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^{nd} and 3^{rd} cases in world)
- Adducted Thumb-Clubfoot Syndrome & *CHST14* mutations (1^{st} case in U.S.)
- Spinocerebellar ataxia, myoclonic epilepsy & *AFG3L2* muts (1^{st} 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 muts
- Waardenburg type 2 due to SOX10 deletion
- SLE with cerebellar ataxia and anti-GWB Abs
- GM2 gangliosidosis and Sanfilippo disease
- TEMPI syndrome with erythrocytosis muts
- Choreo-acanthocytosis due to VPS13A
- Aicardi-Goutieres due to RNASEH2B, A muts
- 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 *TUBB2B* de novo mutation
- Mitochondrial disorder due to *MTATP6* mutation
- Kleefstra Syndrome due to *EHMT1* de novo
- Fahr's due to *SLC20A2* mutations
- XMEN (X-linked immunodef, EBV infection, neoplasia due to *MAGT1* mutation
- Relapsing polychondritis
- Hereditary Spastic Paraplegia 76 & *CAPN1* muts
- AR Limb-Girdle MD 2Z due to *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*

NEJM	5
JAMA	2
Nature Genet	5
Other Nature Journals	5
Am J Hum Genet	16
Genetics in Medicine	11
Human Mutation	11

*** 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deuitch, D. Rowczenio, E. Rominger, K.V. Wells, C.-C.R. Lee, W. Wang, M. Trick, J. Mullikin, G. Wigerblad, S. Brooks, S. Dell'Orso, Z. Deng, J.J. Chae, A. Dulau-Florea, M.C.V. Malicdan, D. Novacic, R.A. Colbert, M.J. Kaplan, M. Gadina, S. Savic, H.J. Lachmann, M. Abu-Asab, B.D. Solomon, K. Retterer, W.A. Gahl, S.M. Burgess, I. Aksentijevich, N.S. Young, K.R. Calvo, A. Werner, D.L. Kastner, and P.C. Grayson

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
5. Bioinformatics Journal Club
6. Weekly patient rounds; ~60 attendees
7. Genetics Fellows rotate through UDP.
8. 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.
4. The UDP shares its Manual of Operations, protocol, and consents worldwide.

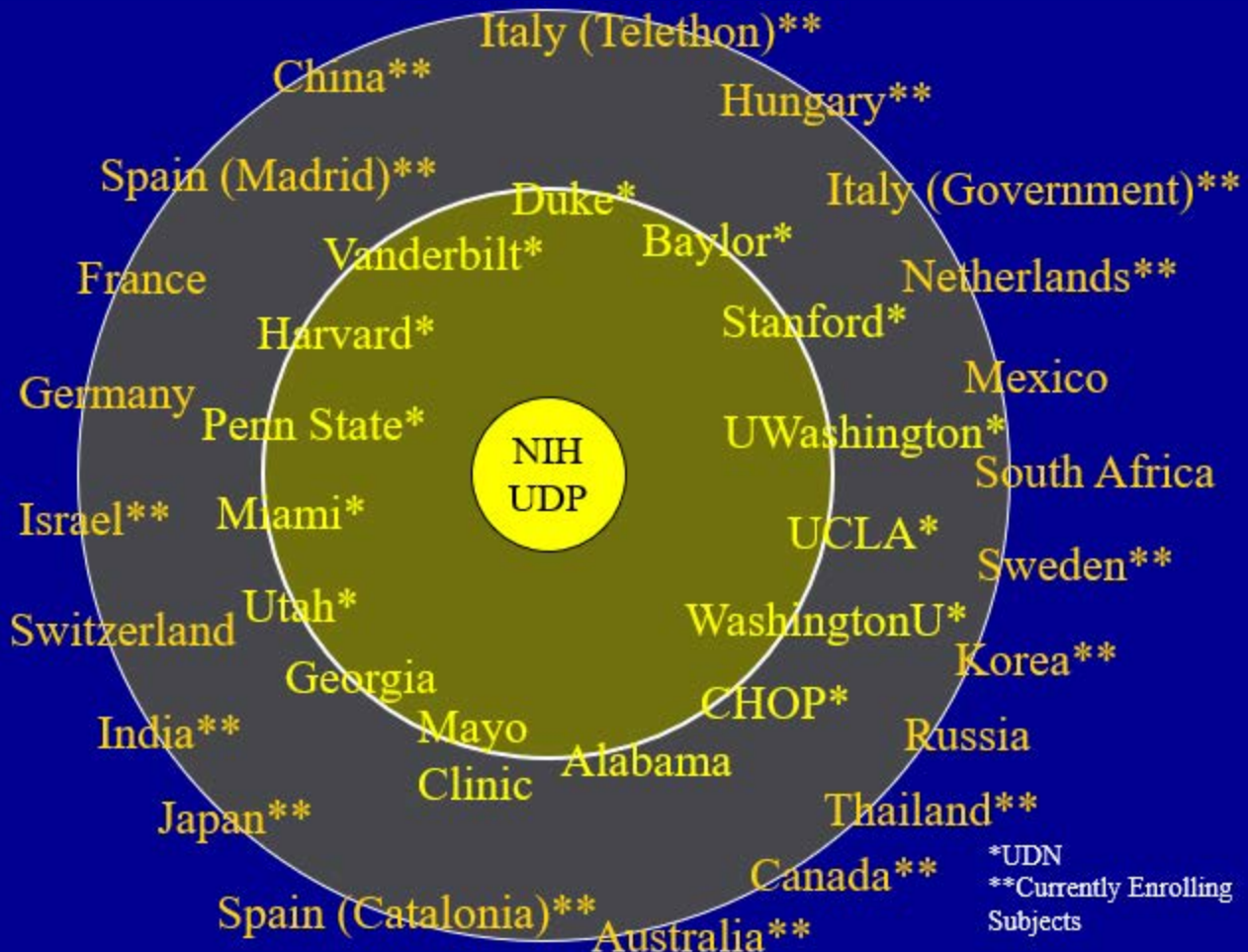
Institutional Impact of the UDP

- ~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



UNDIAGNOSED DISEASES NETWORK

2013: The Undiagnosed Diseases Network (UDN)

- Supported by the NIH Common Fund
- Expansion to extramural clinical sites
- Training, Collaboration & DataSharing
- 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

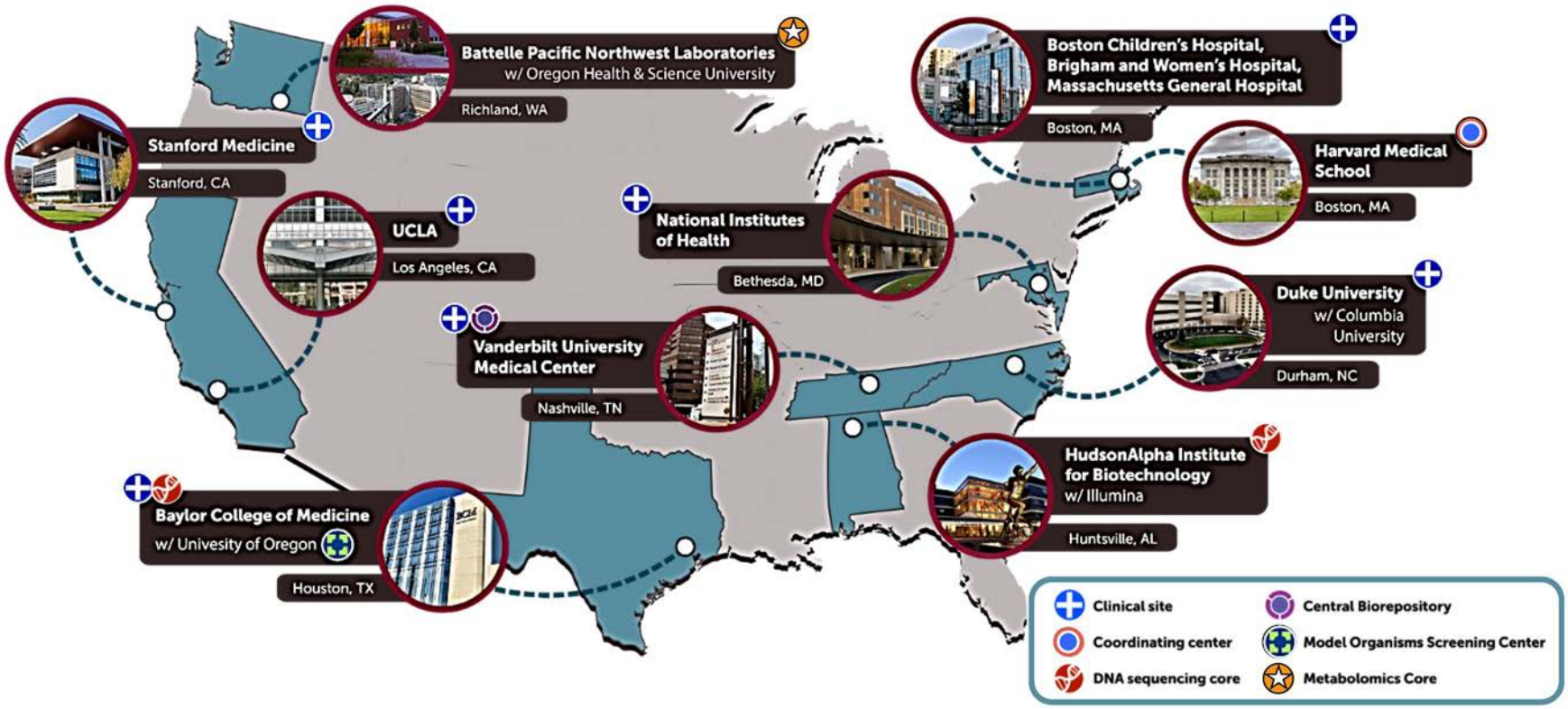
Undiagnosed Diseases Network

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

Undiagnosed Diseases Network

Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository



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

Undiagnosed Diseases Network

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

Undiagnosed Diseases Network

Solving medical mysteries through team science

Phase II:2018-2022

- **Baylor College of Medicine** — Houston, TX
- **Baylor College of Medicine and University of Oregon** — Houston, TX
- **Brigham and Women's Hospital, Boston Children's Hospital, Massachusetts General Hospital** — Boston, MA
- **Children's Hospital of Philadelphia and University of Pennsylvania** — Philadelphia, PA
- **Duke University and Columbia University** — Durham, NC
- **Harvard Medical School and University of Alabama at Birmingham** — Boston, MA
- **Mayo Clinic** — Rochester, MN
- **National Institutes of Health** — Bethesda, MD
- **Stanford Medicine** — Stanford, CA
- **UCLA** — Los Angeles, CA
- **University of Miami School of Medicine** — Miami, FL
- **University of Utah** — Salt Lake City, UT
- **University of Washington School of Medicine and Seattle Children's Hospital** — Seattle, WA
- **Vanderbilt University Medical Center** — Nashville, TN
- **Washington University in St. Louis** — St. Louis, MO

Clinical site | Coordinating center | DNA sequencing core | Central Biorepository | Model Organisms Screening Center | Metabolomics Core

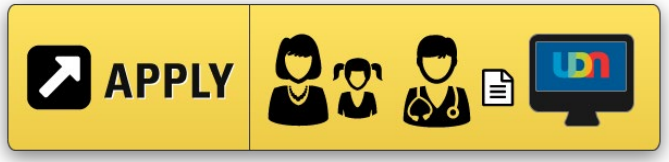
Twelve clinical sites, a coordinating center, a sequencing core, a metabolomics core, two model organism screening centers, and a central biorepository.

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

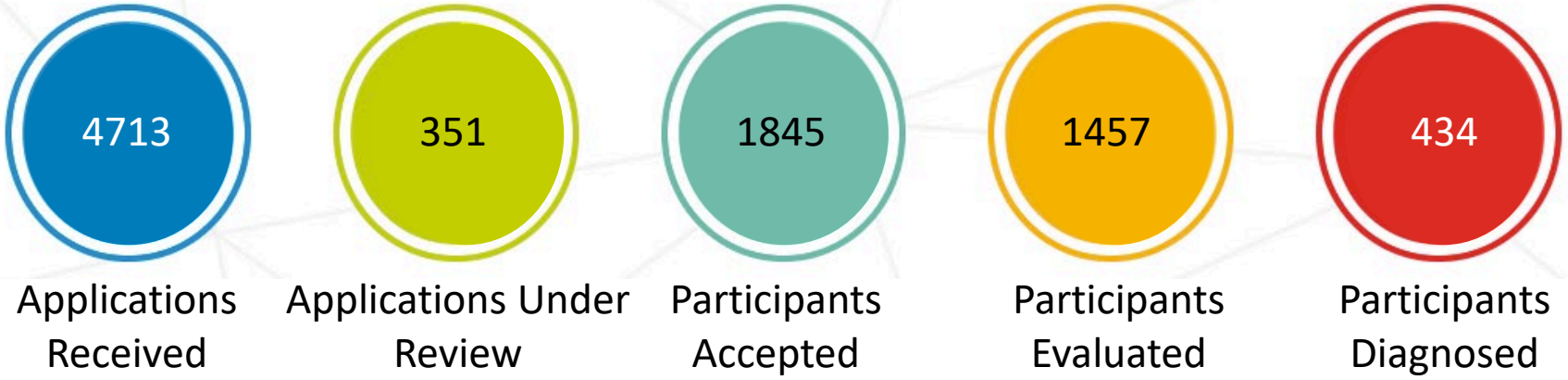
Undiagnosed Diseases Network

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

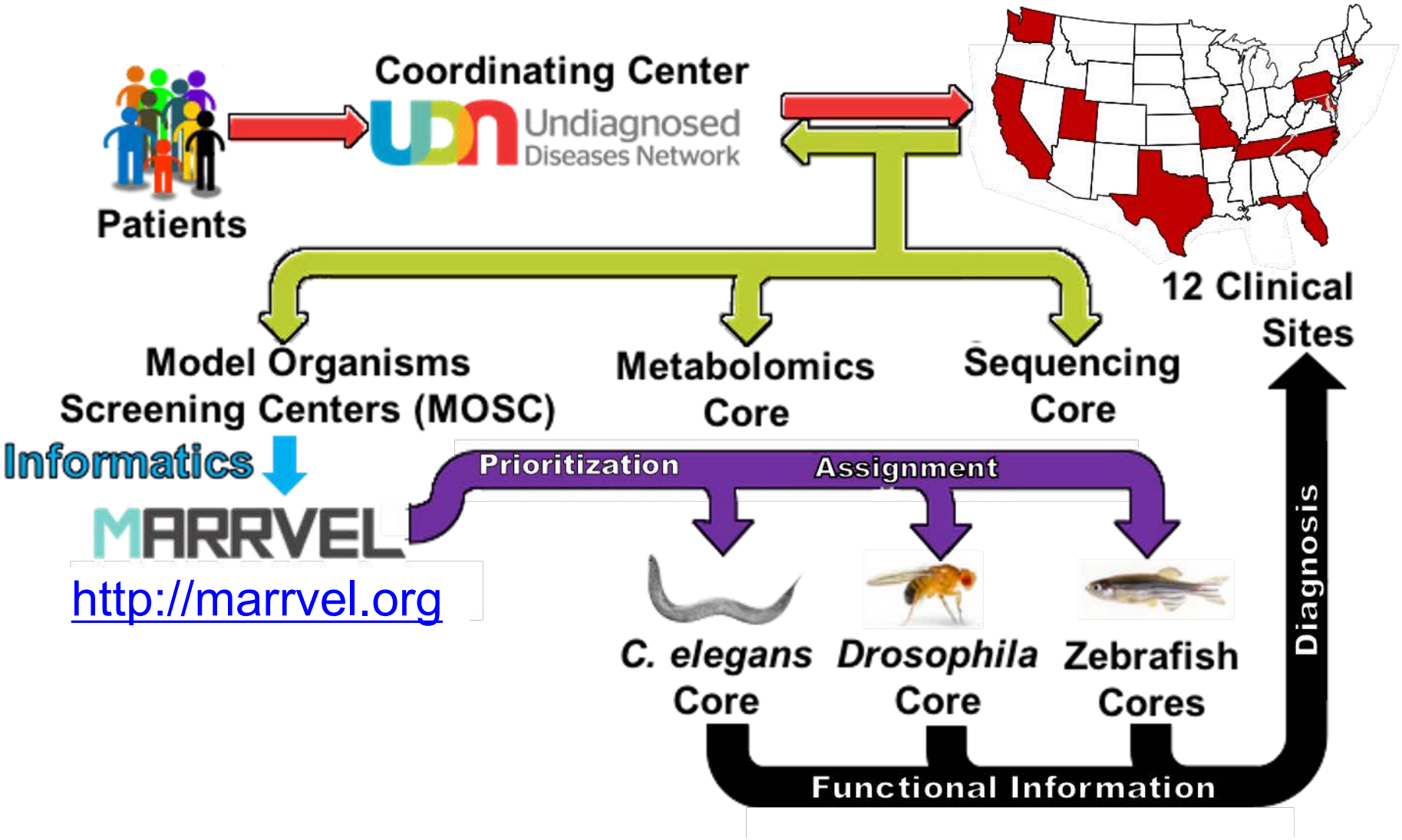
Adult specialties

- 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)



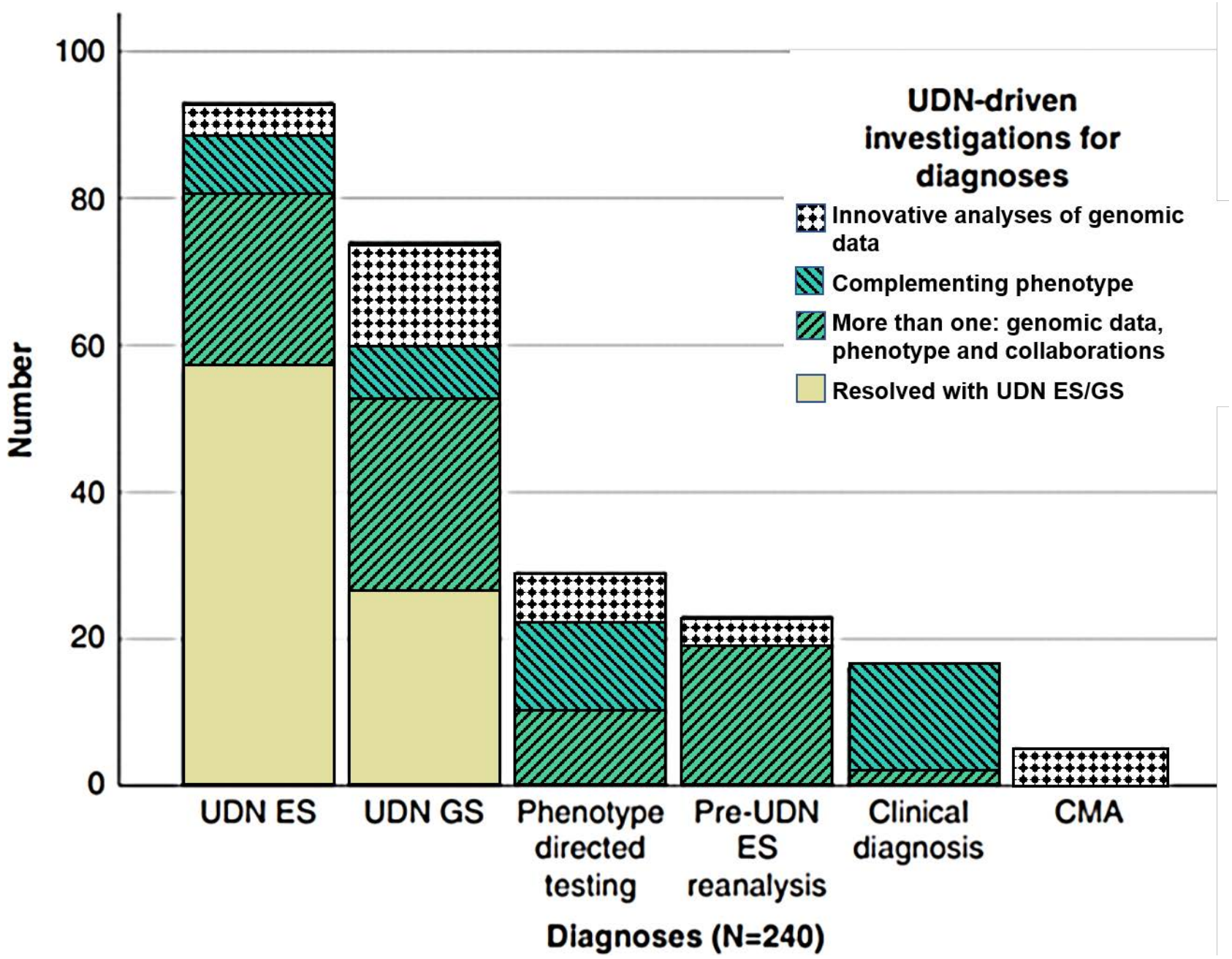
Participants with exome or genome sequencing complete: 1299

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

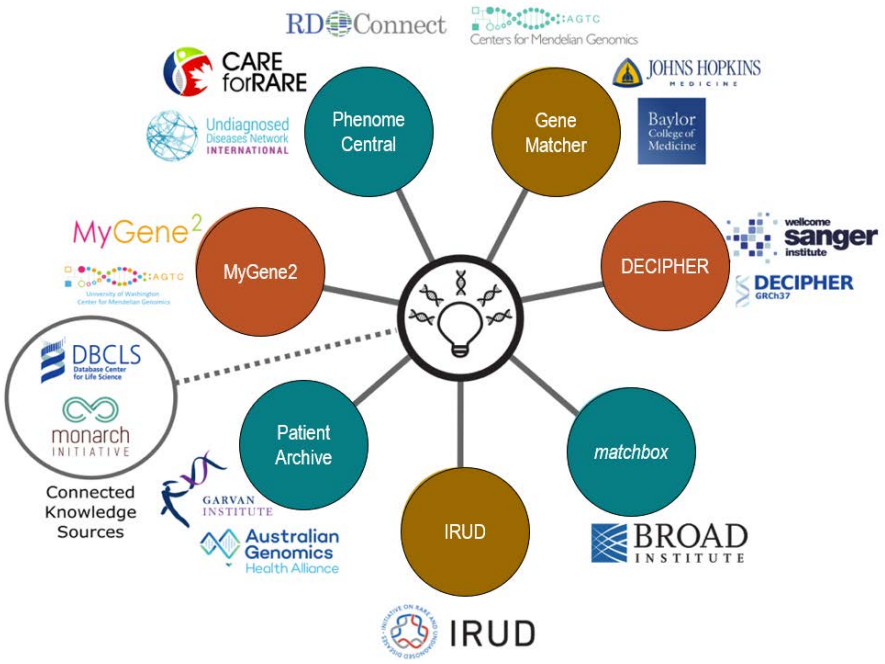
Undiagnosed Diseases Network



Schoch et al 2020

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/

Undiagnosed Diseases Network

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

Undiagnosed Diseases Network

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**