Undiagnosed Diseases Network : **Phase II**

Applicant Information Webinar

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National Institutes of Health
Office of Strategic Coordination - The Common Fund

Outline for Today's Webinar

1. Background on the UDN
2. UDN Phase II FOAs Overview
3. Frequently Asked Questions
4. Applicant Questions

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Overall UDN Objectives

1. **Improve the level of diagnosis and care** for patients with undiagnosed diseases
2. **Facilitate research** into the etiology of undiagnosed diseases
3. **Promote an integrated and collaborative community** to investigate these difficult to diagnose diseases

Undiagnosed Diseases Network

Undiagnosed Diseases Network

APPLY

http://udnconnect.org/apply/

Applications Received	Applications Under Review	Applicants Accepted
1798	344	750

491 Clinical Evaluations

Sequencing
(exome and genome)

Model Organisms
(fly and fish)

Metabolomics

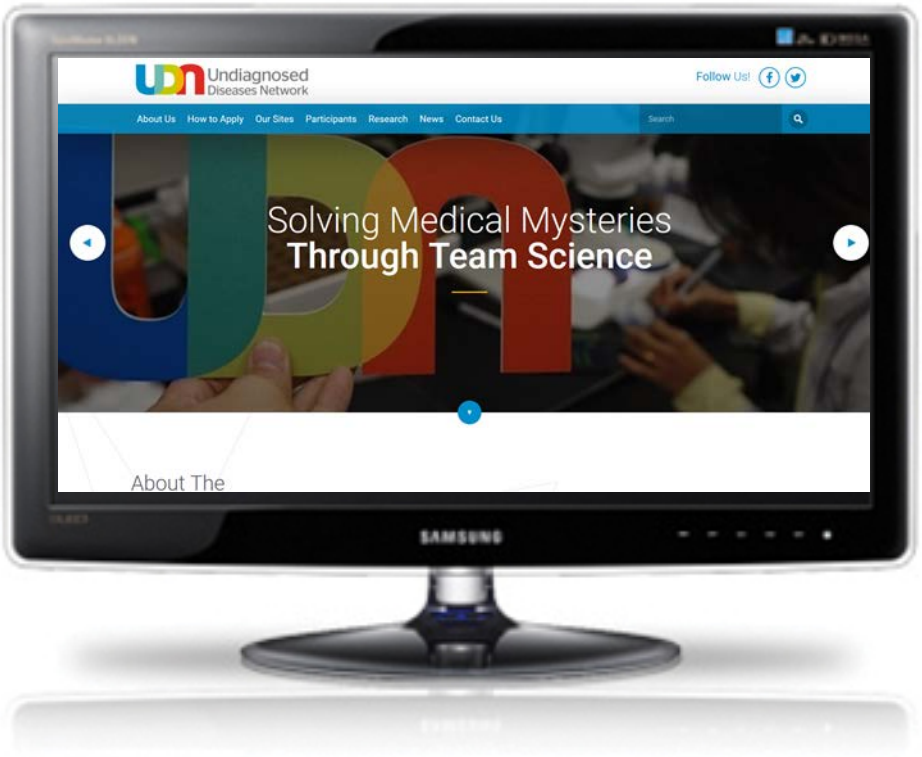
Working Together 128 Diagnoses

(September 2017)

UDN Manual of Operations

UDN Manual of Operations (MOO)

- Network-wide Protocol
- Single (Central) IRB
- Data Sharing and Use Agreement



https://undiagnosed.hms.harvard.edu/udn-manual-of-operations/

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RFA-RM-17-019

Clinical Sites

Award Budget: $1.1M direct costs per year in FY18 and FY19, and $800K direct costs in FY20 and FY21

- Recruit, select, evaluate, and follow participants with disorders in **any clinical specialty, adult and pediatric**
- Provide a **comprehensive clinical evaluation** completed within one week of initiation or a time-efficient alternative
- Establish and maintain clinical evaluations at a rate of **30** affected UDN participants per year

8-10 awards anticipated

RFA-RM-17-018

Coordinating Center

Award Budget: $2.9M direct costs per year in FY18 and FY19, $2.5M direct costs in FY20, and $1.8M direct costs FY21

- **Establish and maintain efficient data systems and infrastructure** necessary for timely collection, submission, and analysis of data from the UDN
- Develop a resource for **linking UDN participants with researchers**
- **Award gene function studies** to follow-up on variants identified in the UDN:
  - Infrastructure to support access
  - Methods for data sharing
  - Process for review of research proposal

RFA-RM-17-017

Model Organisms

Award Budget: $700K direct costs per year in FY18 and FY19, $550K direct costs in FY20, and $350K direct costs in FY21

- Establish a Model Organisms Screening Center (MOSC) resource to assist the UDN in evaluating the pathogenicity and preliminary function of human gene sequence variants identified through the UDN
- Develop a creative, innovative screening pipeline with the capacity to analyze approximately **200 UDN gene variants per year**, including:
  - bioinformatics approaches for screening and evaluation of variants
  - capacity to evaluate variants in *Drosophila* and zebrafish models at a minimum

  - other small animal models or cell-based assays, optionally and as needed, to achieve project goals (up to a maximum of five Resource Cores including *Drosophila* and zebrafish Cores)

RFA-RM-17-017

MOSC NIH Priorities

- Can best assist the UDN in the diagnosis of UDN participants (i.e., the proband and family members) network-wide
- Proposes innovative strategies – e.g., resourceful combinations of bioinformatics tools/genomics resources, model organisms and/or cell-based assays – that can rapidly and efficiently assist the UDN in evaluating the clinical impact of gene variants, including:
  - a screening pipeline and analysis plan that can accommodate the diversity of mutations and clinical phenotypes likely to be encountered by the UDN
  - cutting-edge gene editing/targeting technologies and phenotypic assays that can meet the throughput (~200 variants/year) and turnaround expectations (~6-12 months from variant assignment) of the FOA
- An outstanding, highly qualified team of investigators who are poised to work in a high throughput and interactive/collaborative team environment with the UDN

RFA-RM-17-016

Sequencing

Award Budget: $1.2M direct costs per year in FY18 and FY19, $900K direct costs in FY20, and $600K direct costs in FY21

- Provide both **exomes and genomes** in a CAP-accredited and/or CLIA-certified environment
- Provide raw sequence files, exome and/or genome, as decided by the clinical team within a **two-week turnaround** timeframe. Approximately 1200 participants are anticipated for FY18-19 with a potential ramp down over FY20-21
- Provide **CLIA clinical variant report** with Sanger validation
- Provide **re-analysis** of previously sequenced exomes and genomes and **re-interpretation** as needed for unsolved cases

RFA-RM-17-015

Metabolomics

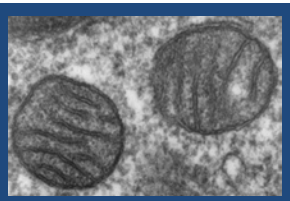
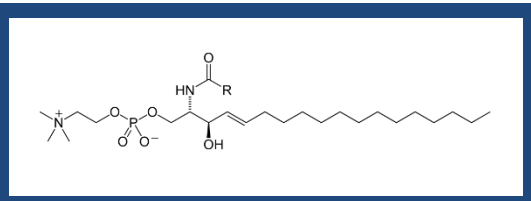
Award Budget: $500K direct costs for FY18 and 19; $375K direct costs for FY20; and $250K direct costs for FY21

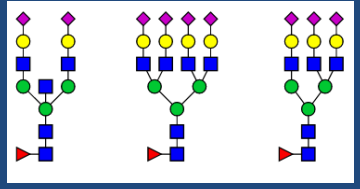
- Provide **metabolomics clinical expertise** and consultation
- Provide **specific expertise in at least two of the three areas** listed below:
    a) Glycans
    b) Lipids
    c) Mitochondria
- Serve as a conduit for the UDN to **access resources and experts** with knowledge in metabolomics beyond their own area of expertise
- Providing **existing cutting edge analytical methods** to examine changes in glycans, lipids and/or mitochondria from a broad range of sample sources

RFA-RM-17-015

Metabolomics

- **Identify rare, abnormal and novel metabolites** as defined by a participant's disease. The Metabolomics Core is not expected to develop new technology
- Participate in **co-interpretation** of metabolomics data alongside other data and help identify candidate causal mutations and critical metabolites
- Apply state-of-the-art metabolomics technology and instrumentation for analyzing **75-125 clinical cases** (this number includes cases referred to alternate sites with special expertise) per year. Each clinical case may require the testing of multiple samples from participant and additional testing of relatives



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Frequently Asked Questions

General for all 5 Phase II FOAs

Frequently Asked Question 1

Will applicants be able to read the current UDN protocol?

Yes. Information on the current protocol can be found in the UDN Manual of Operations at: https://undiagnosed.hms.harvard.edu/udn-manual-of-operations/

Frequently Asked Question 2

The “Funds Available and Anticipated Number of Awards” budget does not seem to match with the “Award Budget”?

The “Funds Available and Anticipated Number of Awards” is in total costs while the “Award Budget” is in direct costs. Your application budget should not exceed the “Award Budget” in direct costs.

Frequently Asked Question 3

Do direct costs include consortium F&A costs requested by a subcontract?

The direct costs are excluding the consortium F&A costs requested by a subcontract following this Guide Notice: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-040.html

Frequently Asked Question 4

Can a PD/PI on a Clinical Site application also be on a different UDN Phase II application (Coordinating Center, Metabolomics Core, Model Organisms Screening Center, or Sequencing Core) in a role other than PD/PI?

The PD/PI on a Clinical Site application may have any role on a different UDN Phase II application other than PD/PI (or co-PI on a multi-PI application). Funding multiple UDN Phase II awards at the same institution would require that potential conflicts and overlaps be resolved before awards are made.

Applies similarly to all FOAs.

Frequently Asked Question 5

Who can be the PD/PI of a Clinical Site application if the institution is submitting an application for a different UDN Phase II award (Coordinating Center, Metabolomics Core, Model Organisms Screening Center, or Sequencing Core)?

The PD/PI (or co-PI on a multi-PI application) of any other UDN Phase II application may not be the PD/PI (or co-PI on a multi-PI application) of a Clinical Site application. However, other individuals located at the same institution may be the PD/PI on a Clinical Site application. Funding multiple UDN Phase II awards at the same institution would require that potential conflicts and overlaps be resolved before awards are made. Applies similarly to all FOAs.

Frequently Asked Question 6

If submitting a multi-PI application, does each PD/PI need to be well-established in clinical research, sequencing, or metabolomics?

PD/PIs on a multi-PI application must as a team be well-established in clinical research, sequencing, or metabolomics as specified in the FOA.

Frequently Asked Question 7

What is expected in a letter of support to document institutional commitment to sustaining the program beyond NIH Common Fund support?

Letters of support should clearly document commitments (including but not limited to staff or monetary commitments) to meet the requirements of the FOA during the period of award. Institutional commitment and willingness to sustain the program beyond NIH Common Fund support should also be indicated, however, a specific monetary commitment level is not required. Additionally, the Sustainability Plan proposed in the Other Attachments section should include the investigators' plan for sustainability as NIH Common Fund funding ramps down.

Frequently Asked Questions

Model Organisms Screening Center FOA (RM-17-017)

Selected MOSC FAQs

Does each variant assigned to the MOSC require analysis using *all* model organisms available to the Center (e.g., in both *Drosophila* and zebrafish models)?

No. The MOSC should strive to maximize the value and cost-effectiveness of all available resources and funds to assist in the diagnosis of UDN participants.

Do all assigned variants require analysis using wet-lab approaches (i.e., in a model organism or cell-based assay)?

No. The primary screening platform could involve a combination of bioinformatics and/or wet-lab approaches.

Is the MOSC expected to confirm or rule out definitively the pathogenicity of all gene variants assigned to the Center?

No. The MOSC is expected to conduct the initial screen and analysis of candidate UDN gene variants; however, deeper analysis of promising variants may be conducted in collaboration with the other UDN sites.

Frequently Asked Questions

Sequencing Core FOA (RM-17-016)

FAQ Sequencing 1

Two-week timeframe for returning raw (unassembled) data from start to stop

Begins with the start of DNA sample preparation for sequencing including but not limited to library preparation, enrichment, capture, and cluster generation for exome or genome sequencing, but excluding DNA extraction. The process is complete when raw (unassembled) sequence data has been returned to either the UDN Coordinating Center and/or a UDN Clinical Site.

FAQ Sequencing 2

Expectation for CLIA clinical variant report with Sanger validation

Description of a plan for development of CLIA clinical reports to be delivered to Clinicians (attach an example in appendix)

Budget for additional research sequencing approaches such as RNAseq, ChIP-seq, etc.

Include budget, must fit within the direct costs of the application budget

FAQ Sequencing 3

Re-analysis

Start with original raw data and rerun entire analysis and interpretation pipeline; recommended with a significant pipeline change

Re-interpretation

Review of variant in context of new data in the literature, both new disease gene associations and changes in variant interpretation

Frequently Asked Questions

Metabolomics FOA (RM-17-015)

FAQ Metabolomics 1

Are letters of support from all alternate sites with special expertise necessary?

Letters of support from all alternate sites with special expertise are not necessary, but may be included.

FAQ Metabolomics 2

For UDN participant sample workup, will the Metabolomics Core have access to clinical and phenotypic information and the full sequencing data from the respective participants?

Yes, the UDN anticipates considerable communication and collaboration amongst the Metabolomics Core and the Model Organisms Screening Center, the Clinical Sites, and Sequencing Cores in evaluating UDN participants and the putative pathogenicity of any candidate gene variants. Clinical and sequencing data will be shared to the fullest extent possible.

FAQ Metabolomics 3

Does the Metabolomics Core need to budget for cases referred to alternate sites with special expertise? Is billing to the Clinical Site or participant allowed?

A plan to meet the FOA expectations of throughput (analysis of approximately 75-125 clinical cases per year including cases referred to alternate sites with special expertise) should be accounted for in the budget. Meeting the FOA expectations should not require billing to the Clinical Sites or participants.

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Applicant Questions

Letter of Intent Due: October 2, 2017

Application Due: November 2, 2017

Any Questions?

Acknowledgments

Thank you to all the UDN patients and their families!

Undiagnosed Diseases Network

http://undiagnosed.hms.harvard.edu/

Acknowledgments

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For More Information on the UDN

https://commonfund.nih.gov/Diseases

http://www.genome.gov/27550959

http://rarediseases.info.nih.gov/undiagnosed

THANKS!

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Undiagnosed Diseases Network

http://undiagnosed.hms.harvard.edu/