NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

The NIH Undiagnosed Network: hope for more families and links to the International Rare Diseases Community

Cynthia J. Tifft, M.D., Ph.D.

RareX/ICORD 2016,

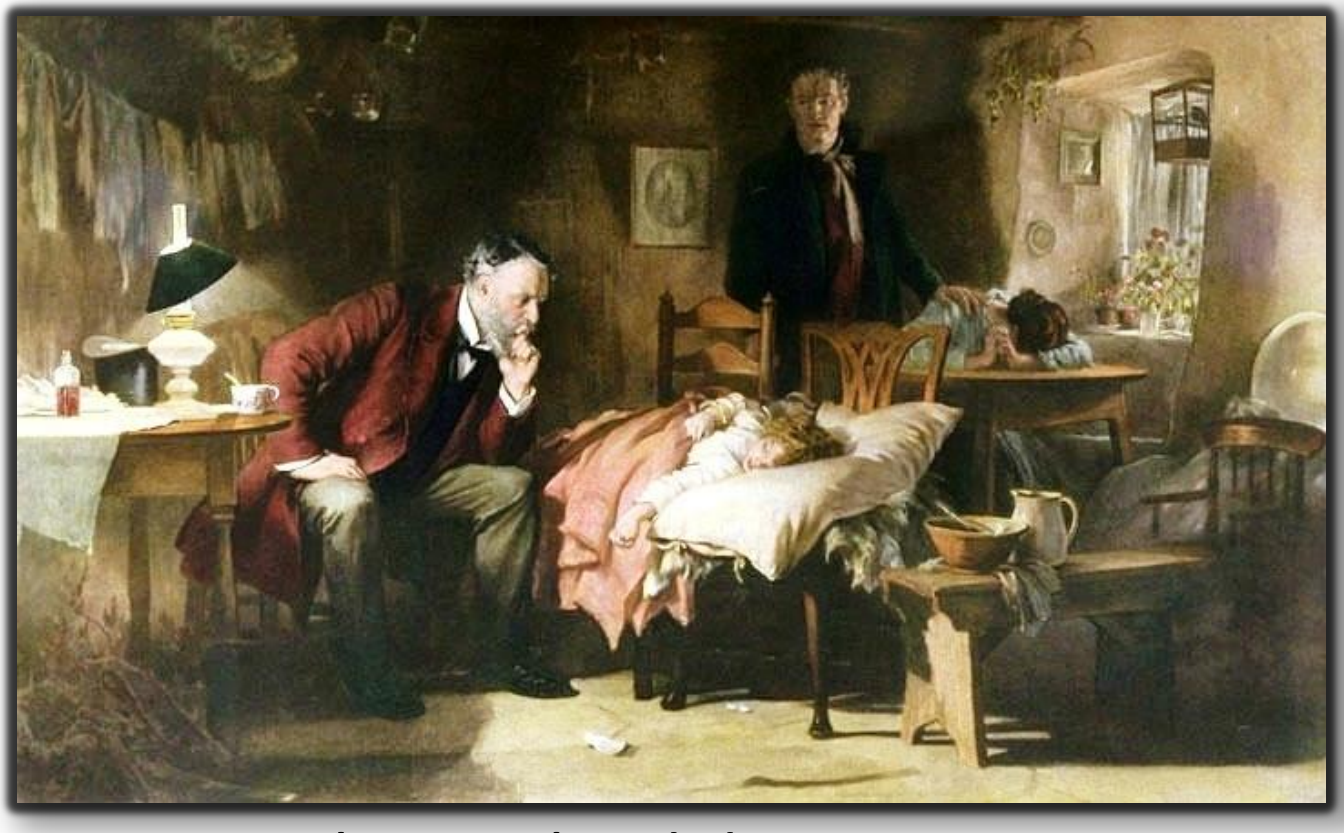
Cape Town, South Africa

20 October 2016

Every rare disease was once an undiagnosed disease!!

In rare and undiagnosed diseases, collaboration is EVERYTHING!!

In the beginning…2007 6% of patients contacting the NIH Office of Rare Disorders Research did not have a diagnosis



For those who did,

33% took 1 to 5 years

15% took > 5 years to obtain it!

The NIH Undiagnosed Diseases Program 2008-2015

Launched in May, 2008 as a 5 year pilot project with two main objectives that reflect the mission of the NIH:

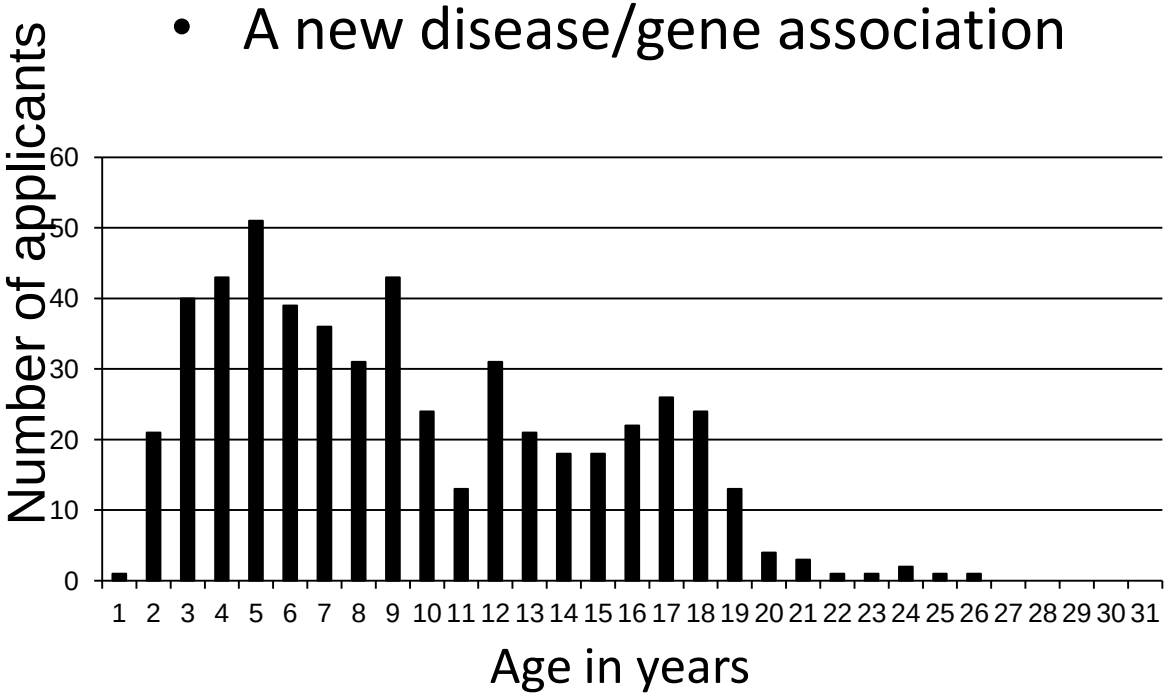
- Public Service
  - To provide answers to patients with mysterious conditions that had long eluded diagnosis
- Biomedical Research
  - To advance medical knowledge by providing insight into human physiology and the genetics of rare and common diseases

All UDP applicants are desperate--

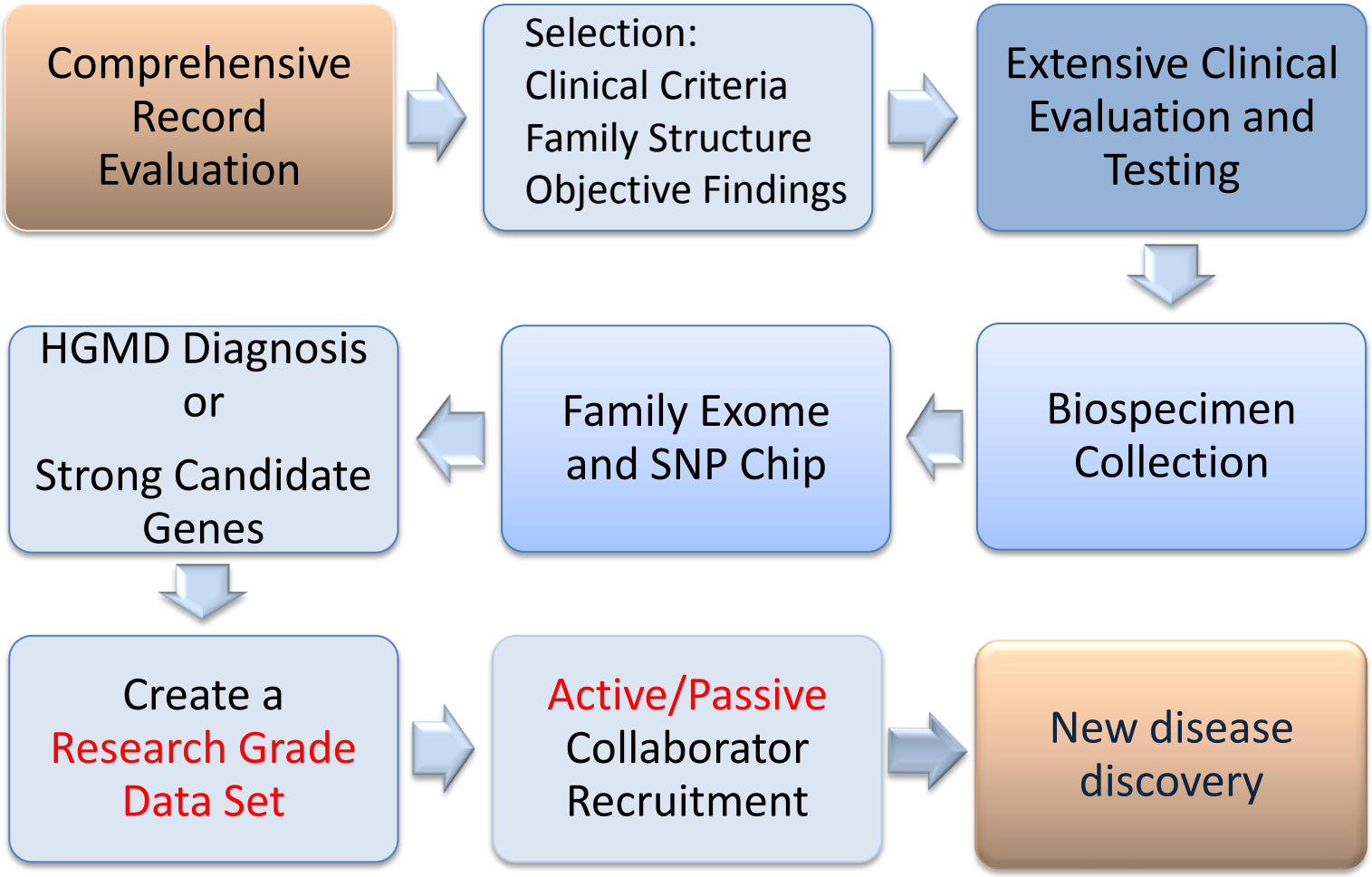
- Everyone gets something from the UDP
  - Complete charts are organized
  - Every chart is read thoroughly by specialists
  - Applicants not accepted (75%) & their physicians receive a personal letter with recommendations for further work up
  - Accepted applicants (25%) receive a one week inpatient evaluation at the NIH Clinical Center in Bethesda, Maryland

Working hypotheses…

- An extremely rare disease with expanded phenotype
- An unusual presentation of a more common disease
- More than one disease….
- A new disease/gene association



UDP Model


Comprehensive Record Evaluation
Selection:
Clinical Criteria
Family Structure
Objective Findings
Extensive Clinical Evaluation and Testing
Biospecimen Collection
Family Exome and SNP Chip
HGMD Diagnosis or Strong Candidate Genes
Create a Research Grade Data Set
Active/Passive Collaborator Recruitment
New disease discovery

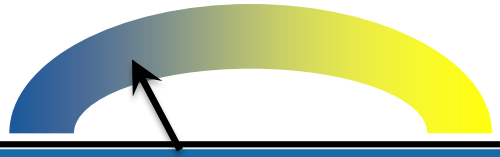
Without accurate phenotyping, exome/genome analysis is uninterpretable!

	F.P.	DOB ********		MR # 71-91-81-9		UDP# 7478			
	Monday 02/10/2014	Tuesday 02/11/2014		Wednesday 02/12/2014		Thursday 02/13/2014		Friday 02/14/2014	
7:00a	Admissions	7:00a		7:00a	Sedate Day	7:00a		7:00a	
7:30a		7:30a		7:30a		7:30a		7:30a	
8:00a		8:00a	EKG	8:00a	Sedated brain MRI/MRS,	8:00a	Speech and swallow study	8:00a	OT w/ Becky
8:30a	Informed Consent	8:30a		8:30a	eye exam, skin biopsy,	8:30a	w/ Beth Solomon in	8:30a	in Rehab Medicine
					and LP		Radiology		
9:00a	History and physical	9:00a	Neuropsych w/ Dr. Thurm	9:00a		9:00a		9:00a	
9:30a	on 1NW Inpatient Unit	9:30a	~ meet at the bedside	9:30a	Genetic	9:30a	Abdominal U/S	9:30a	EEG in 7SW Neuro
					Counseling				Testing
10:00a		10:00a		10:00a		10:00a		10:00a	
10:30a		10:30a		10:30a		10:30a		10:30a	
11:00a		11:00a		11:00a	EMG in PACU	11:00a		11:00a	Clinical Photos
11:30a		11:30a		11:30a		11:30a	Eye appointment	11:30a	
							w/ Dr. Zein in OP-11		
12:00p		12:00p	Neurology w/ Dr. Paul Lee	12:00p		12:00p		12:00p	
12:30p		12:30p	at the bedside	12:30p		12:30p		12:30p	
1:00p	Audiology and ABR	1:15p		1:00p		1:00p		1:15p	DEXA scan in Nuclear
1:30p	in OP-5	1:30p		1:30p		1:30p		1:30p	Medicine
2:00p		2:00p	Pre-Anesthesia Clinic	2:00p	Nutrition w/ Jennifer Myles	2:00p		2:00p	PT w/ Zavera
2:30p		2:30p		2:30p	at the bedside	2:30p		2:30p	
3:00p	Physiatry w/ Dr. Paul	3:00p	Echocardiogram in 5NE-N	3:00p		3:00p		3:00p	
3:30p	in Rehab Medicine	3:30p		3:30p		3:30p		3:30p	
									Wrap-Up
4:00p		4:00p	Neurology w/ Dr. Toro	4:00p		4:00p		4:00p	
4:30p		4:30p	at the bedside	4:30p		4:30p		4:30p	
5:00p		5:00p		5:00p		5:00p		5:00p	
6:00p		6:00p		6:00p		6:00p		6:00p	
7:00p		7:00p		7:00p		7:00p		7:00p	
8:00p		8:00p		8:00p		8:00p		8:00p	
9:00p		9:00p		9:00p		9:00p		9:00p	

PHENOTIPS

HPO terms:
a common language

Specificity meter



QUICK PHENOTYPE SEARCH: Enter keywords and choose among suggested ontology terms

▼CRANIOFACIAL
- ▶ NA Y N Craniosynostosis
- ▶ NA **Y** N **Cleft upper lip**
- ▶ NA Y N Cleft palate
- ▶ NA Y N Abnormal facial shape

Other
(enter free text and choose among suggested ontology terms)

▼EYE DEFECTS
- ▶ NA Y N Visual impairment
- ▶ NA Y N Abnormality of the cornea
- ▶ NA Y N Coloboma
- ▶ NA Y N Abnormality of the anterior chamber
- ▶ NA **Y** N **Cataract**
- ▶ NA Y N Abnormality of the retina
- ▶ NA Y N Abnormality of the optic nerve
- ▶ NA Y N Microphthalmos
- ▶ NA Y N Nystagmus
- ▶ NA Y N Strabismus

Other
(enter free text and choose among suggested ontology terms)

▼EAR DEFECTS

Deafness
- NA Y N Sensorineural
- NA Y N Conductive

- ▶ NA Y N Preauricular pit
- ▶ NA Y N Preauricular skin tag
- ▶ NA **Y** N **Abnormality of the outer ear**
- ▶ NA Y N Abnormality of the inner ear

CURRENT SELECTION

GROWTH PARAMETERS

Decreased body weight Delete · Clear details
Neonatal onset
Slow progression

CRANIOFACIAL

Cleft upper lip Delete · Clear details
No additional information.

EYE DEFECTS

Cataract Delete · Add details

EAR DEFECTS

Abnormality of the outer ear Delete · Add details

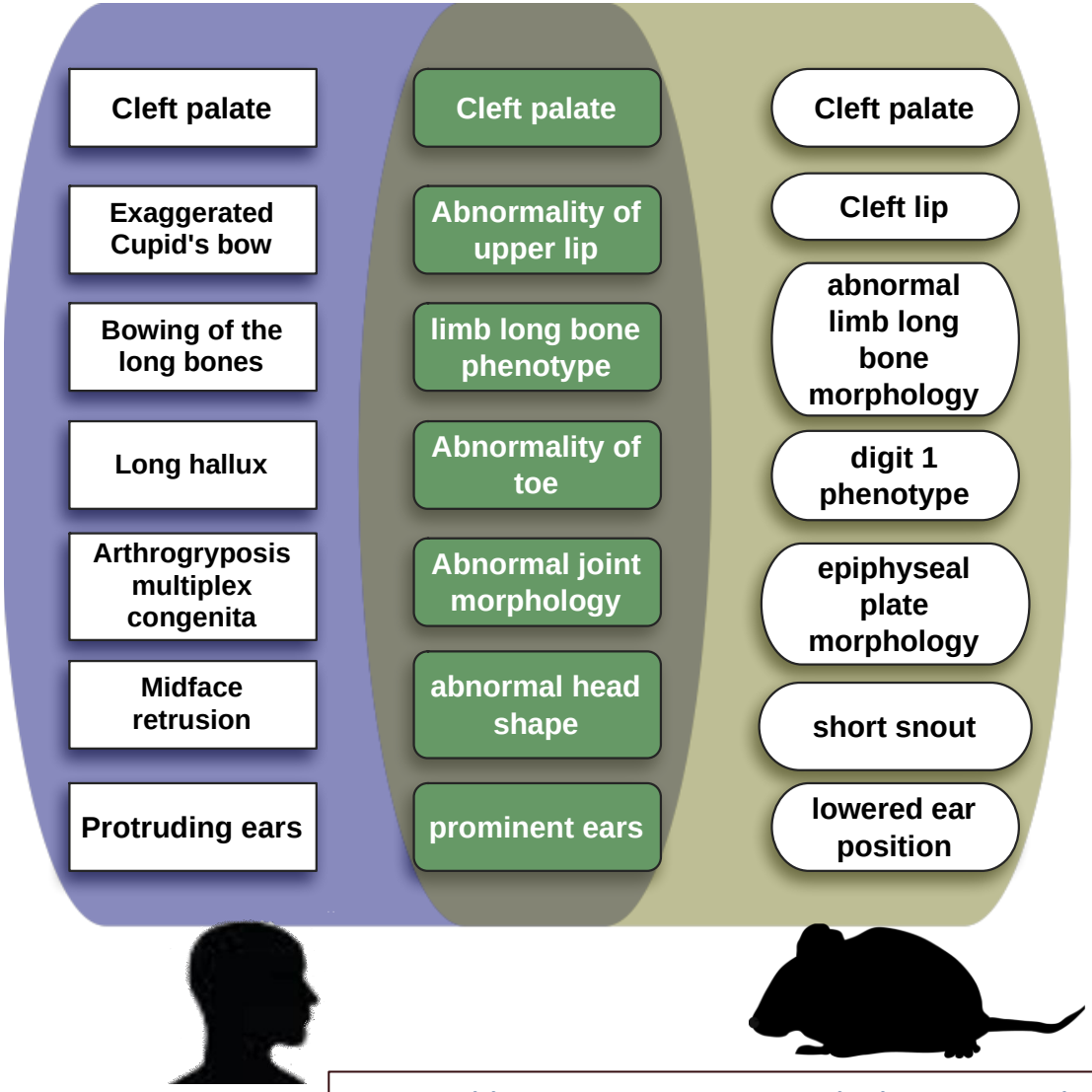
MUSCULOSKELETAL

Hip osteoarthritis Delete · Add details

BEHAVIOR, COGNITION AND DEVELOPMENT

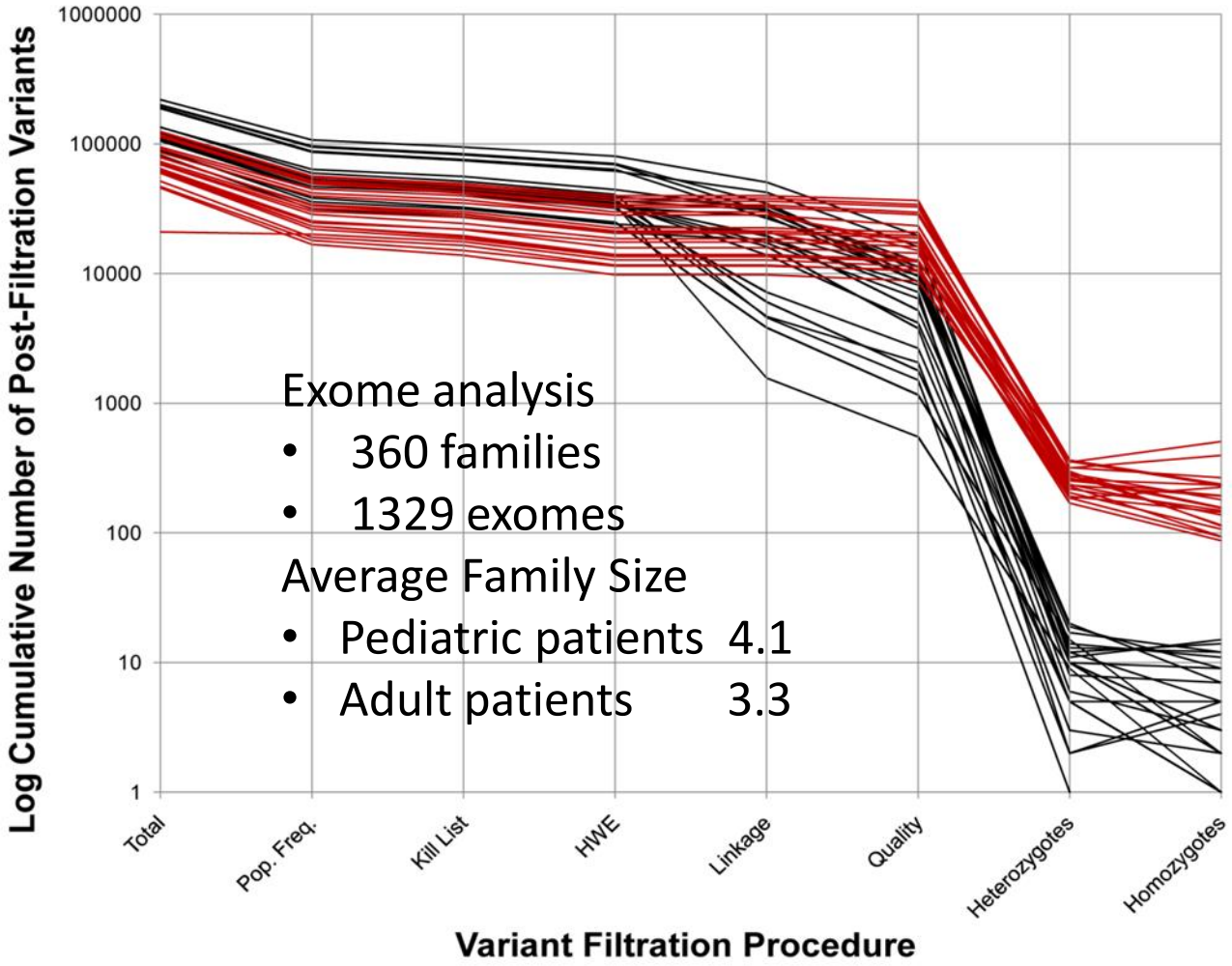
Repetitive compulsive behavior Delete · Add details
Mutism Delete · Add details
Self-injurious behavior Delete · Add details
Attention deficit hyperactivity disorder Delete · Add details
Behavioural/Psychiatric Abnormality Delete · Clear details
No additional information.

Phenotype similarity across patients or ….any organism



https://code.google.com/p/owltools/wiki/OwlSim

Filtered Variants, Family vs No Family



Analysis of DNA Sequence Variants Detected by High-Throughput Sequencing

HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

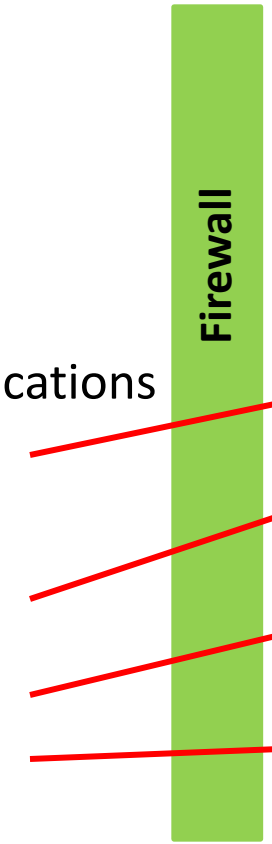
David R. Adams,[1,2*] Murat Sincan,[2] Karin Fuentes Fajardo,[1] James C. Mullikin,[5†] Tyler M. Pierson,[1,4] Camilo Toro,[1] Cornelius F. Boerkoel,[1] Cynthia J. Tifft,[1,3] William A. Gahl,[1,2,3] and Tom C. Markello[3]

NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research

UDP Integrated Collaboration System (UDPICS) Facilitates Active Collaboration

UDP Staff

- Patient identifiers
  - Medical records
  - Photos & videos
  - Consents & Communications
  - Pedigrees
  - Exome/genome
  - HPO phenotyping
  - Candidate genes
  - Biospecimens



Collaborators

- De-identified information
  - Pedigrees
  - HPO clinical phenotype &de-identified medical records
  - List of candidate variants with bioinformatic documentation
  - Available biospecimens

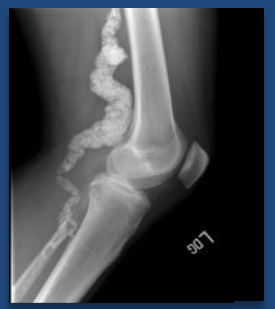
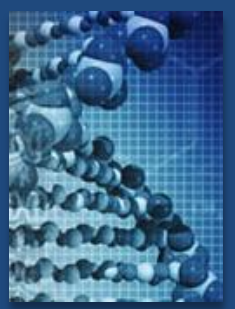
Each patient's disease is a unique research project!

Matchmaker Exchange Facilitates Passive Collaboration

UDP statistics 2008-2015

• Inquiries	7585	
• Medical Records	3124	(41%)
• Acceptances	966	(31%)
– Pediatric probands	348	(36%)
– Female	519	(54%)
– Neurologic phenotype		(>50%)
– International patients		
• Diagnoses	176 in 150	(20%)
– Pediatric diagnoses	93	(33%)



The Undiagnosed Diseases Network

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

UDN Overall Goal

To **extend the success** of the NIH Undiagnosed Diseases Program (UDP) into an Undiagnosed Diseases Network (UDN), composed of UDN Clinical Sites including the UDP, a Coordinating Center, and UDN Core Laboratories, **forming a sustainable national resource** to diagnose both rare and new diseases, **advance laboratory and clinical research**, **enhance global coordination and collaboration** among laboratory and clinical researchers, and **share resulting data and approaches** throughout the scientific and clinical communities.

Undiagnosed Diseases Network

The Undiagnosed Diseases Network

18 Institutions

234 Investigators

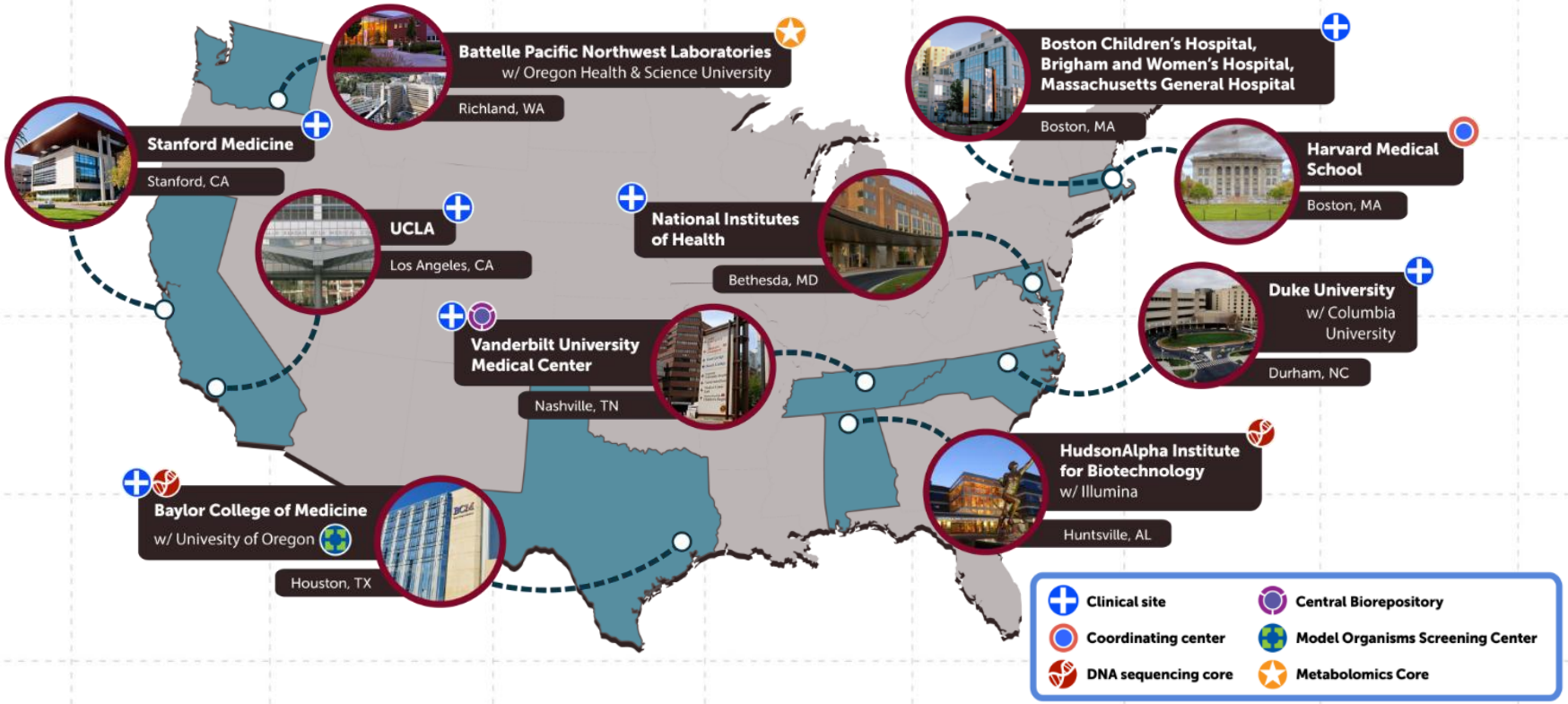
- Network-wide Protocol
- Central IRB
- Data Sharing and Use Agreement
- “Best practices” to share with the clinical and research communities and with patients

Gateway Launched Sept 2015!

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

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.

Identified patient information is available to all sites to aid in diagnosis through a common Date Sharing and Use Agreement

NORD®
National Organization for Rare Disorders

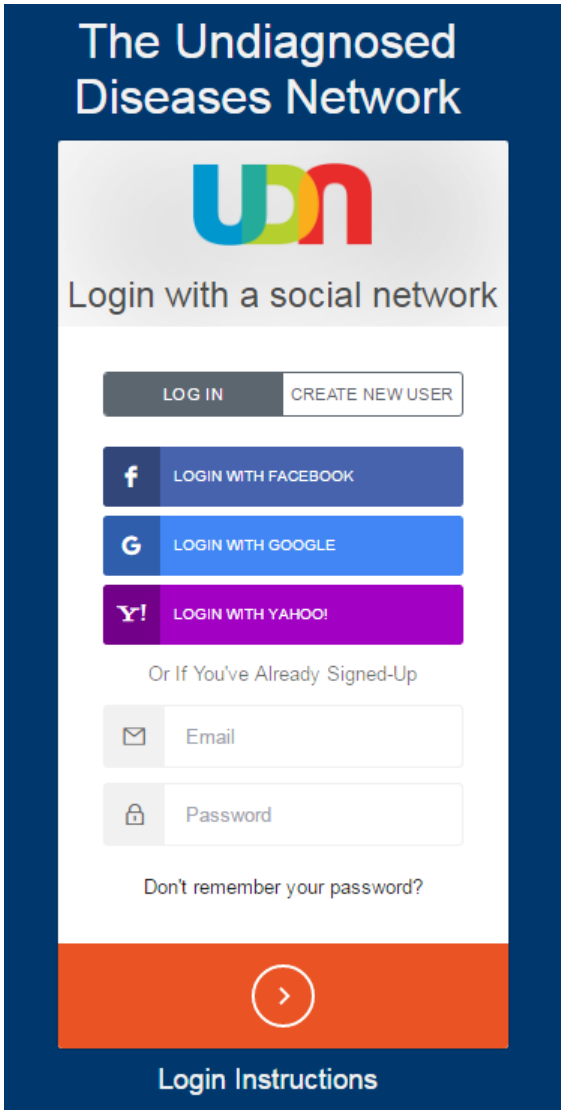
Help from patient advocates…

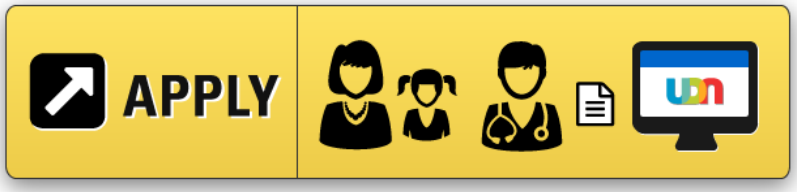
The team is composed of dedicated runners from around the world who will not only spend their personal time training for the marathons, but also host numerous events to raise funds and engage people in the cause. (Learn more about the runners at: www.running4rare.org)

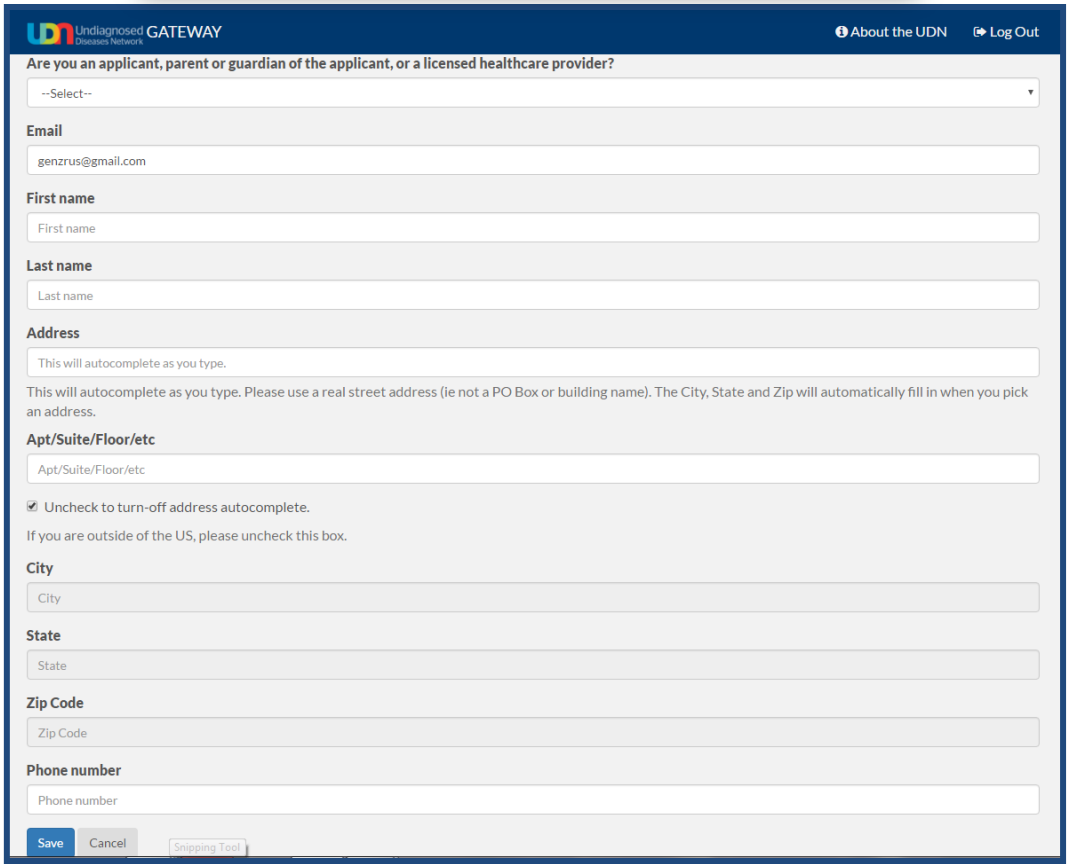
The funds raised by the Running for Rare Team will support the NORD/Undiagnosed Diseases Network (UDN) Patient Assistance Program. This program provides financial assistance to families who have exhausted all other alternatives for seeking a diagnosis. NORD will help cover the basic diagnostic testing needed for patients and families to apply into the Undiagnosed Diseases Network.

Undiagnosed Diseases Network

Patient Online Application





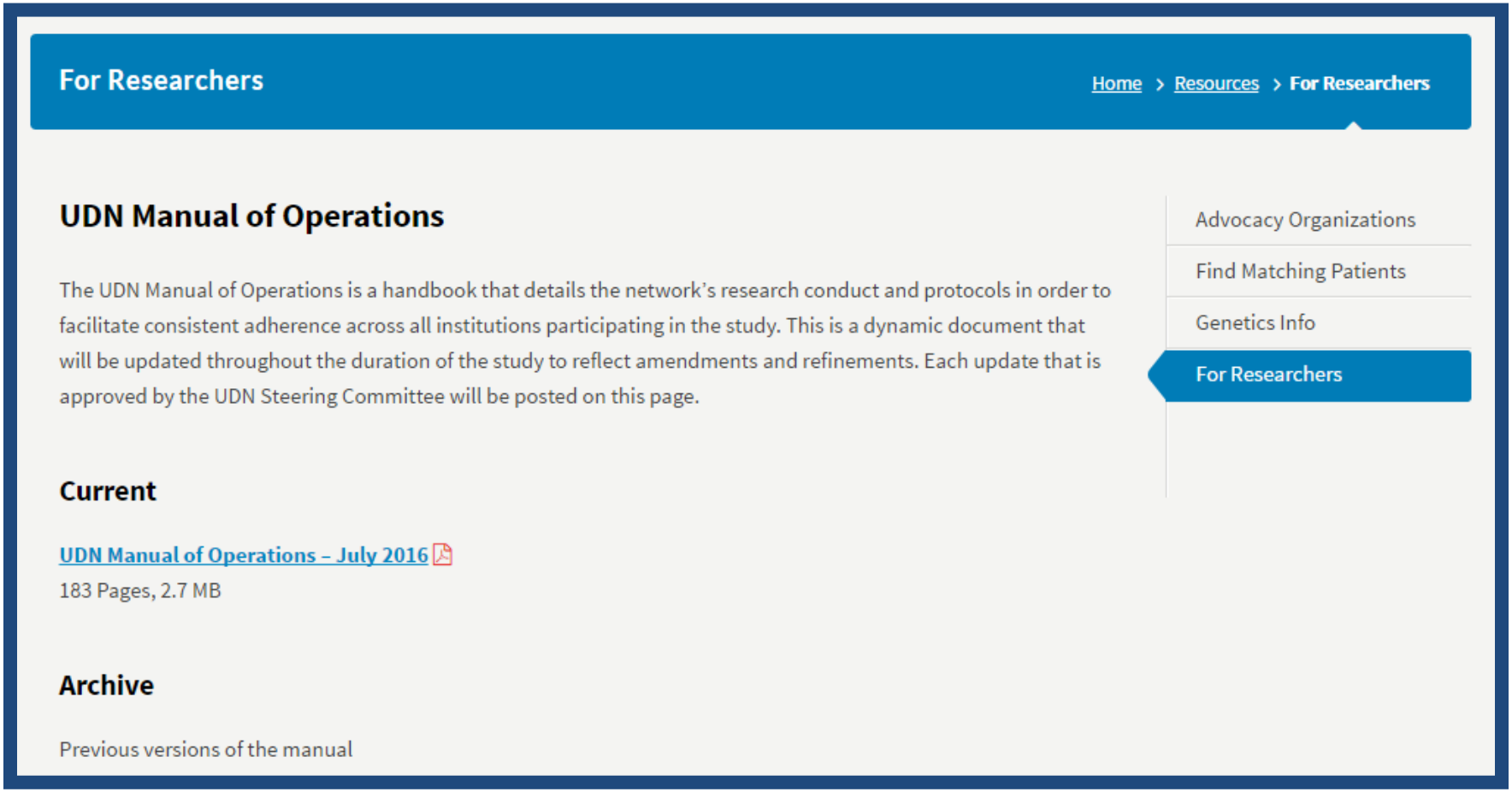


Undiagnosed Diseases Network

https://undiagnosed.hms.harvard.edu/apply/

Undiagnosed Diseases Network

Sharing of “Best Practices”



For Researchers

Home › Resources › For Researchers

UDN Manual of Operations

The UDN Manual of Operations is a handbook that details the network's research conduct and protocols in order to facilitate consistent adherence across all institutions participating in the study. This is a dynamic document that will be updated throughout the duration of the study to reflect amendments and refinements. Each update that is approved by the UDN Steering Committee will be posted on this page.

Advocacy Organizations
Find Matching Patients
Genetics Info
For Researchers

Current

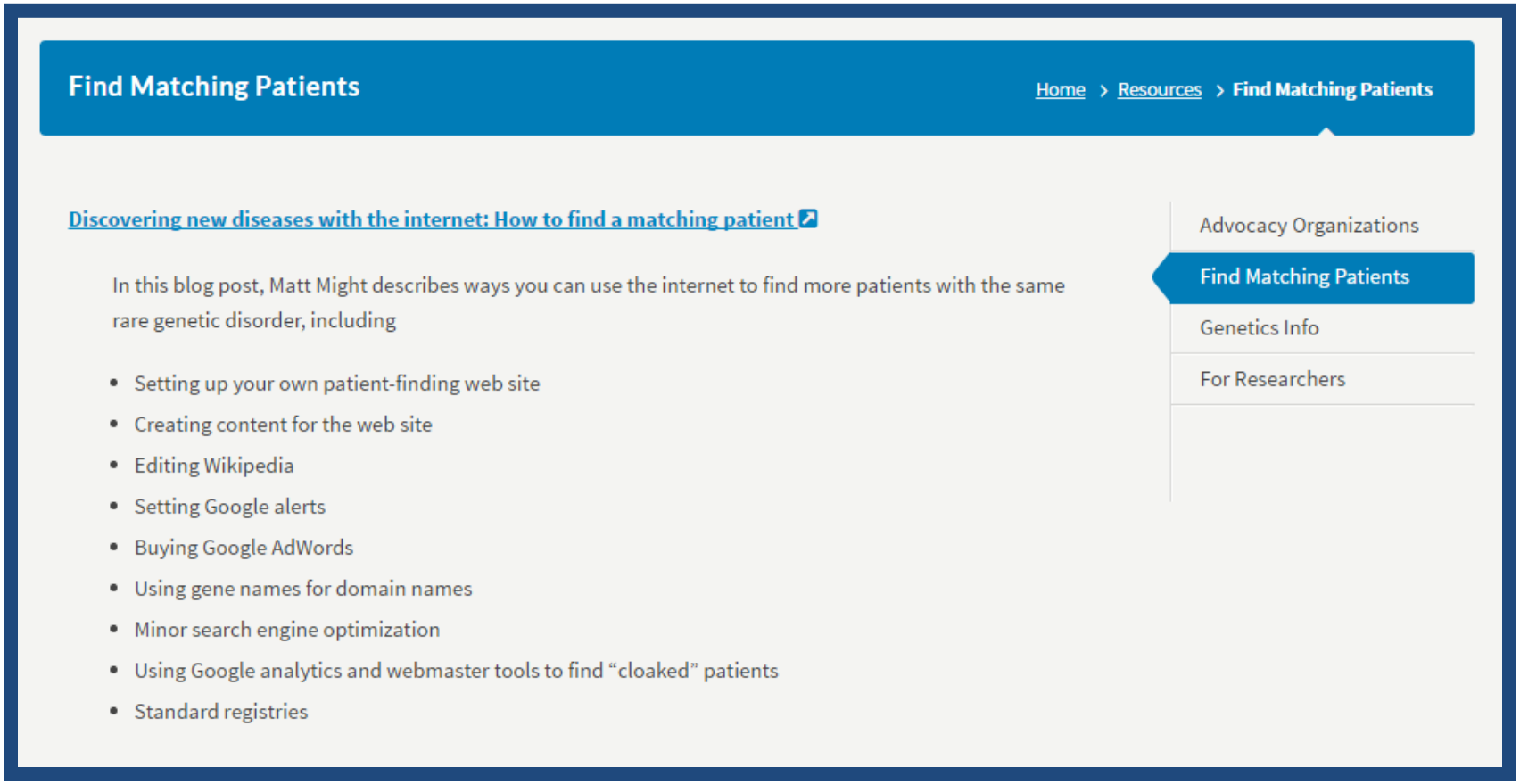
UDN Manual of Operations – July 2016
183 Pages, 2.7 MB

Archive

Previous versions of the manual

Undiagnosed Diseases Network

Empowering Patients

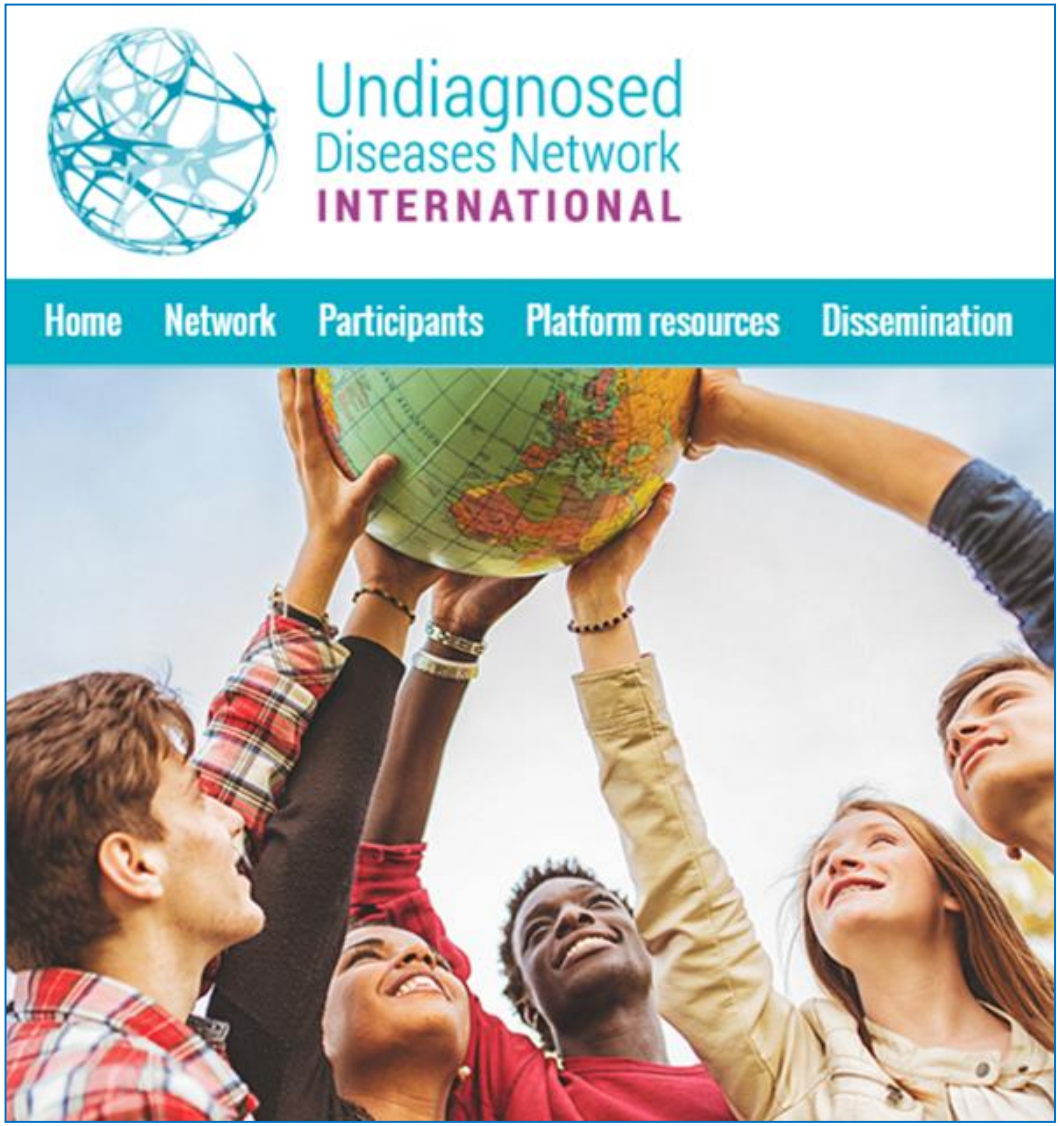


Gateway Launched Sept 2015!

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

- UDN has received 994 applications
  - Accepted 380 participants
  - Completed 137 evaluations
- UDN has made diagnoses*
  - 24 confirmed
  - 10 clinical
  - 11 strong candidates

*numbers as of 10/12/2016



GENERAL AIMS

Improve the level of diagnosis and care for patients with undiagnosed diseases

through the development of ***common protocols*** designed by a large community of investigators.

Facilitate research into the etiology of undiagnosed diseases,

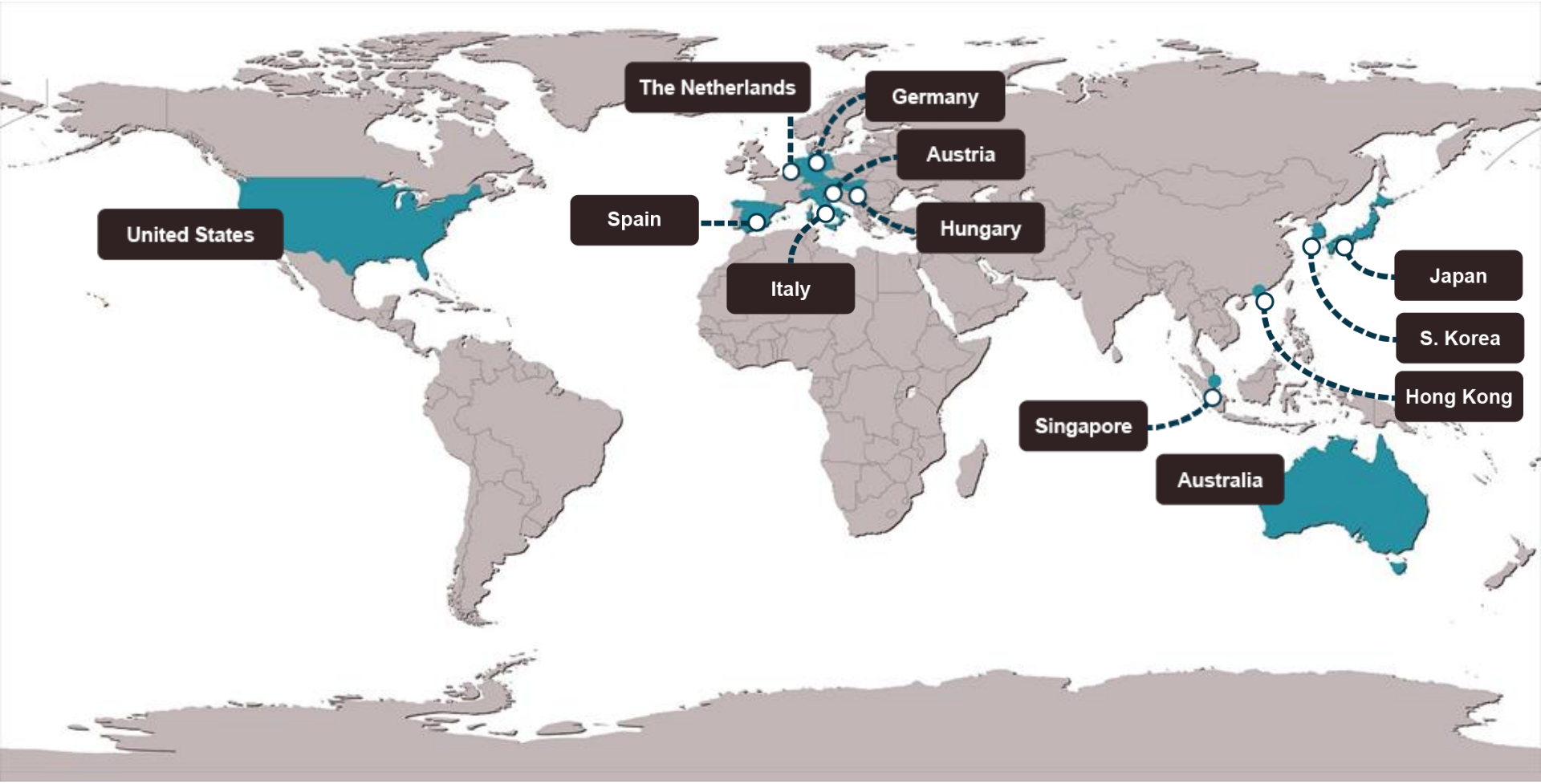
by collecting and sharing standardized, ***high-quality clinical*** and ***laboratory data*** (including genotyping, phenotyping, and documentation of environmental exposures).

Create an integrated and collaborative community across ***multiple Countries*** and ***among laboratory*** and ***clinical investigators*** prepared to investigate the pathophysiology of these newly recognized and rare diseases.

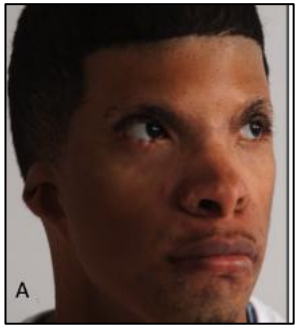
www.udninternational.org
udni@iss.it

Undiagnosed Diseases Network

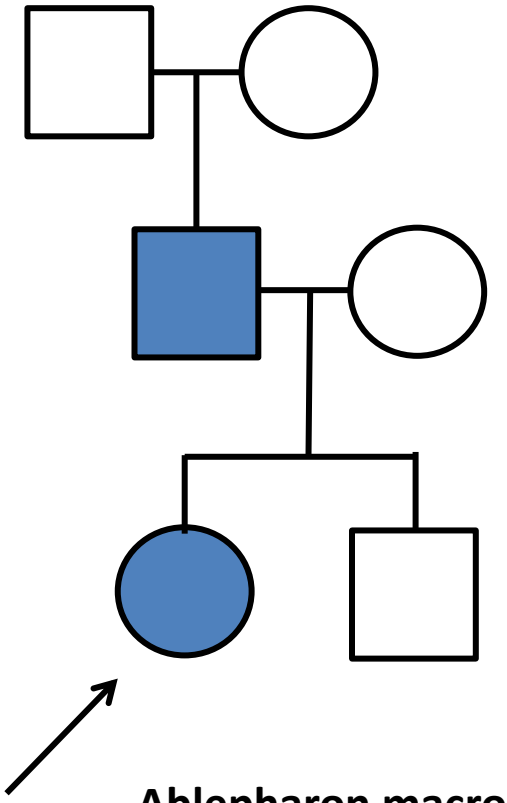
Undiagnosed Diseases Network INTERNATIONAL



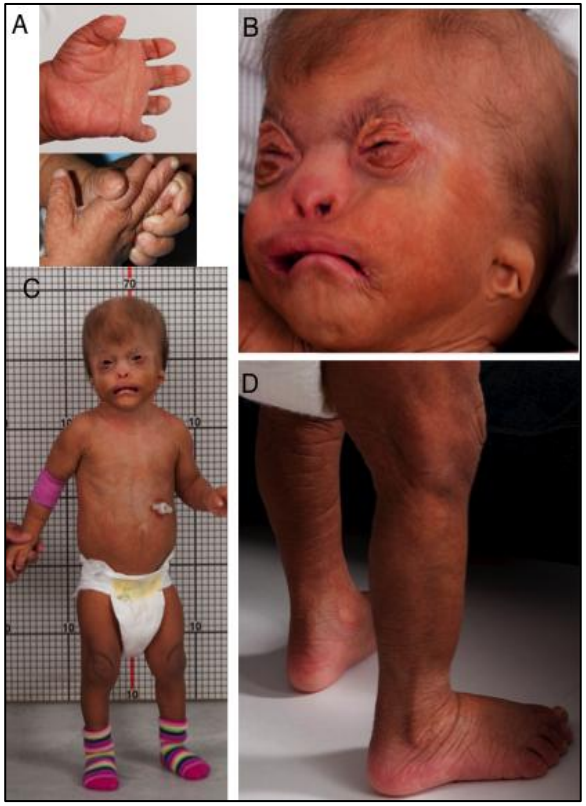
Teamwork and the global community…



Mosaicism in 1st generation (fertile)



Ablepharon macrostomia syndrome



Recurrent Mutations in the Basic Domain of *TWIST2* Cause Ablepharon Macrostomia and Barber-Say Syndromes

Shannon Marchegiani,[1,2,31] Taylor Davis,[1,31] Federico Tessadori,[3,31] Gijs van Haaften,[4] Francesco Brancati,[5] Alexander Hoischen,[6] Haigen Huang,[7] Elise Valkanas,[1] Barbara Pusey,[1] Denny Schanze,[8] Hanka Venselaar,[6] Anneke T. Vulto-van Silfhout,[6] Lynne A. Wolfe,[1,9] Cynthia J. Tifft,[1,9] Patricia M. Zerfas,[10] Giovanna Zambruno,[11] Ariana Kariminejad,[12] Farahnaz Sabbagh-Kermani,[13] Janice Lee,[14] Maria G. Tsokos,[15] Chyi-Chia R. Lee,[15] Victor Ferraz,[16] Eduarda Morgana da Silva,[16] Cathy A. Stevens,[17] Nathalie Roche,[18] Oliver Bartsch,[19] Peter Farndon,[20] Eva Bermejo-Sanchez,[21] Brian P. Brooks,[22] Valerie Maduro,[1] Bruno Dallapiccola,[23] Feliciano J. Ramos,[24] Hon-Yin Brian Chung,[25] Cédric Le Caignec,[26] Fabiana Martins,[27] Witold K. Jacyk,[28] Laura Mazzanti,[29] Han G. Brunner,[6,30] Jeroen Bakkers,[3] Shuo Lin,[7] May Christine V. Malicdan,[1,9,*] Cornelius F. Boerkoel,[1] William A. Gahl,[1,9,*] Bert B.A. de Vries,[6] Mieke M. van Haelst,[4] Martin Zenker,[8,32] and Thomas C. Markello[1,32]

47 authors from 11 countries

TWIST2:c.223G>A(p.E75K)

Transcription factor

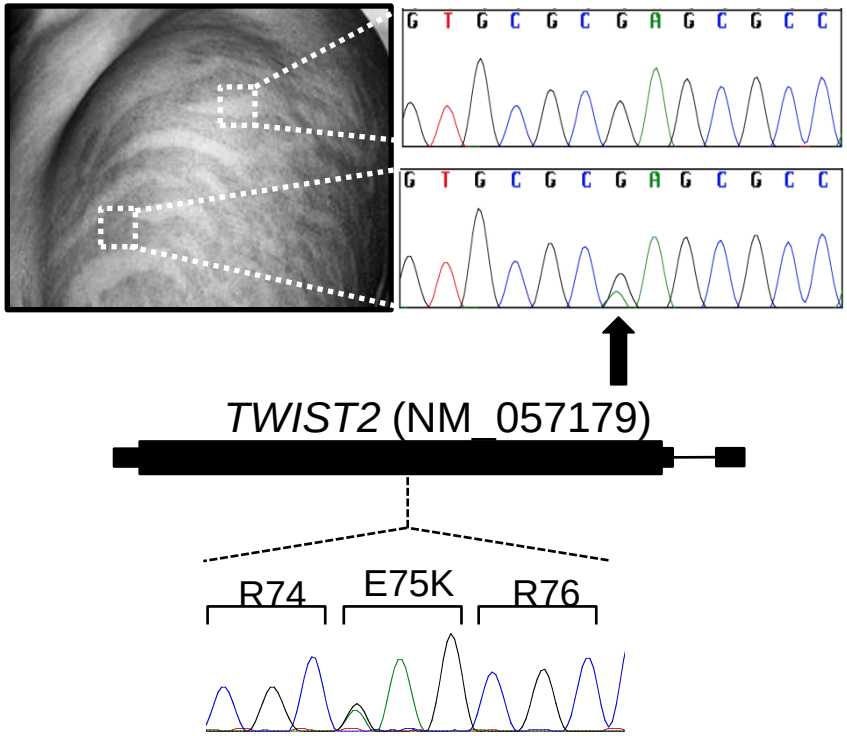
Group A helix-loop-helix transcription factor (E box)

Mesenchyme and craniofacial and dermis in embryogenesis plus cell maintenance

Autosomal dominant

7 families with ablepharon macrostomia

10 families with Barber-Say syndrome



"A small group of thoughtful people could change the world. Indeed, it's the only thing that ever has."

-Margaret Mead

Acknowledgements

UDP

William Gahl
Stephen Groft
David Adams
May Malicdan
Camilo Toro
cast of > 100 others

NIH Undiagnosed Diseases Program

UDN

William Gahl
Anastasia Wise
234 Investigators
many, many others

UDN Undiagnosed Diseases Network

Undiagnosed Diseases Network INTERNATIONAL

UDNI

Domenica Taruscio
William Gahl
Helene & Mikk Cederroth
Investigators from 13 countries