PERIPHERAL NERVE WORKUP (PNW) FORM

The Peripheral Nerve Workup Form (PNW) has to be completed for all new PNRR enrollments. Only laboratory testing within 36 months from study visit should be reported. The exception is genetic testing which should always be reported.

First tier laboratory testing information must be provided for all new idiopathic PN enrollments with the exception of lipid profile. For diabetic PN enrollments, the SIFE/SPEP is not considered mandatory. Lipid profile should be obtained for all new enrollments, but it is understood that the information might not be available for younger study participants.

Second-tier laboratory testing results should be entered into PNRR as they are available.

GENERAL INFORMATION

- **Subject ID:** five-digit PNRR subject ID assigned to research participant
- **Sex:** genetic sex of the PNRR participant
- **Year of visit:** year of the visit this PNW form is associated with
- **Year of birth:** year the PNRR participant was born

FIRST TIER

1. Chemistry 12-18

Only the reported Creatinine level from the most recent Comprehensive Metabolic Panel (CMP) should be considered for normal or abnormal interpretation. Creatinine levels ≥1.4 mg/dL or equivalent should be reported as abnormal. Creatinine levels reported in nmol/L must be converted into mg/dL before they are entered into PNRR database.

Chemistry evaluation:

- **Normal:** creatinine value is within normal range (≤ 1.3 mg/dL)
- **Abnormal:** creatinine value is outside the normal range (≥ 1.4 mg/dL)
- **ND/NA:** no CMP done in the past 36 months, or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Creatinine level: enter measured creatinine value in mg/dL

2. Glucose

Glucose testing information can be provided in form of one of three laboratory testings: (1) glycated hemoglobin (HbA1c), (2) fasting glucose (must be confirmed fasting) or (3) two-hour oral glucose tolerance testing (OGTT). At a minimum, the results from one of these three tests must be provided. If testing results are available for all three, all three should be entered into REDcap.

a. Glycated Hemoglobin (HbA1C)

The glycated hemoglobin value should be reported here in % glycated hemoglobin. For PNRR HbA1c of 5.7% or higher is considered abnormal.

HbA1c interpretation:

- **Normal:** measured HbA1c % was within the reference range (≤ 5.6%)
- **Abnormal:** measured HbA1c % was higher than the reference range (≥ 5.7%)
- **ND/NA:** test was not performed within last 36 months, or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

HbA1C Level: enter measured HbA1c level in % of glycated hemoglobin

b. Blood Glucose (confirmed fasting)

Expresses the amount of glucose in blood after a minimum of 6 hour fasting. Abnormal testing results should only be provided when participant was confirmed fasting at the time of the blood draw. Fasting blood glucose levels ≥ 100 mg/dL are considered abnormal. Fasting glucose levels reported in mmol/L shall be converted to mg/dL.

Fasting glucose interpretation:

- **Normal:** fasting glucose within normal range (≤ 99 mg/dL)
- **Abnormal:** fasting glucose outside the normal range (≥ 100 mg/dL)
- **ND/NA:** not measured within the last 36 months or test results not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Fasting Glucose level: enter measured fasting glucose level in mg/dL

c. Oral Glucose Tolerance test (OGTT)

Blood glucose levels measured fasting and two hours after participant consumed glucose syrup should be reported in milligram per deciliter (mg/dL). Both abnormal high (hyperglycemic, ≥140 mg/dL) and abnormal low (hypoglycemic, ≤70 mg/dL) test results should be reported as abnormal. Testing results reported in mmol/L should be converted to mg/dL.

OGTT interpretation:

- **Normal:** test result within normal range (70-139 mg/dL)
- **Abnormal:** blood glucose levels after two hours were abnormal low (≤ 70 mg/dL) or
- abnormal high (≥140 mg/dL).
- **ND/NA:** test not performed within the last 36 months or test results not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Glucose level: measured glucose level at the two-hour mark in mg/dL

3. Paraproteins

Screening for paraproteins in form of abnormal immunoglobulin (antibodies) and protein levels must be provided in form of one of two screening tests: (1) Serum Immunofixation (SIFE) or (2)

Serum Protein Electrophoresis (SPEP). For participant with normal testing results only the results of one test must be entered into the database. For participants with abnormal testing results, both tests are expected to be done to determine the severity of the paraprotein. Participants with IgM monoclonal gammopathy (MGUS) are not eligible for enrollment into PNRR unless the enrolling physician confirms that IgM MGUS is not the primary cause of the peripheral neuropathy.

SIFE / SPEP interpretation:

- **Normal:** all screened immunoglobulins are within normal range
- **Abnormal:** one or more immunoglobulins are outside of normal range
- **ND/NA:** test was not performed within the last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

If SIFE and/or SPEP were abnormal:

Identification of type of abnormality:

- Monoclonal gammopathy – presence of paraprotein (abnormal high levels)
- Hypoglobulinemia – one or more values are in abnormal low range

And identification of the abnormal immunoglobulins:

- Immunoglobulin A (IgA)
- Immunoglobulin G (IgG)
- Immunoglobulin M (IgM)
- Kappa Light Chain
- Lambda Light Chain
- Other – abnormal finding should be specified in open text data entry field

If SIFE and/or SPEP were abnormal:

Physician must determine if abnormality is clinically significant or not:

- Clinically significant (CS)
- Not clinically significant (NCS)

4. Vitamin B12

Measured Vitamin B12 (or cobalamin) levels in blood reported in picogram per milliliter (pg/mL). Reported values below the normal range (180 pg/mL) should be reported as abnormal. High values are of no concern and are common in participants who take Vitamin B supplements. Abnormally high laboratory testing results should not be reported as an abnormal finding. Vitamin B12 levels measured in nmol/L should be converted to pg/mL before entered into the database.

Vitamin B12 interpretation:

- **Normal:** Vitamin B12 value in normal range or elevated
- **Abnormal:** Vitamin B12 value is below normal range < 180 pg/mL
- **ND/NA:** test was not performed within the last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin B12 Value: enter measured Vitamin B12 level in pg/mL

5. Lipid Profile

Lipid profile or lipid panel screens for abnormal blood lipid levels. Lipid profile is critical component for the evaluation of the presence of metabolic syndrome, and should be obtained for all PNRR enrollments. Lipid profile should be marked abnormal when one or more lipid levels are reported abnormally high or low by the laboratory. All testing results should be reported in milligram per deciliter (mg/dL). The normative values vary between laboratories, however for most labs the normative values are: cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, High Density Lipids (HDL) <30 mg/dL for men or <40 mg/dL for women, and Low Density Lipids (LDL) ≥130 mg/dL.

Lipid Profile Interpretation:

- **Normal:** all measured lipids were in the normal range
- **Abnormal:** one or more measured lipids were outside of normal range
- **ND/NA:** test was not performed within last 36 months or test results are not available.

Year of Test: calendar year test was performed. Must be within 36 months of visit.

The following values are to be recorded:

- **Cholesterol:** measured cholesterol level in mg/dL
- **Triglycerides:** measured triglyceride level in in mg/dL
- **HDL:** measured HDL-cholesterol level in mg/dL
- **LDL:** measured LDL-cholesterol level in mg/dL

SECOND TIER

The Second Tier lists standard laboratory tests which are commonly ordered for participants with a diagnosis of PN to check for common causes as well as other factors that can influence the natural history of the disease. Second-tier testing results should be entered as they are available.

6. Methyl malonic acid (MMA)

Methyl malonic acid is elevated in participants with Vitamin B12 deficiency, even if the deficiency is mild and Vitamin B12 levels are still within the normal range. The normal range for MMA levels in blood can slightly vary between laboratories and the reference range information provided by the laboratory should be used to determine if a value is considered Normal or Abnormal. MMA is usually measured in nmol/L. If another unit is used, it measured value will need to be converted to nmol/L units before value is entered into database.

MMA interpretation:

- **Normal:** MMA level considered to be within normal range
- **Abnormal:** elevated MMA levels above normal range
- **ND/NA:** test was not performed within last 36 months or test results are not available.

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Measured MMA value: measured MMA value in nmol/L

7. Homocysteine

Elevated homocysteine levels can be an indicator for low B-vitamin intake. Homocysteine levels are usually measured in micromoles per liter (µmol/L), and 5-15 µmol/L is considered normal range.

Moderate (16-30 µmol/L), intermediate (31-100 µmol/L) and severely elevated (>100 µmol/L) homocysteine levels should all be reported as abnormal.

Homocysteine interpretation:

- **Normal:** within normal range
- **Abnormal:** elevated level
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Measured homocysteine value: measured homocysteine blood levels in µmol/L

8. Thyroid Stimulating Hormone (TSH)

Thyroid Stimulating Hormone (TSH) is an indicator for thyroid function and elevated TSH levels indicate hypothyroidism, while low TSH levels indicate hyperthyroidism. TSH levels are usually reported in milli-International Units per Liter (mIU/L). The normal range may differentiate between laboratories and laboratory report should be referenced when determining if testing result was normal or abnormal. Usually the normal range for TSH is 0.5-5 mIU/L.

TSH interpretation

- **Normal:** measured TSH level is within normal range
- **Abnormal:** measured TSH level is outside of normal range – both abnormal high and low levels should be reported as abnormal
- **ND/NA:** test was not performed within the last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

TSH value: measured TSH level should be entered in mIU/L.

9. Urine Monoclonal Immunoglobulins

To screen for abnormal protein levels (monoclonal immunoglobulins) in urine, Urine Immunofixation (UIFE) is the most common laboratory screening test. If UIFE is abnormal, then most laboratories perform (2) Urine Electrophoresis (UPEP). Testing results from either UIFE or UPEP should be entered in the database.

Monoclonal Immunoglobulin interpretations:

- **Normal:** no monoclonal immunoglobulins are not found
- **Abnormal:** monoclonal immunoglobulin(s) are detected
- **ND/NA:** test was not performed within the last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

If Abnormal, report abnormality: _____

The abnormal finding from the UIFE or UPEP laboratory report should be entered.

10. Kappa / Lambda Light Chains

Test measures amounts of free kappa and free lambda immunoglobulin light chains in blood serum, and the ratio between kappa and lambda chains is calculated. If the concentration of either kappa or lambda chains or the kappa/lambda ratio are outside of the normal range, the test should be reported as abnormal. Kappa and lambda levels are usually reported in mg/L. The normal range for kappa light chains is 3.3 to 19.4 mg/L. For lambda, the normal range is 5.7 to 26.3 mg/L. If reported in other units, the testing results must be converted to mg/L before values are entered into the database. The K/L ratio is usually reported as a number, with normal range 0.26 to 1.65.

Kappa/Lambda interpretation:

- **Normal:** normal testing result
- **Abnormal:** either kappa, lambda or K/L ratio are outside of normal range
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

- **Kappa/lambda ratio:** ratio from laboratory report should be entered
- **Kappa light chain level:** measured kappa light chain levels in mg/L
- **Lambda light chain level:** measured lambda light chain level in mg/L

11. Charcot-Marie-Tooth (CMT) panel genetic testing

Genetic testing is often order to verify that PN is not inherited and caused by pathogenic genetic variant. Genetic testing results should be entered independent of time elapse since testing was performed.

Genetic testing interpretation:

- **Normal:** no pathogenic variant was found
- **Abnormal:** pathogenic variant was found, participant has inherited neuropathy
- **ND/NA:** genetic screening test was never done

Year of Test: calendar year test was performed (no time limit for genetic testing).

If genetic testing is reported as normal, a pop-up question will appear, asking if genetic variant with uncertain significance (VUS) was found. If VUS is reported by laboratory, the information from the genetic testing report should be entered into the database, including the gene on which the variant was found, the codon change as well as the amino acid change.

- Example for **gene**: MFN2
- Example for **codon change**: c.326A>G
- Example for **amino acid change**: p.Lys109Arg

12. Paraneoplastic Panel (MAYO)

Screening for autoantibodies in blood, including Anti-Hu, -Ri and –Yo plus others. For participants who received chemotherapy, a negative Paraneoplastic Panel is considered a confirmation that the neuropathy is caused by chemotherapy drugs.

Paraneoplastic Panel Interpretation:

- **Normal:** negative result
- **Abnormal:** positive result (autoimmune antibodies present)
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

All antibodies for which abnormal levels were measured should be marked.

ANN1S	Anti-Neuronal Nuclear Ab, Type 1
ANN2S	Anti-Neuronal Nuclear Ab, Type 2
ANN3S	Anti-Neuronal Nuclear Ab, Type 3
AGN1S	Anti-Glial Nuclear Ab, Type 1
PCABP	Purkinje Cell Cytoplasmic Ab Type 1
PCAB2	Purkinje Cell Cytoplasmic Ab Type 2
PCATR	Purkinje Cell Cytoplasmic Ab Type Tr
AMPHS	Amphiphysin Ab, S
CRMS	CRMP-5-IgG, S
STR	Striational (Striated Muscle) Ab, S
CCPQ	P/Q-Type Calcium Channel Ab
CCN	N-Type Calcium Channel Ab
ARBI	ACh Receptor (Muscle) Binding Ab
GANG	AChR Ganglionic Neuronal Ab, S
VGKC	Neuronal (V-G) K+ Channel Ab, S
Other:	abnormality information from lab report should be entered in pop-up field

13. Vitamin E

Vitamin E deficiency is a known cause for PN. Normal ranges vary between laboratories and the provided references should be consulted to determine if the measured Vitamin E levels are within normal range or low. Only Vitamin E deficiencies should be reported as an abnormal result. Testing results should be reported in milligram per liter (mg/L). Lab testing results reported in µg/mL or any other units should be converted to mg/L before entered into the database.

Vitamin E interpretation:

- **Normal:** Vitamin E levels in normal range or elevated
- **Abnormal:** Vitamin E levels below normal range
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin E value: measured Vitamin E value should be entered in mg/L

14. Vitamin B1 (Thiamin)

Vitamin B1 deficiencies are also a known cause of PN. Only abnormal low testing results should be reported as abnormal in PNRR. Vitamin B1 is usually measured in nanomole per liter (nmol/L) and the normal range is 74 to 222 nmol/L. Some laboratories report Vitamin B1 levels in microgram per deciliter (µg/dL). These values must be converted to nmol/L before they are entered into the database.

Vitamin B1 Interpretation:

- **Normal:** Vitamin B1 within normal range or elevated
- **Abnormal:** Vitamin B1 deficiency
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin B1 value: enter measured Vitamin B1 level in nmol/L

15. **Vitamin B6**

Vitamin B6 is involved in the formation of myelin and both B6 deficiency and chronically elevated B6 levels can cause PN, and both abnormal low and high levels of Vitamin B6 should be reported as abnormal in the database.

Vitamin B6 testing results can be reported in either nanogram per milliliter (ng/mL), microgram per liter (µg/L), microgram per deciliter (µg/dL), or in nanomole per liter (nmol/L). Unit in which Vitamin B6 testing results are reported must be indicated in database.

Vitamin B6 interpretation:

- **Normal:** Vitamin B6 level are within normal range
- **Abnormal:** Vitamin B6 levels are either elevated or below normal range.
- **ND/NA:** test was not performed within last 36 months or test results are not available

Year of Test: calendar year test was performed. Must be within 36 months of visit.

Vitamin B6 value: enter measured Vitamin B6 level

Measurement unit: identify measurement unit for Vitamin B6 level

Date Data Entry Completed:

Date should be entered when data entry was completed.

Nerve Workup Form (PNW) Status:

- **Incomplete:** not all data is entered yet
- **Unverified:** data is entered, but not verified
- **Complete:** all information is verified, no additional edits are anticipated