AWARD NUMBER: W81XWH-21-1-0499

TITLE: Host-Based and Pathogen-Based Proteomic Biosignatures for the Diagnosis of Lyme Disease in Children

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REPORT DATE: OCTOBER 2022

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2022	Annual	30SEPT2021 - 29SEPT2022

4. TITLE AND SUBTITLE

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-21-1-0499

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

We propose to identify a novel blood-based biomarker signature to distinguish between patients with Lyme disease and patients with symptoms compatible with Lyme disease but who ultimately were found to have alternate diagnoses, i.e. patients with symptoms mimicking Lyme disease. In pilot studies, we have shown differential abundances of a subset of blood proteins which alone or in combination show promise as a sensitive diagnostic that could be used to improve on currently available diagnostics for early Lyme disease. We hypothesize that a novel blood-based biomarker (or set thereof) has the potential to improve diagnostic accuracy for patients with suspected Lyme disease.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	14	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION

Over the past two decades, Lyme disease has grown from a regional phenomenon to a national epidemic affecting hundreds of thousands of people each year. Current two-tiered diagnostic tests for Lyme disease have well-recognized limitations including false negatives in early disease, false positives after prior infection, and slow turn-around time with wait times of up to three days. Here we propose the **hypothesis that serum proteomics will provide a superior approach to differentiate Lyme disease from its clinical mimics**, focusing on children who represent more than half of new Lyme disease cases annually. To address this diagnostic gap, we have established an interdisciplinary translational research team spanning both clinical (Nigrovic) and proteomics (Steen) expertise in Lyme disease. In 2015, Dr. Nigrovic founded a Lyme disease research network (Pedi Lyme Net) that has collected biospecimens on more than 2,500 children and 200 adults tested for Lyme disease in ten emergency departments in Lyme-endemic areas across the United States. These carefully phenotyped cohorts and high-quality biosamples provide the ideal optimization and validation opportunity for our proteomics strategy.

2. KEYWORDS

Lyme disease, diagnostics, proteomics, children

3. ACCOMPLISHMENTS

What were the major goals of the project?

AIM 1. Derive and validate a serum proteomic signature for Lyme arthritis for use across the age spectrum. **Lyme arthritis** is a clear clinical phenotype for which current two-tier diagnostic testing is highly accurate, if slow. Employing this syndrome as our gold standard and our existing proteomic biosignature as a reference point, we will conduct an unbiased proteomic survey in serum from 130 children with confirmed Lyme arthritis, each paired with three age and symptom-matched non-Lyme arthritis controls. Consistent with Federal Drug Administration (FDA) guidelines for test development, the optimal host- and/or pathogen-based Lyme proteomic signature will be validated in an independent cohort of 100 children and 30 adults with Lyme arthritis and 390 matched controls. *We predict that our biomarkers will distinguish Lyme arthritis from its mimics with high sensitivity and specificity.*

AIM 2. Refine and validate a proteomics strategy for the diagnosis of early-disseminated Lyme disease in children. Unlike Lyme arthritis, patients with **early-disseminated Lyme disease** may not have a detectable serologic response. Using existing and newly-assembled samples from 200 children with early-disseminated Lyme disease with 600 age and symptom-matched non-Lyme mimics, we will apply unbiased proteomics to test our existing proteomic biosignature (as optimized in Aim I), and to derive and validate a new host and/or pathogen-based biomarkers for early Lyme disease. *We predict that a specific set of candidate biomarkers, overlapping but potentially distinct from the panel that is informative in Lyme arthritis, will provide accurate diagnosis in early-disseminated Lyme disease.*

What was accomplished under these goals?

Enrollment Q3-4 Y1

Target prospective enrollment Overall Pedi Lyme Net	***Y1 Q3-4 Target***	***Y1 Q3-4 Actual***
Aim 1: Employ Lyme arthritis to optimize a Lyme proteomic signature *Major task 2: Validation of LC/MS biosignature in children and adults with Lyme arthritis and matched symptomatic controls*		
Target enrollment	*40*	*151*
Boston		*34*
Wilmington		*20*
Providence		*17*
Philadelphia		*13*
Milwaukee		*5*
Pittsburgh		*54*
Minneapolis		*5*
St. Paul		*3*
Aim 2: Test a proteomics strategy for the diagnosis of early-disseminated Lyme disease *Major Task 1: LC/MS analysis of a cohort with early disseminated Lyme patients and symptomatic controls to refine the Lyme arthritis biosignature*		
Target enrollment	*25*	*153*
Boston		*28*
Wilmington		*8*
Providence		*42*
Philadelphia		*17*
Milwaukee		*7*
Pittsburgh		*41*
Minneapolis		*6*
St. Paul		*4*

Statement of work

Specific Aim 1: Employ Lyme arthritis to optimize a Lyme proteomic signature for use across the age spectrum.	**Timeline [months]**	**Completion**
IRB Review and Approval	0	100%
HRPO Review and Approval	1-3	100%
Major Task 1: Derivation of LC/MS biosignature in children with Lyme arthritis and matched symptomatic controls (previously collected from Boston Children's Hospital, A.I. Dupont Children's Hospital and Hasbro Children's Hospital for independent derivation).	4-24	100%
Sub task 1: Processing of the derivation cohort with ~520 serum samples and subsequent LC/MS analysis in discovery mode. *retrospective samples from PediLyme Net (130 Lyme: 390 control samples)	4-5	100%
1.1 Blot sample processing (~520 serum samples) to capture serum proteins	6-9	100%
1.2 LC/MS analysis of the ~520 serum samples on a high accuracy/high resolution mass spectrometry system.	10-11	100%
1.3 LC/MS data analysis	12	100%

1.4 Statistical analysis of the data	13-15	100%
1.5 Biomedical interpretation of the data	16-18	100%
1.6 Identification of biomarker candidates, generation of transition list	18-24	100%
Milestone Achieved: Completion of processing and analysis of the retrospective arthritis cohort; identification of candidate shortlist		
Major Task 2: Validation of LC/MS biosignature in children and adults with Lyme arthritis and matched symptomatic controls (samples collected from Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Children's Wisconsin and Children's Minnesota at Minneapolis and St. Paul for independent validation).	4-24	30%
Sub task 1: Research two-tier Lyme disease testing for prospectively enrolled biosamples. 160 total pediatric samples (across 8 recruitment sites)		
1.1 Perform research Lyme testing on 160 pediatric prospective samples: First tier Diasorin VLSE EIA followed by immunoblot for a positive/equivocal first tier test	12-24	0%
Sub task 2: Processing of the validation cohort with ~520 (130 Lyme: 390 control) serum samples and subsequent targeted LC/MS analysis. (Banked samples ~40 adults: 320 pediatric + Prospectively collected: 160 pediatric from 8 recruitment sites)	18-24	100%
2.1 Blot sample processing of ~520 serum samples	20-21	100%
2.2 Mass spectrometry analysis of the ~520 samples on a fast and highly sensitive triple quadrupole mass spectrometer.	21-23	100%
2.3 Analysis of targeted LC/MS data	23-24	0%
2.4 Statistical analysis of the data	24-26	0%
2.5 Biomedical interpretation of the data	27	0%
Milestone Achieved: Completion of processing and analysis of validation cohort; validation of arthritis biosignature/panel of biomarkers		

Preliminary results

Major Task 1: We identified 520 eligible retrospective samples that have been shipped from clinical collecting sites and processed by the Pedi Lyme Net biobank. The Steen Laboratory has processed all of these samples and mapped all serum proteomes. In collaboration with study biostatistician, we had derived a candidate diagnostic panel of 4 proteins (3 upregulated and one down-regulated) for Lyme arthritis.

Major Task 2: We prospectively enrolled 80 children for the validation of the Lyme arthritis proteomic biosignature (>200% of target for Y1 Q3Q4 targets) including 32 Lyme arthritis cases and 48 matched controls.

Specific Aim 2: Test a proteomics strategy for the diagnosis of early-disseminated Lyme disease in children.	**Timeline [months]**	**Completion**
Major Task 1: LC/MS analysis of a cohort with early disseminated Lyme patients and symptomatic controls to refine the Lyme arthritis biosignature.	4-36	30%
Sub task 1: Research Lyme disease testing for prospectively enrolled early-disseminated biosamples (100 total pediatric samples across 8 sites).		

1.1 Perform research Lyme testing on prospective samples: First tier Diasorin VLSE EIA followed by immunoblot for a positive/equivocal first tier test	4-24	0%
Sub task 2: Processing of the cohort with ~800 pediatric (200 Lyme: 600 control) serum samples and subsequent LC/MS analysis in discovery mode. (700 Banked samples from PediLyme Net + 100 prospective)	24-36	0%
1.2 MStern blotting sample processing of ~800 serum samples	24-26	0%
1.3 LC/MS analysis of the ~800 samples on a high accuracy/high resolution mass spectrometry system.	26-29	0%
1.4 LC/MS data analysis	29-33	0%
1.5 Statistical analysis of the data	33-35	0%
1.6 Biomedical interpretation of the data	36	0%
Milestone Achieved: Completion of processing and analysis of early disseminated Lyme cohort; refinement of arthritis biomarker signature for early disseminated Lyme disease		

Preliminary results
Major Task 1: We prospectively enrolled 153 children evaluated for early-disseminated Lyme disease including 44 early-disseminated Lyme cases and 109 matched controls. Given our brisk enrollment in year 1, we anticipate no challenges to meet enrollment overall enrollment or biosignature development and validation of the proteomic biosignature panel.

Regulatory Protocol and Activity Status
(a) Human Use Regulatory Protocols

TOTAL PROTOCOLS: 8
PROTOCOL (1 of 8 total): Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1a** Title: **Novel diagnostics for Lyme Disease in Children** **Submitted to and Approved by:** Approved through December 1, 2023 **Status:** active **(i)** Number of subjects recruited/original planned target: See Pedi Lyme Net chart above **(ii)** Report amendments submitted to the IRB and USAMRMC HRPO for review: None **(iii)** Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None
PROTOCOL (2 of 8 total): Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1b and Log Number E02436.1c [Rhode Island Hospital]** Title: **Novel diagnostics for Lyme Disease in Children** **Submitted to and Approved by:** Approved through March 20, 2023 **Status:** active **(i)** Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments previously submitted to the IRB and USAMRMC HRPO for review:

1. Site PI changed from Aris Garro to Laura Chapman
2. Enrollment restricted to 1-21 years at Rhode Island Hospital; Miriam Hospital is not enrolling for this research protocol

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (3 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1d [Children's Hospital of Pittsburgh]**

Title: **Novel diagnostics for Lyme Disease in Children**

Submitted to and Approved by: Approved through April 7, 2023

Status: active

(i) Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (4 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1e [Children's Hospital of Philadelphia]**

Title: **Novel diagnostics for Lyme Disease in Children**

Submitted to and Approved by: Approved through June 6, 2023

Status: active

(i) Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (5 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1f [Nemours Children's]**

Title: **Novel diagnostics for Lyme Disease in Children**

Submitted to and Approved by: Approved through October 17, 2023

Status: active

(i) Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (6 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1g [Children's Wisconsin]**

Title: **Novel diagnostics for Lyme Disease in Children**

Submitted to and Approved by: Approved through March 20, 2023

Status: active

(i) Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (7 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.1h [Children's Minnesota]**

Title: **Novel diagnostics for Lyme Disease in Children**

Submitted to and Approved by: Approved through June 14, 2023

Status: active

(i) Number of subjects recruited/original planned target: See Pedi Lyme Net chart above

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

PROTOCOL (8 of 8 total):

Protocol [HRPO Assigned Number]: **HRPO Log Number E02436.2a [Steen Laboratory]**

Title: Plasma/Serum/Urine Proteomics in Children with Lyme disease

Submitted to and Approved by: Approved April 9, 2021 w/out expiration date (active protocol)

Status: active

(i) Number of subjects recruited/original planned target: n/a

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: None

(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

TOTAL ACTIVITIES: 0

ACTIVITES: none

(c) Animal Use Regulatory Protocol

TOTAL PROTOCOL(S): No animal use research protocols are required to complete the statement of work.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

We plan to continue to enrolling children with potential Lyme disease at each of the performance sites with research two-tier Lyme testing at Branda laboratory. We will also continue with proteomics analysis and interpretation in consultation with the Steen laboratory.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Over the past two decades, Lyme disease has grown from a regional phenomenon to a national epidemic affecting hundreds of thousands of people each year. Current Lyme disease two-tiered diagnostic tests have well-recognized limitations including false negatives in early disease, false positives after prior infection, and slow turn-around time. Both children and adults undergoing evaluation for possible Lyme disease pose diagnostic challenges. An accurate and rapid diagnostic test for Lyme disease would be an important asset for acute disease management by avoiding unnecessary invasive procedures and allowing prompt initiation of appropriate therapy for those patients with confirmed Lyme disease.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change.

We have not made any changes in approach.

Actual or anticipated problems or delays and actions or plans to resolve them.

The work is proceeding according to schedule. We did experience a delay with the research Lyme disease testing of samples at the Branda Laboratory at Massachusetts General Hospital (Boston, MA) where laboratory resources had been diverted to the high volume of clinical COVID-19 clinical assays. However, biosamples have been recently delivered to our collaborator (December 2022) with anticipated sample analysis by early 2023. These delays have not required any changes to our enrollment or analytic plans as the research testing does not depend on the clinical Lyme disease testing.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

The site PI for Rhode Island Hospital has changed from Aris Garro, MD MPH to Laura Chapman, MD (change previously approved by the local IRB as well as the DOD HRPO).

6. PRODUCTS

No research products to date.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Founded in 2015 by Dr. Nigrovic, Pedi Lyme Net has grown to include eight enrolling centers located in Lyme disease endemic areas of the in the Northeast, Mid-Atlantic and Upper Midwest. We enroll children who present to the emergency department of a participating center with suspected Lyme disease and collect clinical phenotype as well as research biospecimens. Research biosamples from enrolled children are stored in the Pediatric Lyme Disease Biobank housed at Boston Children's Hospital. Pedi Lyme Net has collaborated with Hanno Steen, PhD, Director of the Proteomics Center at Boston Children's Hospital (Boston, MA). Dr. Steen's laboratory in consultation with study statistician leads the effort to derive and validate the novel proteomic biosignature for acute Lyme disease in children.

Pedi Lyme Net enrolling center	*Location*	*Site PI*
Boston Children's Hospital	Boston, MA	Lise Nigrovic, MD
Children's Hospital of Philadelphia	Philadelphia, PA	Fran Balamuth, MD PhD
Children's Hospital of Pittsburgh	Pittsburgh, PA	Desiree Neville, MD
Children's Hospital of Wisconsin	Milwaukee, WI	Michael Levas, MD MPH
Nemours Children's Hospital	Wilmington, DE	Amy Thompson, MD
Minnesota Children's Hospital	Minneapolis, Minnesota	Anupam Kharbanda, MD MSce
Minnesota Children's Hospital	St. Paul, Minnesota	Anupam Kharbanda, MD MSce
Rhode Island Hospital	Providence, RI	Laura Chapman, MD

What individuals have worked on the project?

Boston Children's Hospital
Name: Lise Nigrovic, MD MPH
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-6369-1656
Nearest Person Month Worked: 1.2 calendar months
Contribution to Project: Oversight of all aspects of the project including clinical enrollment

Name: Hanno Steen, PhD
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-0179-6648
Nearest Person-Month Worked: 0.48 calendar months
Contribution to Project: Oversight of all aspects of laboratory analysis of patient specimens

Name: Benoit Fatou, PhD
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-0317-0243

Nearest Person-Month Worked: 2.4 calendar months
Contribution to Project: Specimen analysis

Name: David Zurakowski, PhD
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID): 0000-0003-3610-6942
Nearest Person-Month Worked: 0.36 calendar months
Contribution to Project: Study design, power calculations, statistical analysis

Name: Mariah Elder
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person Month Worked: 1.8 calendar months
Contribution to Project: Study coordination, data management, sample collection

Name: Rachael Aresco
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person Month Worked: 1.8 calendar months
Contribution to Project: Study coordination, data management, sample collection

Children's Hospital of Philadelphia
Name: Frances Balamuth, MD PhD
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-3709-7160
Nearest Person Month Worked: 0.12 calendar months
Contribution to Project: Oversight of project at site

Name: Tyne Hernandez
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person Month Worked: 1.2 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Children's Minnesota
Name: Anupam Kharbanda, MD MSc
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-523129855
Nearest Person-Month Worked: 0.06 calendar months
Contribution to Project: Oversight of project at site

Name: Brianna Bretscher
Project Role: Research Manager
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person-Month Worked: 0.15 calendar months
Contribution to Project: Study coordination

Name: Julia Kancans
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person-Month Worked: 0.13 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Name: Angela Bornhoft
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person-Month Worked: 0.05 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Name: Serena Miller
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person-Month Worked: 0.02 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Medical College of Wisconsin
Name: Michael Levas, MD MS
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-3685-2478
Nearest Person-Month Worked: 0.12 calendar months
Contribution to Project: Oversight of project at site

Name: Jared Hogeterp
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID):N/A
Nearest Person-Month Worked: 1.0 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Nemours Children's Hospital
Name: Amy Thompson, MD
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-6283-8966
Nearest Person-Month Worked: 0.5 calendar months
Contribution to Project: Oversight of project at site

Name: Claire Loiselle
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): 0000-0001-7633-6449
Nearest Person-Month Worked: 1.2 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

Rhode Island Hospital
Name: Laura Chapman, MD
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0001-7957-2666
Nearest Person Month Worked: 0.12 calendar months
Contribution to Project: Oversight of project at site

Name: Ivan Banhamon
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest Person Month Worked: 1.2 calendar months
Contribution to Project: Subject enrollment, sample, collection, data entry

UPMC Children's Hospital of Pittsburgh
Name: Desiree Neville, MD
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-1927-1682
Nearest Person Month Worked: 0.12 calendar months
Contribution to Project: Oversight of project at site

8. SPECIAL REPORTING REQUIREMENTS

No updates to previously submitted QUAD chart (October 22, 2022).

9. APPENDICES

None.