

PhenX measures for phenotyping rare genetic conditions

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Introduction: The PhenX Toolkit, an online resource of well-established measures of phenotypes and exposures, now has 16 new measures recommended for assessing rare genetic conditions.

Materials and Methods: These measures and their protocols were selected by a working group of domain experts with input from the scientific community.

Results: The measures, which cover life stages from birth through adulthood, include clinical scales, characterization of rare genetic conditions, bioassays, and questionnaires. Most are broadly applicable to rare genetic conditions (e.g., family history, growth charts, bone age, and body proportions). Some protocols (e.g., sweat chloride test) target specific conditions.

Discussion: The rare genetic condition measures complement the existing measures in the PhenX Toolkit that cover anthropometrics,

demographics, mental health, and reproductive history. They are directed at research pertaining to common and complex diseases. PhenX measures are publicly available and are recommended to help standardize assessments across a range of biomedical study designs. To facilitate incorporation of measures into human subjects' research, the Toolkit offers data collection worksheets and compatible data dictionaries.

Conclusion: Widespread use of standard PhenX measures in clinical, translational, and epidemiological research will enable more uniform cross-study comparisons and increase statistical power with the potential for enhancing scientific discovery.

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PhenX uses a consensus-based process to identify measures of phenotypes and exposures for biomedical studies. Funded by the National Human Genome Research Institute and the National Institute on Drug Abuse, with supplemental funding from other National Institutes of Health (NIH) institutes for specific research areas or conditions (e.g., mental health, sickle cell disease, tobacco regulatory research, and substance use), the PhenX Toolkit is a Web-based catalog that includes more than 450 measures that broadly address 23 research domains and add depth to four research areas. As of 5 May 2016, the PhenX Toolkit had been recommended in 166 NIH funding opportunity announcements. Measures in the PhenX Toolkit are publicly available at <http://www.phenxtoolkit.org>.

Originally, when the PhenX Toolkit was made available in 2008, it was mainly a resource for genome-wide association studies; however, with the addition of research domains and more specific disciplines it expanded to epidemiological and biomedical research. The PhenX Toolkit is ideal for investigators who want to expand their disease-specific studies into disciplines outside the focus of their research. This gives investigators without expertise in these disciplines an opportunity to incorporate high-quality measures into their studies at the study design stage.¹

The PhenX steering committee (SC), which consists of 10 researchers recommended because of their broad genetic,

epidemiology, and biomedical research expertise, provides guidance to the project.² In 2013, the SC decided that the field of genetics would benefit from a set of standard measures to encourage research in rare (i.e., very-low-prevalence) diseases and syndromes.³ This paper describes the process of selecting the measures in the Rare Genetic Conditions domain, details the measures selected for inclusion in the PhenX Toolkit, and describes the challenges in identifying these measures. Investigators are encouraged to utilize this carefully selected set of standard measures in a wide variety of study designs.

METHODS

The PhenX Rare Genetic Conditions Working Group (WG) consisted of medical and clinical geneticists, including three physicians, a pediatrician, a certified genetic counselor, an epidemiologist, a registered nurse, and a patient advocate, and was supported by an SC liaison and staff from RTI International. The WG was charged with identifying up to 15 high-priority measures to assess rare genetic conditions, the scope of which included organ systems, family health history, and genetic mutations. The WG used the definition of a rare disease enacted by the Orphan Drug Act of 1983—having a prevalence of fewer than 200,000 affected individuals in the United States—and focused on rare conditions that have a known genetic component.⁴

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Each WG member was assigned one or more scope elements and reviewed the existing relevant Toolkit measures and protocols, appropriate literature, and current clinical and research tools used for data collection to recommend measures and protocols to vet. Most of the WG review occurred during a 1-day in-person meeting; additional discussions were accomplished via teleconferences. All of this occurred over an 8-month time period in 2014–2015 and resulted in the WG achieving a consensus regarding 16 measures after identifying and vetting a total of 51 measures. The WG used the SC criteria (e.g., clearly defined, well-established, reproducible, low burden, used in a major study) for this selection and were mindful of the need to complement existing PhenX Toolkit content.

RESULTS

Sixteen new measures (see **Table 1**) were added to the PhenX Toolkit in April 2015 (see <https://www.phenxtoolkit.org/index.php?pageLink=browse.measures&id=220000>). Most measures (e.g., family history, growth charts, bone age, and body proportions) are broadly applicable to rare genetic conditions research. Measures were not identified and subsequently were not recommended for each organ system because standardized protocols are not available (e.g., skin conditions) or tools for those phenotypes were already covered by existing Toolkit measures (e.g., ocular). Ideally, PhenX measures include nonproprietary protocols, but two proprietary protocols—the Disability Index and the Scale of Developmental Domains of Early Childhood—were included in this domain because they were the most commonly used. Owing to the complexity of assessing rare genetic condition phenotypes, nine of these are considered high-burden measures (e.g., two require specialized training, two take more than 15 minutes to administer to an unaffected individual, and five require both training and more time). Details regarding the burden appear in the Requirements section for each protocol.

Guidelines from the Human Genome Variation Society (HGVS), which were used to properly name genetic variants, were added as Supplemental Information (SI) as an additional resource for researchers. Although highly relevant to rare genetic condition research, the guidelines were not a standardized protocol and did not meet the SC selection criteria for inclusion in the Toolkit.

To illustrate the content of the Toolkit, three of the rare-genetic-condition measures are described below.

Family health history

A multigenerational pedigree is the gold standard for family health history. Many pedigrees are proprietary instruments. The WG selected the US Surgeon General's Web-based tool My Family Health Portrait (<http://www.familyhistory.hhs.gov/FHH/html/index.html>). It is nonproprietary and customizable and captures an individual's family health history through structured and open-ended questions. My Family Health Portrait is widely used; the website was accessed more than 1.7 million times between 2011 and September 2015 (S. Pandya, personal communication, 27 October 2015).

Growth charts

Abnormal growth is a feature of many rare genetic conditions, including Turner syndrome, Marfan syndrome, Noonan syndrome, and various forms of skeletal dysplasia. Growth charts provide information regarding deviations from typical growth patterns. This information, along with other clinical and laboratory findings, can assist investigators with their research. The World Health Organization and the Centers for Disease Control and Prevention growth charts were selected for the Growth Charts measure because they are the most common standard methods used in clinical and research practice to record growth.^{5,6}

Ataxia rating scale

Ataxia is a symptom of several rare neurologic conditions, including ataxia telangiectasia and the various forms of spinocerebellar ataxia (SCA). Because disorders that affect the cerebellum cause most genetic forms of ataxia, ataxia rating scales are used to assess the severity of cerebellar ataxia. The Scale for the Assessment and Rating of Ataxia (SARA) was selected because it has good metric properties and interrater reliability and is easily administered.⁷ The validation procedures for the SARA involved three large multicenter trials including patients with SCA and non-SCA ataxia as well as controls. The SARA has been shown to be a reliable and valid scale for measuring ataxia, with scores that correlate closely with other scales of ataxia as well as with activities of daily living.

DISCUSSION

Clinicians and researchers may wish to seriously consider incorporating PhenX measures into their own practice and research efforts because meta-analyses with the standardized measures could lead to genetic discoveries. Because the PhenX Toolkit resource facilitates cross-study analyses, the measures should be of particular interest to rare-condition researchers because of the limited sample size in each trial or study. In addition, these approaches may expand the existing understanding of some genetic conditions and lead to improved services and health for those with these conditions.

The rare-genetic-condition measures can be accessed by users with varying levels of experience with rare genetic conditions. For instance, protocols are applicable to study designs that include individuals who have already been diagnosed or are being evaluated, or both. As a result, they are beneficial to researchers who have experience with a specific rare condition, such as cystic fibrosis, as well as researchers who work with diseases for which a diagnosis is elusive.

Along with the research benefits to investigators of the rare-genetic-condition measures, there are limitations. For instance, the WG could not identify standard low-burden measures for certain organ or sensory systems, such as gastrointestinal, ocular, and auditory systems. Another challenge was identifying a standard measure for newborn screening. Although each state conducts such screening, the conditions for which each state screens vary, as do their cutoffs for what constitutes disease. As

Table 1 PhenX measures in the Rare Genetic Conditions domain

Measure name	Protocol source	Description of measurement protocol
Ataxia rating scale ^a	Scale for the assessment and rating of ataxia (SARA)	The SARA is a clinical scale used to assess cerebellar ataxia. The scale consists of eight items related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test.
Body proportions	Lifshitz, ⁹ Lohman, ¹⁰ NHANES 2007–2008, ¹¹ NHANES III ¹²	Arm span–to–height comparison is determined by measuring the individual's arm span and standing height and then comparing the two measurements (e.g., arm span is 3 cm greater than height).
Bone age ^a	Tanner and Whitehouse method	The latest Tanner and Whitehouse method, sometimes referred to as TW2, involves the interpretation of a radiograph of the left hand and wrist by a trained radiologist.
Child oral health pain	Child Oral Health Impact Profile–Short Form 19 (COHIP-SF 19) ¹³	The COHIP-SF 19 is a 19-item, interviewer-administered questionnaire about the oral health of a child to assess the child's quality of life.
Complete blood count (CBC)	NHANES 2010 ¹⁴	The complete blood count (CBC) protocol is a standard blood panel from the NHANES and is performed for participants age 1 year and older.
Disability index	Oswestry Disability Index (ODI)	ODI version 2.1a is a 10-item, proprietary, self-administered questionnaire that asks questions regarding how an individual's back (or leg) trouble affects the ability to perform routine daily activities.
Disease progression and regression ^a	Newcastle Paediatric Mitochondrial Disease Scale (NPMDS) and Newcastle Mitochondrial Disease Adult Scale (NMDAS)	The NPMDS and the NMDAS can be used to evaluate the progression of mitochondrial disease. Each of the three versions of the NPMDS addresses a specific age range (0–24 months, 2–11 years, and 12–18 years). The NMDAS is for adult patients older than 16 years.
Disorders of respiratory control with inherent autonomic dysregulation ^a	Weese-Mayer <i>et al.</i> ¹⁵	The American Thoracic Society policy statement regarding congenital central hypoventilation syndrome (CCHS) is a comprehensive guide for diagnosing an individual with CCHS by evaluating his or her phenotype and determining the paired-like homeobox gene (<i>PHOX2B</i>) genotype.
Echocardiography phenotypes ^a	British Society of Echocardiography (BSE) website	The BSE Education Committee guidelines for a standard transthoracic echocardiogram consist of a minimum data set and a recommended sequence on how to perform a comprehensive assessment.
Family health history	My Family Health Portrait (MFHP)	MFHP is a free, Internet-based tool that allows individuals to record their family health history (in the form of a pedigree). It is used to collect information regarding an individual and his or her close biological relatives.
Growth charts	World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) websites	WHO and CDC growth charts include standard graph lines and a series of percentile curves that demonstrate the distribution of certain body measurements.
Quality of life	PROMIS-25 Profile v.1.1	Pediatric: this profile consists of seven item banks: physical function mobility, anxiety, depressive symptoms, fatigue, peer relationships, pain interference, and pain intensity.
	PROMIS-29 Profile v2.0 Adult Profile	Adult: this protocol includes 29 self-administered, quality-of-life-type questions from the PROMIS Profile-29 for adults. The quality-of-life questions address physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain intensity.
Scale of developmental domains of early childhood ^a	Mullen Scales of Early Learning	Five scales that provide information regarding an infant's or child's cognitive and motor ability and also assess a child's readiness for school.
Scoliosis – physical assessment ^a	Adam's forward-bend test, X-ray, Cobb technique	The aggregate protocol includes Adam's forward-bend test and an X-ray with Cobb technique to determine whether an individual has scoliosis.
Scoliosis – quality of life ^a	Pediatric Outcomes Data Collection Instrument (PODCI)	The PODCI consists of 86 items and is designed to collect data regarding an individual's general health and problems related to bone and muscle conditions.
Sweat chloride test ^a	Clinical and Laboratory Standards Institute, ¹⁶ LeGrys <i>et al.</i> ¹⁷	Quantitative pilocarpine iontophoresis is also known as the sweat chloride test.
Genetic variant nomenclature standards (in supplemental information) ^b	Human Genome Variation Society (HGVS) guidelines for sequence variant nomenclature; Wildeman <i>et al.</i> ¹⁸	The HGVS guidelines for sequence variant nomenclature are a comprehensive guide on how to describe (i.e., name) any identified variant by a standardized method. Mutalyzer is a free online tool that is primarily used to check that the sequence variant descriptions follow the HGVS nomenclature guidelines.

All the measures are available at the following website, under the measure of interest: <https://www.phenxtoolkit.org/index.php?pageLink=browse.measures&id=220000>.

^aHigh-burden measure. ^bSupplemental Information describes the scope of each PhenX domain or collection and includes other measure(s) considered by the working group (not selected for the Toolkit) and additional comments from the working group.

a result, there was no WG consensus on a measure for newborn screening so it was not included in the Toolkit. Similarly, no standard screening panel for rare metabolic genetic conditions was identified. Instead, health-care providers base their laboratory-test orders on an individual's clinical evaluation and family history. Therefore, the WG did not include a measure for a metabolic screening panel.

In addition to the measures in the Rare Genetics Conditions domain, other measures and resources in the Toolkit are relevant to research in both common and rare genetic conditions. A collection of measures for sickle cell disease research was added to the Toolkit in July 2015. In addition, the Genetic Alliance (<http://www.geneticalliance.org>) led a crowd-sourcing effort to annotate PhenX measures for specific genetic conditions. Researchers are encouraged to use this tool to annotate protocols for other rare genetic conditions. For example, the Exercise Capacity/Six-Minute Walk Test is used to measure the response to medical interventions in patients with moderate to severe heart or lung disease, and it is used as an outcome measure for people with Duchenne muscular dystrophy.⁸ The annotation tool is available on the Resources tab of the PhenX Toolkit.

The Toolkit has several features that make it a user-friendly resource. Investigators can use the search function to find measures of interest and then add them to their personalized Toolkit to be downloaded as needed. In addition to the measures, data-collection worksheets and data dictionaries are available for each measure; these can be easily downloaded via the “My Toolkit” feature, which functions similarly to an online retailer's shopping cart. Investigators who become registered users of the PhenX Toolkit may save their work, share measures with colleagues, and receive updates about changes to the Toolkit. PhenX protocols are now available as “instrument zip” files on the Research Electronic Data Capture (REDCap) Shared Library website (<https://redcap.vanderbilt.edu/consortium/library/search.php>), making it easy for investigators to include PhenX measures in REDCap study designs.

CONCLUSION

Researchers of rare genetic conditions are encouraged to use the PhenX Toolkit when designing studies or adding measures to their research protocols. The use of standard measures facilitates cross-study analysis with limited sample sizes. The Toolkit gives investigators the capacity to expand original research and to look at common risk factors and overlapping phenotypes across rare genetic conditions and common and complex diseases.

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DISCLOSURE

The authors declare no conflict of interest.

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