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Genet Med. Author manuscript; available in PMC 2017 July 14.

Published in final edited form as:

Genet Med. 2017 July ; 19(7): 834–837. doi:10.1038/gim.2016.199.

PhenX Measures for Phenotyping Rare Genetic Conditions

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Abstract

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 cover life stages from birth through adulthood, and 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.

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DISCLOSURE

The authors declare no conflict of interest.

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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.

Keywords

phenotypes; rare genetic conditions; standardized measures; PhenX; PhenX Toolkit

INTRODUCTION

PhenX uses a consensus-based process to identify measures of phenotypes and exposures for biomedical studies. Funded by the National Human Genome Research Institute (NHGRI) and the National Institute on Drug Abuse (NIDA), with supplemental funding from other 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 which includes more than 450 measures which broadly addresses 23 research domains and adds depth in four research areas. As of May 5, 2016, the PhenX Toolkit has been recommended in 166 NIH funding opportunity announcements. Measures in the PhenX Toolkit are publicly available at www.phenxtoolkit.org.

Originally, when the PhenX Toolkit was made available in 2008, it was a resource mainly for genome-wide association studies (GWAs) but 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 other disciplines that are 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 (Hamilton et al., 2011).

The PhenX Steering Committee (SC), which consists of 10 researchers who were recommended because of their broad genetic, epidemiology and biomedical research expertise, provides guidance to the project (Maiese et al., 2013). In 2013, the SC decided that the field of genetics would benefit from a set of standard measures to encourage research in rare (very low prevalence) diseases and syndromes (De La Paz et al., 2010). This paper describes the process to select 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, 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 (a prevalence of fewer than 200,000

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affected individuals in the United States), and focused on rare conditions that have a known genetic component (Orphan Drug Act, 1984).

Each WG member was assigned with one or more scope elements and reviewed 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 with the WG. Most of the WG review occurred during a one day in-person meeting and additional discussion was held via multiple teleconferences. All of this occurred during an eight-month time period during 2014–15, and resulted in the WG coming to a consensus on 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 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 (Disability Index, Scale of Developmental Domains of Early Childhood) were included in this domain because they were the most commonly used. Due 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 have both training and greater time requirements). Details about the burden appear in the Requirements section for each protocol.

Guidelines from the Human Genome Variation Society (HGVS), used to properly name genetic variants, was added as Supplemental Information (SI) as an additional resource for researchers. While 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 (RGC) measures are described below:

Family Health History

A multi-generational pedigree is the gold standard for family health history. Many pedigrees are proprietary instruments. The WG selected the U.S. Surgeon General's web-based tool, My Family Health Portrait (MFHP, 2015). It is nonproprietary, customizable and captures the 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

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between 2011 and September 2015 (Sima Pandya, personal communication, October 27, 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 (WHO) and the Centers for Disease Control and Prevention (CDC) growth charts were selected for the Growth Charts measure because they are the most common standard method used in clinical and research practice to record growth (CDC 2010, WHO 2016).

Ataxia Rating Scale

Ataxia is a symptom of several rare neurologic conditions, such as ataxia telangiectasia and the various forms of spinocerebellar ataxia (SCA). Disorders that affect the cerebellum cause most genetic forms of ataxia; hence, there are ataxia rating scales 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 inter-rater reliability, and is easily administered (Schmitz-Hübsch et al., 2006). The validation procedures for the SARA involved three large multi-center 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 activities of daily living.

DISCUSSION

Clinicians and researchers may strongly wish to consider incorporating PhenX measures into their own practice and research efforts because meta-analyses with the standardized measures could lead to genetic discoveries. Since 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 may lead to improved services and the health of 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, are being evaluated, or both. As a result, they are beneficial to researchers with 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 from 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. Another challenge was to identify a standard measure for newborn screening (NBS). While each state

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conducts NBS, the conditions for which each state screens vary, as do their cut offs for what constitutes disease. As a result, there was no WG consensus on a measure for NBS, so it was not included in the Toolkit. Similarly, no standard screening panel for rare metabolic genetic conditions was identified. Instead, health care providers order laboratory tests based upon 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, there are other measures and resources in the Toolkit that 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 (www.geneticalliance.org) led a crowdsourcing 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; it is used as an outcome measure in people with Duchenne muscular dystrophy (McDonald et al., 2013). The annotation tool is available in the Resources tab of the PhenX Toolkit.

The PhenX Toolkit has several features which 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, which can be easily downloaded via a "My Toolkit" feature that 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 making it easy for investigators to include PhenX measures into REDCap study designs (REDCap).

CONCLUSION

Rare genetic condition researchers 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 PhenX 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.

Acknowledgments

The PhenX team would like to thank Dr. Erin Ramos, the NHGRI Project Officer, and the Rare Genetic Conditions Working Group Members including Peter Byers (Chair), Lisa Heral, Janine Lewis, Cynthia Powell, and Sarah Soden. We are also grateful to the Genetic Alliance for their assistance with the PhenX Annotation Tool. Funding provided by a Genomic Resource Grant (U41 HG007050) from NHGRI, with co-funding from NIDA.

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Table 1

PhenX Measures in the Rare Genetic Conditions Domain (all of the measures are available by going to the following website and then opening the measure of interest https://www.phenxtoolkit.org/index.php?pageLink=browse.measures&id=220000)

Measure Name	Protocol Source	Description of Measurement Protocol
Ataxia Rating Scale *	Scale for the Assessment and Rating of Ataxia (SARA)	The SARA is a clinical scale used to assess cerebellar ataxia. The scale includes eight items that are related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test.
Body Proportions	Lifshitz, F. (Ed.). (2007); Lohman, T. G., et al (Eds.). (1988); National Health and Nutrition Examination Survey (NHANES) 2007–2008 and NHANES III: Body measurements (anthropometry)	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 centimeters greater than height).
Bone Age *	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)	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	The Complete Blood Count (CBC) protocol is a standard blood panel from the NHANES and is performed on participants ages 1 and older.
Disability Index	The Oswestry Disability Index (ODI©)	The 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 *	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. There are three versions of the NPMDS, each for a specific age range (0–24 months, 2–11 years, and 12–18 years). The NMDAS is for adult patients over 16 years.
Disorders of Respiratory Control with Inherent Autonomic Dysregulation *	Weese-Mayer, D. E., et al. 2010	The American Thoracic Society (ATS) 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 their paired-like homeobox gene (PHOX2B) genotype.
Echocardiography Phenotypes *	The British Society of Echocardiography (BSE) web site	The BSE Education Committee guidelines for a standard transthoracic echocardiogram (TTE) 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) and that is used to collect information regarding the individual and his or her close biological relatives.
Growth Charts	The 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: PROMIS® Profile 25 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 include physical function, anxiety,

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Measure Name	Protocol Source	Description of Measurement Protocol
		depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain intensity.
Scale of Developmental Domains of Early Childhood *	The Mullen Scales of Early Learning	The Mullen Scales of Early Learning includes five scales that provide information on an infant's or child's cognitive and motor ability and also assess a child's readiness for school.
Scoliosis – Physical Assessment *	Adam's forward bend test, X-ray, Cobb technique	The aggregate protocol includes the Adam's forward bend test and an x-ray with Cobb technique to determine if an individual has scoliosis.
Scoliosis – Quality of Life *	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 *	Clinical and Laboratory Standards Institute, 2009; LeGrys, V. A., et al., (2007)	Quantitative pilocarpine iontophoresis is the procedure also known as the sweat chloride test.
Genetic Variant Nomenclature Standards (in Supplemental Information) **	The Human Genome Variation Society (HGVS) guidelines for sequence variant nomenclature Wildeman, M. et al., (2008)	The HGVS guidelines for sequence variant nomenclature is a comprehensive guide on how to describe (i.e., name) any identified variant by a standardized method. Mutalyzer is a free online tool which is primarily used to check that sequence variant descriptions follow the HGVS nomenclature guidelines.

*High burden measure.

**Supplemental Information describes the scope of each PhenX Domain or Collection, includes other measure(s) considered by the Working Group (not selected for the Toolkit) and additional comments from the Working Group.