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Smoking cessation, harm reduction, and biomarkers protocols in the PhenX Toolkit: Tools for standardized data collection

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Abstract

The use of standard protocols in studies supports consistent data collection, improves data quality, and facilitates cross-study analyses. Funded by the National Institutes of Health, the PhenX (consensus measures for **Phen**otypes and e**X**posures) Toolkit is a catalog of recommended measurement protocols that address a wide range of research topics and are suitable for inclusion in a variety of study designs. In 2020, a PhenX Working Group of smoking cessation experts followed a well-established consensus process to identify and recommend measurement protocols suitable for inclusion in smoking cessation and smoking harm reduction studies. The broader scientific community was invited to review and provide feedback on the preliminary recommendation of the Working Group. Fourteen selected protocols for measuring smoking

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cessation, harm reduction, and biomarkers research associated with smoking cessation were released in the PhenX Toolkit (https://www.phenxtoolkit.org) in February 2021. These protocols complement existing PhenX Toolkit content related to tobacco regulatory research, substance use and addiction research, and other measures of smoking-related health outcomes. Adopting well-established protocols enables consistent data collection and facilitates comparing and combining data across studies, potentially increasing the scientific impact of individual studies.

Keywords

Smoking cessation; Harm reduction; PhenX Toolkit; Standardized data collection

1. Introduction

1.1. Need for standardized measurement protocols for smoking cessation and harm reduction and potential for their use

Cigarette smoking continues to be one of the leading causes of morbidity and mortality in the world. In 2020, 12% of U.S. adults reported smoking cigarettes (30 million people) [1] , and worldwide, more than 1 billion people smoke [2] . Though most people report wanting to stop smoking, nicotine in combustible cigarettes is addictive, and successful smoking cessation remains a challenge for most people. Only 5% of people who smoke will quit per year [3] .

Pharmacological and behavioral treatments are effective in promoting successful smoking cessation. The Food and Drug Administration has approved three pharmacological treatments (nicotine replacement therapy, varenicline, and bupropion) to aid smoking cessation, and many behavioral approaches have been shown to successfully increase quitting [4 , 5]. Though pharmacological and behavioral treatments can improve smoking cessation, the magnitude of improvement is modest at best [4–8]. In most treatment trials, interventions increase smoking cessation to 30% of participants. Thus, a large treatment gap remains, and more successful interventions are needed to help most people stop smoking.

The emergence of tobacco products such as electronic cigarettes (e-cigarettes) and heated tobacco products raises the potential for a harm reduction approach for those who smoke combustible cigarettes. Harm reduction focuses on minimizing the adverse health effects from the persistent use of smoked tobacco products (i.e., cigarettes, cigars, pipe tobacco), rather than focusing solely on complete abstinence from tobacco. E-cigarettes expose the user to markedly lower levels of harmful constituents and carcinogens when compared to combustible cigarettes [9], and switching from combustible cigarettes to e-cigarettes has the potential to greatly decrease exposure to adverse biomarkers related to smoking behaviors [10]. In addition, among adults who smoke combustible cigarettes, using e-cigarettes is one of the most common strategies used to aid in quitting [3]. Reducing the adverse health effects of tobacco use, particularly cigarette smoking, is most important from a public health perspective.

To increase scientific knowledge of how to improve smoking cessation and reduce harm associated with smoking behaviors, key valid protocols that can be used across research studies are needed. The goal of providing a common foundation of protocols is to enhance reproducibility of studies and facilitate cross study comparison. In addition, by using standardized protocols, results can be more easily combined for large cross-study meta-analysis and research. The PhenX (consensus measures for **Phen**otypes and e**X**posures) Toolkit (https://www.phenxtoolkit.org/) supports this goal by providing a catalog of recommended standard measurement protocols across many scientific domains for investigators to use to address their research questions. The National Institute on Drug Abuse (NIDA) and the National Institutes of Health (NIH) Tobacco Regulatory Science Program recognized the need for smoking cessation research and funded an expansion of the PhenX Toolkit to include key smoking cessation and harm reduction protocols, including biomarkers, associated with smoking behaviors.

1.2. Introduction to the PhenX Toolkit

The objective of PhenX is to identify and promote the use of standard measurement protocols that improve the consistency of data collection with human participants, allowing for cross-study analyses, increased statistical power, and direct data comparability across studies. PhenX began in 2007 and is funded by the National Human Genome Research Institute (NHGRI) with additional funding from other NIH institutes and centers. The PhenX Toolkit is a web-based resource that researchers can use to inform their selection of data collection protocols. An important goal of the PhenX Toolkit is to provide investigators with a centralized location to examine a curated list of protocols recommended by domain experts and to facilitate the broadening of studies by adding protocols outside investigators' areas of expertise. Investigators may select the protocols from the Toolkit that meet their needs within the context of their available resources, study design, or research questions. Measurement protocols are selected by working groups of experts using an established consensus process [11], vetted in consultation with the broader research community, and made available to the public via the PhenX Toolkit [12]. Protocols are selected from available, well-established sources that are typically low burden for both investigators and study participants.

As of January 2023, the PhenX Toolkit includes measurement protocols relevant to 30 research domains and six specialty collections that provide additional depth for research in substance use disorder, mental health, tobacco regulatory science, blood sciences (i.e., sickle cell disease, hemophilia), social determinants of health, and COVID-19. PhenX measurement protocols are available as Research Electronic Data Capture (REDCap) data dictionaries that can be uploaded directly to REDCap for electronic data collection. As of January 2023, the PhenX Toolkit has more than 4200 registered users and has been recommended in more than 600 NIH funding opportunity announcements and notices. Use of PhenX protocols has been cited in 147 publications across a range of topics, including reactions to e-cigarette prevention advertisements [13] and timing of smoking cessation treatment [14] .

2. Materials and methods

The initial scope (Table 1) for a Smoking Cessation domain was developed with input from NIDA. In addition to focusing on smoking cessation, biomarkers associated with smoking behaviors was identified as a key area of focus. This scope guided the selection of an eight-member Smoking Cessation Working Group. The expertise of the Working Group members reflects the depth and diversity of the smoking cessation field, including by discipline. The members include physicians, clinical and behavioral psychologists, and a pharmacologist. Two co-chairs led the Working Group, and a liaison from the PhenX Steering Committee guided the group in its deliberations.

The PhenX consensus process includes defined criteria for inclusion of a measurement protocol in the PhenX Toolkit [11]. In general, the protocols must be well-established and relatively low burden to both investigators and participants, and preferably open source. The goal of the Working Group process is to identify protocols that can be recommended for the Toolkit that experts and nonexperts alike can use. Because the PhenX Toolkit provides protocols for a wide range of research topics, many smoking-related protocols were already in the Toolkit when the Smoking Cessation Working Group convened. The Working Group was tasked with building upon the existing Toolkit protocols, focusing on those specifically addressing smoking cessation and harm reduction.

The Working Group first convened in March 2020, at which time each Working Group member took responsibility for one or more scope elements within their area of expertise. At their next meeting in June 2020, each Working Group member presented the findings of their literature review and their recommendations about which protocols met PhenX criteria and could be considered as candidates for the Toolkit. Two key decisions developed during this process: a focus on cigarette smoking rather than all tobacco products, and a recognition of harm reduction as an important outcome. Combustible cigarettes are the most harmful tobacco product, and combustible cigarette smoking is highly prevalent. In addition, the strongest research base for tobacco products is focused on combustible cigarette smoking. These issues led the Working Group to decide to focus on cigarette smoking cessation. Next, the Working Group also recognized the dynamic nature of tobacco products and the emergence of e-cigarettes as a product often used by people who smoke to potentially aid in smoking cessation. The switch from combustible cigarettes to e-cigarettes represents a harm reduction approach to smoking that can be monitored through the measurement of smoking-related biomarkers. The Working Group added the topic of harm reduction as an important measurable goal with important public health significance. As a result of these deliberations, the Working Group recommended 16 preliminary measurement protocols to address the elements in the scope of Smoking Cessation, Harm Reduction, and Biomarkers (Table 1). These 16 protocols were included in an outreach email invitation to the broader scientific community to review and provide feedback. The scientific community included PhenX-registered users and NIDA-funded investigators. Outreach occurred from December 1 through 18, 2020, during which more than 100 individuals viewed the PhenX portal page that included the measurement protocols. Forty-two people provided feedback that generally supported the Working Group recommendations. The Working Group reviewed the feedback at their final meeting in January 2021. The lack of public access to one protocol

resulted in the Working Group recommending a publicly available alternative for the Toolkit. Noting that the fields of DNA methylation and polygenic risk scores were part of a fast moving and growing research base, the Working Group decided that these protocols were more suitable as reference materials in the PhenX Toolkit Supplemental Information. The Working Group made their final recommendations to the PhenX Steering Committee, which reviewed and approved the protocols for inclusion in the new Smoking Cessation, Harm Reduction, and Biomarkers domain. Information about the protocols, as with all PhenX Toolkit protocols, was processed using a bioinformatics pipeline for loading into the Toolkit, and protocol-specific data dictionaries and data collection worksheets were developed [15]. The Smoking Cessation, Harm Reduction, and Biomarkers domain was added to the PhenX Toolkit in February 2021.

3. Results

The Smoking Cessation, Harm Reduction, and Biomarkers domain includes 14 measurement protocols, with an additional two protocols in the PhenX Toolkit Supplemental Information as reference materials. They are listed alphabetically in Table 2 with the source of the protocol. The selected protocols include outcomes of cessation (e.g., abstinence from cigarettes); others may be mediators (e.g., adherence to medication regimens), moderators (e.g., social support for quitting smoking), or attitudes about smoking (e.g., perception of harm). For each protocol, the PhenX Toolkit provides information on how to administer the protocol, any specific instructions for using the protocol, and whether special training or resources are needed to administer the protocol. The Toolkit also lists references documenting the development and use of the protocols intended to help users understand potential limitations, such as use with diverse populations and availability in other languages. The Toolkit provides the tools to administer these protocols (with data dictionaries and data collection worksheets) to facilitate incorporation of the protocols into studies. In addition, PhenX data dictionaries fully support submission to the database of Genotypes and Phenotypes and are in a format suitable for upload to studies being implemented in REDCap [15].

3.1. Measurement protocols recommended for the PhenX Toolkit

3.1.1. Adherence to medication regimens—Adherence to smoking cessation medications is important to measure in smoking cessation studies [16 , 17]. If a person does not take the medications to promote smoking cessation, the medications cannot be effective. The Adherence to Refills and Medications Scale (ARMS) protocol is a series of 12 self-reported questions to assess how often an individual did not take medications. The answer choices are on a four-point Likert scale ranging from none of the time to all of the time. Within the 12 questions, there are two subscales. An eight-item subscale assesses the ability to administer a prescribed medication regimen. A four-item subscale assesses the ability to refill prescriptions on schedule. The lower the score, the better the adherence.

3.1.2. Cessation milestones - abstinence from cigarettes—Though long-term, continuous abstinence is the ultimate goal with smoking cessation, analyzing cessation outcome milestones allows researchers to identify the time course of treatment effects (i.e.,

examine earlier effects of treatment) and identify whether treatments can prevent relapse after an initial lapse [18–20]. It is important to define the primary outcome of abstinence in a research study a priori, whether it is point prevalence abstinence (no smoking in the previous 7 or 30 days) or continuous abstinence (no smoking over 12 weeks or more). Smoking cessation milestones address the real-world clinical course of quitting smoking, where some participants may be unable to quit on a targeted quit date or have some lapses and smoke, but then achieve successfully long-term abstinence. This protocol includes milestones of initial abstinence, initial lapse, and relapse to ascertain abstinence from cigarettes as well as longer-term abstinence.

3.1.3. Heaviness of smoking index—Understanding the heaviness of smoking provides insight into nicotine dependence, which can provide insight into relapse likelihood and withdrawal severity [21] . The Heaviness of Smoking Index includes two self-reported items about how soon after waking a person has their first cigarette and how many cigarettes the person smokes in a day. The answers to these questions can be used to guide dosing decisions in nicotine replacement therapy. These are a subset of questions from the Fagerström Test for Nicotine Cigarette Dependence.

3.1.4. Methods of quitting smoking cigarettes - adults—This protocol captures interventions for smoking cessation [22]. Various pharmacological and behavioral strategies are common and, when used in combination, are likely to lead to higher levels of cessation success. This protocol includes two self-administered questions that ask current smokers about their attempts to quit smoking cigarettes during the last 3 months. Respondents who attempted to quit are asked what methods they used.

3.1.5. Nicotine metabolite ratio - serum and saliva—The nicotine metabolite ratio is a genetically informed biomarker of nicotine clearance that is associated with smoking cessation success and pharmacological treatment response in clinical trials [23]. This is a laboratory protocol from the National Health and Nutrition Examination Survey (NHANES) to measure cotinine and trans-3-hydroxycotinine in serum or saliva. This ratio relates to the rate of nicotine metabolism in people who smoke and can help select an appropriate smoking cessation medication.

3.1.6–3.1.10 Perception of tobacco product harm - cigarettes, cigars, e-cigarettes, pipe tobacco, smokeless tobacco—Perceptions of harm of tobacco products are important in predicting willingness to try to quit and continued use of tobacco products. Also, many people switch tobacco products while attempting to quit smoking cigarettes [3]. These questions from the Population Assessment of Tobacco and Health (PATH) Study ask about a respondent’s thoughts about the physical and health harms associated with using several different types of tobacco products, including e-cigarettes, cigars, pipe tobacco, and smokeless tobacco.

3.1.11. Point-prevalence abstinence from tobacco products—Point-prevalence abstinence is the primary outcome in many cessation studies [20] . Point-prevalence abstinence is defined as complete abstinence, not even a puff, from combustible cigarette usage in a defined time period. It is important to define the duration of the abstinence

period, usually 7 or 30 days. This assessment from the Program for Lung Cancer Screening and Tobacco Cessation (PLUTO) identifies participants who have achieved abstinence following treatment in cessation clinical trials [24] . In most studies, a lapse by smoking a cigarette or even continuing to smoke after a quit date may not be considered a smoking cessation failure. This approach recognizes that smoking cessation is difficult and takes much effort and potentially passes through several smoking cessation milestones such as initial abstinence and lapses. The two questions to define point prevalence abstinence ask about the use of defined tobacco products in the past 7 days and the past 30 days. It is important to recognize that switching from combustible cigarettes to e-cigarettes can be discerned with this protocol.

3.1.12. Prolonged abstinence from tobacco products—Long-term abstinence from smoking leads to improved health and is the ultimate goal of smoking cessation [20 , 25]. This protocol assesses long-term abstinence following treatment in cessation clinical trials. These questions ask current tobacco users about their use of specific tobacco products since the end of an initial grace period following a target quit date, which enables abstinence to be established. The grace period is typically 1 to 2 weeks after the target quit date.

3.1.13. Self-Efficacy for not smoking—Self-efficacy for not smoking is a risk factor that is predictive of smoking relapse or failure to quit smoking [26] . This 12-item instrument measures current and former smokers' confidence in their ability to abstain from smoking in certain social or emotional situations. The Smoking Self-Efficacy Questionnaire (SEQ-12) has two subscales measuring confidence in ability to refrain from smoking when facing internal stimuli (e.g., feeling depressed) and external stimuli (e.g., being with smokers).

3.1.14. Social support for quitting smoking—Support from family and friends is positively associated with a person's intention to quit smoking. This protocol from the Partner Interaction Questionnaire (PIQ-20) determines social support specific to quitting smoking [27] . This 20-item questionnaire assesses the nature of partner behaviors supporting quitting and maintenance of abstinence. It includes two subscales assessing positive and negative behaviors of a spouse or romantic partner, close friend, or family member.

3.2. PhenX Toolkit Supplemental information

PhenX Toolkit Supplemental Information includes two additional protocols that were deemed to be important and at the cutting edge of the biological science for understanding smoking cessation and harm reduction. Because research is actively ongoing with these biomarkers and the knowledge base underlying these protocols is dynamic and growing, these were determined to be suitable for the PhenX Toolkit Supplemental Information.

3.2.1. Polygenic risk score—A polygenic risk score is an estimate of risk based on the presence of hundreds to thousands of variants across a person's genome. A single scored value that quantifies an individual's propensity can be used to estimate the risk of disease or

other clinically relevant outcomes compared with others with a different genetic constitution [28] .

3.2.2. Epigenetics of smoking—Epigenetic changes can reflect predisposing factors related to smoking and consequences of smoking [29] . A genome-wide DNA methylation analysis provides an epigenetic signature of current and lifetime cigarette smoking exposure for individuals.

3.3. Existing related PhenX Toolkit protocols

The PhenX Toolkit addresses a wide range of research topics that had protocols in the Toolkit already when the Smoking Cessation Working Group was formed. As a result, the Working Group identified protocols from elsewhere in the Toolkit that are relevant to smoking cessation and harm reduction research. These protocols are organized into folders at the bottom of the Smoking Cessation domain page to allow users to easily identify additional protocols for consideration. They are grouped into Additional Relevant Protocols for Smoking Cessation and Health Outcomes (Tables 3 and 4) and a Core Collection.

3.3.1. Core collection of measurement protocols for smoking cessation studies—The Working Group identified 16 core protocols that are deemed relevant for all smoking cessation studies. The list includes protocols for basic demographic information that would be collected in most research studies (e.g., current age, ethnicity, and race) and protocols specific to smoking cessation research (e.g., heaviness of smoking, smoking quit attempts). Consistent use of these core protocols will ensure collection of comparable data across studies:

1. Amount, Type, and Frequency of Recent Cigarette Use
2. Biological Sex Assigned at Birth
3. Biomarker of Exposure to Nicotine-Containing Products - Saliva
4. Biomarker of Exposure to Nicotine-Containing Products - Serum
5. Biomarker of Exposure to Nicotine-Containing Products - Urine
6. Current Age
7. Ethnicity and Race
8. Expired Carbon Monoxide
9. Gender Identity
10. Heaviness of Smoking Index
11. Motivation to Quit - Multiple Item
12. Motivation to Quit - Single Item
13. Point-Prevalence Abstinence from Tobacco Products
14. Prolonged Abstinence from Tobacco Products
15. Self-Efficacy for Not Smoking

16. Smoking Quit Attempts

4. Discussion

4.1. Use of standardized data collection protocols

A more rapid increase in knowledge about smoking cessation and harm reduction will be facilitated using valid standard protocols that make the resulting data directly comparable across studies. By using standardized protocols, studies can be compared and results combined to more efficiently and reliably answer important questions of what works best to reduce smoking, a major public health problem. Using standardized measures also obviates the need to perform time-consuming data harmonization. The Working Group identified 14 protocols, with an additional two protocols in the PhenX Toolkit Supplemental Information. This PhenX domain includes measurements of perceived harm from tobacco products, medication adherence, social support for quitting, nicotine metabolite ratio measures, and smoking cessation milestones. The Working Group also referenced other existing protocols in the Toolkit that are related to smoking cessation and harm reduction.

4.2. Challenges and special considerations

Identifying measurement protocols to recommend for smoking cessation and harm reduction was challenging. One challenge is that the landscape of tobacco products is rapidly changing. The Working Group recognizes that within the last 15 years, new tobacco and nicotine products have emerged, including e-cigarettes. These different tobacco products raise the issue of whether the focus of the domain should be on all tobacco products or on combustible cigarette smoking. The Working Group came down on the side of focusing on combustible cigarette smoking for two key reasons. First, combustible cigarettes are by far the most prevalent and deadly tobacco product in use. Second, the greatest number of validated protocols target combustible cigarette use. However, the Working Group recognizes that many of these protocols have been or can be modified to ask about other tobacco products.

The emergence of new tobacco products also raised the potential focus on harm reduction as an important outcome that the Working Group recognizes requires additional study. The use of non-combustible tobacco products such as e-cigarettes is not going away and offers cigarette smokers an alternative to smoking that could yield public health benefits if smokers used these alternatives to substitute completely for tobacco. However, there is legitimate concern that nonsmokers, especially youth, will take up these non-combustible products, and it is not clear if e-cigarette use will persist beyond experimentation and result in long-term exposures that could cause serious health problems.

One issue faced by the Working Group was how to make protocol recommendations when research gaps remain. Two new powerful biomarkers are genetic measures: polygenic risk scores and epigenetic measures. Polygenic risk scores, a summation of a person’s genetic risk across thousands of variants, could identify those at greatest risk of developing nicotine use disorder and failing smoking cessation [30 , 31]. Epigenetic measures, which can represent changes in activation of genes, may be able to identify those with the greatest

burden of combustible cigarette smoking exposure across a lifetime. Techniques to measure genetic and epigenetic variation are standardized, but the predictive accuracy is changing and only generalizable within some ancestries. However, the knowledge base is growing, and we expect such tools to become increasingly useful for predicting population risk, understanding individual risk, and improving study designs (e.g., clinical trials).

The Working Group came to consensus that these two genetic biomarkers, though not yet fully validated, were important to include in the PhenX Toolkit. The tension between recommending important, but not fully validated, protocols and the PhenX principle of including only validated standard protocols must be balanced in the pursuit of scientific progress. How can research programs close these gaps in knowledge if the scientific experts cannot recommend promising but not fully standardized protocols to the research community? After due deliberation and consultation with the PhenX Steering Committee, a compromise was made to include these two protocols in the PhenX Toolkit Supplemental Information. The Working Group hopes that these genetic measurement protocols will be included in future research on smoking cessation and harm reduction. Because the PhenX Toolkit is a resource that evolves over time, these genetic biomarkers are likely to be promoted to recommended protocols after further validation and standardization.

5. Conclusion

In summary, the PhenX Toolkit provides an important resource for investigators studying smoking cessation and harm reduction that will accelerate knowledge gained from their research. Results across studies can be better compared and combined to more efficiently and reliably determine what helps people cut down and quit smoking, reduces their health risks, and improves health outcomes.

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Data availability

No data were used for the research described in the article.

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Table 1

Initial scope for the Smoking Cessation, Harm Reduction, and Biomarkers Domain (6).

Biomarkers (focus on therapeutics)
Mechanism of cessation
Mediators of treatment effects
Outcomes
Risk factors
Treatment

Table 2

Protocols included in the PhenX Toolkit Smoking Cessation, Harm Reduction, and Biomarker Domain.

Protocol name	Source of protocol
Adherence to Medication Regimens	Dharmapuri, S., Best, D., Kind, T., Silber, T. J., Simpson, P., & D'Angelo, L. (2015). Health literacy and medication adherence in adolescents. *Journal of Pediatrics, 166* (2), 378–382. Kripalani, S., Risser, J., Gatti, M. E., & Jacobson, T. A. (2009). Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value in Health, 12* (1), 118–123.
Cessation Milestones - Abstinence from Cigarettes	Japuntich, S. J., Leventhal, A. M., Piper, M. E., Bolt, D. M., Roberts, L. J., Fiore, M. C., & Baker, T. B. (2011). Smoker characteristics and smoking-cessation milestones. *American Journal of Preventive Medicine, 40* (3), 286–294. Shiffman, S., Scharf, D. M., Gwaltney, C. J., Dang, Q., Paton, S. M., & Clark, D. B., 2006. Analyzing milestones in smoking cessation: Illustration in a nicotine patch trial in adult smokers. *Journal of Consulting and Clinical Psychology, 74* (2), 276–285.
Heaviness of Smoking Index	Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., Rickert, W., & Robinson, J. (1989). Measuring the heaviness of smoking: Using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *British Journal of Addiction, 84* (7), 791–799. National Institute on Drug Abuse (NIDA) Data Share Website. (2016). *Heaviness of Smoking Index* (scoring instructions). National Institutes of Health.
Methods of Quitting Smoking Cigarettes - Adults	Caraballo, R.S., Shafer, P. R., Patel, D., Davis, K. C., & McAfee, T. A., 2017. Quit methods used by US adult cigarette smokers, 2014–2016. *Preventing Chronic Disease, 14* , E32.
Nicotine Metabolite Ratio - Serum and Saliva	Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). (2018). *Cotinine and hydroxycotinine in serum laboratory procedure manual* . U.S. Department of Health and Human Services.
Perception of Tobacco Product Harm - Cigarettes	U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2018, Wave 3 Adult Annotated Instrument, items AC9019, AX0723, AX0724. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research.
Perception of Tobacco Product Harm - Cigars	U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2016, Wave 1 Adult Annotated Instrument, items AG1001, AG9002, AG1099, AG1106, AG1107. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research. U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2018, Wave 3 Adult Annotated Instrument, items AG9062, AG1110. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research.
Perception of Tobacco Product Harm - E-Cigarettes	U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2016, Wave 1 Adult Annotated Instrument, items AE1001, AE1099. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research.
Perception of Tobacco Product Harm - Pipe Tobacco	U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2016, Wave 1 Adult Annotated Instrument, items AP1001, AP1099, AH1001, AH1099. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research.
Perception of Tobacco Product Harm - Smokeless Tobacco	U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2016, Wave 1 Adult Annotated Instrument, items AS1001, AS1105. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research. U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse; and U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Population Assessment of Tobacco and Health (PATH) Study, 2018, Wave 3 Adult Annotated Instrument, items AU1105, AU9040. Distributed October 21, 2020, by Inter-university Consortium for Political and Social Research.
Point-Prevalence Abstinence from Tobacco Products	Fu, S. S., Rothman, A. J., Vock, D. M., Lindgren, B., Almirall, D., Begnaud, A., Melzer, A., Schertz, K., Glaeser, S., Hammett, P., & Joseph, A. M. (2017). Program for lung cancer screening and tobacco cessation: Study protocol of a sequential, multiple assignment, randomized trial. *Contemporary Clinical Trials, 60* , 86–95.

Protocol name	Source of protocol
Prolonged Abstinence from Tobacco Products	Hughes, J. R., Keely, J. P., Niaura, R. S., Ossip-Klein, D. J., Richmond, R. L., & Swan, G. E. (2003). Measures of abstinence in clinical trials: Issues and recommendations. *Nicotine & Tobacco Research, 5* (1), 13–25.
Self-Efficacy for Not Smoking	Etter, J., Bergman, M. M., Humair, J., & Perneger, T. (2000). Development and validation of a scale measuring self-efficacy of current and former smokers. *Addiction, 95* (6), 901–913.
Social Support for Quitting Smoking	Cohen, S., & Lichtenstein, E. (1990). Partner behaviors that support quitting smoking. *Journal of Consulting and Clinical Psychology, 58* (3), 304–309.
PhenX Toolkit Supplemental Information (2)	
Polygenic Risk Score	Wand, H., Lambert, S. A., Tamburro, C., Iacocca, M. A., O'Sullivan, J. W., Sillari, C., Kullo, I. J., Rowley, R., Dron, J. S., Brockman, D., Venner, E., McCarthy, M. I., Antoniou, A., C., Easton, D. F., Hegele, R. A., Khera, A. V., Chatterjee, N., Kooperberg, C., Edwards, K., Vlessis, K., et al. (2021). Improving reporting standards for polygenic scores in risk prediction studies. *Nature, 591* (7849), 211–219.
Epigenetics of Smoking	Joehanes, R., Just, A. C., Marioni, R. E., Pilling, L. C., Reynolds, L. M., Mandaviya, P. R., Guan, W., Xu, T., Elks, C. E., Aslibekyan, S., Moreno-Macias, H., Smith, J. A., Brody, J. A., Dhingra, R., Yousefi, P., Pankow, J. S., Kunze, S., Shah, S. H., McRae, A. F., Lohman, K., et al. (2016). Epigenetic signatures of cigarette smoking. *Circulation: Genomic and Precision Medicine, 9* (5), 436–447. Xing, X., Zhang, B., Li, D., & Wang, T. (2018). Comprehensive whole DNA methylome analysis by integrating MeDIP-seq and MRE-seq. In Tost, J. (Ed.), *DNA methylation protocols. Methods in molecular biology* (Vol. 1708, pp. 209–246). Humana Press. 10.1007/978-1-4939-7481-8_12

PhenX Toolkit Supplemental information includes protocol(s) considered by the Working Group that were not selected for the PhenX Toolkit.

Table 3

Additional Smoking Cessation Protocols in the PhenX Toolkit (23).

Cigarette Smoking Status - Adolescent
Cigarette Smoking Status - Adult
History of Switching to Lower Tar and Nicotine Cigarettes
Nicotine Content
NNAL in Urine
Passive Exposures to Tobacco Products
Passive Smoke Exposure
Personal Perception and Knowledge of Smoking-related Cancer Risk
Social Norms about Tobacco - Adult
Social Norms about Tobacco - Youth
Susceptibility to Tobacco Products
Tobacco (non-cigarette) - Product Use
Tobacco - 30-Day Quantity and Frequency - Adolescent
Tobacco - 30-Day Quantity and Frequency - Adult
Tobacco - Age of Initiation of Use - Adolescent
Tobacco - Age of Offset of Cigarette Use - Adolescent
Tobacco - Age of Offset of Cigarette Use - Adult
Tobacco Brand and Variety - Cigarettes
Tobacco Brand and Variety - Cigars
Tobacco Brand and Variety - Smokeless Tobacco
Tobacco Product Adulteration - Vent or Filter Blocking
Tobacco Warning Label Exposure and Recall
Use of Tobacco Products

Table 4

Additional Health Outcomes Protocols in the PhenX Toolkit (24).

Adipocytokines
Anxiety Disorders Screener - Adult
Birth Weight - Measured Weight at Birth
Blood Pressure (Adult/Primary)
Cancer: Personal and Family History
Depression Screener - Adults
Fasting Serum Insulin
Gestational Age - Maternal Interview
History of Stroke - Ischemic Infarction and Hemorrhage
Myocardial Infarction
Peak Expiratory Flow Rate (PEFR)
Periodontal Disease - Prevalence
Personal and Family History of Respiratory Symptoms/Diseases - Adult
Personal and Family History of Respiratory Symptoms/Diseases - Child
Personal History of Allergies, Infectious Diseases, and Immunizations - Adult
Personal Medical History of Allergies, Infectious Diseases, and Immunizations - Child
Personal History of Type I and Type II Diabetes
Pulmonary Embolism
Quality of Life - Adult
Respiratory Rate - Adult Respiratory Rate - Child
Spirometry - Adult Spirometry - Child Weight Loss/Gain