The Extreme of “No One Left Behind”: Undiagnosed Patients

Rare Disease Day at the United Nations

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UDP
(May 19, 2008)

• Goals:
  – To assist patients with unknown disorders reach an accurate diagnosis
  – To discover new diseases that provide insight into human physiology and genetics
Intramural UDP Operations

- Applicants submit medical records
- Referring physician sends summary letter
- UDP Director triages submitted records
- Intramural NIH consultants review records
- UDP Director makes final disposition
- Patients/physicians receive a standard letter; advice conferred in ~25% of cases
- If accepted, 1-week inpatient CC admission
UDP Numbers (2008-2019)

- Medical Records: >4000
- Admitted & Evaluated: >1200
- Children: ~40%
- Neurological: ~50%
- Some diagnosis: ~30%
- Publications 180
65 Year-old Man with Recurrent Meningitis

- Age 59 - First episode of meningitis; followed by autoimmune sensorineural hearing loss
- Acute: Headache, unsteady gait
- Chronic: Uses wheelchair, memory decline
- Age 59-65 – 27 more episodes
- LPs: Lymphocytic pleiocytosis
- Aseptic; steroid responsive
- Negative imaging; negative rheumatology evaluation
- Normal labs, including CRP, ESR
- No diagnosis at Emory, Cleveland Clinic, Mayo (Fl), Hopkins
65 Year-old Man with Recurrent Meningitis

- Exomes: Thr915Met in NLRP3
- NLRP3: Familial cold autoinflammatory syndrome or Muckle-Wells syndrome
- Heterozygous; gain of function

Donna Novacic, MD
- NLRP3 is part of the Inflammasome.
- A gain of function mutation will increase IL-1 activity.
- We treated with the IL-1 receptor inhibitor, anakinra
- In 4 hours, he walked and talked normally
Diagnoses
Very Very Rare Diagnoses

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

- EMARRD (Early myopathy, AReflexia, Respiratory distress, Dysphagia) due to \textit{MEGF10} mutations
- Neurodegeneration due to \textit{BTK} mutation
- Cognitive & motor decline with \textit{C19orf12} muts
- Waardenburg type 2 due to \textit{SOX10} deletion
- SLE with cerebellar ataxia and anti-GWB Abs
- GM2 gangliosidosis and Sanfilippo disease
- TEMPI syndrome with erythrocytosis muts
- Choreo-acanthocytosis due to \textit{VPS13A}
- Aicardi-Goutieres due to \textit{RNASEH2B, A} muts
- SPG11, NPC1, STIM1, GARS, A-T, NGLY1, MNGIE, CAV3
Expansion
The Undiagnosed Diseases Network (UDN)

- UDP, 7 (now 12) Clinical Sites, Coordinating Center, 2 Sequencing Cores, Metabolomics Core, Model Organisms Screening Center, Central Repository
- Formal data sharing agreements
- Consent: PII to be shared within UDN, de-identified data with others.
- First patients: August 2015.

Website: [http://www.udninternational.org/](http://www.udninternational.org/)
UDNI Meetings

(NIH Common Fund, Wilhelm Foundation, Local Sponsors)

- Rome September 2014
- Budapest – June 2015
- Vienna – February 2016
- Tokyo – November 2016
- Stockholm – August 2017
- Naples – June 2018
- Delhi – April 2019
Undiagnosed Diseases Programs

- W. Australia
- Japan
- Austria
- Spain
- Sweden
- India
- Turkey
- Canada
- Hong Kong
- China
- Korea
- France
- Thailand
- Italy
CONCLUSIONS: Rare and Undiagnosed Diseases Programs

- Require strong phenotyping of patients
- Foster new disease discovery
- Lead to insights into common diseases
- Help desperate patients
- Often require functional studies
- Sometimes do not need NGS
- Hugely benefit from data sharing
- Have captured the interest of industry
- Are needed throughout the world