NIH Undiagnosed Diseases Program (UDP) Precursor of the Undiagnosed Diseases Network (UDN)

- **UDP**
  
  Component of the NIH Intramural Research Program
  Hosted by NHGRI but trans-NIH
  Seed funding: NIH Office of Rare Diseases (2008)
  Initial funding arranged by Elias Zerhouni (2009-12)
  In-kind support from NIH Clinical Center and NHGRI

- **UDN**
  
  Established 2013 to expand the UDP nationally
  Supported by the NIH Common Fund with 10-year limit ending after FY22
  Brendan Lee will discuss
UDP Numbers (2008-20)

- Medical Records: >4000
- Admitted & Evaluated: >1400
- Children: ~40%
- Neurological: >50%
- Diagnoses: ~350
- New Diseases: ~25
Very Rare Diagnoses

- Congenital Disorder of Glycosylation type 2b (2<sup>nd</sup> and 3<sup>rd</sup> cases in world)
- Adducted Thumb-Clubfoot Syndrome & CHST14 mutations (1<sup>st</sup> case in U.S.)
- Spinocerebellar ataxia, myoclonic epilepsy & AFG3L2 muts (1<sup>st</sup> AR case)
- Autosomal Dominant Leukodystrophy & LMNB1 duplication (~10 in world)
- Adenylosuccinate lyase def. (~60 cases)
- Hereditary Muscular Neuropathy type 6 due to IGHMBP2 muts (oldest pt. known)
- Fatty acid 2-hydroxylase def. (~50 cases)
More Diagnoses

- EMARRD (Early myopathy, AReflexia, Respiratory distress, Dysphagia) due to *MEGF10* mutations
- Neurodegeneration due to *BTK* mutation
- Cognitive & motor decline with *C19orf12* mutants
- Waardenburg type 2 due to *SOX10* deletion
- SLE with cerebellar ataxia and anti-GWB Abs
- GM2 gangliosidosis and Sanfilippo disease
- TEMPI syndrome with erythrocytosis mutants
- Choreo-acanthocytosis due to *VPS13A*
- Aicardi-Goutieres due to *RNASEH2B, A* mutants
- SPG11, NPC1, STIM1, GARS, A-T, NGLY1, MNGIE, CAV3
Recent Diagnoses

- Tremor & spasticity due to GAN de novo mutation
- Connective tissue and GI disorder due to \textit{TUBB2B} de novo mutation
- Mitochondrial disorder due to \textit{MTATP6} mutation
- Kleefstra Syndrome due to \textit{EHMT1} de novo
- Fahr’s due to \textit{SLC20A2} mutations
- XMEN (X-linked immunodef, EBV infection, neoplasia due to \textit{MAGT1} mutation
- Relapsing polychondritis
- Hereditary Spastic Paraplegia 76 & \textit{CAPN1} muts
- AR Limb-Girdle MD 2Z due to \textit{POGLUT1} muts
New Disease-Gene Associations as of 3/19

1. Arterial calcifications  NT5E
2. Spastic paraplegia, spinocerebellar ataxia AFG3L2
3. Skin/skeletal lesions, FGF23 abnormal NRAS
4. Upregulated interferon signaling IFIH1
5. Stroke and vasculopathy ADA2
6. Epileptic encephalopathy AARS
7. Ablepharon macrostomia TWIST2
8. York Platelet Syndrome STIM1
9. Developmental delays CAD
10. Cirrhosis, developmental delays PP1R15B
11. Dystonia KMT2B
12. Neurodevelopmental disorder EBF3
13. Mitochondrial encephalopathy TIMM50
14. Developmental and growth delays GARS
15. Infantile parkinsonism WARS
16. Developmental neuroregression UBTF
17. Saul-Wilson syndrome COG4
18. Microcephaly, seizures, cerebral atrophy VARS
19. Developmental delays, dysmorphisms TRAF7
20. Delays, cardiac defects, dysmorphisms TMEM94
21. Delays, hair & liver defects, dysmorphisms CCDC47
22. Neuropathy, ataxia, dystonia COX20
23. Delays, microcephaly, brittle hair & nails CARS
Publications as of 3/19 = 182*

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<td>NEJM</td>
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* Non-UDP investigators were coauthors on >100 of these and first or last author on 31.

New Disease, *NT5E* Gene, 2011
Manfred Boehm, now NHLBI Senior Investigator

New mechanism of disease resistance, MOGS-CDG, 2014
Sergio Rosenzweig, now CC Senior Investigator
Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease

UDP Communications as of 3/19

Lectures, Seminars, Grand Rounds (180)
- Two Keystone Conferences

Awards (~10)
- AMA Nathan Davis Award
- Service to America Medal
- Lasker Public Service Award to NIH CC

Media
- Press (NY Times & Magazine (3), Newsweek, WSJ, LA Times, Wash Post)
- TV (CNN, NBC Nightly News, PBS, ABC Today, 60 Minutes, Discovery)
- Journals (Science, Nature, Cell, JAMA)
Congressional and Administration Interactions

Congress
  Inquiries 42
  Visits 6
NIH Director 40
Secretary HHS 5
White House 1
Training as of 3/19

1. 13 postdoctoral fellows; 6 in bioinformatics.
2. 55 postbacc IRTAs -> Grad & Med Schools.
3. Trainees are first authors of 26 UDP articles.
4. Short course on UDP exome analyses for NIH, Berkeley, UC-Santa Cruz trainees
6. Bioinformatics Journal Club
7. Weekly patient rounds; ~60 attendees
8. Genetics Fellows rotate through UDP.
9. Guests from around the world.
UDP Data Sharing

1. The UDP’s IRB-approved protocol and consent allow for data sharing in the UDN.
2. The UDP database, UDPICS, is searched and its phenotypes & genotypes are shared.
3. PhenomeCentral & Matchmaker Exchange receive UDP cases.
Institutional Impact of the UDP

- ~100 NIH physicians from 12 institutes
- 139 clinical protocols enrolled >570 UDP patients.
- Provides umbrella for specialty patients.
- Advanced careers of students & faculty
- Source of collaborations, discovery, new clinical protocols
- Enhances reputation of institution
International Impact of the UDP

- Founded Undiagnosed Diseases Network International in 2014
  - 8 international meetings
  - Charter, Committees, Policies, Sharing
  - Developing Nations Working Group
- Promoted the establishment of UDPs throughout the world
- Pursuing collaborations with WHO, IRDiRC, United Nations, etc.
UDP as ‘Center’ of Undiagnosed Diseases Ecosystem

NIH UDP

*UDN
**Currently Enrolling Subjects

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UNDIAGNOSED DISEASES NETWORK
2013: The Undiagnosed Diseases Network (UDN)

- Supported by the NIH Common Fund
- Expansion to extramural clinical sites
- Training, Collaboration & Data Sharing
- Phase I: 2014-2018
- Phase II: 2018-2022
UDN Objectives

1. Improve level of diagnosis and care for patients with undiagnosed diseases
2. Facilitate research into etiology of undiagnosed diseases
3. Discover new biochemical and cell biological pathways amenable to broad therapeutic interventions
4. Create an integrated and collaborative research community to improve options for optimal patient management
The UDN: Phase I

- UDP, 7 Extramural Clinical Sites, Coordinating Center, 2 Sequencing Cores, Metabolomics Core, Model Organisms Screening Center, Central Biorepository
- Central NHGRI IRB; Reliance Agreements
- Formal data sharing agreements
- Consent: PII to be shared within UDN, de-identified data with others
- First patients: July 2015
The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.
UDN Phase I: 7/2015-8/2018

- Applications: 2613
- Acceptances: 1268
- Evaluations: 921
- Diagnoses: 227
- Exomes done: 403
- Genomes done: 432
Primary applicant Phenotypes

• Neurologic: 40%
• Musculoskeletal: 10%
• Immunologic: 7%
• Gastrointestinal: 7%
• Rheumatologic: 6%

Splinter et al. 2018
UDN Phase II: 9/2018-2022

- 11 Extramural Clinical Sites (Baylor, CHOP-Penn, Duke, Harvard, Miami, Stanford, UCLA, Utah, U. Washington, Vanderbilt, Wash U) plus Intramural Site
- Coordinating Center, Sequencing Core, Metabolomics Core, 2 Model Organisms Screening Centers, Central Biorepository
- Sunset of Common Fund support after 2022
Phase II: 2018-2022

Twelve clinical sites, a coordinating center, a sequencing core, a metabolomics core, two model organisms screening centers, and a central biorepository
Evaluation tools and approaches

• Clinical evaluation by multiple specialists
• Standardized phenotyping ontology
• (Family?) exome or genome sequencing performed in clinical lab:
  • Research sequencing analysis
  • Close interactions with clinical team
  • Data sharing with entire UDN
• Incorporation of research approaches, including RNA sequencing, model organisms, metabolomics
The UDN Gateway

Click “Apply” button on any UDN website for more information

http://undiagnosed.hms.harvard.edu/apply/
29 Conditions Newly Described
# BCM UDN Clinical Site Participation

## Adult specialties
- Audiology
- Cardiology
- Dermatology
- Endocrinology*
- Gastroenterology*
- Genetics*
- Hematology
- Immunology
- Infectious Disease
- Nephrology
- Neurology*
- Neuropsychology
- Nutrition
- Ophthalmology*
- Otolaryngology
- Pathology
- Psychology
- Pulmonology
- Radiology
- Radiology – CAMRI
- Rheumatology*
- Speech Pathology
- Surgery
- Toxicology

## Pediatric specialties
- Audiology
- Calorimetry – Children’s Nutritional Research Center
- Cardiology
- Dermatology
- Endocrinology
- Gastroenterology
- General Pediatrics
- Genetics*
- Hematology
- Hepatology
- Immunology*
- Infectious Disease
- Nephrology
- Neurology*
- Neuropsychology
- Ophthalmology*
- Pathology
- Plastic surgery/craniofacial
- PM&R
- Pulmonology
- Radiology
- Rheumatology*
- Speech Pathology
- Surgery
- Toxicology
- Urology
Overall workflow of the UDN and MOSC (Phase II)

1. Patients → Coordinating Center → UDN
   - Undiagnosed Diseases Network

2. UDN → Model Organisms Screening Centers (MOSC)
   - Informatics
   - MARRVEL
   - http://marrvel.org

3. MOSC
   - Metabolomics Core
   - Sequencing Core

4. Prioritization → Assignment
   - C. elegans Core
   - Drosophila Core
   - Zebrafish Cores

5. Functional Information → Diagnosis

6. 12 Clinical Sites
Participants with exome or genome sequencing complete: 1299

Participants with metabolomic analyses complete: 177

Participants with variants studied by the Model Organisms Screening Center: 316

Participants with samples in the Central Biorepository: 1062
Data sharing

• Internal: online cloud portal for patients to apply and clinicians/researchers to share participant data
• External: PhenomeCentral, dbGaP, ClinVar, webpages

https://www.matchmakerexchange.org/
PUBLIC COVERAGE – Primary Stories

- MIT Technology Review
- U Magazine (UCLA Health)
- Wired UK
- The Washington Post
- Stanford Magazine
- The New York Times
- NPR
- CBS News
- San Francisco Chronicle
- ABC7 News (San Francisco)
- ABC11 (Durham)

- Associated Press
- The Scientist
- Los Angeles Magazine
- CNN
- Houstonia Magazine
- STAT (via Kaiser Health News)
- Proto Magazine (MGH)
- Scope Blog
- WCVB Channel 5 Boston
- Vanderbilt Medicine
- The New Yorker
- NBC News
Multi-omic Approach in Clinical Research

• Integrated clinical phenotyping still absolutely required
  • Inform discovery hypotheses
  • Variable expressivity and incomplete penetrance
  • Medical actionability
  • Management without an identifiable cause

• WES and WGS powering a genotype first approach
  • ~35% discovery with research analysis

• Functionalization of the genome
  • Metabolomics clinically available and can lead to biomarker discovery while correlating with WES & WGS
  • Transcriptomics – both complementing interpretation of WES & WGS as well as RNAseq first approach

• Model organism study is critical for interpreting both VUS in known and unknown disease genes
Summary

• UDN approach involves a multidisciplinary evaluation incorporating clinical and research tests and procedures

• Basic research collaborations have the potential to increase knowledge of rare conditions

• Data sharing efforts are crucial to rare disease diagnosis and improving understanding of these conditions
SCIENTIFIC IMPACT

• Laboratory for implementation of the future of genomic medicine
• Strategy for basic discovery by leveraging humans as the emerging best model system; **all the pathways and defects found are by definition functional in humans**
• A model for collaboration, cooperation, and data sharing locally, regionally, nationally, and internationally, AND INTERDISCIPLINARY
SCIENTIFIC FUTURE

- Integrate widely into clinical practice
- Make personalized therapies a realistic consideration for patients with unmet needs
- Drive multidisciplinary research at academic centers while recruiting point of care clinical providers to research enterprise
- Interface with other rare disease discovery, natural history, and treatment consortia
  - NCATS ORDR Rare Disease centers
  - Mendelian Genomic Centers
  - FDA’s new Rare Disease Clinical Trials