



Data Collection Worksheet

Please Note: The Data Collection Worksheet (DCW) is a tool to aid integration of a PhenX protocol into a study. The PhenX DCW is not designed to be a data collection instrument. Investigators will need to decide the best way to collect data for the PhenX protocol in their study. Variables captured in the DCW, along with variable names and unique PhenX variable identifiers, are included in the PhenX Data Dictionary (DD) files.

Autonomic Nervous System Questionnaire (ANSQ):

First we are going to draw your family tree. Be sure to include any abortions (spontaneous and elective) and any infant deaths including sudden infant death syndrome (SIDS). (See step by step family tree diagram.)

Now that we've drawn your family tree, I'm going to ask you specific questions that you should answer first about the individual with CCHS (might be you or your child) and then about anyone you've described in your family tree.

Are you or any other adults (18 years of age or older) in your family:

Over 6'2?

Under 4'8?

Over 200 lbs?

Under 90 lbs?

Have any minors (under 18 years of age) in your family had atypical growth patterns?

Delayed growth?

Accelerated growth?

Have you or anyone in your family ever been diagnosed with obesity?

Yes ___ No ___

Do you or anyone in your family have growth hormone deficiency or excess?

Yes ___ No ___

Do you or anyone in your family have any known significant medical problems?

Yes ___ No ___

Remember when you answer these questions we would like to know if you ever experienced these problems at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

Such as:

Endocrine problems:

Have you ever had low blood sugar (hypoglycemia) or high blood sugar?

Diabetes: childhood onset, pregnancy related, or adult onset

Thyroid disease

Phenochromocytoma

Parathyroid tumor

Carcinoid

Tumors of neural crest origin such as neuroblastoma,
ganglioneuroma, ganglioneuroblastoma

Heart disease:

Hypertension

Cardiac pacemaker

Bypass surgery

Heart attack

Mitral valve prolapse

Cancer and type:

GI cancer - type

cancers of/in the chest

brain tumor

other cancers

Hearing problems:

Waardenberg syndrome - a white forelock of hair

GI problems:

Hirschsprung disease

Colic as an infant

Any unusual skin color - increase or decrease in pigmentation?

Are there any genetic disease that run in your family? Inborn errors?

Any history of Parkinson's disease?

Have you ever had a wandering eye/told you have strabismus?

Other

Other

Other

Use the following scoring system to rate the following questions:			
Frequency Score:	0= never or insignificant	Severity Score:	0= never
	1= mild or infrequent (once per month)		1= mild symptoms 2= moderate symptoms
	2= frequent (once per week)		3= severe symptoms
	3= consistent once every 2-3 days		
	4= consistent (every day)		

Cardiovascular System Questions:

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

1. Have you experienced episodes of dizziness in the past?

How severe is this problem?

Severity score 0-1-2-3

How often:

Frequency score 0-1-2-3-4

Age at onset of symptoms

When do symptoms occur:

Are there ever any precipitating or aggravating factors:

Early morning

After a meal

Prolonged standing

Exertion/walking

Is the dizziness ever associated with:

palpitations

nausea

vertigo

blurred vision

weakness

tremulousness

anxiety

pallor

clammy skin

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

2. Have you experienced episodes of blurred vision or glare in the past?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with anything? Dizziness? Loss of consciousness?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

3. Have you experienced episodes of loss of consciousness in the past?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with anything? Dizziness? Overheating? Blurred vision?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

4. Have you experienced throbbing pounding headaches (not migraine) in the past?

How severe is this problem?

Severity score 0-1-2-3

Are any associated with your face becoming pale or becoming flushed or with sweating

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

5. Have you ever had facial pallor - paleness of the face associated with sweating?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

6. Have you ever had really cold fingers or toes?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

7. Have you ever had Raynaud's phenomenon where your fingers go white, then blue and red?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

8. Have you ever been told by a doctor that you have:

- postural hypotension
- vasovagal syncope
- paroxysmal hypertension
- cardiac dysrhythmia
- decreased heart rate variability
- altered vascularity of face
- decreased perfusion to extremities

Gastrointestinal System Questions

With these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

9. Have you ever had profuse oral secretions/drooling?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

10. Have you ever had dysphagia - difficulty swallowing?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

11. Have you ever had any of the following symptoms (gastroparesis)

Anorexia

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Early satiety

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Persistent sense of bloating/Fullness with abdominal distension

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Frequent nausea

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Recurrent vomiting

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

12. Have you ever had abdominal surgery? Do you have any scars on your body?

Date and reason

13. Have you ever been diagnosed or evaluated for Hirschsprung disease?

14. Have you ever had had constipation defined as inability to defecate without strenuous effort, presence of hard stools, bowel movements twice a week on average, regular use of mineral oil or other mild laxative?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for this?

If yes, was a diagnosis made?

15. Have you ever had (autonomic) diarrhea unrelated to a viral illness?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

16. Have you ever had abdominal pain? Have you experienced colic as an infant?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Neurologic System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

17. Have you ever had migraine or cluster headaches?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with

ipsilateral (same side as the headache) eye watering

ipsilateral nasal drainage

miosis (pupil constriction)

ptosis (dropping eyelid)

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

18. Have you ever been told you had decreased muscle tone in your arms or legs?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

19. Have you ever had severe burning pain or causalgia of any body part? (For example - ears, fingers, toes, etc)

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

20. Have you ever had an altered perception of pain-either a high pain tolerance/not feel pain or a low pain tolerance/very sensitive to pain?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Ocular Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

21. Do you have unequal pupils?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

22. Do you have droopy eyelids?

Right Left Both

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made? Did they call it ptosis?

23. Were you told that your eyes do not respond well to light?

Right Left Both

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

24. Do you have tightly constricted pupils?

Right Left Both

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made? Was this called miosis?

25. Have you had problems with tearing?

Too little

absent

too much

inappropriate

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

26. Have you ever had trouble with your vision accommodating or converging, i.e. fixing your gaze from far to near?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Psychological System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

27. Have you ever had problems with anxiety?

Absent anxiety

Heightened anxiety

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

28. Have you ever been diagnosed as having a learning disability, either verbal or non-verbal?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Was medication such as ritalin? prozac? caffeine? ever prescribed?

29. Have you ever had problems with recognizing social cues around you?

Have you ever had problems making eye contact?

Do you comprehend facial expression, body language, gesture, and tone of voice?

Do you have social interests but lack the ability to initiate and maintain social relationships?

Renal and Urinary System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

30. Have you ever had problems with retaining your urine or incomplete emptying of your bladder?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

31. Have you ever had problems with frequent urination?

During the day or at night?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

32. Have you ever had problems with urgency to urinate?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

33. Have you ever had problems with urinary incontinence?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Reproductive System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree

34. Have you ever had problems with loss of libido?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

35. Adult male only: Have you ever had problems with erection or ejaculation?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

36. Adult male only: Have you ever had problems with priapism (the penis remains erect when not in use)?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Respiratory System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

37. Have you ever had problems with stridor?

Inspiration

Expiration

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

38. Do you notice or have you been told that you either sigh a lot or do not sigh at all?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

39. Have you ever had problems with apnea or an apparent life threatening event?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

40. Have you ever been given a diagnosis of alveolar hypoventilation?

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

41. Have you ever had problems with breath holding spells?

pallid

cyanotic

with/without loss of consciousness

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

42. Has there ever been a SIDS death in your family?

43. Has anyone in the family been on a home monitor? As an infant, child, or adult?

Sudomotor System Questions

Remember when you answer these questions we would like to know if you ever experienced these symptoms at any time - as an infant, child or adult. Also, tell me first about you and then about any of the people you told me about when we drew the family tree.

44. Have you ever had problems with difficulty sweating?

Lack of sweating

local

generalized

Profuse sweating

face body

relation to ingestion of food

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

45. Have you ever had problems with body temperature?

Too hot/hyperpyrexia

Too cold/hypothermia

How severe is this problem?

Severity score 0-1-2-3

Age at onset of symptoms

When do symptoms occur

Associated with any other symptoms?

How often:

Frequency score 0-1-2-3-4

Last event

Did you seek medical attention for these events?

If yes, was a diagnosis made?

Additional Questions (Answer "yes" or "no"):

Have any members of your family tree been diagnosed with the following:

1. Obstructive sleep apnea
2. Asthma
3. Snoring
4. Depression (any kind)
5. Seizures
6. Multiple Sclerosis
7. Prematurity
8. Down syndrome
9. Ulcerative colitis
Crohn's disease
Irritable bowel syndrome
10. Gastroesophageal reflux
11. Stillbirths
12. Issues related to menses

Genetic Testing:

Genetic testing (stepwise) is used to identify a CCHS-related *PHOX2B* mutation (required to confirm the diagnosis of CCHS). If Step 1 testing is negative, then Step 2 testing should be performed. If Step 2 testing is negative, then Step 3 testing should be performed. Normal *PHOX2B* genotype is 20/20 reflecting the number of

alanines on each allele. Patients with CCHS are heterozygous for a disease-causing *PHOX2B* mutation. This testing should be done via a CLIA-certified laboratory. Information regarding these laboratories is located on www.genetests.org

- Step 1. *PHOX2B* Screening Test (also known as Fragment Analysis or Genotyping Analysis): identifies all polyalanine repeat expansion mutations (PARMs)(genotypes 20/24-20/33), the large frameshift non-PARMs (NPARMs), and somatic mosaicism. It is the only clinically available test that will identify low level somatic mosaicism.
- Step 2. *PHOX2B* Sequencing Test: identifies all known PARMs (genotypes 20/24-20/33) and all NPARMs. Does NOT identify low level somatic mosaicism.
- Step 3. *PHOX2B* MLPA Test: identifies whole gene or whole exon deletions and duplications.

Physiologic and other clinical testing:

Physiologic and other clinical testing that follows the 2010 ATS Statement on CCHS recommendations is optimal to diagnose and provide conservative management of affected patients, with aim for longitudinal follow-up and objective measures before and after pharmacological intervention.

- Detailed recording in a pediatric respiratory physiology laboratory for documentation of hypoventilation or absent spontaneous breathing asleep (most severe in non-REM sleep) and in varied activities of daily living while awake over the course of 4 days and 4 nights to adequately represent the patient's needs. A subset of individuals with CCHS will hypoventilate awake and asleep. Testing should be completed during spontaneous breathing as well as with artificial ventilatory support.
 - Tidal volume (pneumotachograph) measurement
 - In CCHS *below* 7 cc/kg (usually below 5 cc/kg and lower asleep)
 - Normal range in healthy controls is 7-10 cc/kg
 - Movement (respiratory inductance plethysmography) of the chest and abdomen
 - Respiratory frequency
 - In CCHS, respiratory rates will typically be *above* norms for age.
 - General ranges for healthy norms is provided below:
 - Birth to 6 weeks: 30-60 breaths per minute (bpm)
 - 6 months: 25-40 bpm
 - 3 years: 20-30 bpm
 - 6 years: 18-25 bpm
 - 10 years: 12-15 bpm
 - Adults: 12-20 bpm
 - Hemoglobin saturation with visible pulse waveform and beat-to-beat

- measures
 - In CCHS *below* 92% during sleep and, if awake hypoventilation, when awake
 - End tidal carbon dioxide with visible breath-to-breath measures
 - In CCHS *above* 50 mmHg during sleep, and if awake hypoventilation, when awake
 - ECG
 - In CCHS *decreased* heart rate variability and in a subset of cases sinus pauses
 - If possible, measures of blood pressure and cerebral oxygenation/regional blood flow should be included
- Exogenous and endogenous ventilatory challenges in response to hypoxemia and hypercarbia (awake and asleep)
 - In CCHS lack of a consistent or sustained normal ventilatory or cardiovascular response to clinical challenges with Hypercarbia (5%)/Hyperoxia (95%), Hypercarbia (7%)/Hypoxia (14%), and Hypoxia (5 breaths of nitrogen).
- 72-hour Holter recording annually to evaluate for cardiac sinus pauses
- Neurocognitive testing
- Evaluation for tumors of neural crest origin if *PHOX2B* genotype 20/28-20/33 or NPARM
- Evaluation for Hirschsprung disease
- Age and symptom-specific autonomic testing
 - Birth through adult Poincaré plots of r-r +1 vs. r-r (cigar pattern in CCHS), pupillometry (typically decreased pupillary response to light but *PHOX2B* genotype-specific), and peripheral skin temperatures (typically mildly reduced)6 years through adult: head-up tilt (typically uncoupling of blood pressure and heart rate and altered cerebral regional blood flow), thermoregulatory sweat test (typically altered sweating pattern and reduced peripheral skin temperature), heart rate-deep breathing, Valsalva maneuver, and more depending on child's symptoms and ability to cooperate.

Protocol source: <https://www.phenxtoolkit.org/protocols/view/220801>