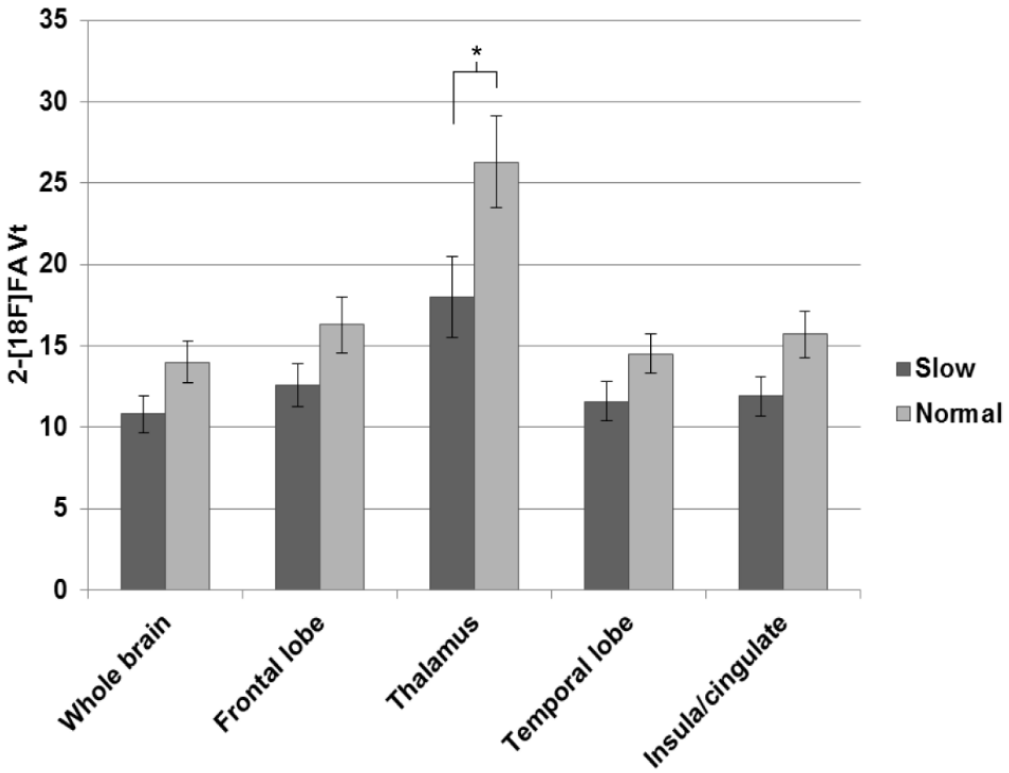

Figure 1 Legend: Smokers with normal nicotine metabolism (NMR ≥0.26) demonstrated increased V_t in brain compared to those with slower metabolism including in the thalamus (p=0.037) and marginally in the insula/cingulate gyrus (p=0.05). This relationship persisted and approached significance when comparing V_t between low (bottom quartile) and normal NMR groups for the entire brain (p=0.07). P values were calculated using one-way ANOVA. Error bars show standard error of the mean.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

___X__Yes
_____ No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X_Yes
_____No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

__2___Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

___48___Number of subjects originally targeted to be included in the study
___24___Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
__11____Males
__13____Females
_____Unknown

Ethnicity:
_____ Latinos or Hispanics
__24___Not Latinos or Hispanics
_____ Unknown

Race:
_____American Indian or Alaska Native
_____Asian
__17__Blacks or African American
_____Native Hawaiian or Other Pacific Islander
___7__White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

USA

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X__No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the

publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation	Lerman C, Schnoll R, Hawk L, Cinciripini P, George T, Wileyto E, Swan G, Benowitz N, Heitjan D, and Tyndale R	Lancet Respiratory Medicine	July 2014	☐Submitted ☐Accepted ☒Published
2. Decreased nicotinic receptor availability in smokers with slow rates of nicotine metabolism	Dubroff J, Doot R, Falcone M, Schnoll R, Tyndale R, Brody A, Lerman C	Journal of Nuclear Medicine	February 2015	☒Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No___X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be

single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

We discovered that slow and normal metabolizers of nicotine exhibit differences in brain nicotinic receptor availability. Decreased hepatic nicotine metabolism may help explain recent evidence that smokers with less up-regulated nAChR availability, also determined using 2-[^{18}F]FA PET imaging, were more likely to quit smoking. Manipulation of nicotine hepatic metabolism could be critical to raising poor nicotine cessation rates. This study further reinforces prior evidence that PET imaging of the α4β2* nAChR subtype represents a promising predictive biomarker of nicotine cessation therapy. Additionally, it raises the underappreciated issue of how psychoactive drug metabolism influences neuronal receptor expression and availability.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No_X__

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes___ No_

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
   Yes___ No__
   If yes, indicate number of patent, title and date issued:
   Patent number:
   Title of patent:
   Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No__

   If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

   If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Dubroff, Jacob Gershom	POSITION TITLE Assistant Professor of Radiology
eRA COMMONS USER NAME (credential, e.g., agency login) jdubroff	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A.S., B.A.	1993-1997	Biomedical Engineering History of Science
SUNY Upstate Medical University, Syracuse, NY	M.D., Ph.D.	1998-2006	Medicine, Neuroscience
Frankford Hospitals, Jefferson Health System Philadelphia, PA		2006-2007	Transitional Year Internship
Hospital of the University of Pennsylvania Philadelphia, PA		2007-2010	Nuclear Medicine Residency

A. Personal Statement

My long-term career goal is to establish an independent career in patient-oriented research (POR), focusing on understanding the changes in brain that occur in nicotine dependence and how they can be shaped to achieve cessation and improve public health. My training objectives progress in a logical fashion to prepare me to achieve this goal. I will accomplish these objectives through a combination of coursework, research experience and guidance from my primary mentors (Dr. Mach and Dr. Lerman) as well as my mentorship committee (Drs. Mankoff, Kranzler and Dani). The research project I propose, to examine the dynamics of nicotine's interaction with the nicotinic acetylcholine receptor (nAChR) in smokers with different rates of hepatic nicotine metabolism, builds on compelling preliminary data I have attained through generous time and support of one of my primary mentors (Lerman). On January 1, 2012, I was appointed Assistant Professor of Radiology at UPenn, allowing me to pursue a career in translational POR on neuroreceptor imaging of nicotine addiction. The K23 mechanism will enable me to focus 75% of my time and effort to develop a career as an independent clinical researcher. This comprehensive, interdisciplinary mentored approach will significantly enhance my clinical research skills and ability to successfully compete for R01 funding and establish an independent program of research.

B. Positions and Employment

Employment

2010-2011 Clinical Instructor of Radiology, Hospital of the University of Pennsylvania
2012-Present Assistant Professor of Radiology, Hospital of the University of Pennsylvania

Professional Memberships

2000- Sigma Xi
2001- Society for Neuroscience
2007- Society of Nuclear Medicine and Molecular Imaging
2009- Radiologic Society of North America

Honors

1997 Outstanding Undergraduate Service Award, University of Pennsylvania
2009-2010 Chief Resident, Nuclear Medicine, Hospital of the University of Pennsylvania
2013 Radiological Society of North America Clinical Trials Methodology Workshop Selection
2014 Best Poster, Neuroscience "Effect of nicotine metabolism on nicotinic acetylcholine receptor availability and craving." Society of Nuclear Medicine and Molecular Imaging, St Louis, MO.

C. Peer Review Publications

Most relevant to the current application

1. Falcone M, Gold AB, Wileyto EP, Ray R, Ruparel K, Newberg A, **Dubroff J**, Logan J, Zubieta JK, Blendy JA, Lerman C.: μ-Opioid receptor availability in the amygdala is associated with smoking for negative affect relief. Psychopharmacology 222(4): 701-8, 2012.
2. Arnold SE, Vega IE, Karlawish JH, Wolk DA, Nunez J, Negron M, Xie SX, Wang LS, **Dubroff JG**, McCarty- Wood E, Trojanowski JQ, Van Deerlin V.: Frequency and Clinicopathological Characteristics of Presenilin 1 Gly206Ala Mutation in Puerto Rican Hispanics with Dementia. J. Alzheimers Dis. 2013;33(4):1089-95.
3. Nasrallah IM and **Dubroff JG**: An Overview of PET Neuroimaging. Semin Nucl Med. 43(6): 449-61, Nov 2013.
4. Doty RL, Beals E, Osman A, **Dubroff J**, Chung I, Leon-Sarmiento FE, Hurtig H, Ying GS. Suprathreshold odor intensity perception in early-stage Parkinson's disease. Mov Disord 2014 Aug;29(9):1208-12.
5. Doty RI, Gandhi SS, Osman A, Hurtig HI, Pawasarat I, Beals E, Chung I, **Dubroff J**, Newberg A, Ying GS, and Leon-Sarmiento FE.: Point pressure sensitivity in early stage Parkinson's disease. Physiology and Behavior 2014 Notes: (accepted, awaiting publication).
6. Nayate AP, **Dubroff JG**, Schmitt JE, Narallah I, Kishore R, Mankoff D, and Pryma DA.: Use of SUVr decreases inter-reader variability of (F-18) Florbetapir PET brain scan interpretation. American Journal of Neuroradiology 2014. Notes: (accepted with revisions).

Additional recent publications of importance to the field (in chronological order)

7. Hodge CJ Jr., Huckins SC, Szeverenyi NM, Fonte MM, **Dubroff JG**, Davaluri K. Patterns of Lateral Sensory Cortical Activation Determined using Functional Magnetic Resonance Imaging. J Neurosurg. 1998 Nov; 89(5):769-79.
8. Hodge CJ Jr., Stevens R, Yamamoto T, Nguyen T, **Dubroff JG**, Zhu W, and McCasland JS. A new model of cortical plasticity using rat whisker barrel cortex. Developments in Neuroscience: Proceedings of the 2nd Mt. BANDAI Symposium for Neuroscience, Bandai, Japan. (27 October 2001), Volume 1247 December 2002, pp. 383-393.
9. **Dubroff JG**, Stevens RT, Hitt J, Maier DL, McCasland JS, and Hodge CJ Jr. Use-Dependent Plasticity in Barrel Cortex: Intrinsic Signal Imaging Reveals Functional Expansion of Spared Whisker Representation into Adjacent Deprived Columns. Somatosensory and Motor Research. 2005 Mar; 22(1/2): 25-35.
10. **Dubroff JG**, Stevens RT, McCasland JS, and Hodge CJ Jr. Fuctional Organization of Barrel Cortex in GAP-43 Deficient Mice. Neuroimage. 2006 Feb 15;29(4):1040-8.
11. **Dubroff JG**, Segal S, Wintering NA, Alavi A and Newberg AB. FDG PET Findings in Patients with Galactosemia. Molecular Metabolism and Genetics J Inherit Metab Dis. 2008 Aug;31(4):533-9.
12. **Dubroff JG** and Newberg AB. Neuroimaging of Traumatic Brain Injury. Seminars in Neurology. 2008 Sep;28(4):548-57.
13. **Dubroff JG**, Alavi A, Friedberg JS and Cengel KA. Postsurgical atypical f-18 fluorodeoxyglucose positron emission tomography uptake. Clinical Nuclear Medicine. 2009 Nov;34(11):808-10.
14. **Dubroff JG** and Newberg AB: PET Imaging for Traumatic Brain Injury. PET Clinics: PET in CNS Disease 5(2), Apr 2010.
15. Allison KC, Studt SK, Berkowitz RI, Hesson LA, Moore RH, **Dubroff JG**, Newberg A, Stunkard AJ.: An open-label efficacy trial of escitalopram for night eating syndrome. Eat Behav. 14(2): 199-203, April 2013.
16. Ficicioglu C, **Dubroff JG**, Thomas N, Gallagher PR, Burfield J, Hussa C, Randall R, Zhuang H.: A Pilot Study of Fluorodeoxyglucose Positron Emission Tomography Findings in Patients with Phenylketonuria before and during Sapropterin Supplementation. J. Clin. Neurol. 9(3): 151-6, July 2013.
17. Thaker AA, Schmitt SE, Pollard JR, Dubroff JG.: Natalizumab-Induced Progressive Multifocal Leukoencephalopathy. Clin Nucl Med 39(7): 365-6, Jul 2014.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Lerman, Caryn	Mary W. Calkins Professor
eRA COMMONS USER NAME CLERMAN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MO/YRS	FIELD OF STUDY
Pennsylvania State University, University Park, PA	B.S.	05/1981	Psychology
University of Southern California, Los Angeles, CA	M.A.	05/1982	Psychology
University of Southern California, Los Angeles, CA	Ph.D.	05/1984	Clinical Psychology

A. Personal Statement

Dr. Lerman is the Mary W. Calkins Professor in the Department of Psychiatry and the Deputy Director of the Abramson Cancer Center at the University of Pennsylvania. She is an Elected Member of the Institute of Medicine of the National Academy of Sciences, and has served as a member of the National Cancer Institute Board of Scientific Advisors and the National Human Genome Research Institute Advisory Council. She is a current member of the National Institute on Drug Abuse Advisory Council and past President of the Society for Research on Nicotine and Tobacco. Her research focuses on translating research in pharmacology, neuroscience, genetics, and behavioral science to develop improved treatments for tobacco dependence.

B. Positions and Honors

Positions and Employment

1985-1986 Assistant Professor of Psychiatry, Director of Health Psychology, Medical College of Pennsylvania, Philadelphia, PA
1986-1988 Assistant Professor of Medicine and Psychiatry, Temple University School of Medicine, Philadelphia, PA
1988-1993 Associate Member, Director of Behavioral Oncology Research, Fox Chase Cancer Center, Philadelphia, PA
1993-1998 Associate Professor, Departments of Medicine and Psychiatry, Georgetown University Medical Center (GUMC), Washington, DC
1998-2001 Professor, Departments of Oncology and Medicine, Georgetown University Medical Center (GUMC), Washington, DC
2001-2006 Associate Director, Cancer Control and Population Sciences, Abramson Cancer, University of Pennsylvania, Philadelphia, PA
2001-pres. Mary W. Calkins Professor, Department of Psychiatry and Annenberg Public Policy Center, University of Pennsylvania, Philadelphia, PA
2010-2011 Interim Director, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
2006-pres. Deputy Director, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
2013-pres. Director, Neuroscience of Behavior Initiative, University of Pennsylvania, Philadelphia, PA

Honors

1981 Phi Beta Kappa
1981 Magna Cum Laude, Pennsylvania State University
1989 New Investigator Award, Society of Behavioral Medicine
1991 Preventive Oncology Academic Award, National Cancer Institute/National Institutes of Health
1995 Award for Outstanding Contributions to Health Psychology, American Psychological Assn.
2004 Joseph Cullen Memorial Award, American Society of Preventive Oncology
2007 Alton Ochsner Award Relating Smoking and Health, American College of Chest Physicians
2007 American Cancer Society, Cancer Control Award - Southeastern Pennsylvania
2008 Arthur Asbury Outstanding Faculty Mentor Award, University of Pennsylvania
2009 Elected President of the Society for Research on Nicotine and Tobacco
2010 Elected Member, Institute of Medicine of the National Academy of Sciences
2011 William Osler Patient-Oriented Research Award, University of Pennsylvania

C. Selected Peer-Reviewed Publications (Out of 352)

Lerman C, et al. BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision-making and outcomes. Journal of the American Medical Association, 1996; 275(24):1885-1892.

Lerman C, et al. Genetic testing in families with hereditary nonpolyposis colon cancer. Journal of the American Medical Association, 1999; 281(17):1618-1622.

Lerman C, et al. Individualizing nicotine replacement therapy for the treatment of tobacco dependence. Annals of Internal Medicine, 2004; 140(6):426-433.

Lerman C, et al. Translational research in medication development for nicotine dependence. Nature Reviews Drug Discovery, 2007; 6(9)746-762.

Wang Z, Faith M, Patterson F, Tang K, Kerrin K, Wileyto EP, Detre JA, **Lerman C**. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. Journal of Neuroscience, 2007; (27):14030-14040.

Patterson F, Schnoll RA, Wileyto EP, Pinto A, Epstein LH, Shields PG, Hawk LW, Tyndale RF, Benowitz N, **Lerman, C**. Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. Clinical Pharmacology & Therapeutics, 2008; 84, 320-325 (PMID18388868; PMC in Progress).

Loughead J, Wileyto EP, Valdez NJ, Sanborn P, Tang K, Strasser AA, Ruparel K, Ray R, Gur RC, **Lerman C**. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. Molecular Psychiatry, 2009; 14(8):820-826 (PMID19065145; PMC3896978).

Langleben DD, Loughead JW, Ruparel K, Hakun JG, Strasser A, Holloway MX, Cappella JN, **Lerman C**. Reduced prefrontal and temporal processing and recall of high “sensation value” ads. Neuroimage, 2009; 46(1):219-225 (PMID19457412; PMC2896241; NIHMS183449).

Schnoll RA, Patterson F, Wileyto EP, Heitjan D, Shields AE, Asch D., **Lerman C**. Effectiveness of extended-duration transdermal nicotine therapy: a randomized trial. Annals of Internal Medicine, 2010; 152(3):144-151 (PMID20124230; PMC3782858).

Loughead J, Ray R, Wileyto EP, Ruparel K, Sanborn P, Siegel S, Gur RC, **Lerman C**. Effects of the $\alpha 4\beta 2$ partial agonist varenicline on brain activity and working memory in abstinent smokers. Biological Psychiatry, 2010; 67(8):715-721 (PMID20207347; (PMC in Process).

Lerman C, et al. Genetic variation in nicotine metabolism predicts the efficacy of extended duration transdermal nicotine therapy. Clinical Pharmacology & Therapeutics, 2010; 87(5):553-557 (PMID20336063; PMC3896974).

Ray R, Ruparel K, Newberg A, Wileyto E., Loughead J, Divgi C, Blendy JA, Logan J, Zubieta JK, **Lerman C**. Human mu opioid receptor (OPRM1 A118G) polymorphism is associated with brain mu opiod receptor binding potential in smokers. Proceedings of the National Academy of Sciences USA, 2011; 108(22):9268-9273 (PMID21576462; PMC3107291).

Lerman C, Gu H, Loughead J, Ruparel K, Yang Y, Stein EA. Large scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. JAMA Psychiatry, 2014; 71(5):523-530 (PMID24622915; PMC4097018)

Loughead J, Wileyto EP, Ruparel K, Falcone M, Hopson R, Gur R, **Lerman C.** Working memory-related neural activity predicts future smoking relapse. Neuropsychopharmacology, 2014; Epub Ahead of Print (PMID: 25469682; PMCID in Process).

Lerman C, et al. A randomized placebo-controlled trial to test a genetically-informed biomarker for personalizing treatment for tobacco dependence. The Lancet Respiratory Medicine, 2015; S2213-2600(14)70294-70292 (PMID25588294; PMC in Process).