PhenX Guidance Document for Working Group Members

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1 Introduction

Thank you for agreeing to participate in a PhenX Working Group (WG). This document provides guidance for the process of selecting measures and finalizing the content for the PhenX Toolkit (www.phenxtoolkit.org). Background about the PhenX research resource grant (2013-2017) and the cooperative agreement (2007-2013) between the National Human Genome Research Institute (NHGRI) and RTI International can be found at www.phenx.org. This Website also provides multiple fact sheets about the project. We encourage you to read those documents to better understand the background and organization of this project, including information on the PhenX Steering Committee (SC). The PhenX Website also includes a private portal where draft documents will be posted for your review and comment. Instructions for accessing the portal will be provided for the first conference call.

PhenX is a consensus-building project of the research community. The end product is a PhenX Toolkit of high-priority **Phen**otype and e**X**posure measures for genome-wide association studies (GWAS). Because of your expertise, you have been asked to contribute to the discussions that will lead to the identification and inclusion of up to 15 measures in the Toolkit from this WG.

1.1 The PhenX Toolkit – Purpose and Contents

Purpose

The purpose of the Toolkit is to:

- Provide measures for consideration and inclusion in future human genomics, epidemiology, and biomedical research.
- Facilitate wider acceptance and consistent use of existing measures.
- Serve as a reference of recommended standards for a variety of uses.

Contents

The PhenX Toolkit is a Web-based catalog of measures that are in the public domain. Initially released on February 6, 2009, the Toolkit has measures for 21 research domains and a Substance Abuse and Addiction Collection. As new domains and specialty areas are added, the Toolkit will include additional measures and protocols. The goal is to provide researchers with high-priority measures for a wide range of research domains.

For each PhenX measure, the following information is provided:

- brief description of the measure
- protocol(s) for collecting the measure
- rationale for the WG's selection of the protocol(s)
- details about the personnel and equipment needed to collect the measure

PhenX Measures

The PhenX measures are high-priority measures for inclusion in human genomics, epidemiology, and biomedical research by experts in the field, and they have well-established protocols associated with them. These measures have the potential to be the common link across studies, in particular between studies with different primary goals. When PhenX measures are included in a wide range of genomic studies, the ability to combine and compare data across studies will be increased.

The Toolkit is a Web-based resource that makes it easier for researchers to confirm their choice of measures and/or to broaden their studies by adding a few measures outside of the scope of their original study or range of expertise. A researcher might use the PhenX toolkit as a starting point for selecting measures they are planning to include in their studies. Of course, they will probably elect to include additional measures not included in the PhenX Toolkit that provide more information to address a particular research question. A researcher may also want to consider including the PhenX measures most relevant to the focus of their study, thereby being assured of consistency with other researchers using PhenX measures.

- references and other information, including links to resources that include the measures (e.g., CaBIG, dbGaP, and P3G)

The Toolkit can be accessed by a researcher who is planning a new study or looking to add measures to an ongoing study. The Toolkit is a particularly useful resource for researchers seeking to add measures outside of their primary research focus. In the Toolkit, researchers can browse by domains or measures or search using keywords. The PhenX measures that are selected are saved in "My Toolkit" from which the researcher can generate a report with information about the measures.

The Toolkit provides a glossary of terms, frequently asked questions (FAQs), and a basic guidance document. Also provided are links to supplemental information about the other measures considered by the WGs and to additional resources. The Toolkit also has a section asking for feedback from Toolkit users.

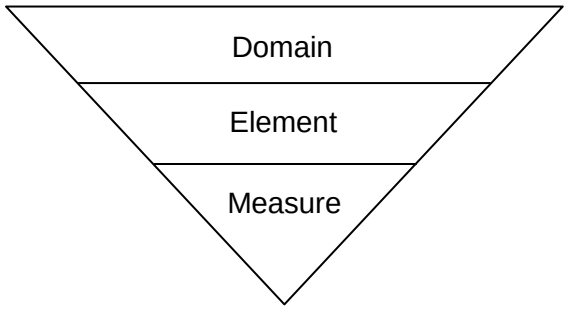
1.2 Domains, Elements, Measures and Specialty Areas and Collections

The PhenX Toolkit will include 21 domains. For this project:

- A **domain** is a field of research with a unifying theme and easily enumerated quantitative and qualitative measures.

Examples of domains that have been identified by the SC include demographics, anthropometrics, organ systems (e.g., Respiratory, Neurology), complex diseases (e.g., Cancer, Cardiovascular), and lifestyle factors, including use of Alcohol, Tobacco, and Other Substances. A complete list of domains will be provided as your WG begins deliberations.

Exhibit 1. Hierarchy of a domain, element, and measure



Within the domains, the SC has identified a preliminary list of domain elements that help the WG conceptualize the full scope of the domain. For this project:

- An **element** categorizes a group of measures and conditions that enclose similar assessments and concepts.

Some examples of domain elements include race and ethnicity in the Demographics domain; height and weight in the Anthropometrics domain; and blood pressure, lipids, and family history of heart attack in the Cardiovascular domain.

The SC recognizes that the preliminary list of domain elements may be refined by each WG. However, the SC expects that, at a minimum, the WG will consider measures that

cover the preliminary list of domain elements. If the WG chooses to include additional domain elements, those elements can be recommendations from the WG to the SC.

You have been engaged as a subject matter expert to help work through a process of determining the high-priority, established measures for a particular domain. For this project:

- A **measure** refers broadly to a standardized way of capturing data on a certain characteristic of or relating to a study subject. Measures may include exposures, clinical assessments, and quantitative and qualitative traits.

A **specialty area** is a relatively narrow field of research with a unifying theme and easily enumerated quantitative and qualitative measures. Specialty areas are intended to add depth to the Toolkit. A **specialty collection** is a collection of measures relevant to a specialty area. Measures included in specialty collections are selected by WGs and are primarily intended for use by investigators who conduct research in that field.

The SC recommends several principles to guide your deliberations on measures. These include:

- When choosing measures, the WG should limit its review to ***existing well-established measures that are in the public domain***. The purpose of PhenX is not to develop new measures, but to recommend well-established measures.
- Measures should be assessed in terms of the requirements on both study participants and investigators. Each WG is permitted only ***four high burden*** measures for Community Outreach, and only ***two high burden*** measures for the Toolkit. Burden is assessed by time, equipment, training, and biospecimen collection.
- While ensuring compatibility with prior measurements, the WG should take the dynamic movement of measures in their field into account and consider ***measures that will be accepted for the foreseeable future***; that is, not to recommend measures that have been supplanted by newer, more well-established methods.
- This being a U.S. effort means that the primary focus is on measures found in domestic research, but with recognition that ***international standards should be considered***.
- Measures may have more than one protocol, for instance, age-specific or gender-specific protocols. That is, a measure indicates a single concept of "what" is being evaluated, but the ***"how" of that measurement may have multiple methods that are comparable***.
- ***When multiple protocols are included for the same measure, they should be comparable***. For example, in demographics, for several measures both computer-assisted personal interview and self-assessed paper and pen protocols are included; these are different protocols for collecting data for these measures, but the results are comparable.
- ***Comparability of equipment models / types should be considered.***
- Measures can be ***independently informative***. For instance, height and weight may be combined in a derived index, such as body mass index. However, height and weight are also each independently informative. Thus, they are two measures. (Derived indices are not measures.)

- Measurement ***protocols may contain other data***, called “essential data,” that are required to interpret the measure. For instance, time of last food intake is essential data for interpreting lipid levels.
- Domain elements that have ***multi-part questionnaires or repeated measures can be considered as a single measurement***.
- A measure can be removed from the Toolkit only if it is recognized that the measure does not meet the selection criteria.

Because the NHGRI would like the PhenX Toolkit to provide high-priority measures for the domain, it is critical that the 15 measures encompass the scope of the domain.

1.3 Who Is in the WG?

Each WG comprises six to eight researchers selected to broadly represent the scope of the domain that the WG will address. The composition of the WG has been balanced to include the perspectives of the research community, with representatives from the nongovernmental sector including academic institutions and private sector organizations, as well as the federal government scientists. Other staff of the National Institutes of Health (NIH) who are serving as liaisons to the PhenX SC may also attend the WG meetings to provide additional expertise and perspective on their related projects. While the WG members may seek input from other researchers, only the WG members will have votes on the decisions of the WG.

One person has been chosen as the WG chairperson (with a co-chair if applicable) and each WG will have a PhenX SC member serving as ex officio liaison to the WG. The SC Liaison provides advice and guidance about the process, the reports, and the end products that are expected in the course of the eight months of WG discussions and consensus building. The SC Liaison is empowered to represent the interests of the SC within the WG and will seek guidance from the SC when appropriate. In the case of Specialty Areas, each WG will have a Research Panel (RP) Liaison who will serve the same role as the SC Liaison.

2 Operations of the WG

2.1 How Will the WG Work?

While the WG will determine the scientific direction of the WG activities, the WG will be supported by staff of RTI International. The RTI staff will work closely with the WG Chair to develop the agendas and provide logistics for the meetings. RTI staff performs the background literature searches to obtain information required by the WG and communicate with the authors and developers of the measurement protocols as needed. RTI staff organizes and prepares meeting materials and develops minutes and action items from the meetings to ensure that the meetings run as productively as possible. In addition, RTI staff assists the SC/RP Liaison and WG chair to facilitate communications with the SC.

RTI staff takes the content developed by the WG and uses it to collect input from the research community on the selected measures. Finally, the RTI staff supports the WG in finalizing the data sheets (See Appendix 1) for the selected measures and measurement protocols for inclusion in the Toolkit (www.phenxtoolkit.org).

The RTI staff consists of WG Managers who can engage other staff to assist with specific tasks, such as logistics specialists, health librarians, substantive experts, survey

specialists, and administrative assistants. The WG Managers report to an RTI WG Supervisor, thus ensuring that the WG processes across PhenX are run in a similar fashion.

The WG makes decisions by consensus. The SC can assist with difficult decisions that are cannot be resolved within the WG. The WG Chair and SC/RP Liaison periodically report to the SC and discuss communications from the SC with the WG.

The PhenX portal is used for most of the communication within the WG. This private workspace is accessible only to the WG members, the SC/RP Liaison, NHGRI, and the RTI team. The RTI WG Manager provides access codes and instructions for use of this space. Prior to each meeting the RTI WG Manager places documents onto the portal, including meeting agendas, data sheets with the measures and measurement protocols, supporting documents, etc., for the WG members' review. Discussion forums on the portal facilitate discussion and communication between WG members and with the RTI staff. Each WG's section of the portal is open only to members of that WG.

2.2 What Is the Time Frame for the Working Group?

The time frame for selection of measures for each domain is approximately eight months. The time frame may be somewhat shorter or longer to accommodate logistical issues, but not, in principle, to accommodate specific domain issues. Table 1 lays out the meetings and tasks in this time frame. Timelines for Specialty Area WGs vary and will be communicated during initial WG meetings.

Table 1. Time Frame for Domain Working Group Activities

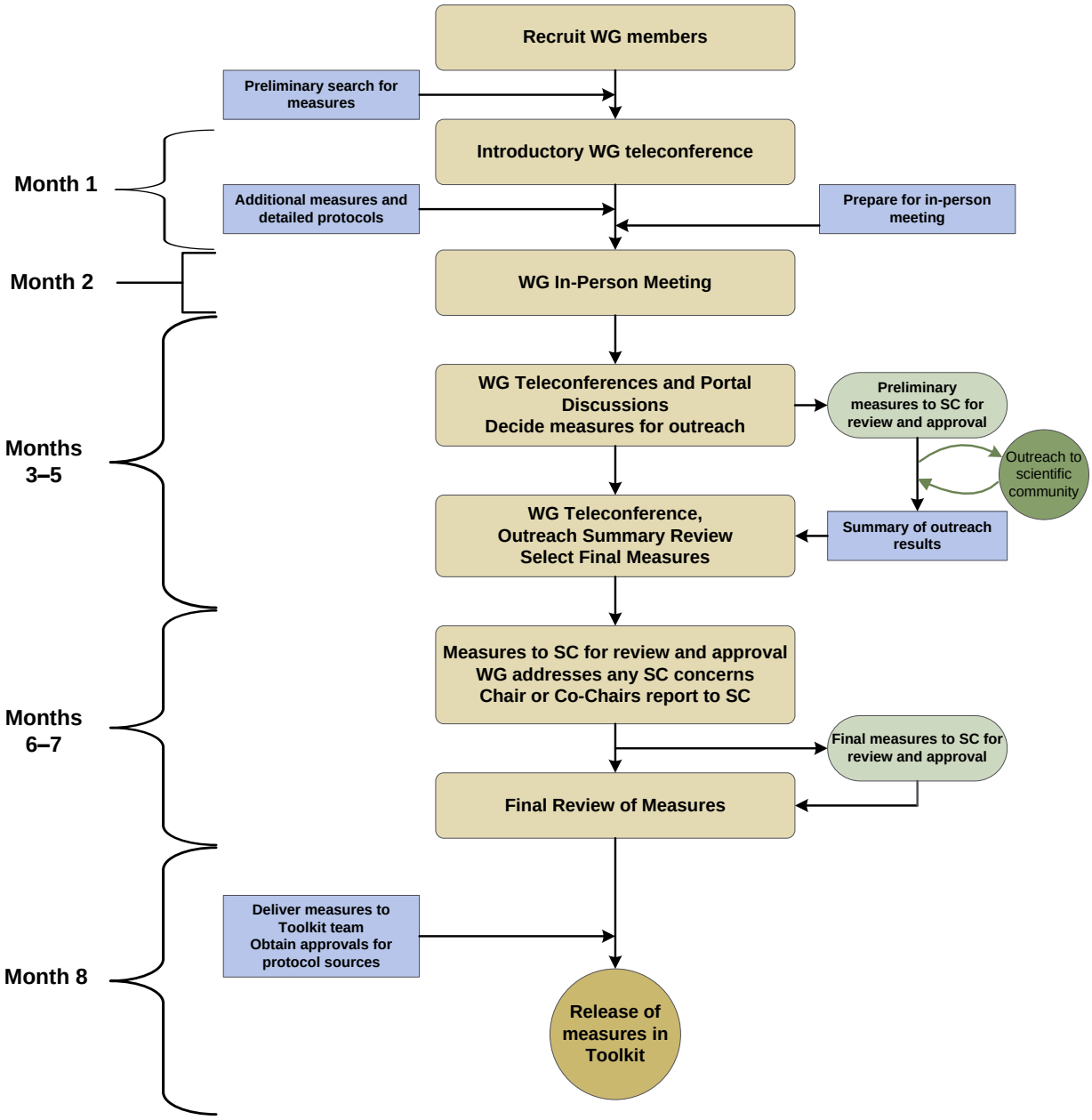
#	Domain-specific Working Group Activities	Month							
		1	2	3	4	5	6	7	8
1	WG has a conference call for a PhenX orientation and for planning the domain scope and identifying source studies/surveys for measure identification. Additional WG discussions leading up to the in-person meeting may occur by phone or on the portal.	●							
2	WG in-person meeting is held in the Washington, D.C. metropolitan area to review measures and protocols.		●						
3	WG discusses potential measures and measurement protocols via conference calls. WG members identify scientists for inclusion in the community outreach process.			●	●				
4	WG prioritizes and recommends up to 15 measures and measurement protocols. The WG Chair reports to the SC via conference call, seeking approval to go to community outreach.				●				
5	RTI makes the measures and measurement protocols available by e-mail to acquire comments from the scientific community. WG members encourage review and comments by their professional colleagues.				●	●			

#	Domain-specific Working Group Activities	Month							
		1	2	3	4	5	6	7	8
6	WG incorporates comments from the scientific community and makes final recommendations of priority measures and their measurement protocols to the SC.						•	•	
7	WG works with RTI to complete information about the measures and to make the domain available through the PhenX Toolkit on the Internet.							•	•

2.3 What Does the WG Need to Do?

The following sections of this guide are laid out chronologically based on the timetable above. Exhibit 2 provides a graphic representation of the WG activities overall.

Exhibit 2. Working Group Process



2.3.1 First WG Call(s)

Shortly after a WG is composed, an introductory conference call is held. The purpose of this initial call is to introduce the members of the WG to one another and to orient them to the PhenX project. In this 90-minute call, presentations by NHGRI Project Scientist Dr. Erin Ramos and RTI Principal Investigator Dr. Carol Hamilton address the background of the project and a review of the steps envisioned for the WG to produce 15 high-priority measures for the Toolkit.

The WG is provided with a list of the domain elements that have been identified by the SC, sometimes with the input of the WG Chair. The goal of the first WG call is to review and refine the scope of the domain that serves as the framework for identifying measures and measurement protocols. This first discussion of the scope is based on the data elements that the SC has initially set forth for the domain.

The WG will be asked to recommend new data elements and to consider whether any data elements should be excluded. Because of the potential interactions with other domains and since the WG is limited to 15 measures in the PhenX Toolkit, the SC/RP Liaison guides the WG to expand and/or narrow the scope. The WG is encouraged to choose data elements that cover the scope of their domain, being mindful of the domains that precede them as well as those that may be developed. If the WG considers particular elements important to measures in their domain, they are encouraged to address the element and not expect that it will be covered by another WG.

Another part of the call is a presentation about this Working Group Guidance document. A list of preliminary measures and the minutes of the call are posted on the WG area of the PhenX portal. WG members are asked to suggest additional measures relevant to the domain scope. This information is used to build a more complete list of measures to be considered at the in-person meeting.

At the discretion of the WG Chair, additional calls may be convened before the in-person meeting. The purpose of such calls might be to

- introduce new WG members to the project,
- continue the discussion of the scope, or
- refine the search strategy when the resources are particularly vast.

WG Chairs will tap the expertise of their WG members, asking them to take responsibility and work with the RTI team to identify the most relevant measures and well-established protocols to cover the scope of the domains. The WG members will then report their findings back to the entire WG at the in-person meeting and in subsequent telephone calls. All of the work between the first call and the in-person meeting is designed to support a productive discussion at the only face-to-face meeting of the WG.

2.3.2 WG In-Person Meeting

Approximately one month after the first WG call, a face-to-face meeting is held in the Washington, D.C. metropolitan area. The purpose of the one-day meeting is to review the results of the search strategy vis-à-vis the scope of the domain and work to develop a broad list of possible measures. Prior to the meeting, the WG Manager prepares a list of measures related to the elements identified by the WG. In addition, the WG Manager can assist the WG members in preparing their presentations for the in-person meeting should the WG decide to use this presentation model. More specific instructions on this presentation method are provided in Appendix 2.

While the WG may come to the meeting with anywhere from 20–40 measures, the ultimate goal of the in-person meeting is to produce a list of up to 15 measures to take to community outreach. With the assistance of the RTI staff, the WG reviews the extent to which the measures have been used in either GWAS or other major epidemiologic studies, and then makes their recommendations accordingly. The review is facilitated by criteria that have been set forth by the SC. (See Section 3.1.)

While the face-to-face meeting is primarily focused on arriving at a first set of measures with well-established protocols, additional agenda items are likely to include a discussion of the plans for community outreach and the identification of individuals and groups who should be asked to provide their input regarding the proposed measures. There is also an introductory presentation about the PhenX Toolkit so that WG members understand the end product of their deliberations.

Draft documents and minutes of the meeting are posted on the WG area of the PhenX portal to capture the decisions about the measures and next steps.

To ensure that the PhenX Toolkit reflects the most current measures and is coordinated with other NIH measurement efforts (e.g., dbGaP, and CaBIG), the RTI WG Manager will provide the WG with the most current information about measures relevant to their deliberations. One role for the SC/RP Liaison will be to inquire about sources for protocols. In addition, the SC/RP Liaison and RTI staff should be proactive in engaging people and making sure that all WG members are heard.

2.3.3 WG Conference Calls and Reviews Prior to Community Outreach

To continue the discussion that began at the in-person meeting and to refine the list of measures posted in community outreach, the WG comments on draft documents that are posted on the portal, and meets periodically by conference calls. Another telephone call is scheduled shortly after the in-person meeting, and the WG Chair decides how often they need to meet to complete their work. During this time, the WG refines the selected measures based on feedback from the SC and additional information provided by the RTI WG Manager.

Each call is structured to prioritize the list of measures and to select protocols. At the end of the first two months of the WG process, the WG generates a list of up to 15 possible measures that are recommended for inclusion in outreach to the research community. The WG also has input into questions that may be useful to include in the outreach about the measures and measurement protocols presented. The community outreach is used to vet the measures with the broader scientific community as a means to develop consensus.

The end product of these WG calls is to present to the SC with a set of approximately 15 measures for inclusion in community outreach. Through a conference call, the WG Chair and SC/RP Liaison will provide a first pass of the 15 measures to the SC. The SC will provide feedback to the WG on whether the measures cover the scope of the domain, are of the highest priority, and pose low burden to the study participants and investigators. The SC relies on the expertise of the WG members to select well-established sources for the measurement protocols.

Information about the measures is presented in data sheets, an example of which is included in Appendix 1. The data sheet is the mechanism by which the measure information is included in community outreach, and ultimately in the Toolkit. Ensuring the accuracy of the information in the data sheets requires extensive review by RTI staff and the WG. To facilitate this review, each WG member is assigned to be the primary reviewer for a few measures and a secondary reviewer for a few others. The RTI WG Manager coordinates the sequential review by the primary and secondary reviewers. The WG Chair and SC/RP Liaison will resolve any outstanding issues. When 15 measures go to outreach, only portions of the data sheet are completed. The WG will complete the remainder when the final 15 measures are selected for the Toolkit.

We advise WGs to have no more than two high burden measures in the set of measures proposed to the SC for community outreach. By adhering to this policy, the WG will be in a good position to ensure that no more than two high burden measures are selected by the WG for inclusion in the Toolkit.

The WG will also get an opportunity to pose questions to the research community. For example, should the protocol be used for a different age group? This can help to resolve issues the WG has struggled with and been unable to resolve on their own.

The WG Chair and the SC/RP Liaison participate in an SC conference call to finalize the content for community outreach. If there are tie votes or other unfinished business, the SC/RP Liaison can bring the issues to the SC in this call.

RTI will acquire any permissions (e.g., copyright or trademarks) needed for inclusion in the Toolkit. However, we strongly discourage including measures that require additional permissions as this will reduce accessibility to the research community. The RTI WG Manager conducts telephone calls with the lead authors as needed about the measures, the measurement protocols, and the algorithms required to interpret the results.

RTI asks the WG to identify throughout its discussions individuals and professional organizations that RTI should contact to encourage participation during the community outreach period. This list will be available on the PhenX portal. Outreach by WG members to their colleagues is encouraged. RTI can provide e-mail text that can be easily forwarded to your colleagues to promote the community outreach.

2.3.4 Outreach to the Larger Scientific Community

Vetting the proposed PhenX measures with the research community helps the WG refine the list of measures for the Toolkit and aids in building consensus. To support these goals, RTI conducts an e-mail-based community outreach effort for each domain to query potential users about the proposed measures. Community outreach is e-mailed to potential and current Toolkit users and any other individuals or groups whose expertise and insights might be of value to the WG. The use of community outreach facilitates consensus and acceptance of the measures throughout the research community

The purpose of the domain-specific outreach effort is to obtain opinions regarding the priority and appropriateness of the measures and utility of the measurement protocols. The outreach includes the definition of the domain, a list of up to 15 measures with their definitions, and measurement protocols.

The outreach e-mail asks respondents about the acceptability, feasibility, and usability of each of the measures. Respondents are asked to indicate whether they would definitely include or definitely exclude the measure and protocol in their study. In addition, the e-mail invites respondents to suggest new measures and alternative measurement protocols as appropriate.

After a two-week comment period, the WG Manager compiles the results of the outreach. This feedback helps guide the WG to finalize the 15 measures for inclusion in the PhenX Toolkit.

2.3.5 WG Conference Calls after Community Outreach

After the RTI WG Manager summarizes the community outreach results, the WG may meet at least twice by conference call. In preparation for the first call, the RTI WG

Manager posts a summary of the community outreach results on the PhenX WG Portal and works with the WG Chair to frame an agenda that addresses the issues raised by the research community. The summary is also posted for SC review.

During the calls, the WG deliberates on incorporating the research community's perspectives based on the community outreach results. This may involve the refinement, substitution, addition, or deletion of measures. To the extent that issues require the WG to review the prioritization of measures, the WG Chair may employ a voting process. Results of the community outreach and recent publications may inform the final choice of up to 15 measures by the WG. The measures that are not selected for the Toolkit will be posted for the research community in another section of the PhenX portal as Supplemental Information.

2.3.6 WG Review of the Materials for the Toolkit

The final measures are presented in the data sheets to facilitate the transition of this information into the Toolkit. WG members are asked to conduct a final review of the content of the data sheets for which they were originally assigned as the primary or secondary reviewer prior to outreach. The RTI WG Manager coordinates the sequential review of the comments by the primary and secondary reviewers. The WG Chair will resolve any outstanding issues.

The SC/RP Liaison and the WG Chair will sign off on the data sheets before they go to the SC for final approval for Toolkit inclusion. If the SC has questions about the recommended measures, the WG will be asked to reconsider the measures in light of those comments. The RTI staff works with the WG and the SC/RP Liaison to finalize the information that is included in the Toolkit.

A final call with the WG is conducted to obtain sign-off that the information about the measures to be included in the Toolkit is complete and accurate to the satisfaction of the WG. Subsequent maintenance of the Toolkit measures will be the responsibility of the SC and the RTI team. Additional phone calls may be needed with the WG Chair or individual WG members if unforeseen issues arise concerning the protocols for the final measures in the Toolkit.

3 Selection of Measures

3.1 Criteria for Evaluating Measures

A number of criteria have been suggested by the SC to guide the selection of the measures to be included in the PhenX Toolkit. The WG uses these criteria, to the extent possible throughout the process, to prioritize measures. Similarly, the SC will use these criteria in its reviews of the WG reports.

The measures should be:

- Clearly defined
- Well established
- Broadly applicable and generally accepted
- Low burden to participants and investigators
- Well-established and demonstrated utility
- Reproducible
- Specific

- Reliable
- Standard measurement protocols exist

Additional criteria for selecting the measures include:

- Crosscutting relevance for population groups as well as diseases and conditions
- Prior use in GWAS
- Use in major reference study (e.g., NHANES)
- Open-source software and nonproprietary instruments preferred
- Brevity
- Expectation of acceptance by the research community

The final set of measures should cover the scope of the domain.

The protocol reflects the mode of administration used in the reference source. The protocols range from self-administered questionnaires, interviews, and examinations, to biospecimen protocols. If different, but comparable, modes of administration exist, the WG is encouraged to provide additional protocols. If data exist on the comparability in different modes of administration, the WG is encouraged to provide that information for the Toolkit. Similarly, the WG is asked to note the age of the study participants.

The WGs are also encouraged to identify quality-control issues in the measurement protocols and specify how the investigator can address these issues, e.g., specific training and instructions for personnel administering the protocol. The WG is encouraged to address safeguards for ensuring the integrity of the data collected.

3.2 Difficulty Selecting Measures

In the event that the WG has difficulty identifying a reasonable number of measures for inclusion in community outreach, one suggestion for helping in the selection of the 15 is to give each member of the WG 5 votes. The votes could be collected via the WG work area on the PhenX portal. One advantage of this approach is that the measures may cluster, helping get away from the exact 15 number of measures. The WG may also ask each WG member to prioritize the measures. RTI and the WG Chair will work together to identify the best approach for reducing the number of measures to be included.

3.3 What Are Some Possible Challenges to Prioritizing 15 Measures?

Existing measures: The WG is encouraged to take advantage of other groups/Websites that may list more detailed measures relevant to a specific phenotype.

Multiple protocols: The measure may have multiple existing measurement protocols. Two situations are possible: There may be different protocols for different populations (such as for different ages), or there may be alternative protocols. If it is appropriate to have different measurement protocols, they will be included in the toolkit. If multiple protocols are relevant for different populations (e.g., measurement of height depending on age of the participant), the definitions for these populations should be provided. If multiple commonly utilized protocols may be used in the same populations (such as measurement of height versus self-reported height), it may be necessary to pick a single protocol. If a single protocol cannot be selected, alternative measurement protocols for the measure can be specified, but the WG is encouraged to provide a preference and information on how the investigator can harmonize the results to findings from other measurement protocols.

Assessment batteries: Some measures require multiple questions as part of the measurement protocols. The objective of PhenX is to recommend measures that can be widely integrated into research protocols. Consequently, measures that require extensive instruments are discouraged as these measures may place substantial burden on the participant and/or the investigator.

Broad inclusion in studies: The WG may recommend that multiple measures be included in most studies. Other measures, however, may be recommended for only some types of studies. In addition, some measures may be broadly applicable to all population groups, while others may be specific to particular age groups, races, or sexes. The Toolkit will specify the mode of administration of the measures.

Other measurement recommendations: The WG should review the work of other PhenX WGs (both content already in the Toolkit and content being considered by active WGs) in an effort to reduce duplication in the Toolkit. For example, both the Physical Activity and Physical Fitness WG and the Cancer WG were interested in a measure to assess cumulative lifetime physical activity. By sharing the measures that both WGs were considering, they avoided including the same measure in the Toolkit. The SC will continually assess whether any particular subject is being overemphasized in the context of measures being added to the PhenX Toolkit. As reflected in the statement of purpose, it is important that the Toolkit meet the needs of the research community.

Appendix 1: Example Data Sheets

The data sheet is used at two points in the WG process. If the WG has more than 18 measures for community outreach, only the following fields in the data sheet are completed: Domain, Name of Measure, Definition, Description of Measure Protocol, Participant, and Source. The entire data sheet will be completed when the WG is using the fast track approach for the outreach effort and when the measures go into the Toolkit. Note that the essential data field is defined as:

> *Essential data are only those items that are critical to the collection of the measure or are necessary for the interpretation of results. Essential data are integral to the measure. Without such information, the data collected would be incomplete and/or misleading.*

Below are examples of completed data sheets for the "Caffeine Intake" and "Color Vision" measures that are in the Toolkit.

CAFFEINE INTAKE

About the Measure	
Domain (included in Survey & Supplemental Information)	Nutrition and Dietary Supplements
Measure (included in Survey & Supplemental Information)	Caffeine Intake
Definition (included in Survey & Supplemental Information)	A measure to estimate an individual's caffeine intake.
Purpose	There are functional and health effects associated with caffeine consumption. Some of these benefits include promoting enhanced energy expenditure for weight loss, slowing early memory loss, keeping alert, and preventing fatigue. Epidemiological and experimental studies have shown positive effects associated with caffeine consumption, especially from regular coffee-drinking, on various aspects of health, such as psychoactive responses (alertness, mood change), neurological (infant hyperactivity, Alzheimer's and Parkinson's diseases) and metabolic disorders (diabetes, gallstones, liver cirrhosis), and gonad and liver function

About the Protocol

Description of Protocol
(included in Survey & Supplemental Information)

These self-administered questions can be used to inquire about the frequency of an individual's consumption of beverages containing caffeine. Various timeframes ranging from once per Month to 6 or more times per day are arrayed on the response card for the respondent to use in assessing caffeine intake. The protocol also includes scoring procedures to convert an individual's responses to an estimate of caffeine intake in milligrams.

Selection Rationale

The Working Group felt it was important to include a protocol to measure caffeine intake and specific sources due to the increased consumption of caffeinated beverages.

Specific Instructions

None

Protocol text
(included in Survey & Supplemental Information)

Supplemental Beverage Questions

	HOW OFTEN DID YOU DRINK THE BEVERAGE? (MARK ONE)									AMOUNT			
	Never or less than once per month	1 – 3 per month	1 per week	2 - 4 per week	5-6 per week	1 per day	2 - 3 per day	4 - 5 per day	6+ per day	Medium serving Size	Your Serving Size		
											S	M	L
Decaffeinated coffee (Instant & brewed)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Instant coffee, not decaffeinated (Including flavored types)	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O
Brewed coffee, not decaffeinated	O	O	O	O	O	O	O	O	O	1 Cup (8 oz)	O	O	O

	Decaffeinated espresso and espresso drinks (Latte, Mocha, Americano)	○	○	○	○	○	○	○	○	○	1 Shot of espresso	○	○	○
	Espresso and espresso drinks, not decaffeinated (Latte, Mocha, Americano)	○	○	○	○	○	○	○	○	○	1 Shot of espresso	○	○	○
	Herbal or decaffeinated tea (Instant, bottled, and brewed)	○	○	○	○	○	○	○	○	○	1 Cup (8 oz)	○	○	○
	Green tea (Not decaffeinated-instant, bottled, and brewed)	○	○	○	○	○	○	○	○	○	1 Cup (8 oz)	○	○	○
	Black tea such as Lipton®, or Earl Grey (Not decaffeinated-instant, bottled, and brewed)	○	○	○	○	○	○	○	○	○	1 Cup (8 oz)	○	○	○

Jolt®, Surge®, Mountain Dew®, Red Bull® and other highly caffeinated sodas	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Regular colas and root beer (With caffeine, not diet)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Diet colas and diet root beer (With caffeine)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Regular colas and root beer (Caffeine free, not diet)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O
Diet colas and diet root beer (Caffeine free)	O	O	O	O	O	O	O	O	O	1 Can (12 oz)	O	O	O

Scoring Procedure:
The first phase of processing is to calculate the number of annual servings for each Beverage Questionnaire item. This is done by multiplying the reported frequency by the reported portion size. For example, a participant reporting a frequency of 5-6 per week and a portion size of Large for the beverage item “Espresso and espresso drinks, not decaffeinated” would be assigned 414 annual servings of “Espresso and espresso drinks, not decaffeinated”. That represents – that’s 276 annual servings for 5-6 per week (see Table 1. for beverage frequencies) multiplied by 1.5 for Large (see Table 2. for portion size below).

Table 1. Formats for beverage frequencies

Code	Label	Annual Servings
1	1 per week	52
2	2 to 4 per week	144
3	5 to 6 per week	276
4	1 per day	365
5	2 to 3 per day	852
6	4 to 5 per day	1560
7	6+ per day	2190

Table 2. Formats for beverage portion size

Code	Label	Serving Ratio
1	S	0.5
2	M	1.0
3	L	1.5

Caffeine Database

The second phase of processing involves calculating annual caffeine consumed. For each beverage item the annual servings are multiplied by the single serving caffeine data for that food item, which is found in the caffeine database. Each record in the caffeine database represents the caffeine content of a single serving of a single food item. For example, when calculating annual caffeine consumed for "Espresso and espresso drinks, not decaffeinated", the caffeine value is multiplied by the annual servings for "Espresso and espresso drinks, not decaffeinated" (arrived at in the first phase), and divided by 365 resulting in the average daily intake of caffeine for "Espresso and espresso drinks, not decaffeinated".

Beverage Item	Amount	Caffeine (mg)
Decaffeinated coffee (instant & brewed)	1 cup	2.51
Instant coffee, not decaffeinated (including flavored types)	1 cup	75.41
Brewed coffee, not decaffeinated	1 cup	137.34
Decaffeinated espresso and espresso drinks	1.5 oz or 1 shot of espresso	0.73
Espresso and espresso drinks (Latte, Mocha, Americano)	1.5 oz. or 1 shot of espresso	51.50
Herbal or decaffeinated tea (Instant, bottled, and brewed)	1 cup	0
Green tea Not decaffeinated-instant, bottled, and brewed)	1 cup	47.36
Black tea such as Lipton®, or Early Grey(Not decaffeinated-instant, bottled , and brewed)	1 cup	37.80
Jolt®, Surge® Mountain Dew®, Red Bull® and other highly caffeinated sodas	1 can, 12 fl.Oz.	71.68
Regular colas and root beer (with caffeine, not diet)	1 can, 12 fl.Oz.	37.16
Diet colas and diet root beer (with caffeine)	1 can, 12 fl.Oz.	49.73
Regular colas and root beer (Caffeine free, not diet)	1 can, 12 fl.Oz.	0
Diet colas and diet root beer	1 can, 12 fl.OZ	0

	Lipton® is a registered trademark, Unilever United States, Inc.; Jolt® is a registered trademark, Wet Planet Beverages; Surge® is a registered trademark, The Coca-Cola Company; Mountain Dew® is a registered trademark, PepsiCo, Inc.; Red Bull® is a registered trademark, Red Bull GmbH.
Participant (included in Survey & Supplemental Information)	An Individual aged 18 or older.
Source (included in Survey & Supplemental Information)	Fred Hutchinson Cancer Research Center, Caffeine Questionnaire, 2004.
Language of Source	English
Personnel and Training Required (included in Supplemental Information)	None
Equipment Needs (included in Supplemental Information)	None
Protocol Type	Self-administered questions.

Burden:

Requirements Category	Required: (Yes/No)
Major equipment	No
Specialized training	No
Specialized requirements for biospecimen collection	No
Average time of greater than 15 minutes in an unaffected individual	No

Definitions:

Equipment: this measure requires a specialized measurement device that may not be readily available in every setting where genome wide association studies are being conducted. Examples of specialized equipment are DEXA, Echocardiography, and Spirometry.

Training: this measure requires staff training in the protocol methodology and/or in the conduct of the data analysis.

Cost Fee to obtain or use measure: there is a cost or licensing fee that the investigator must pay to obtain and use this measurement protocol. The cost category would only indicate that the protocol / instrument is not freely available to the general public. .

Cost associated with data analysis: this cost may include manuals, data storage; and proprietary algorithms.

Biospecimen: this protocol requires that blood, urine, etc. be collected from the study participants.

Common Data Element (CDE):

Person Caffeine Intake Value in Milligram (2944784)

National Cancer Institute. CDE Browser, Version 3.2.05 Build 1.

General References:

(included in Supplemental Information)

Song, J.Y., Kristal, A.R., Wicklund, K.G.,Cushing-Haugen, K.L., Rossing, M. (2008) Coffee, Tea, Colas, and Risk of Epithelial Ovarian Cancer. Cancer Epidemiology Biomarkers & Prevention. 2008; 17(3).

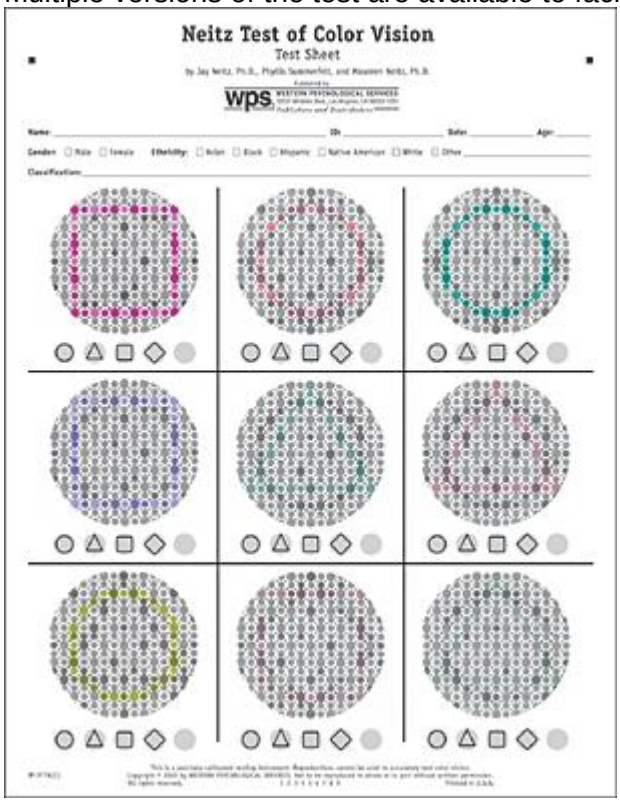
Dórea, J, da Costa, T. Is coffee a functional food? British Journal of Nutrition. 2005 Jun; 93(6):773-82.

	Additional Information About the Measure
Essential Data	Age, gender
Related PhenX Measures	Total dietary intake
Derived Variables	None
Keywords / Related Concepts	Nutrition and Dietary Supplements, Caffeine, Caffeinated beverages, Dietary Supplements, Coffee.

COLOR VISION

About the Measure	
Domain: (included in Survey & Supplemental Information)	Ocular
Measure: (included in Survey & Supplemental Information)	Color Vision
Definition: (included in Survey & Supplemental Information)	A screening test to determine color blindness.
Purpose:	Color blindness is a common inherited disorder. Eight to 10 percent of all males are color blind, as well as approximately one-half of 1 percent of all females (Neitz, Summerfelt, and Neitz, 2001).

About the Protocol	
Description of Protocol: (included in Survey & Supplemental Information)	Red-green and blue-yellow color blindness are tested using the Neitz Test of Color Vision, a disposable 1-page test which consists of 1 demonstration and 8 test panels. In each plate, colored dots of three different sizes and two different saturations form the outline of a geometrical shape. The shapes, presented as multiple choices, are a circle, a square, a triangle, a diamond, and nothing. The examinee marks the option that represents what he or she sees in the grey dot pattern.
Selection Rationale:	The ***Neitz*** detects the presence and severity of the two main classes of color blindness: blue-yellow (tritan) and red-green. It further distinguishes the two subtypes of red-green color blindness (deutan and protan). The Neitz test can be administered in group environments in less than 5 minutes, is suitable for persons of almost any age, including very young children, and requires no specialized training to administer or score.
Specific Instructions:	Because the test is a precisely calibrated instrument, reproductions of the forms will not yield satisfactory results. Color copiers cannot adequately reproduce the colors that are necessary for the test to yield a valid classification. Furthermore, the test is copyrighted and it is therefore impermissible to photocopy test materials for reuse. Test sheets, scoring key and users manual can be purchased from Western Psychological Services, 12031 Wilshire Blvd. Los Angeles, CA 90025-1251, Telephone: (800) 648-8857 - FAX: (310) 478-7838. *Prices of each item are listed below (prices may be subject to change): Item No. Description Price W-377A Test sheets (package of 50) $54.50 W-377B Manual $38.50 W-377C Scoring Key $14.00 *prices obtained October 15, 2009.
Protocol text: (included in Survey & Supplemental	Lighting: the Neitz Test. must be given in a well-lit area, and the light must not come from an incandescent source (regular light bulb). The test works properly under light

Information)	coming from a strong fluorescent source or a combination of natural light (sunlight) and fluorescent light. As shown in Figure 1, the Neitz Test presents a grid including one demonstration item and eight test items, which consist of a gray-scale and color pattern. The Neitz Test detects the two main classes of color blindness, *red-green* and *blue-yellow.* The Neitz Test detects both subtypes of red-green color vision (deutan and protan), and it can give an indication of the severity of red-green color blindness. Each of the nine gray-scale and color patterns has a geometric shape embedded in it. The test panel contains a vanishing-type, desaturated geometric shape against a neutral background. A set of darker dots on each plate suggests an alternate shape that serves as a distractor. Below each pattern are five response options: a circle, a triangle, a square, a diamond, and nothing. The examinee simply marks the option that represents what he or she sees in the grey dot pattern. Alternatively, small children are instructed to trace the shape they see in each panel with a pencil or crayon. The manual provides scripted instructions for an investigator to use in administering the protocol. The demonstration item is visible to even severely color-blind individuals and is designed to make the instructions clear. Anyone who makes one error or more on a test should be re-tested with different version of the form. The scoring key is used to obtain the test results and to identify the possible type and severity of the participant's color vision deficiency. Multiple versions of the test are available to facilitate group administration.  **Figure 1. Example of Neitz Test Sheet** **Sample Test Sheet for the *Neitz Test of Color Vision* copyright © 2001 by Western Psychological Services.**

<table>
<tr><td></td><td>Reprinted by RTI International for the sole purpose of illustration, by permission of WPS, 12031 Wilshire Boulevard, Los Angeles, California, 90025, U.S.A., www.wpspublish.com. Not to be reprinted in whole or in part for any additional purpose. All rights reserved.</td></tr>
<tr><td>Participant:

(included in Survey & Supplemental Information)</td><td>Individuals aged 4 years and older</td></tr>
<tr><td>Source:

(included in Survey & Supplemental Information)</td><td>Neitz J., Summerfelt P., Neitz M. (2001) The Neitz Test of Color Vision Manual. Los Angeles, CA: Western Psychological Services.

Neitz, M., Neitz, J. (2001). A new mass screening test for color-vision deficiencies in children. Color Research and Application, 26(S1), S239-S249.</td></tr>
<tr><td>Language of Source:</td><td>English</td></tr>
<tr><td>Personnel and Training Required:

(included in Supplemental Information)</td><td>None</td></tr>
<tr><td>Equipment Needs:

(included in Supplemental Information)</td><td>The test is copyrighted and it is therefore impermissible to photocopy test materials for reuse. The testing materials include:
The Neitz Test of Color Test Sheets (WPS Product No. W-377A(1), (2), and (3))
The Scoring Key (WPS Product No. W-377C)
The Manual (WPS Product No. W-377B)

Available for purchase from:
Western Psychological Services
12031 Wilshire Blvd. Los Angeles, CA 90025-1251
Telephone: (800) 648-8857 - FAX: (310) 478-7838</td></tr>
<tr><td>Protocol Type:</td><td>Self-administered screener</td></tr>
<tr><td>Requirements:</td><td>
<table>
<tr><th>Requirements Category</th><th>Required</th></tr>
<tr><td>Average time of greater than 15 minutes in an unaffected individual</td><td>No</td></tr>
<tr><td>Major equipment</td><td>No</td></tr>
<tr><td>Specialized requirements for biospecimen collection</td><td>No</td></tr>
<tr><td>Specialized training</td><td>No</td></tr>
</table>
</td></tr>
<tr><td>Common Data Element (CDE):</td><td>Person Color Vision Text (3008667)</td></tr>
</table>

General References: (included in Supplemental Information)	Barnhardt C, Block SS, Deemer B, Calder AJ, DeLand P. (2006). Color vision screening for individuals with intellectual disabilities: a comparison between the Neitz Test of Color Vision and Color Vision Testing Made Easy. *Optometry,* 77(5):211-6.
Protocol ID:	110200

	Additional Information About the Measure
Essential Data:	None
Related PhenX Measures:	Age, Gender
Derived Variables:	None
Keywords / Related Concepts:	Ocular, Color Vision, Color blindness, Neitz
Collections / Used By:	110000
Measure ID:	110200

Appendix 2: Guidance for Protocols and Instrument/Questionnaire Presentation to the WG Members during the In-person Meeting

Within each domain, there are many different protocols and instruments / questionnaires that can be used to measure a research subjects' characteristics and environmental exposures in genome-wide association studies (GWAS) and other large-scale genomic efforts. Because you are an expert on the Working Group (WG), we are asking you to take the lead for a subset of the elements in this domain. You will be helping to sort through the many choices of measures for that element and presenting your recommendations at the in-person meeting.

While the RTI WG Manager can assist you in conducting the necessary searches, we need your help in identifying the relevant studies, Websites, and literature to obtain the protocols and instruments / questionnaires that you feel should be included in the reference materials for the WG to review. This search need not be exhaustive. Rather, it is important to identify protocols and instruments / questionnaires that meet the PhenX criteria: particularly low burden, broadly applicable and useful to a wide audience. Remember, we are seeking standardized and well-established protocols found in the public domain for each of the elements that you have been assigned.

At the in-person meeting, we are asking that you make a brief presentation that covers the following:

- a list of the protocols and instruments / questionnaires that you propose the WG review;
- the pros and cons of the measurement protocols;
- the limitation(s) of the various approaches; and
- your recommendations to the WG as to which should be proposed for outreach and adopted by the Toolkit.

An example presentation taken from the Environmental Exposures WG meeting is provided as a rough guide (see Sample Presentation A).

The WG Manager will work with you to obtain any documentation of protocols and instruments/questionnaires as necessary. In addition, the WG Manager can also assist you in developing your presentation.

A few helpful points to remember:

1. You only have 5 to 10 minutes to present your findings for ALL assigned elements. Thus, please focus your presentation on your specific recommendations. This will also maximize the time for discussion with the rest of the WG during the remaining meeting time.
2. We expect that the other WG members have at least a basic knowledge of the subject material. Therefore, please limit the background information you provide.
3. To the extent that no protocols meet the PhenX criteria, then it is appropriate to discuss with the WG the possibility of querying other scientists during the community outreach to identify and suggest protocols. Another possibility is to suggest that an element be considered low priority and thus not likely to become one of the final 15 measures in the Toolkit.

Contact the WG Manager if you have any questions or if they can be of any assistance in obtaining any materials or organizing the presentation.

Sample Presentation A: Example of a presentation – Biomarkers of Environmental Exposure
Courtesy of Susan Teitelbaum, Mount Sinai School of Medicine

Biologic Specimens

Susan Teitelbaum, PhD
Mount Sinai School of Medicine

Biologic Specimens Commonly Collected

- Blood
- Urine
- Saliva
- Nail clippings
- Hair
- Breast milk / breast duct epithelia
- Semen
- Buccal epithelia
- Cord blood
- Nasal epithelia
- Expired air
- Extracted teeth
- Cervical epithelia
- Bronchial, esophageal, GI tract epithelia
- Amniotic fluid
- Bone marrow
- Adipose tissue

Adapted from: Holland et al. Toxicology and Applied Pharmacology 206 (2005) 261– 268

Collection & Processing Issues

- Adherence to established protocols
  - Decreases variance in stability between samples
  - Increases stability of biomarker assessment within each sample
- Timing between collection and processing
  - Some processes can be done 24–48 h after collection
  - Some must be started immediately after collection
  - Samples that must be shipped to a processing laboratory cannot be used for the most unstable biomarkers or processing should begin in the field to ensure stability during transportation.
- Temperature control
  - Between collection and processing
  - During storage
  - Repeat freeze–thaw cycles
- Degradation
- Contamination

Adapted from: Holland et al. Toxicology and Applied Pharmacology 206 (2005) 261– 268

Recommended Biospecimen Protocols

- NHANES
  - http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/LAB.pdf
  - Blood and urine collection and processing
- NHEXAS
  - http://www.epa.gov/heds/16979doc.pdf
  - Blood and urine collection and processing
- NCI Best Practices for Biospecimen Resources
  - http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf
  - General guidelines for biospecimen collection and processing
- Salimetrics
  - http://www.salimetrics.com/AllThingsSaliva/SalivaCollection/tabid/125/Default.aspx
  - Saliva collection and processing

Biomarker Potential

- Blood
  - Variety of fractions: plasma, serum, white cells (including peripheral blood lymphocytes), red cells.
  - Wide range of biomolecules: DNA, RNA, proteins, products of metabolism (including xenobiotics).
  - Wide physiological coverage: genome, proteome, metabolome, hematological parameters.
  - Suitable for a wide range of assays.
  - Ease and low cost of collection.
- Urine
  - Wide range of biomolecules: electrolytes, products of metabolism (including xenobiotics).
  - Wide physiological coverage: metabonome (including gut microbiome).
  - Suitable for many assays.
  - Ease and low cost of collection (spot urine)
- Saliva
  - Wide range of biomolecules: salivary enzymes, hormones, cotinine, others
  - Ease and low cost of collection

From: Elliott et al. International Journal of Epidemiology 2008;37:234–244 and Salimetrics website: http://www.salimetrics.com/