The NIH Undiagnosed Diseases Program: A Work in Progress

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TMF-Workshop:
Registries for patients with undiagnosed rare diseases
21 November 2013

6% of patients contacting the NIH Office of Rare Disorders do not have a diagnosis

In the United States 6% of the general population suffers from a rare disorder

The NIH Undiagnosed Diseases Program

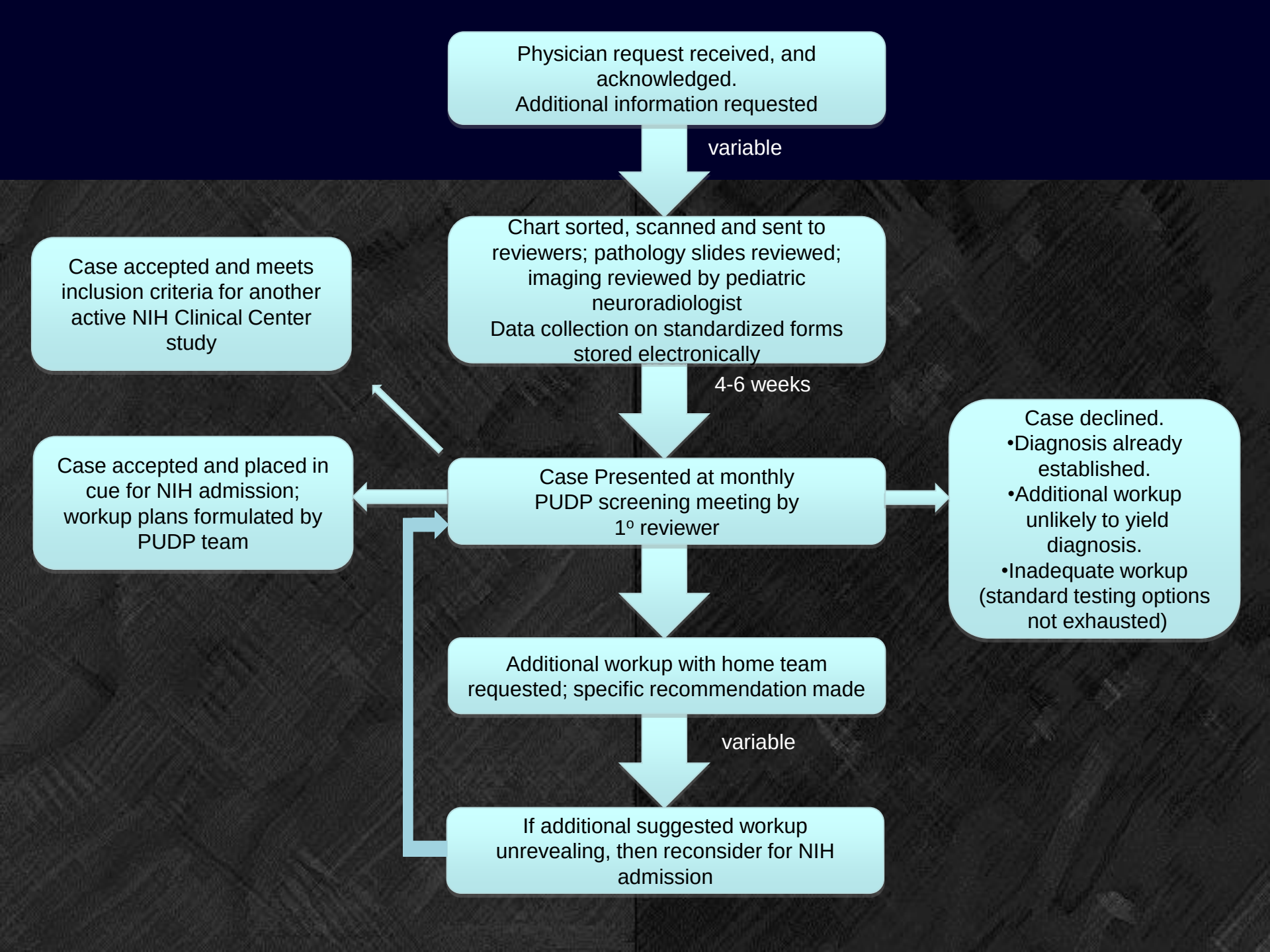
Launched in May, 2008 as a 5 year pilot project with two main objectives:

- 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

The "House of Hope"

UDP Operations

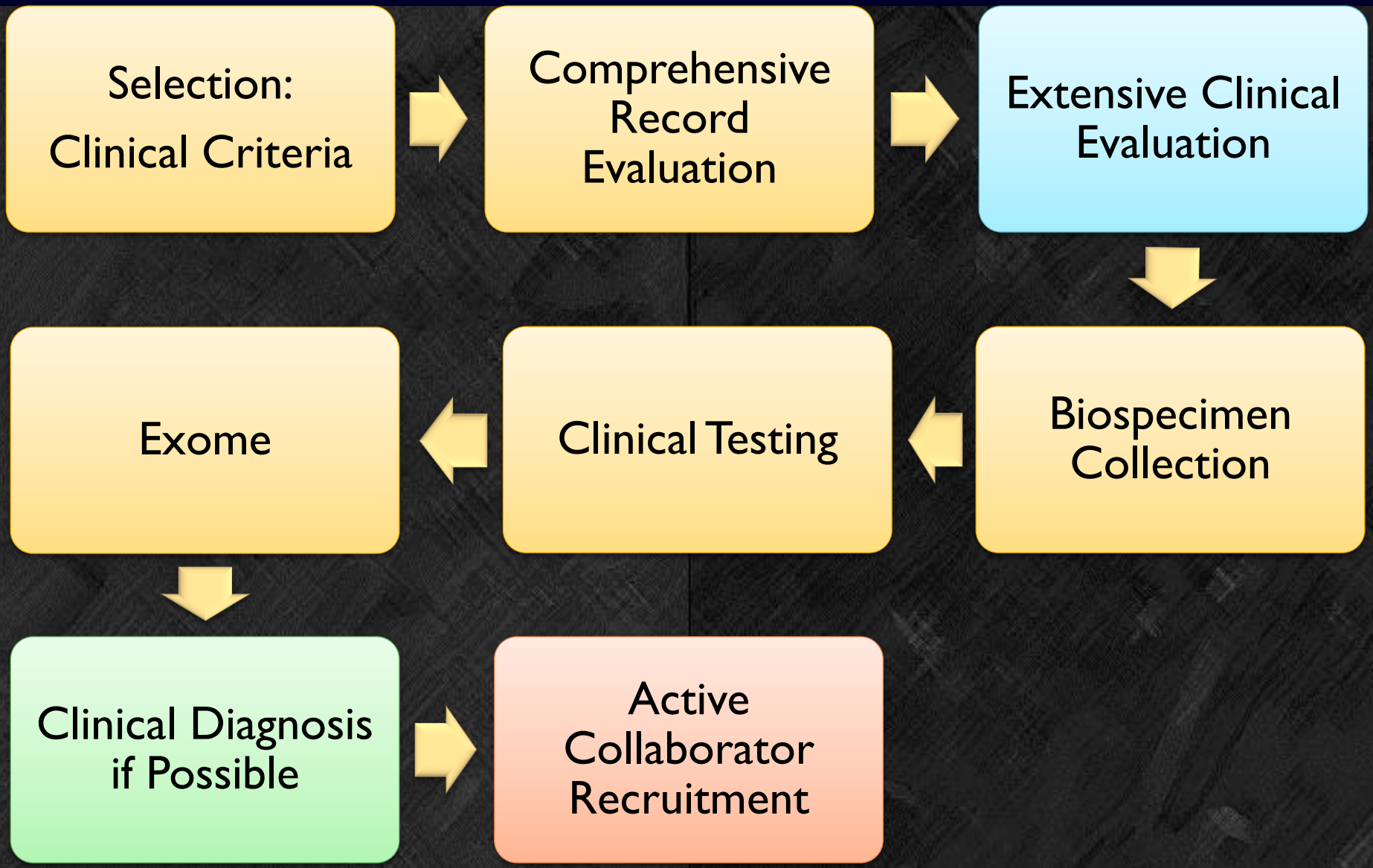
- Adult and pediatric directors triage records for review by appropriate specialists
- Directors synthesize reviews and make a final disposition
- Patients/referring physicians are informed
  - Accepted patients are admitted for a 1 week evaluation
  - The majority of patients who are not accepted receive personalized letters with recommendations for further work up


Physician request received, and acknowledged.
Additional information requested
variable
Chart sorted, scanned and sent to reviewers; pathology slides reviewed; imaging reviewed by pediatric neuroradiologist
Data collection on standardized forms stored electronically
4-6 weeks
Case accepted and meets inclusion criteria for another active NIH Clinical Center study
Case accepted and placed in cue for NIH admission; workup plans formulated by PUDP team
Case Presented at monthly PUDP screening meeting by 1º reviewer
Case declined.
•Diagnosis already established.
•Additional workup unlikely to yield diagnosis.
•Inadequate workup (standard testing options not exhausted)
Additional workup with home team requested; specific recommendation made
variable
If additional suggested workup unrevealing, then reconsider for NIH admission

Optimizing Selection Criteria

- Patients more likely to be selected
  - Objective documented physical or biochemical finding
  - Completely evaluated in an academic medical setting
  - Family structure favorable to genetic analysis
    - Both parents available for blood samples
    - Unaffected sibling
    - Additional affected members with the same or very similar phenotype
    - Consanguineous families

UDP Process


Selection:
Clinical Criteria
Comprehensive Record Evaluation
Extensive Clinical Evaluation
Biospecimen Collection
Clinical Testing
Exome
Clinical Diagnosis if Possible
Active Collaborator Recruitment

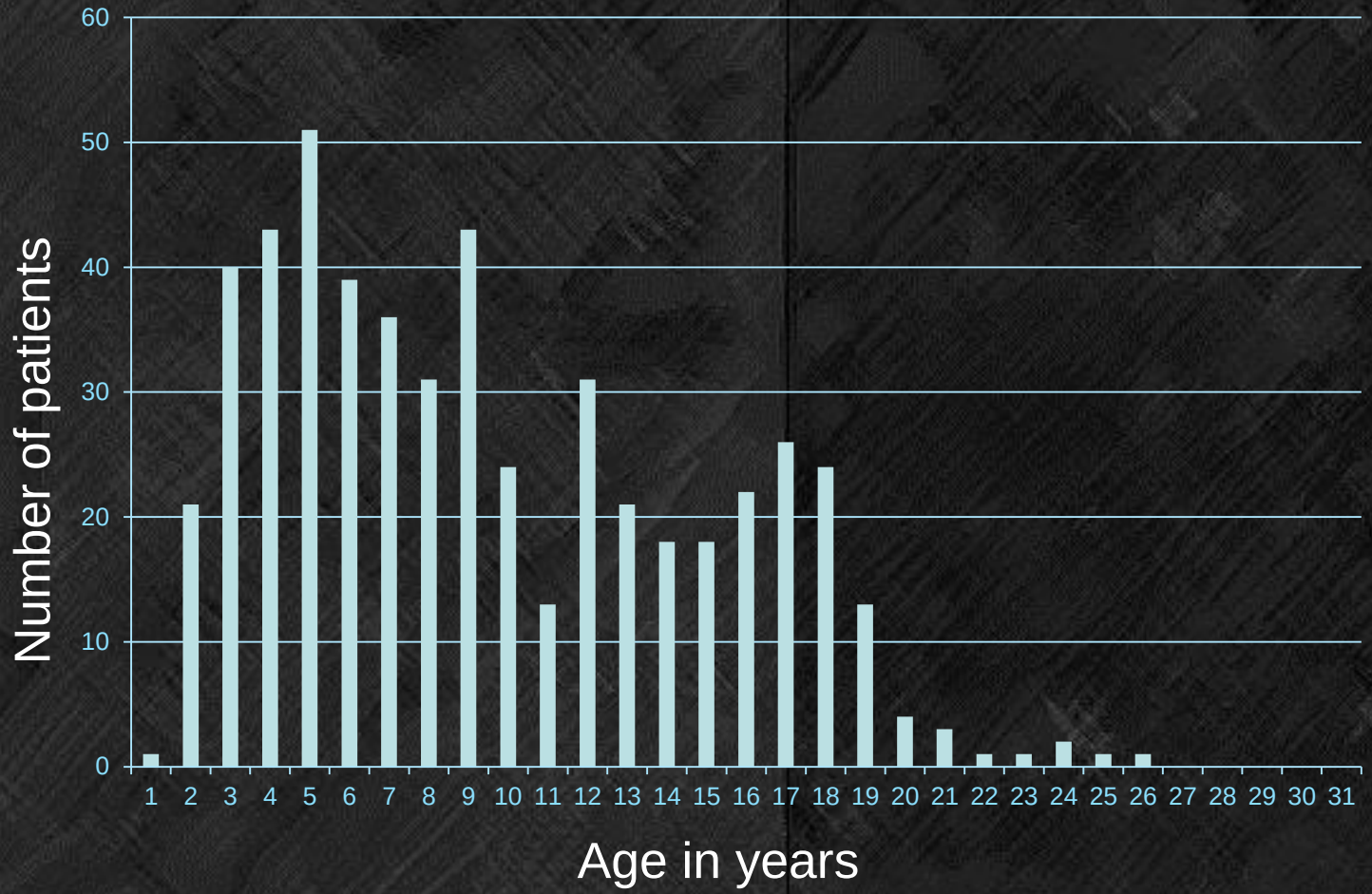
Good Response/Some Success

- 8000 inquiries
  - 3000 medical records reviewed
    - 650 participants accepted into program
    - Diverse symptoms, > ½ neurologic, ~⅓ pediatric
    - 24% offered some diagnostic results/clarification
      - Range from named syndromes to well understood diseases
    - 76% not able to be provided any diagnostic clarification

Major Phenotypes

	Applicants	Accepted
Cardiovascular	40	22
Dermatology	47	8
Endocrine	33	13
Fibromyalgia/CFS	79	3
Gastrointestinal	106	13
Hematology	23	7
Immunology	63	15
Neurology	512	164
Pulmonary	28	14
Renal	19	10
Rheumatology	56	19
Female	60%	56%

Age distribution of PUDP applicants



Pediatric UPD 2008-2013

- Patients Evaluated — 215 (193 families)
  - Patients diagnosed — 56 (26%)
    - Two families had 3 diagnoses each
    - Nine families had 2 or more affected sibs
    - Two patients had a deceased sib with the same phenotype
  - Genetic diagnoses made — 50
    - Next Gen/SNP analysis — 22
    - Conventional testing — 28

Selected Diagnoses

NT5E/calcification	KCTD7/ataxia	*SMS*/neuro and bone
Call Fleming	MBTPS2/Ichthyosis	*ARH3*/neuropathy
SPG7/HSP	C19orf12/neuro	*SOX10*/Waardenburg
ABCA4/Stargardt	C9orf72/dementia	*AFG3L2*
Joubert Syndrome	24 hydroxylase def	*GRIN2A*/neuro
IgG4 sclerosing fibrosis	*CHST14*	*GRIN2B*/neuro
Dejerine-Sottas	*LMNB1*/leukodyst.	*DNAH1*/ciliopathy
Pitt Hopkins	FA2H	*RAI1*/Smith Magenis

What about the 75% of cases unsolved…

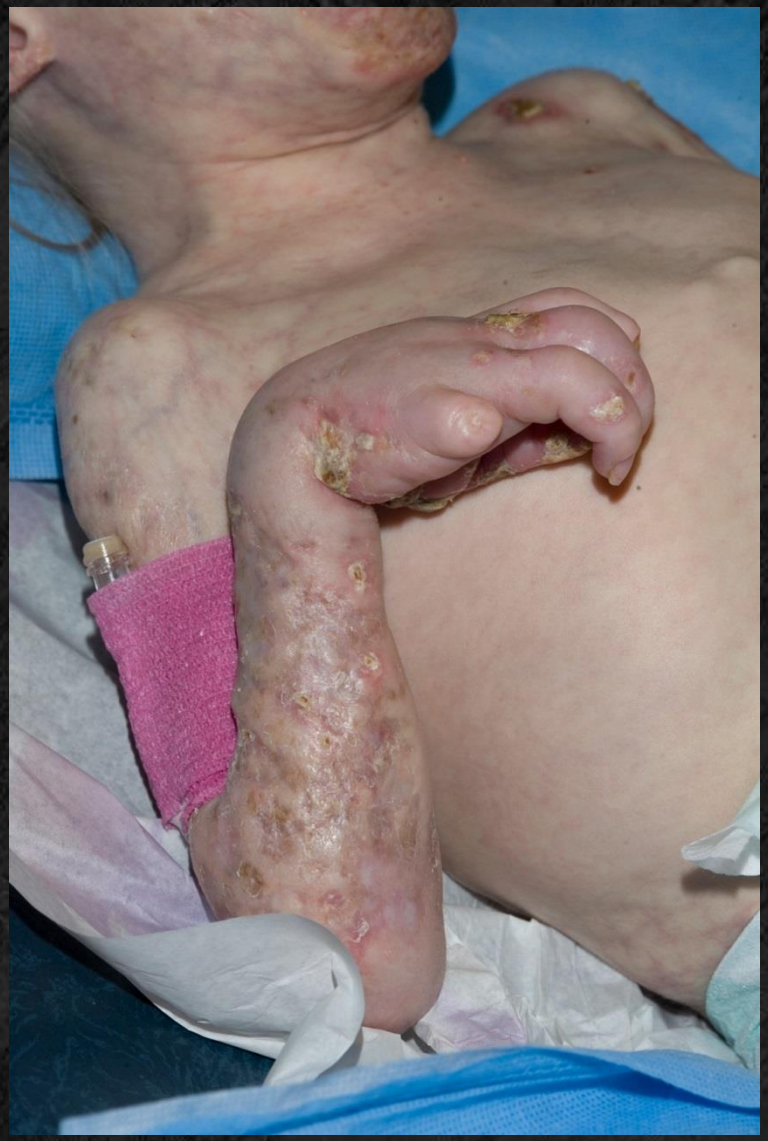
- Good candidate genes in an additional 59 families (quartets on average)
  - Mendelian consistent, rare, good coverage, and predicted deleterious, BUT
  - Gene is not associated with any known disease
  - Gene associated with known disease, but not our phenotype

Challenge: Establishing Disease Causation

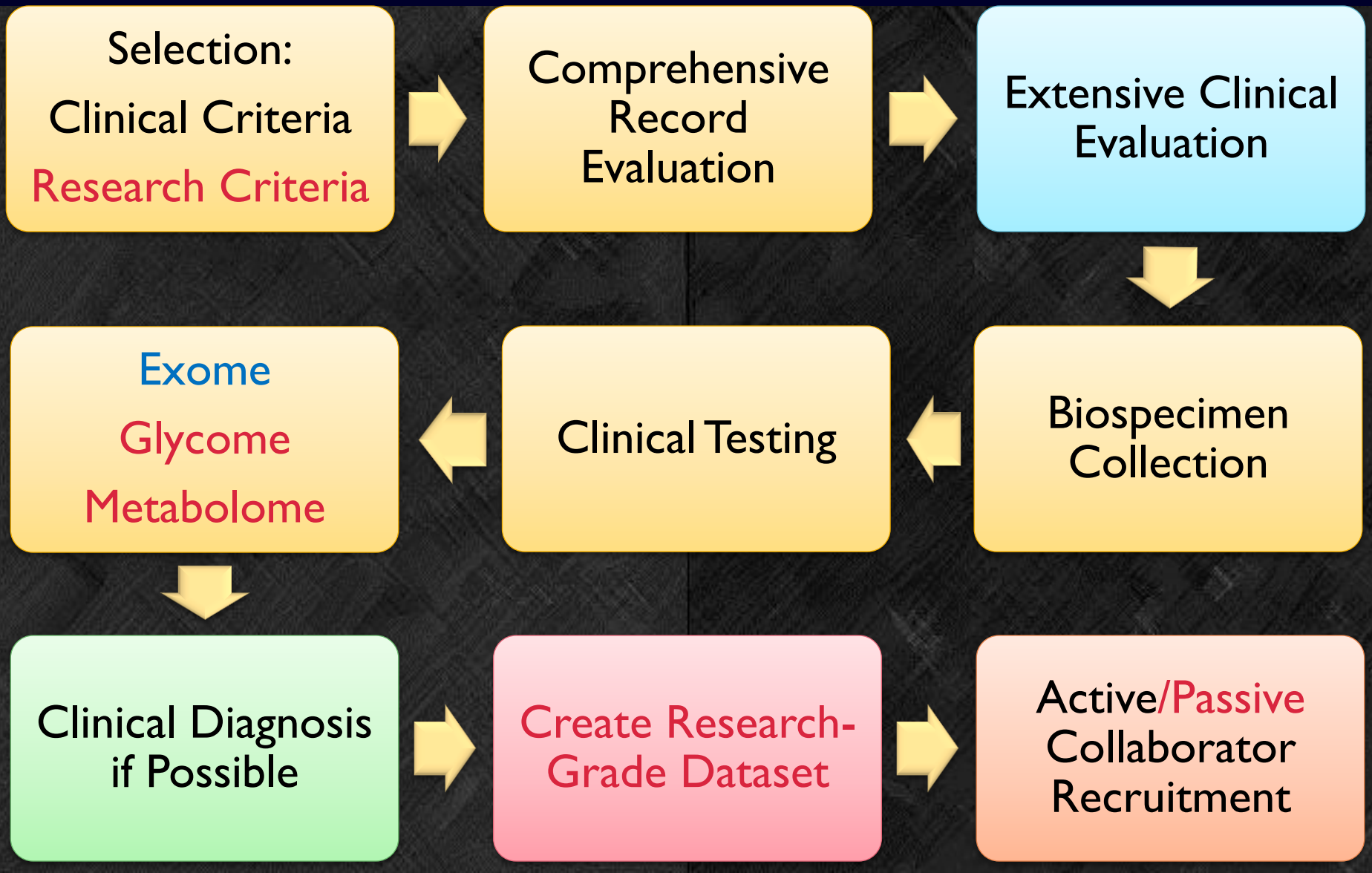
- Given our selection criteria, a minority of *well-worked-up* undiagnosed diseases will be known diseases.
- We hypothesize that a significant number of the remainder have "new" diseases:
  - Undiscovered disease-gene associations
  - Multiple contributing genes
  - Environment-gene interactions
  - Diseases caused by non-coding DNA changes

19 y/o, 9 kg

Each patient, each family becomes a research project…

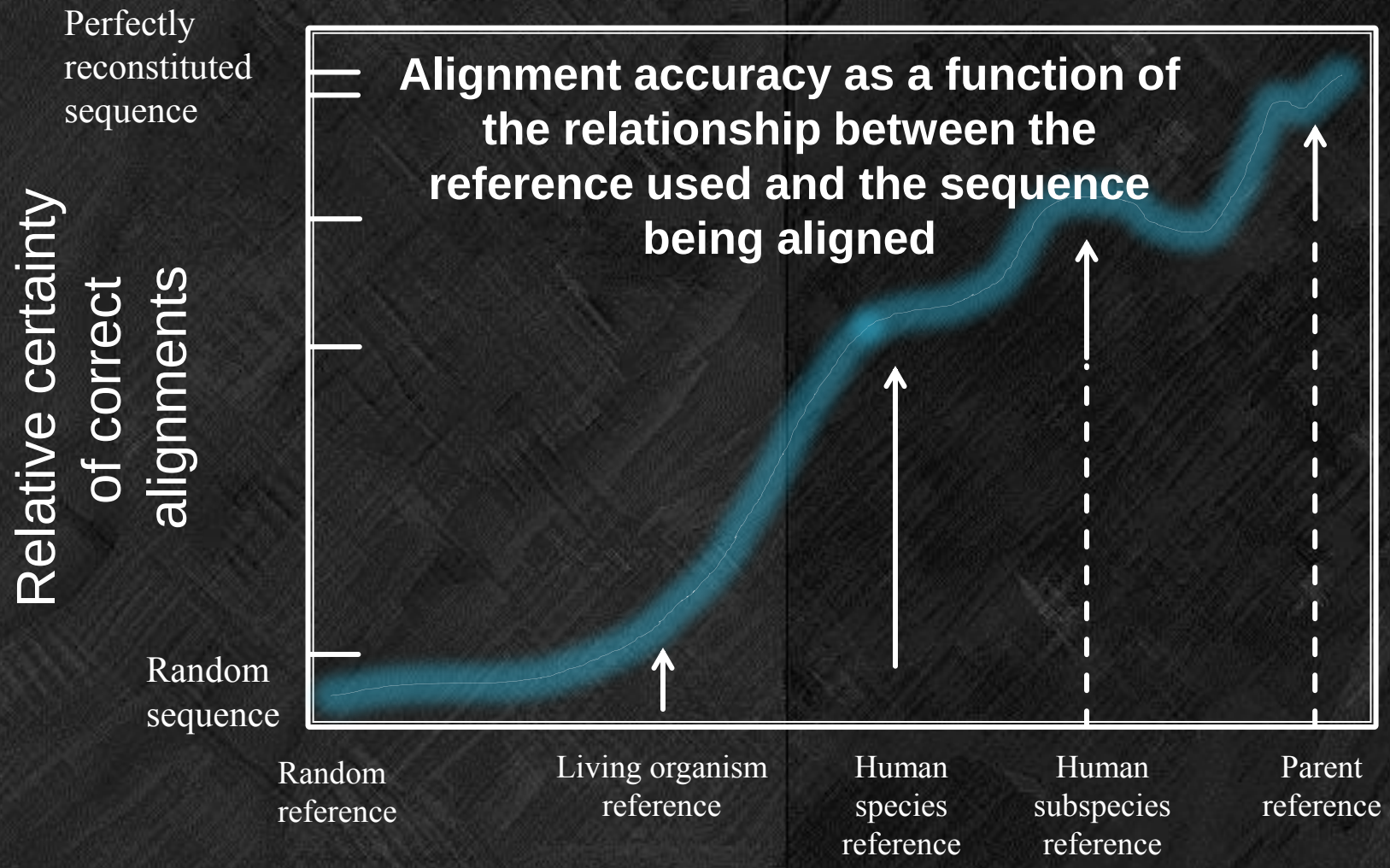


Revised UDP Process



Improve Exome Analysis for Families: The Diploid Aligner

NextGen Sequencing that is Population and Parent Aware at both Alignment and Genotyping



Ontological Mapping of Phenotype

Create Research-Grade Dataset

PHENOTIPS

- Signs and Symptoms (Phenotype) mapped to standard ontology (HPO)

GROWTH PARAMETERS

Small for gestational age Delete · Clear details

assuming near term birth. Exact gestational age at birth not a...

Severe short stature Delete · Add details

Decreased body weight Delete · Add details

Short stature Delete · Add details

CRANIOFACIAL

Craniofacial disproportion Delete · Clear details

cranium > face

Frontal bossing Delete · Add details

Expanded Hypothesis Generation from Untargeted (Agnostic) Screens

Exome

Glycome

Metabolome

- Exome/Genome sequencing
- CSF, Plasma, Urine N- and O-linked glycans
- CSF and Urine Metabolomics
- CSF Lipidomics
- CSF/plasma/urine isoprostanes
- CSF/plasma/urine acylcarnitines

Prioritize/deprioritize DNA sequence candidates +/- stand alone findings

Broaden Opportunities for Collaboration

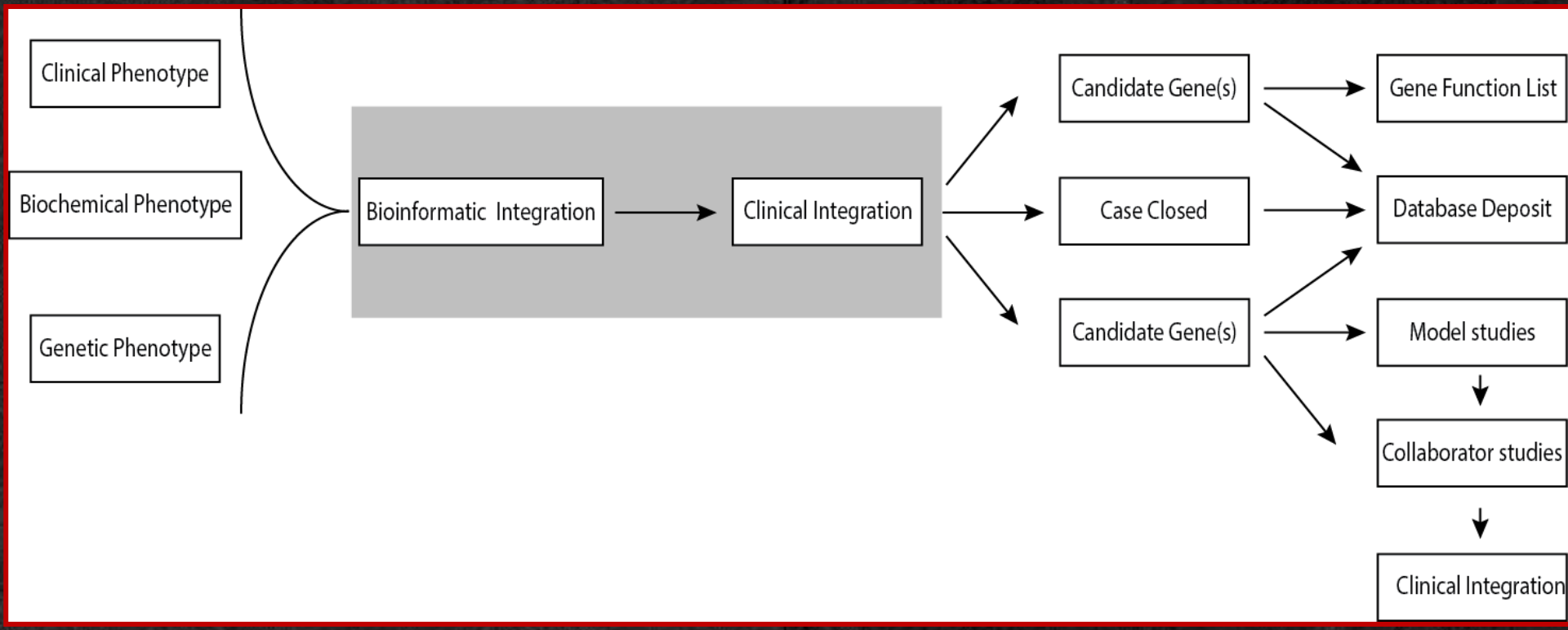
Active/Passive Collaborator Recruitment

- Active Collaborator Discovery
  - Identify established investigators
    - Automate from phenotypes
- Passive Collaborator Discovery
  - Searchable case database
    - dbGaP
    - PhenomeCentral
- Cohort Creation
  - Automate from phenotypes

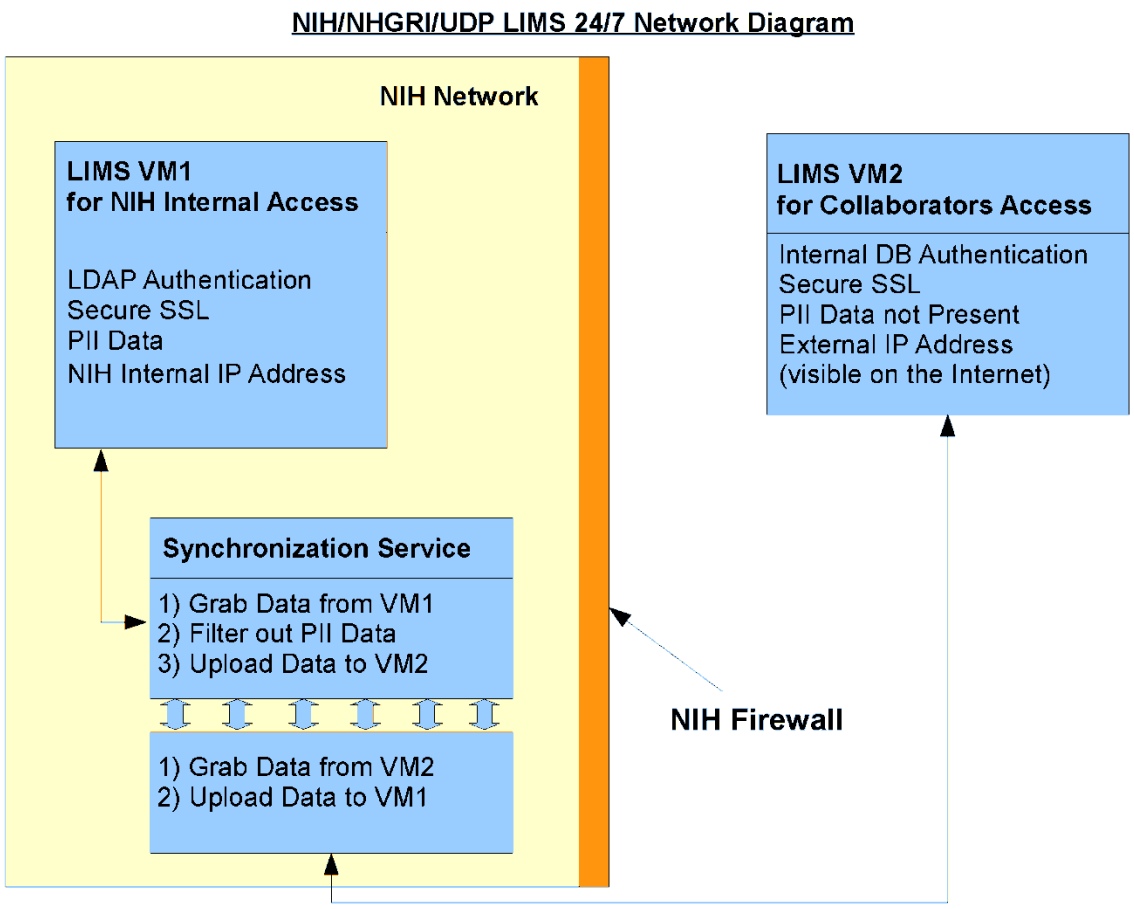
UDP Integrated Collaboration System

- A patient centric information, process management and communications system designed to improve productivity and collaboration.
- Enables UDP leaders to manage each patient's disease as a unique research project with unique experimental design and cohort of collaborators.

UDPICS Work Flow

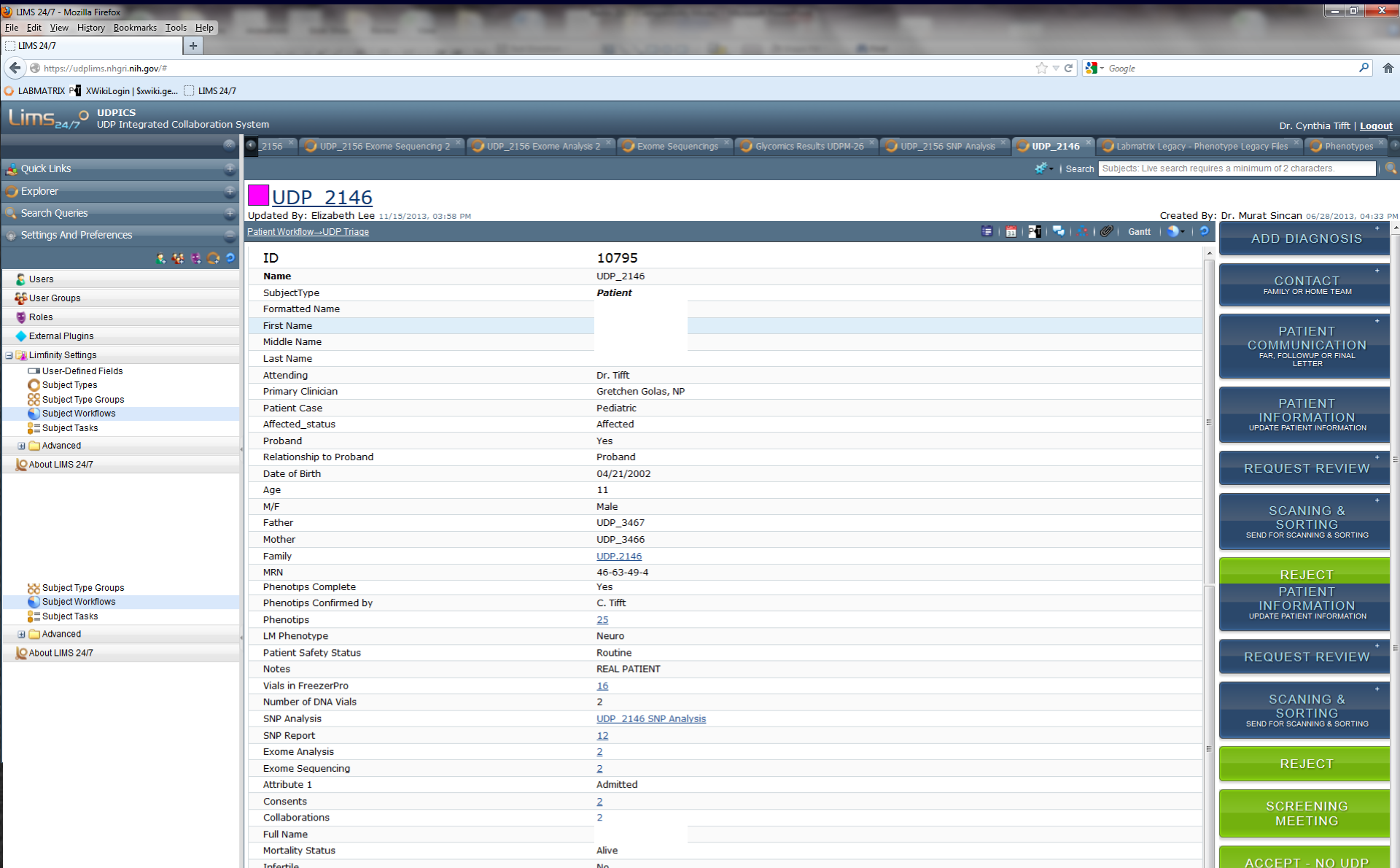


UDPICS Design



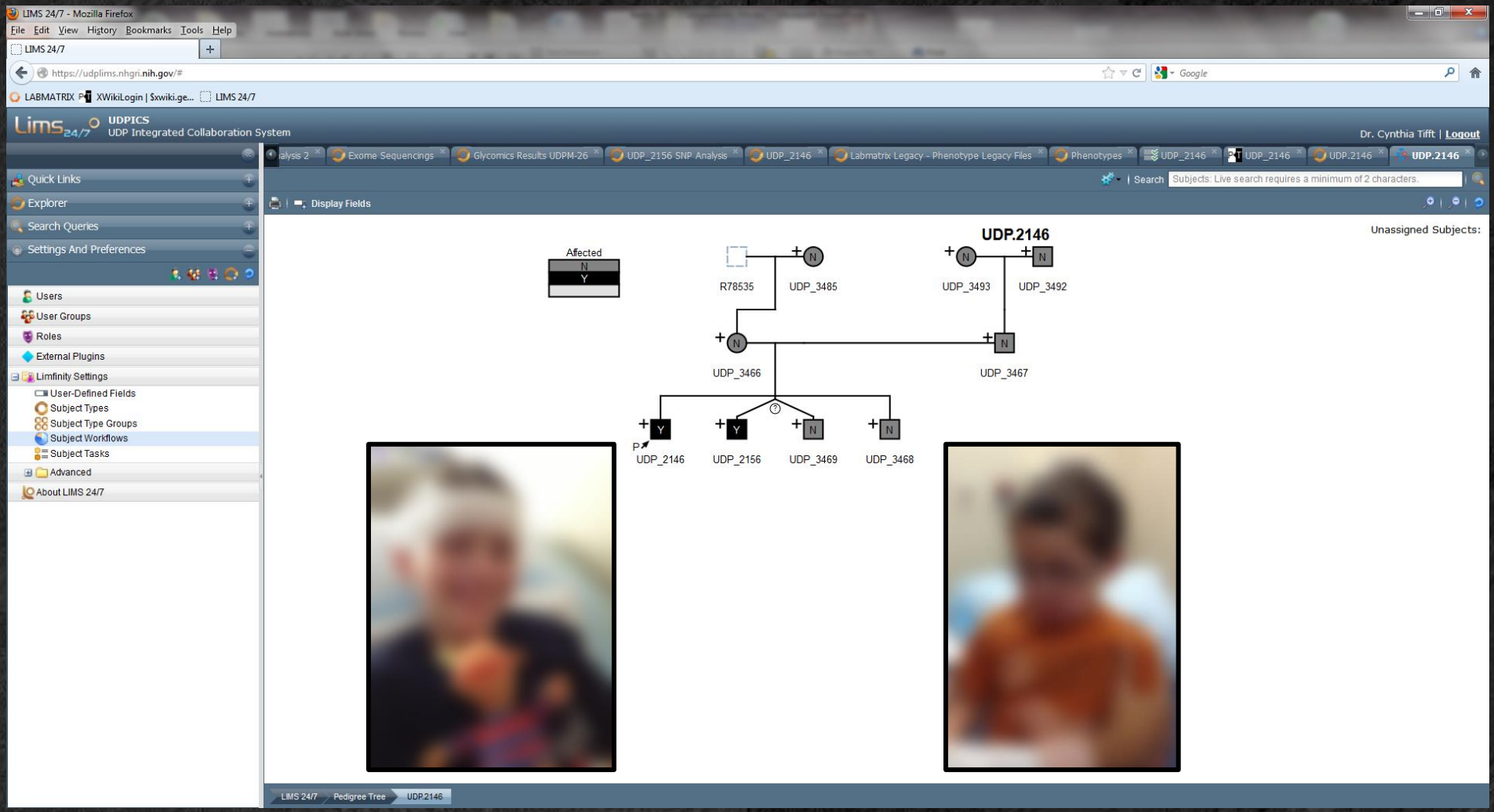
- UDPICS is fully integrated with
  - Phenotips
  - FreezerPro
  - Sciency
  - EzColony
- The system can be customized to meet specific individualized requirements

UDP 2146/2156



ID	10795
Name	UDP_2146
SubjectType	***Patient***
Formatted Name	
First Name	
Middle Name	
Last Name	
Attending	Dr. Tifft
Primary Clinician	Gretchen Golas, NP
Patient Case	Pediatric
Affected_status	Affected
Proband	Yes
Relationship to Proband	Proband
Date of Birth	04/21/2002
Age	11
M/F	Male
Father	UDP_3467
Mother	UDP_3466
Family	UDP.2146
MRN	46-63-49-4
Phenotips Complete	Yes
Phenotips Confirmed by	C. Tifft
Phenotips	25
LM Phenotype	Neuro
Patient Safety Status	Routine
Notes	REAL PATIENT
Vials in FreezerPro	16
Number of DNA Vials	2
SNP Analysis	UDP_2146 SNP Analysis
SNP Report	12
Exome Analysis	2
Exome Sequencing	2
Attribute 1	Admitted
Consents	2
Collaborations	2
Full Name	
Mortality Status	Alive
Infertile	No

UDP 2146/2156

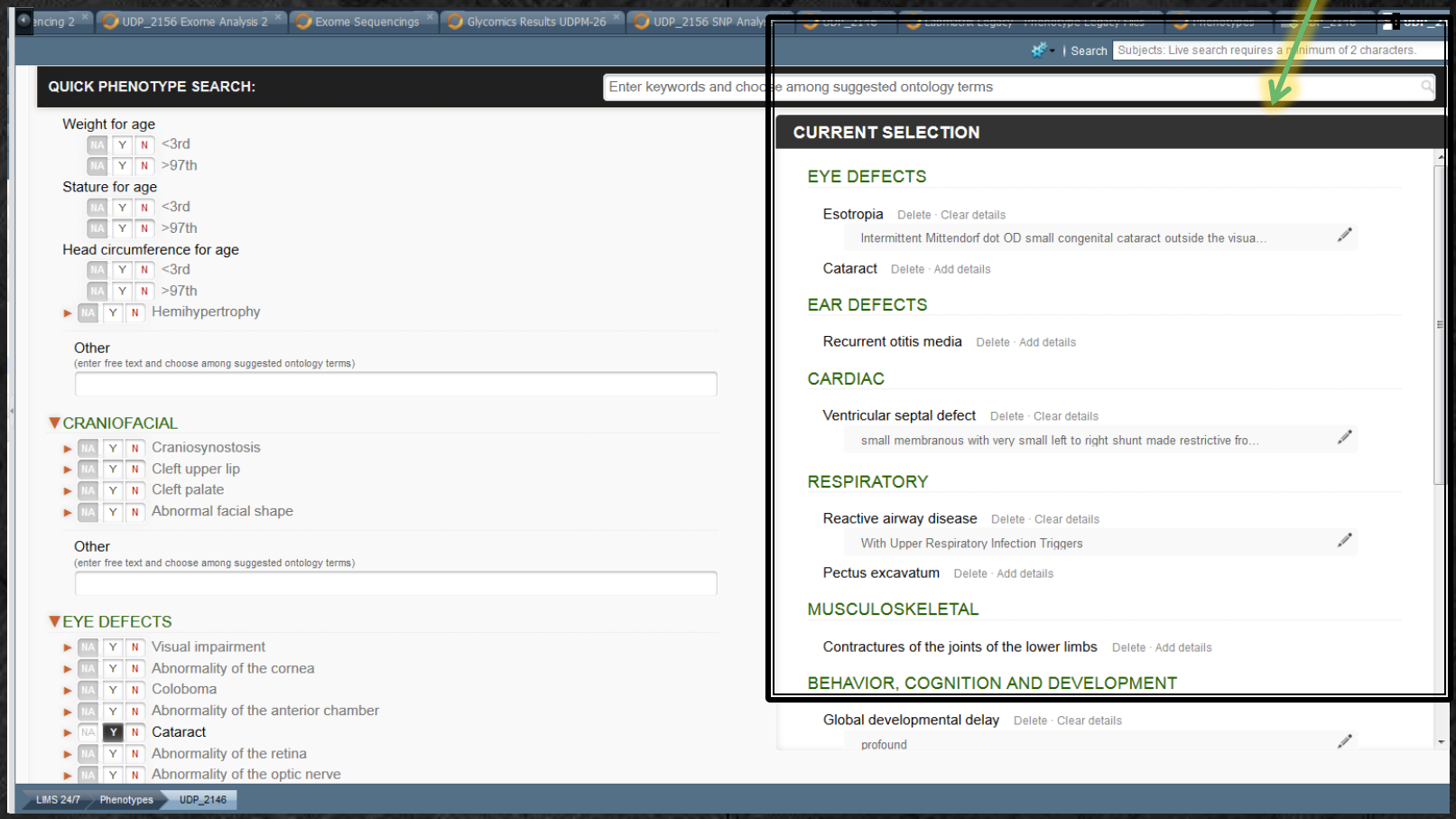


NIH Clinical Center Phenotyping

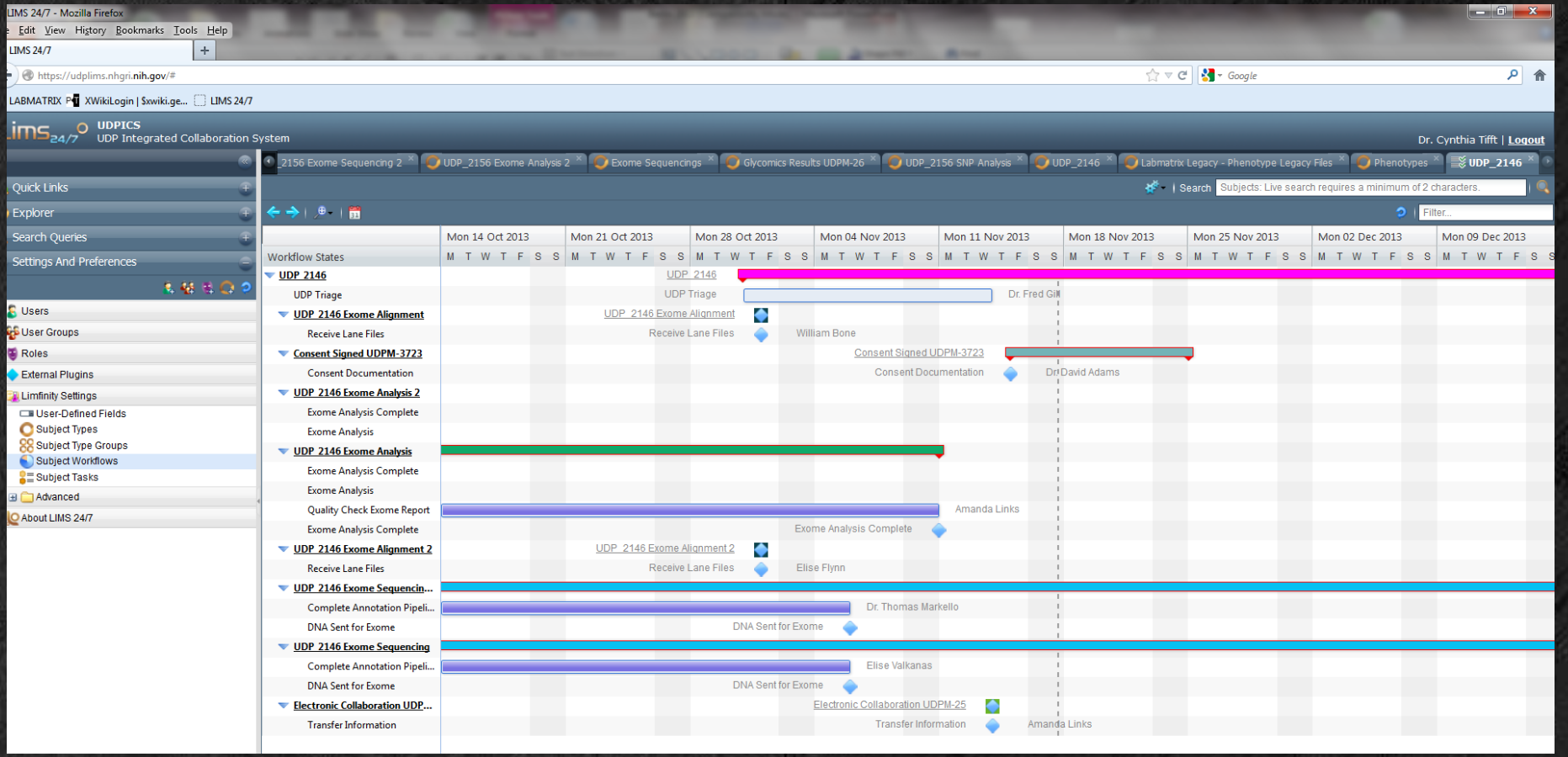
Monday 08/12/13		Tuesday 08/13/13		Wednesday 08/14/13		Thursday 08/15/13		Friday 08/16/13	
7:00a	Admissions	7:00a		7:00a		7:00a		7:00a	
7:30a		7:30a		7:30a		7:30a		7:30a	
8:00a		8:00a		8:00a	DEXA	8:00a		8:00a	
8:30a		8:30a	Skeletal survey	8:30a		8:30a	OT with Hanna	8:30a	
							if additional time needed		
9:00a		9:00a		9:00a	Physiatry w/ Dr. Paul	9:00a		9:00a	
9:30a		9:30a	EEG in 7SW Neuro Testing	9:30a		9:30a	Nutrition consult at bedside	9:30a	
							w/ Jennifer Myles		
10:00a	Neuropsych w/ Dr. Thurm	10:00a		10:00a		10:00a		10:00a	
10:30a	- meet at the bedside	10:30a		10:30a	OT w/ Hanna	10:30a		10:30a	
11:00a		11:00a	PT w/ Mina	11:00a		11:00a	Sedated brain MRI and eye	11:00a	
11:30a		11:30a		11:30a		11:30a	exam	11:30a	
							EMG in the PACU w/		
12:00p		12:00p		12:00p		12:00p	*Dr. Floeter*	12:00p	
12:30p		12:30p		12:30p	Eye consult in OP-11	12:30p		12:30p	
					w/ Dr. Zein				
1:00p		1:00p	Neuro w/ Paul Lee	1:00p		1:00p		1:00p	
1:30p		1:30p	at the bedside	1:30p		1:30p		1:30p	
2:00p	Pre-anesthesia	2:00p		2:00p		2:00p		2:00p	
2:30p		2:30p		2:30p		2:30p		2:30p	
3:00p		3:00p		3:00p		3:00p		3:00p	
3:30p		3:30p		3:30p		3:30p		3:30p	
4:00p		4:00p		4:00p		4:00p		4:00p	
4:30p		4:30p		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	

Phenotype entry populates

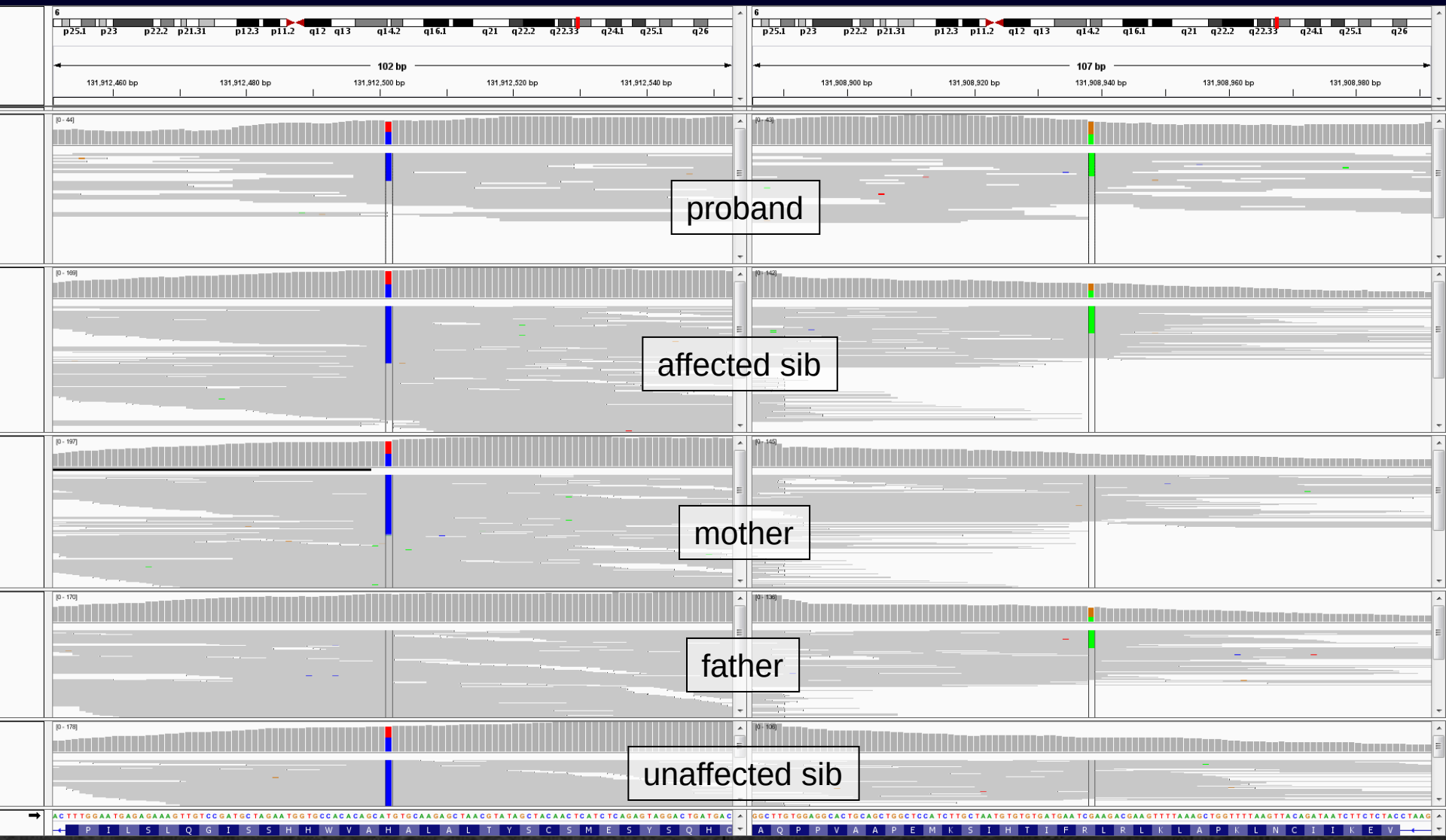
PHENOTIPS



GANTT chart tracks progress of project



UDP 2146/2156 Compound Het for MED23



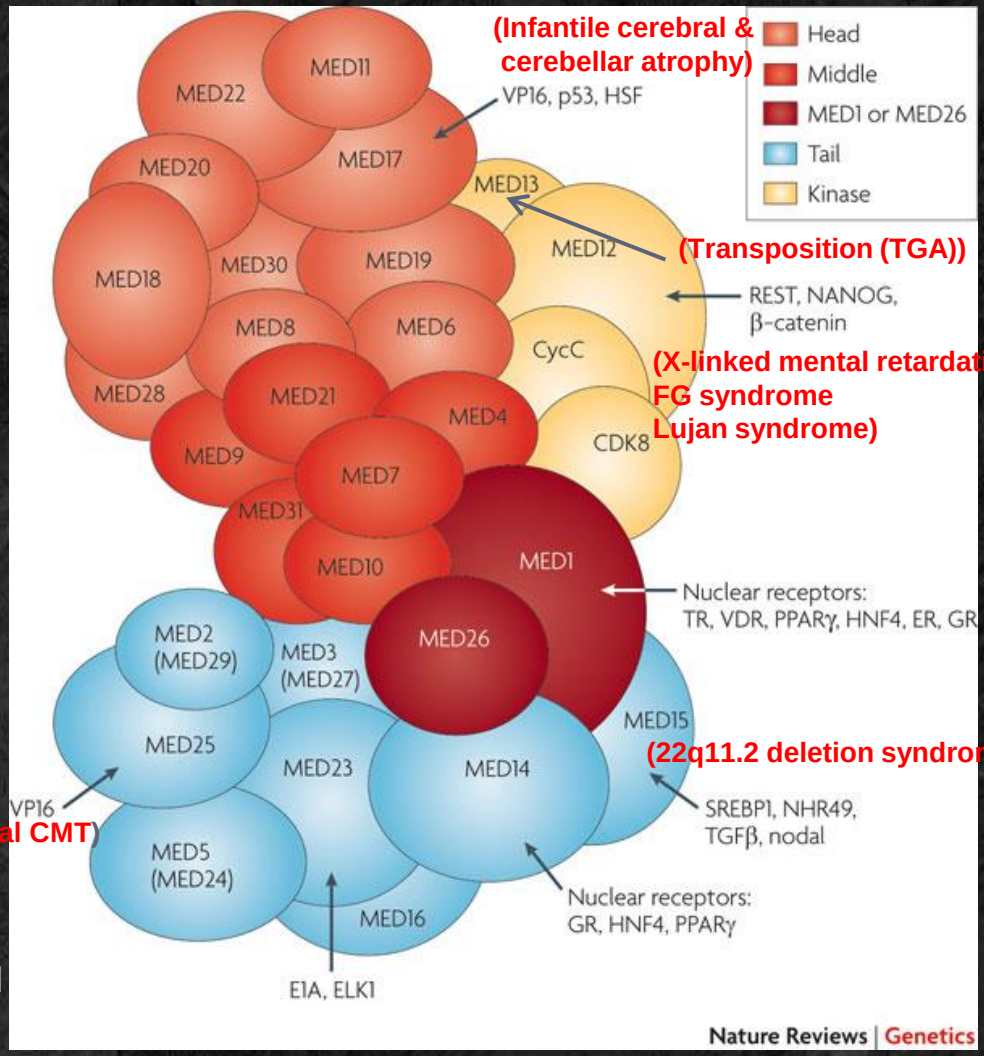
exon26:c.3638A>G:p.H1213R

exon29:c.3988C>T:p.R1330X

Mediator Complex

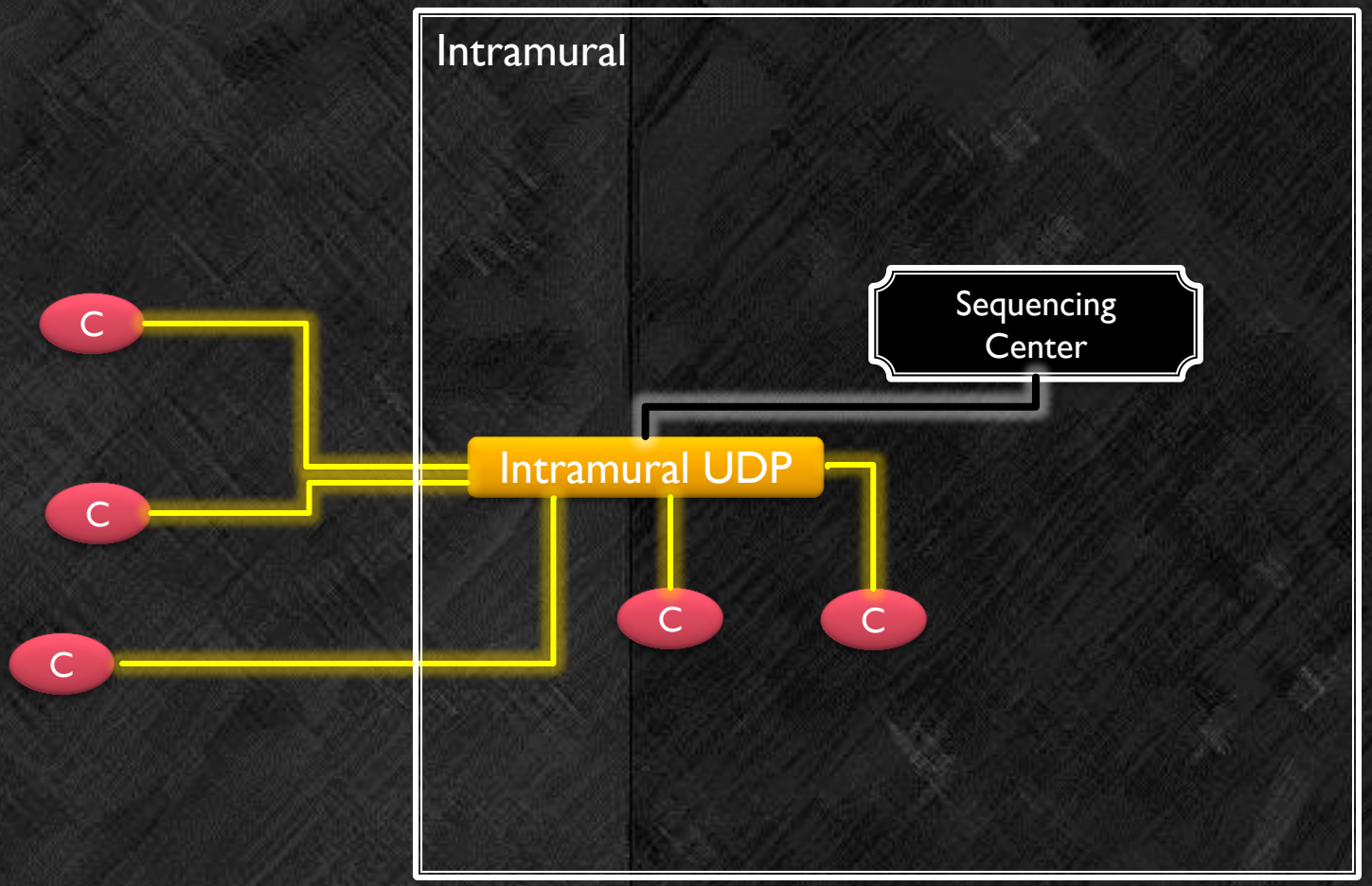
Multi-subunit RNA polymerase II transcriptional regulator

Collaboration with Dr. Zhao to generate drosophila model to functionally validate phenotype has promising preliminary results.



Hashimoto S, Boissel S, Zarhrate M, Rio M, Munnich A, Egly JM, Colleaux L. MED23 mutations links intellectual disability to dysregulation of immediate early gene Expression. (2011) *Science* 333:1161-3.

Undiagnosed Diseases Program



Program Snapshot

With advances in genomic sequencing and medicine, it is now possible to examine patients with rare genetic diseases at a level that allows physicians and scientists to find the "needle in a haystack". Often times, one small change (mutation) in a genetic sequence can cause an individual to develop disease symptoms. To increase the capacity for this type of research, the **Undiagnosed Diseases Program (UDP)** is establishing an Undiagnosed Diseases Network (UDN) to diagnose both rare and new diseases. Furthermore, through the support of mechanistic studies, the Network hopes to aid in management strategies for the patients. This program will advance laboratory and clinical research, building upon the experience and expertise of the NIH Intramural UDP and similar programs, to enhance coordination and collaboration among laboratory and clinical researchers across multiple centers. The Network will benefit from having the capacity to share data and approaches widely throughout the scientific community.

Read more...

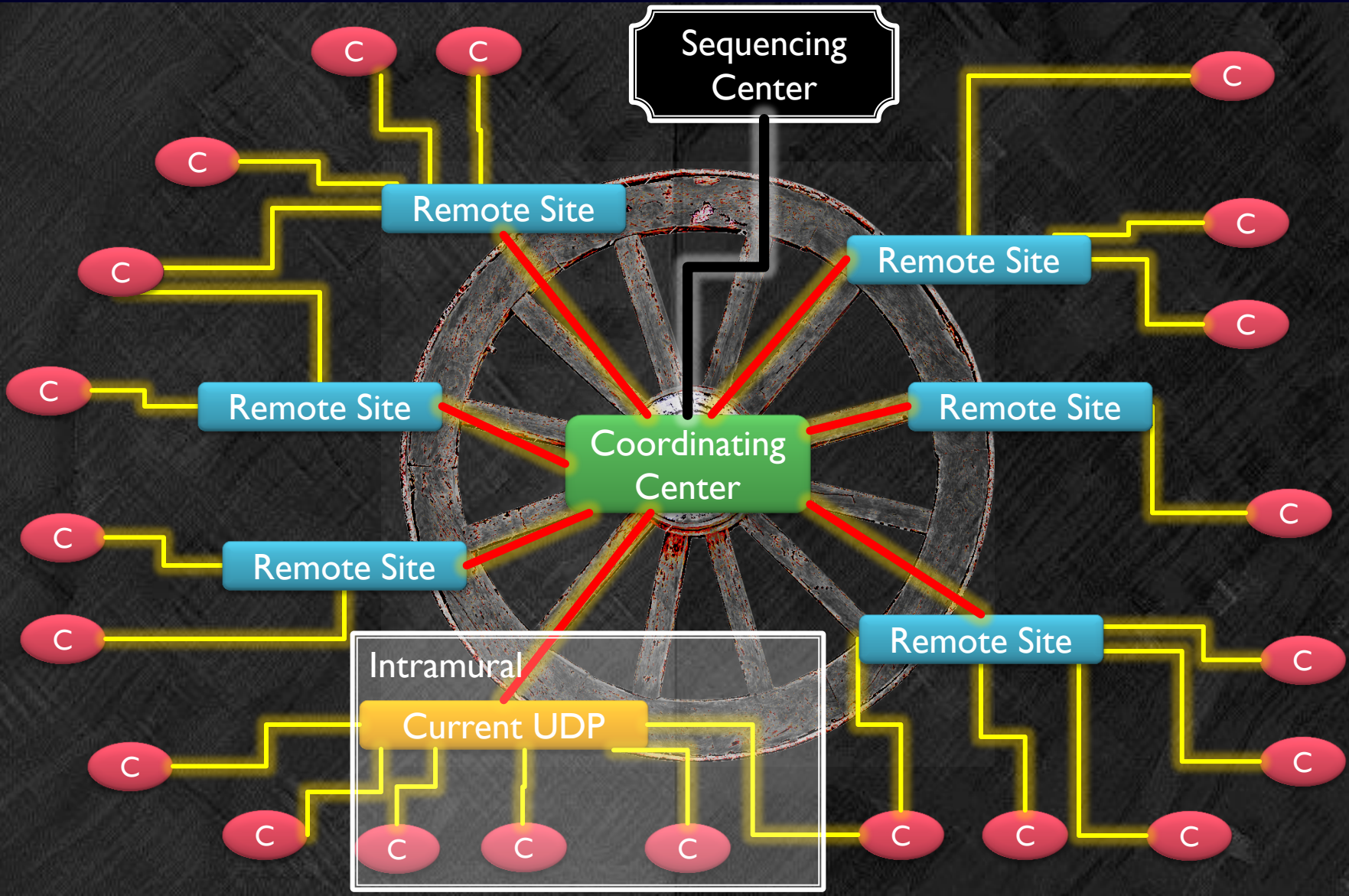
New Funding Opportunity Announcement (Administrative Supplement)!

The Undiagnosed Diseases Program is seeking applications for gene function studies to investigate rare and undiagnosed diseases. Please see the full details here.

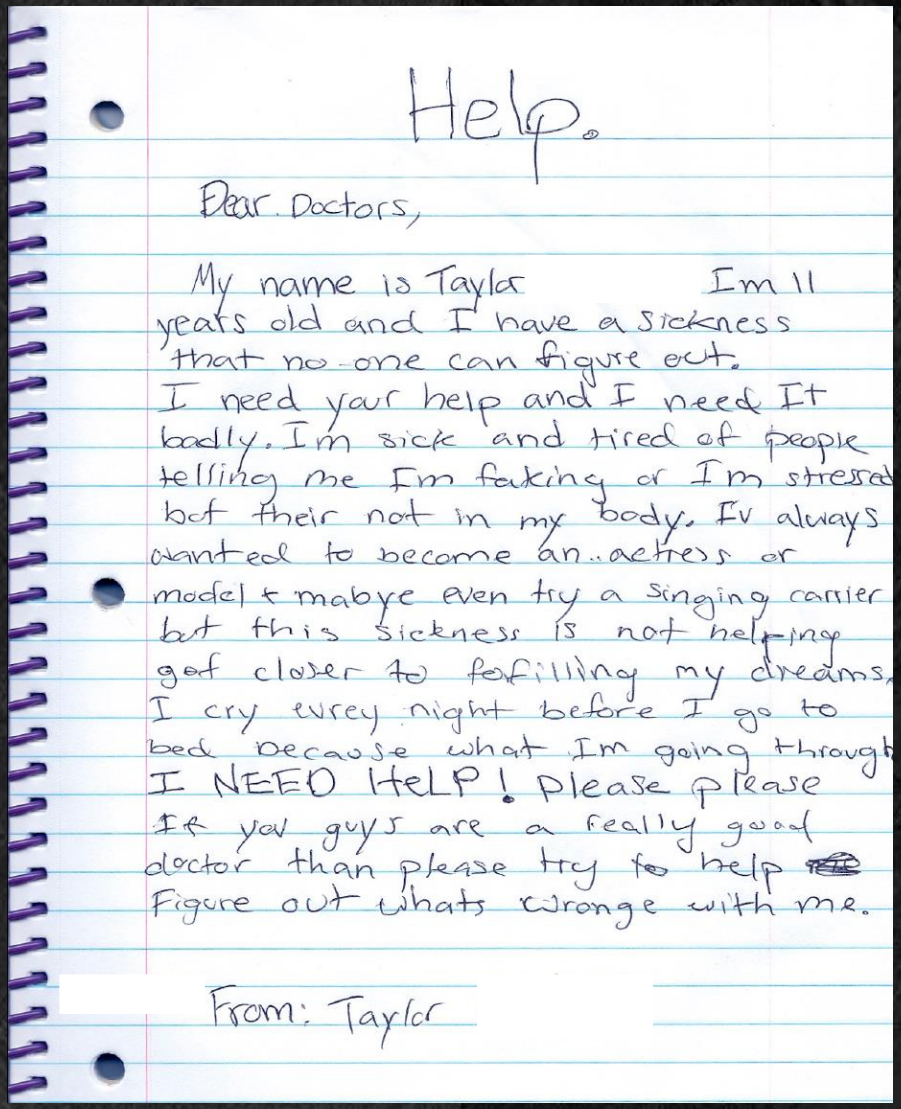
New Funding Opportunity Announcement!

The Undiagnosed Diseases Program is seeking applications for a Coordinating Center for an Undiagnosed Diseases Network (UDN). Please see the full details here.

Undiagnosed Diseases Network



A cry for help.....



Help.

Dear Doctors,

My name is Taylor Im 11 years old and I have a sickness that no one can figure out. I need yaur help and I need It badly. Im sick and tired of people telling me Im faking or I'm stressed but their not in my body. Iv always wanted to become an actress or model + mabye even try a singing carrier but this sickness is not helping get closer to fefilling my dreams. I cry every night before I go to bed because what Im going through I NEED HELP! please please If yaw guys are a really good doctor than please try to help Figure out whats wrong with me.

From: Taylor

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

-Margaret Mead

It Takes a Village…

Willam A. Gahl

Cynthia Tifft
David Adams
Camilo Toro
Dennis Landis
Fred Gill
Grace Park
John Schreiber
Ariane Soldatos
Johannes Dastgir
Paul Lee
Tyler Pierson

Gretchen Golas
Lynne Wolfe
Catherine Groden
Michele Nehrebecky
Colleen Wahl
Rena Godfrey

Joy Bryant
Jean Johnston
Casey Hadsall
Val Robinson
David Draper

Cheryl Hipple
Jose Salas
Joan Rentsch
Anabella Roman
Lisa Gardner
Quentin Whitley

Neil Boerkoel
Tom Markello
Murat Sincan
Praveen Cherukuri

Karin Fuentes Fajardo
Valerie Muduro
Hannah Carlson-Donohoe
Jacqueline Brady
Aditi Trehan
Dimitre Simeonov
John Accardi
May Malicdan
Yan Huang
Shira Ziegler
Tim Gall
Taylor Davis
Charles Markello
Roxanne Fischer
William Bone
Amanda Links
Elise Flynn
Elise Valkanas

Collaborators…the expanded village

Charité Hospital, Berlin
Peter Robinson

University of Toronto
Michael Brudno

Oregon Health Sciences University
Melissa Haendel and the
Monarch Consortium

Children's Hospital Philadelphia
Michael Bennett
Miao He

Case Western Reserve University
Charles Hoppel

Sanger Institute, Cambridge University
Damian Smedley

University of Cinncinati
Bruce Aronow

NHGRI
Shawn Burgess

University of Miami
Grace Zhai
Gennaro D'Urso

University of California, Los Angeles
Shuo Lin

NIH Intramural Sequencing Center
Jim Mulliken

NIH Clinical Center
> 50 physician scientists who volunteer their time and expertise