The NIH Undiagnosed Diseases Network

NIH Council of Councils

May 20, 2016

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Clinical Director, NHGRI

Director, NIH Undiagnosed Diseases Program

A Common Fund Program, FY2013-2017

Testing the feasibility of a national network that extends and expands upon the success of the intramural NIH Undiagnosed Diseases Program to:

- **Improve the level of diagnosis and care** for patients with undiagnosed diseases by developing 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 lab data including genotyping, phenotyping, and environmental exposure histories

- **Create an integrated and collaborative research community** across multiple clinical sites and among lab and clinical investigators to investigate the pathophysiology of new and rare diseases

The UDN

1. The NIH Undiagnosed Diseases Program (UDP)
   - Background
   - Discoveries
   - Mysteries/Treatment
   - Diagnoses
2. Expansion to a Network
3. The Future

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
  - Many different specialties involved
  - Research oriented; not financially driven
- 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

- Medical Records: ~3500
- Admitted & Evaluated: ~1000
- Children: ~40%
- Neurological: ~50%
- Some diagnosis: ~25%
- Publications ~70

UDP Investigations

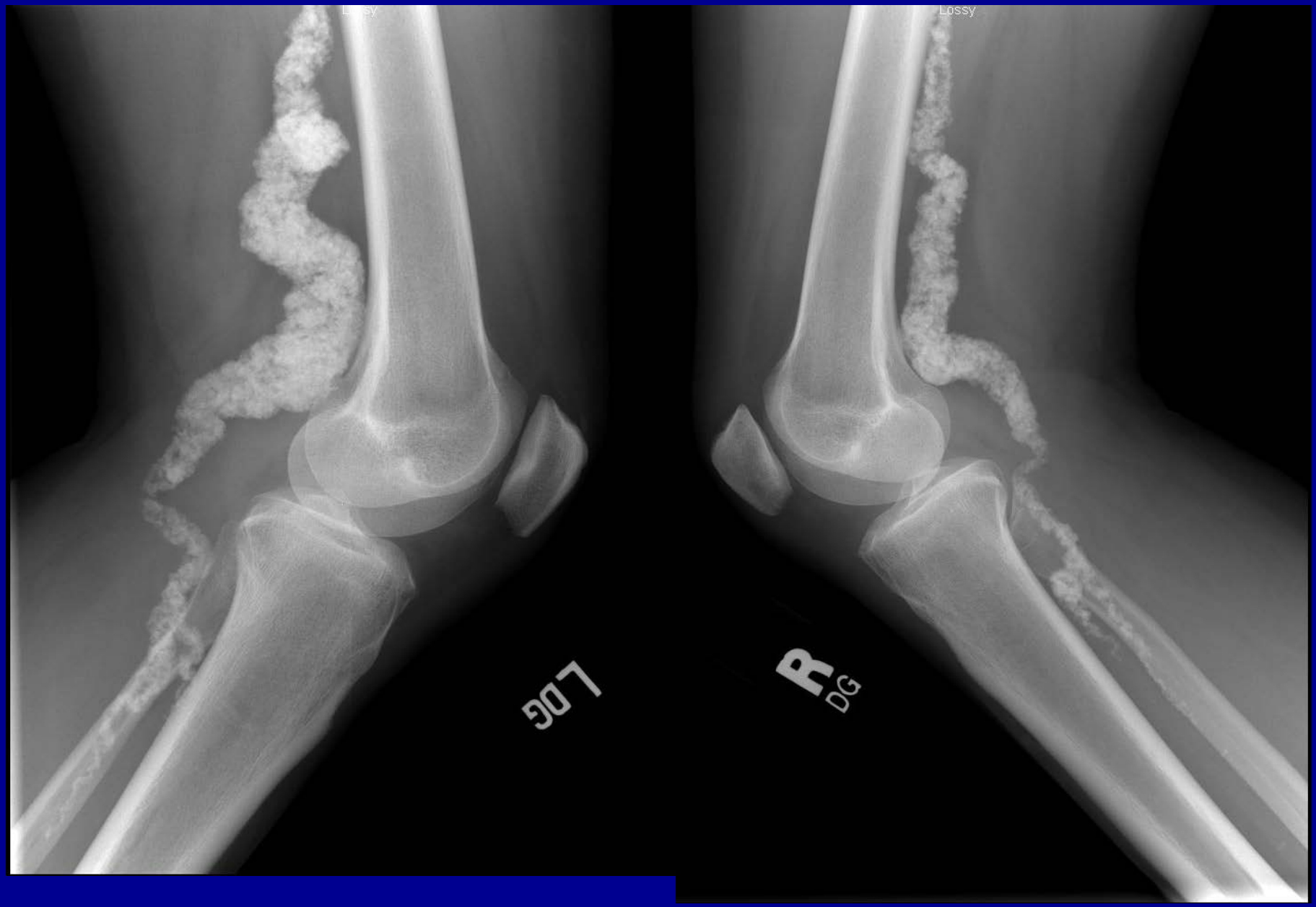
1. Patient phenotyping to rule out known diseases and describe new ones.
2. Genetic studies
   a. Commercial testing
   b. SNP arrays
   c. Exome sequencing
3. Functional studies (assays, model systems)

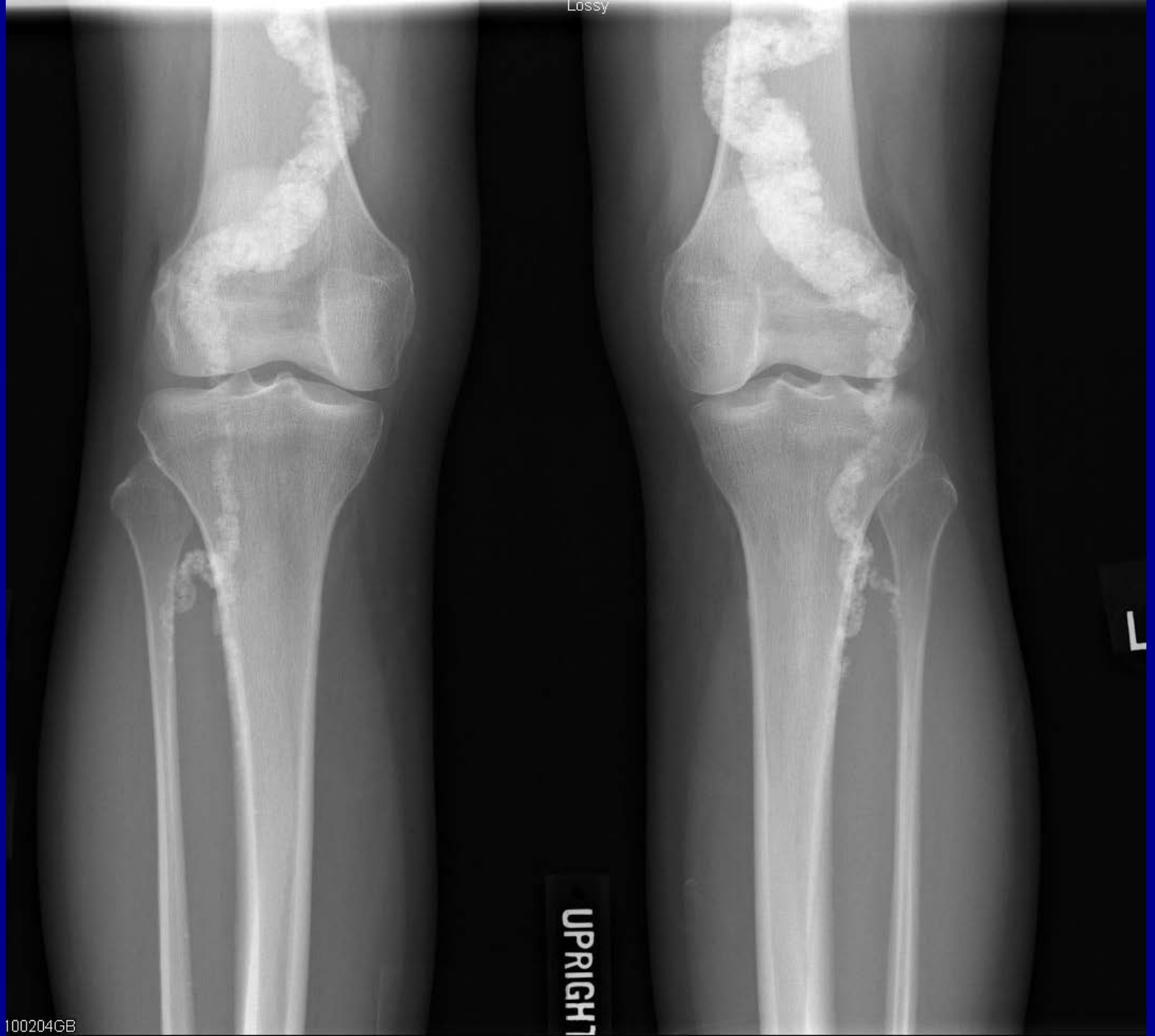
Discovery

5 Adult Siblings with these Clinical Symptoms and Signs:

- Intermittent claudication of calves, thighs, buttocks
- Chronic ischemic pain of the feet
- Joint pain in the hands
- Arterial calcification of lower extremities
- Spared coronary arteries

Femoral-Popliteal Artery Calcification

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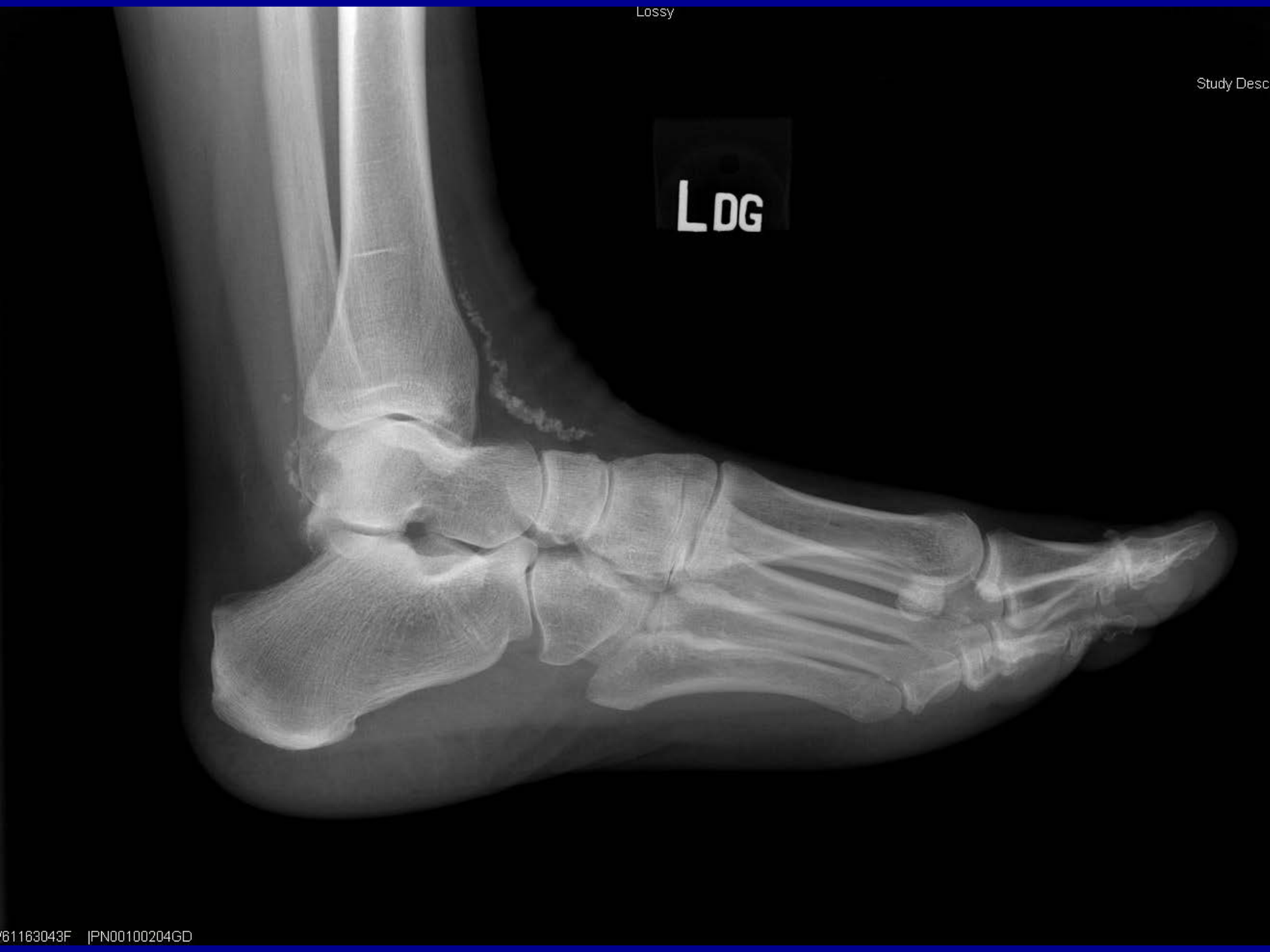
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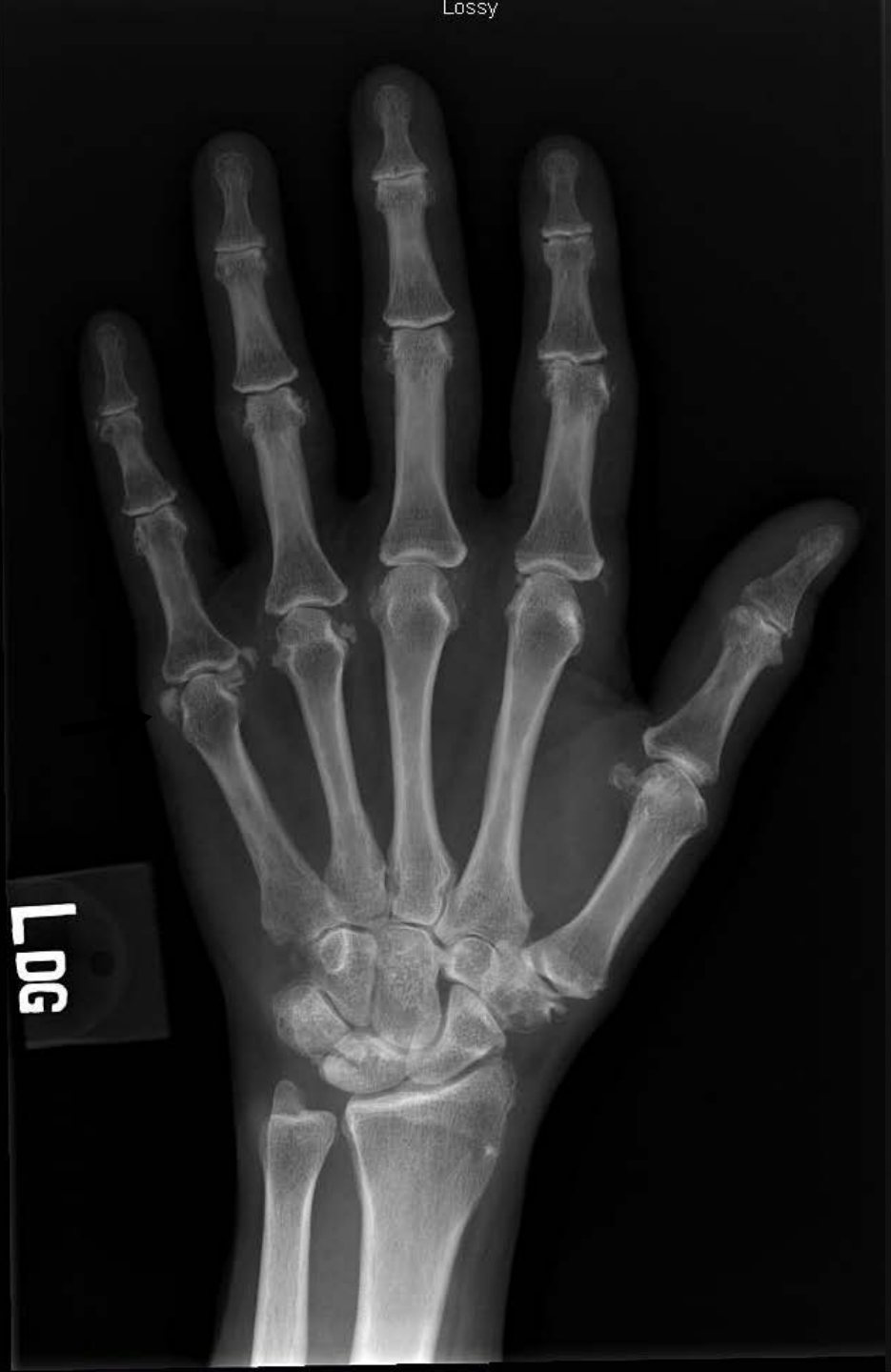
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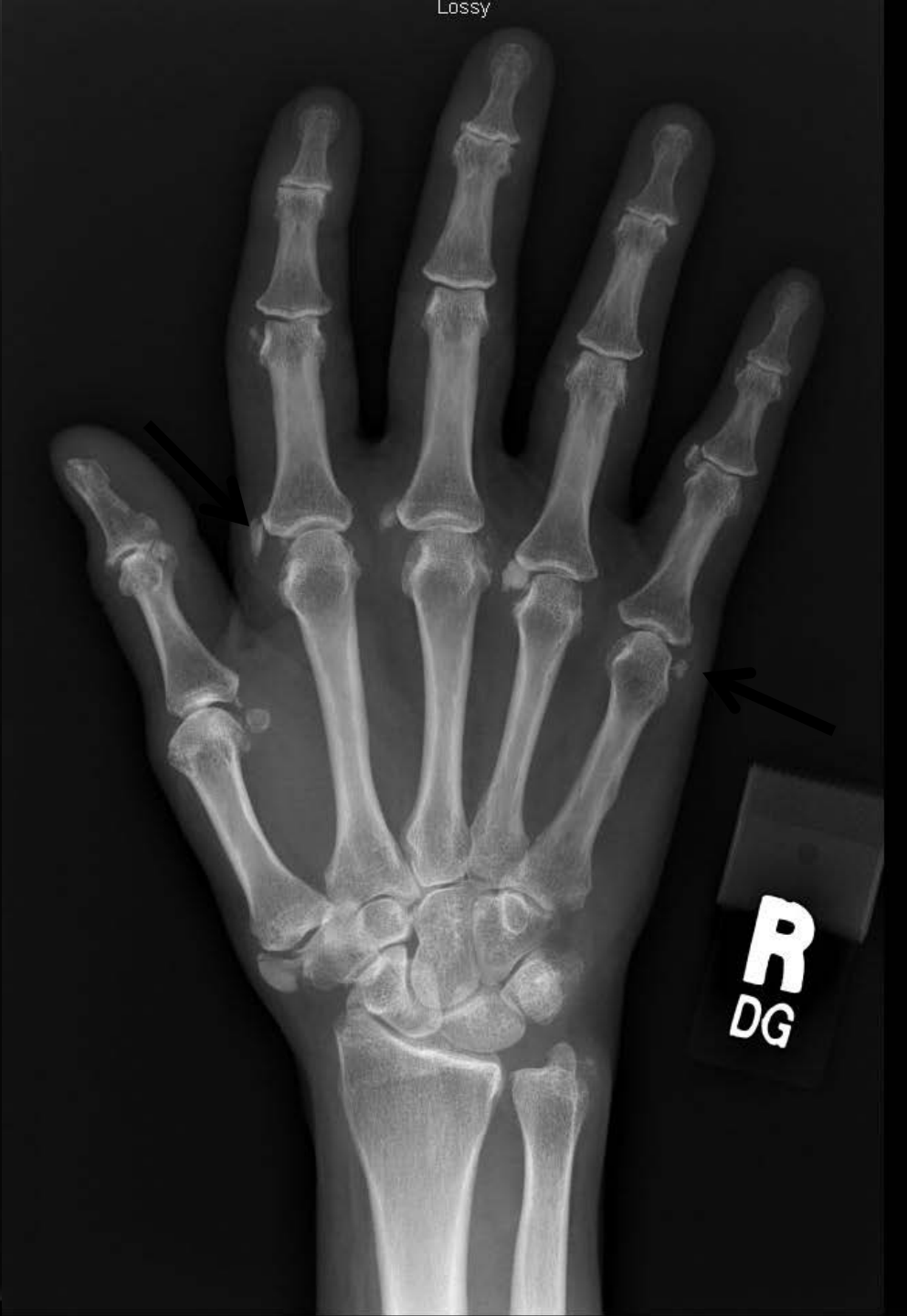
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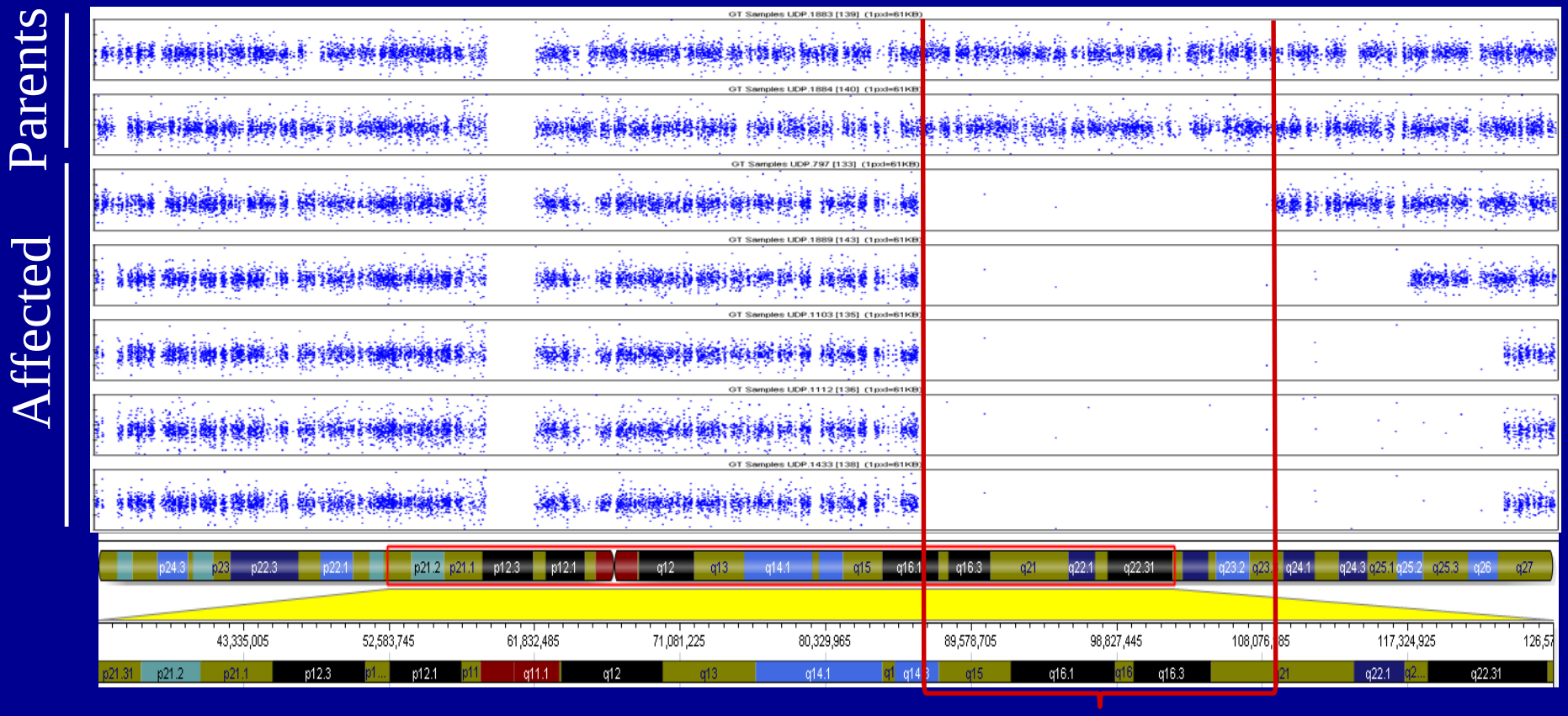
R
DG

Parents were 3rd Cousins
SNP Array: Chromosome 6q14.3-6q21



Region of Identical Homozygosity

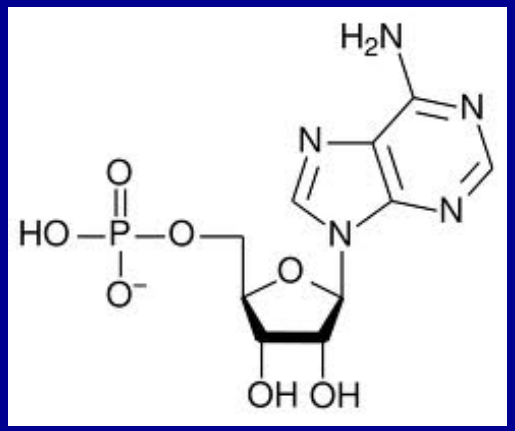
Dr. Tom Markello

Linkage Region

- Region of homozygosity: **22.4MB**
- 7977 total SNPs without a single A/B genotype in any locus
- 92 genes, about 902 exons
- No structural genes of the extracellular matrix
- One good candidate gene: ***NT5E***, encoding CD73, an ecto-5'-nucleotidase

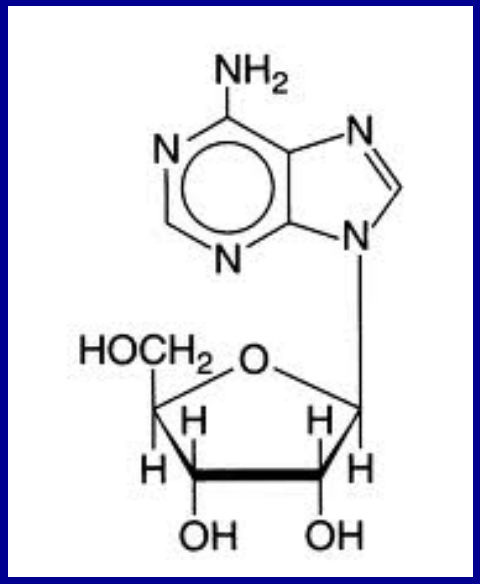
T. Markello, C. St. Hilaire

NT5E Encodes CD73



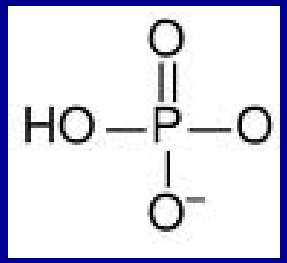
AMP

CD73



Adenosine

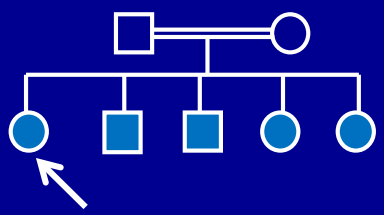
+



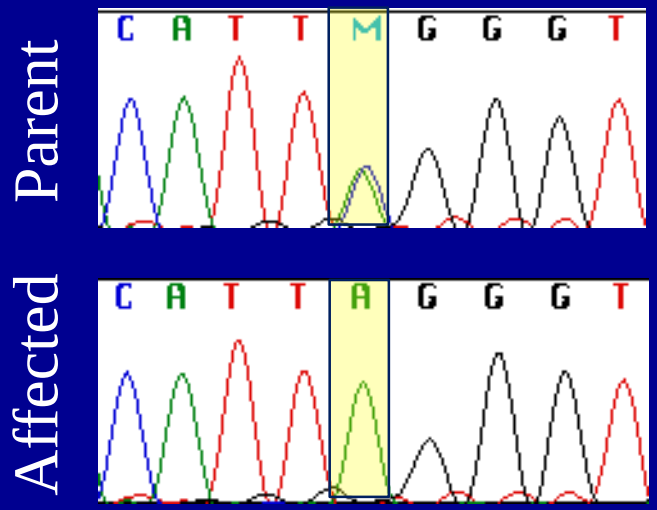
Pi

NT5E Sequencing Analysis

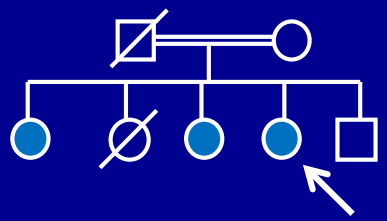
Family 1 (UDP)



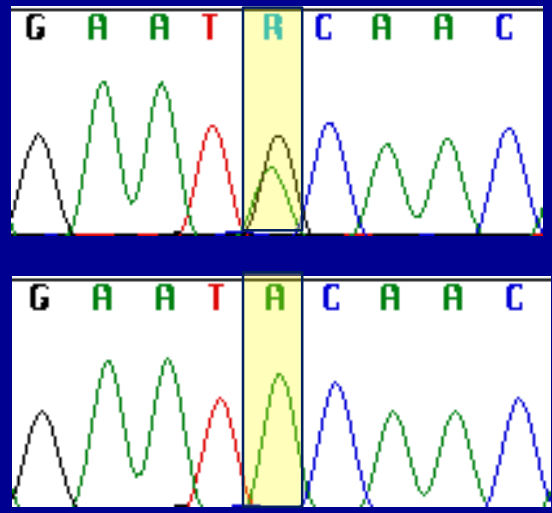
c.662C>A, S>X



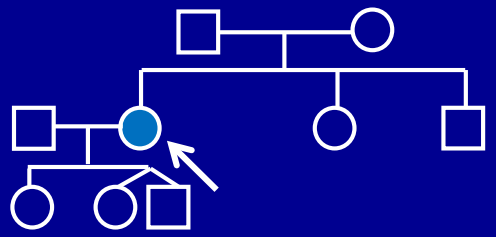
Family 2 (Kleta)



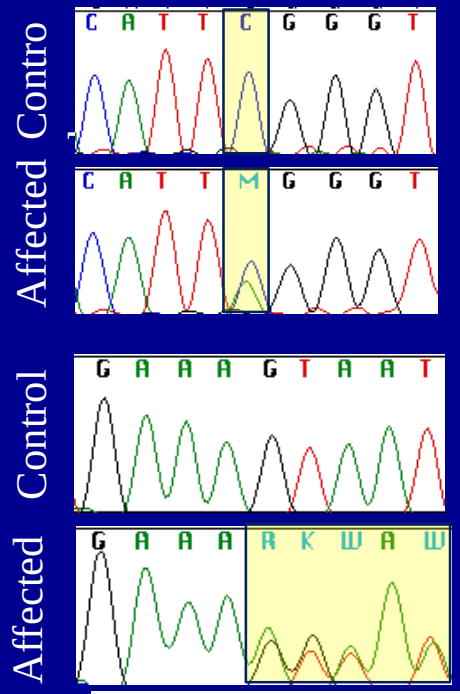
c.1073G>A, C>Y



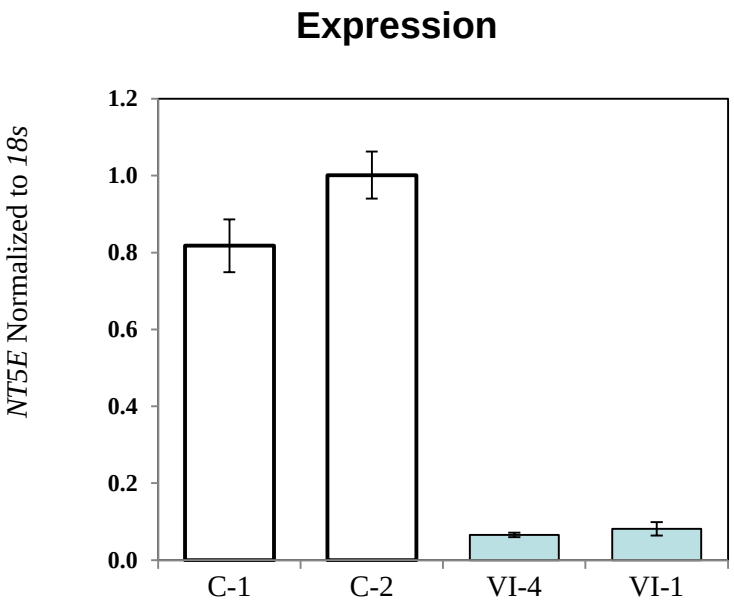
Family 3 (Nussbaum)

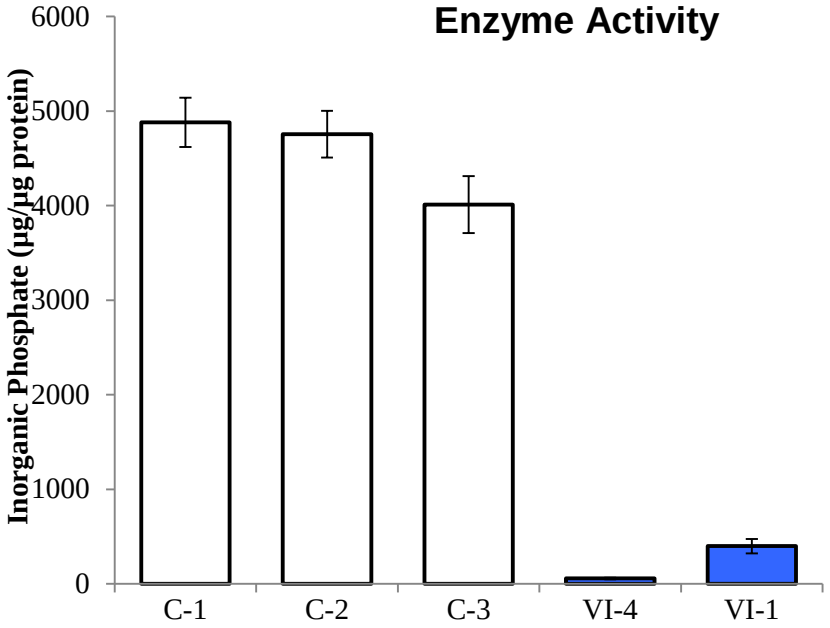


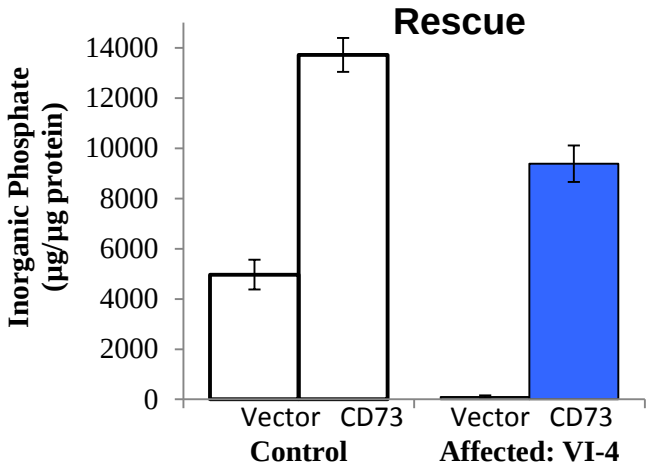
c.1069dupA/c.662C>A



S. Ziegler



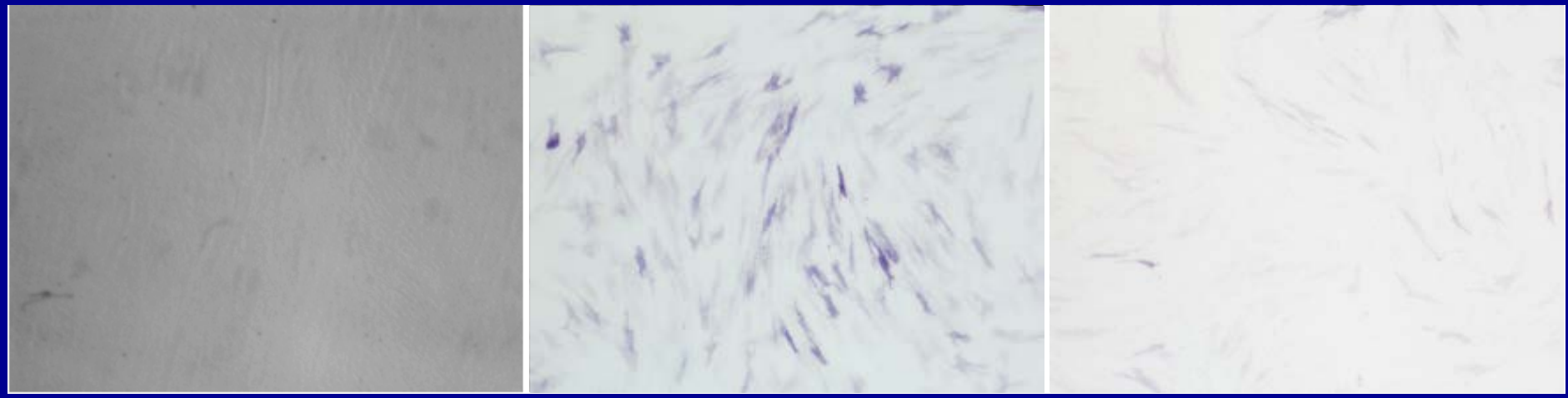




Drs. C. St. Hilaire, M. Boehm

Increased Fibroblast Staining for Alkaline Phosphatase

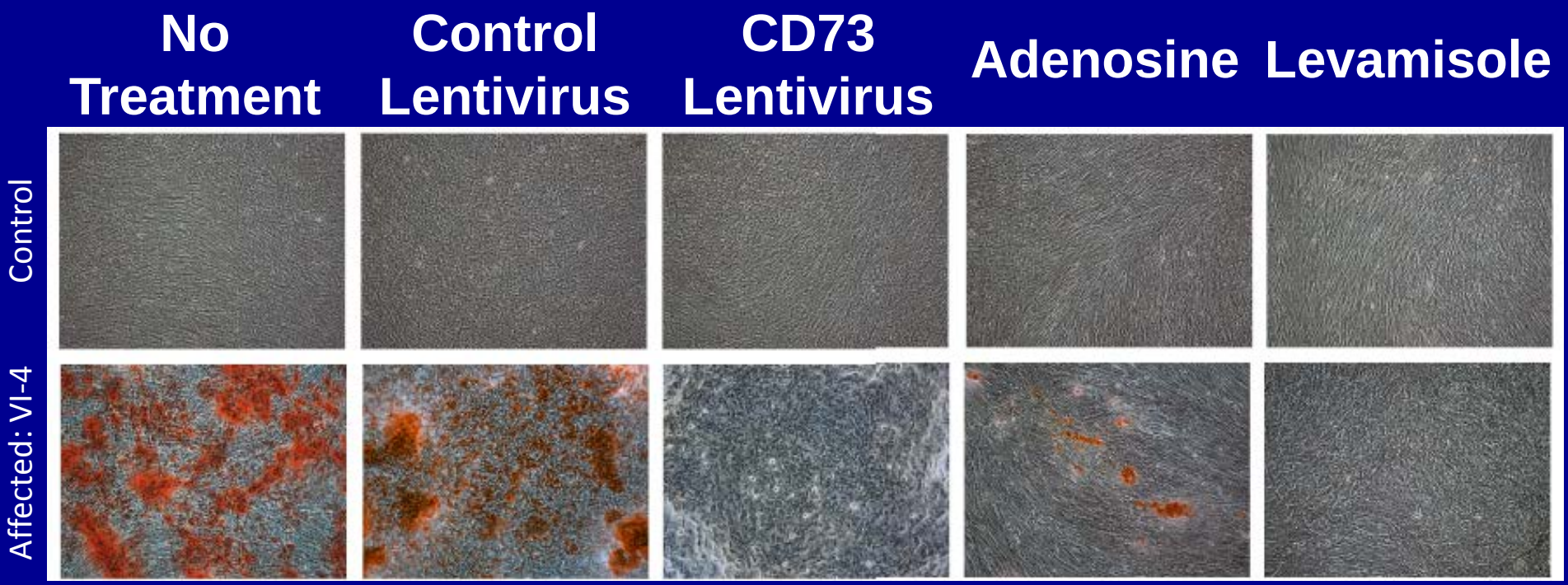
Control | Affected | Affected + Adenosine



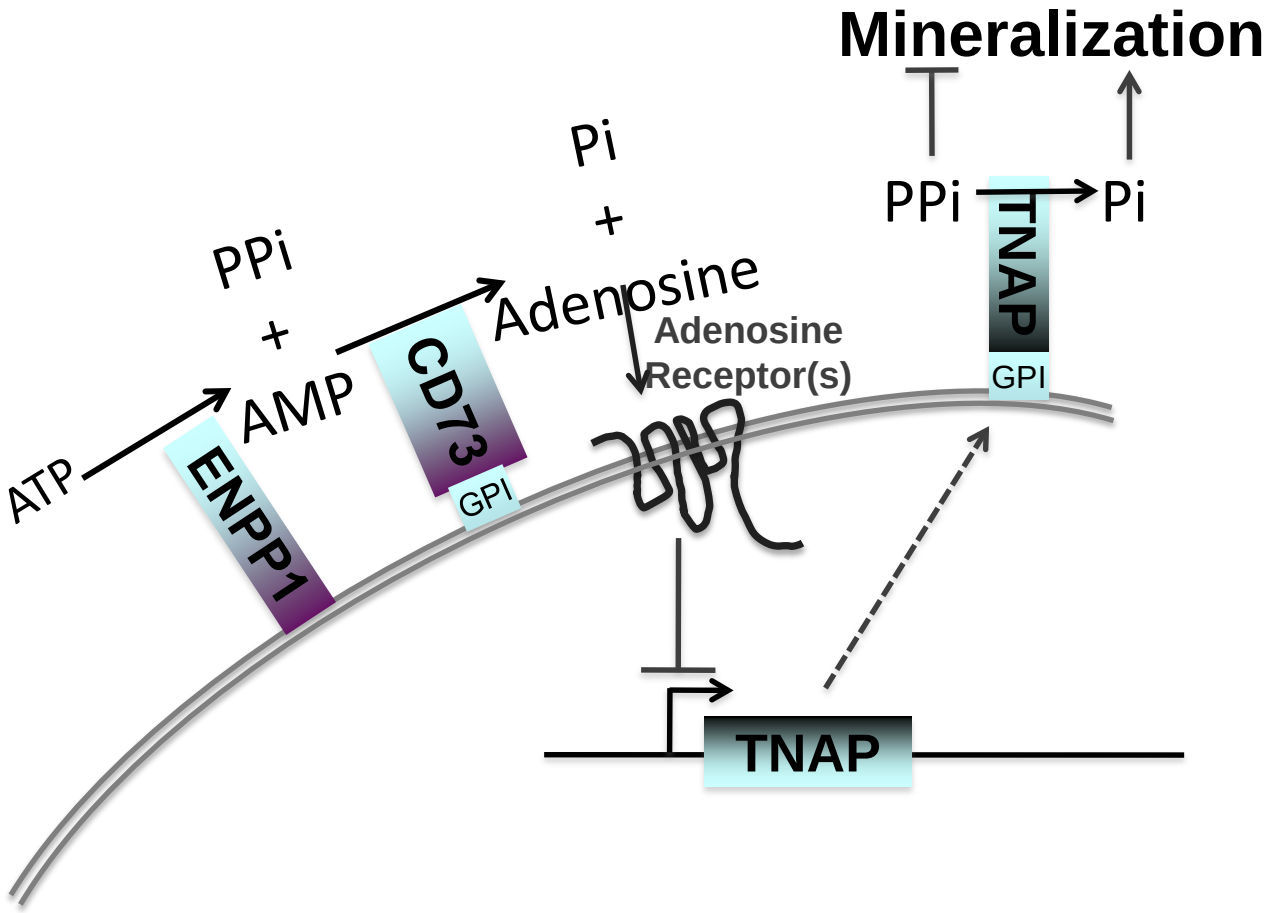
Adenosine treatment of cells reduces alkaline phosphatase staining.

St. Hilaire C, Ziegler SG, et al. NEJM 2011.

Rescue of Cell Calcification by a CD73 Lentivirus, Adenosine, or an Alkaline Phosphatase Inhibitor (Levamisole)



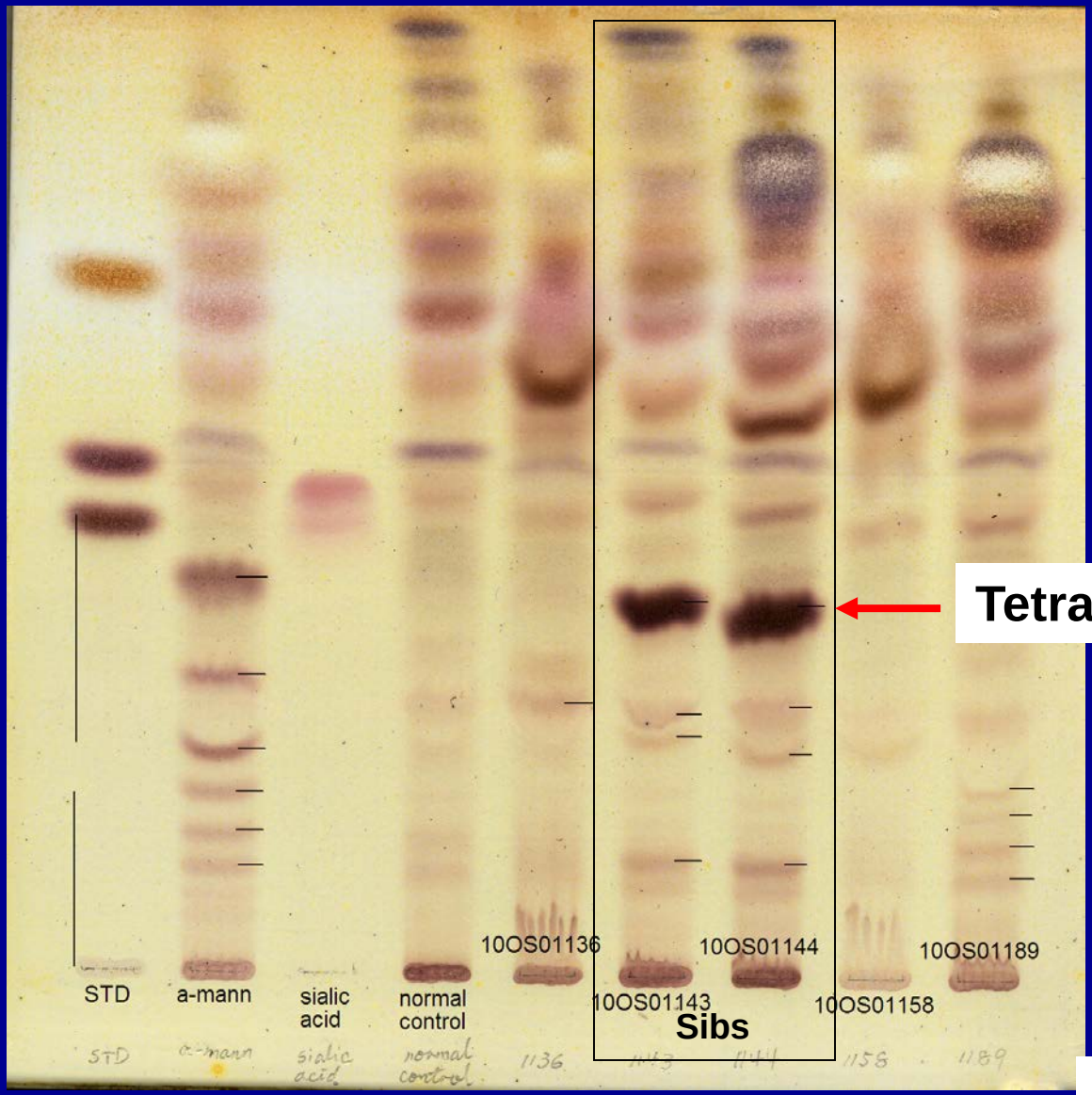
St. Hilaire C, Ziegler SG, et al. NEJM 2011.


Mineralization
PPi
Pi
TNAP
GPI
Pi
+
PPi
+
Adenosine
Adenosine
Receptor(s)
ATP
AMP
CD73
GPI
ENPP1
TNAP

10 year-old boy and 5 year-old girl

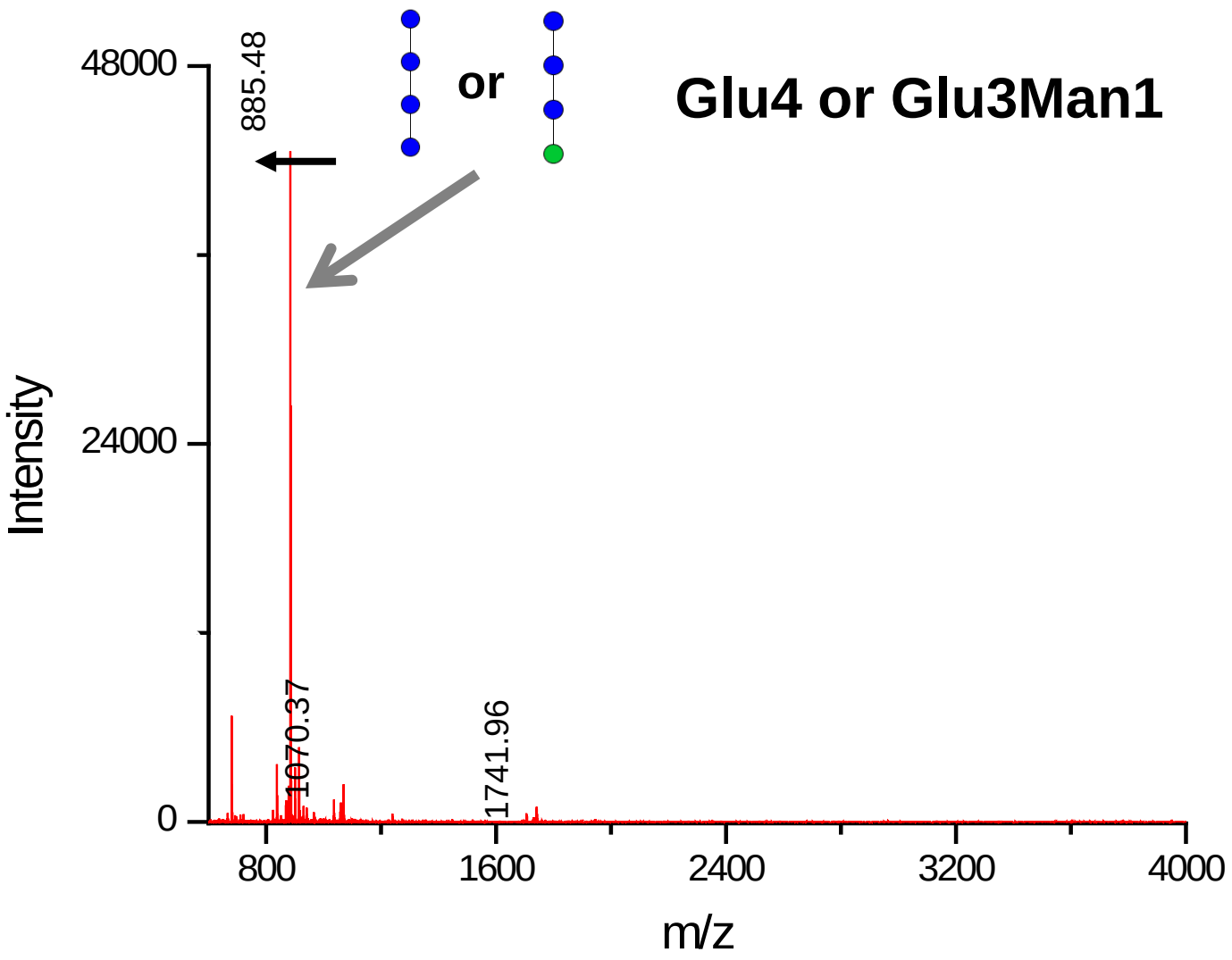
- Facial dysmorphisms, hypotonia, delays, hearing loss, nystagmus, seizures
- MRI: Diffuse atrophy, especially periventricular
- Labs normal, including transferrin IEF
- Urine glycan screening by MALDI (Dr. Miao He, Emory) confirmed hex4 band seen on TLC.

Oligosaccharide TLC



Dr. Miao He

Urine glycan MALDI profile



Dr. Miao He

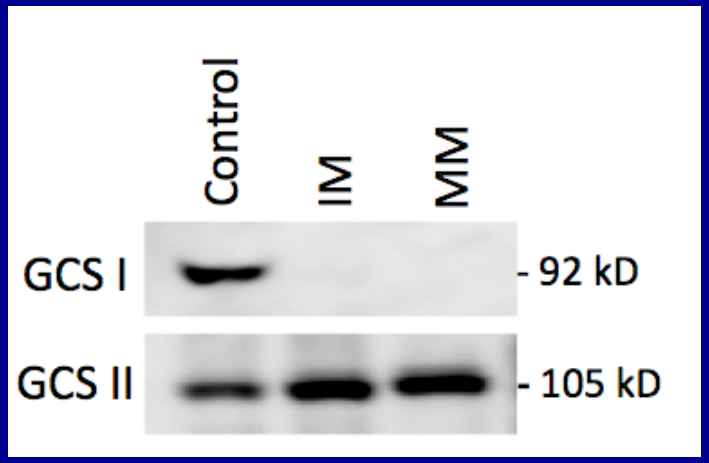
Deficiency of Glucosidase I?

- In N-linked glycoprotein synthesis, $Glc_3Man_9GlcNac_2$ is transferred to polypeptides in the ER.
- Glucosidase I is the first trimming enzyme, removing the terminal glucose.
- Further trimming allows for creation of complex oligosaccharide on N-linked glycoproteins
- Glucosidase I deficiency is Congenital Disorder of Glycosylation IIb (1 patient).

Mutation Analysis of Glucosidase I Gene

Both affected children are compound heterozygous for:

- **Exon 1: c.65C>A, p.A22E; c.329G>A, p.R110H**
- **Exon 2: c.370C>T, p.124Q>X**

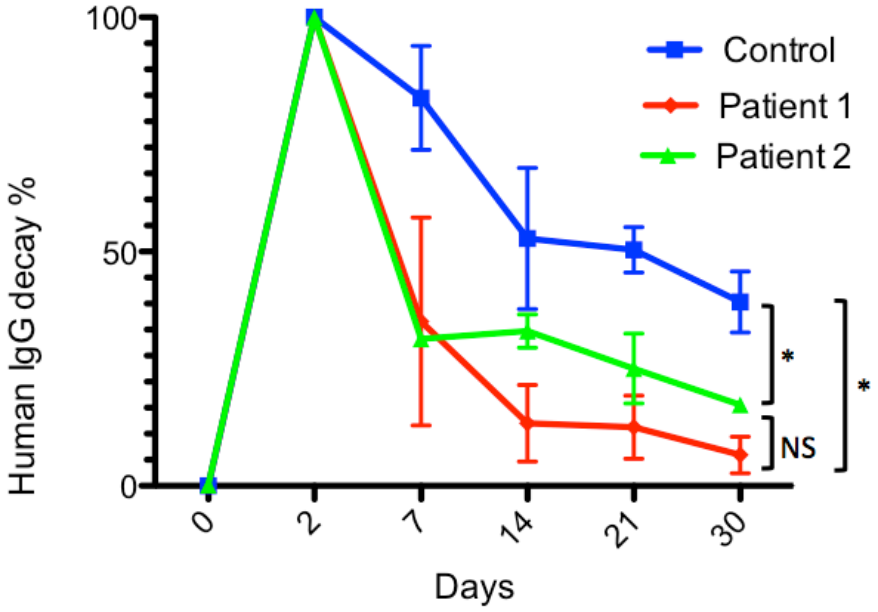


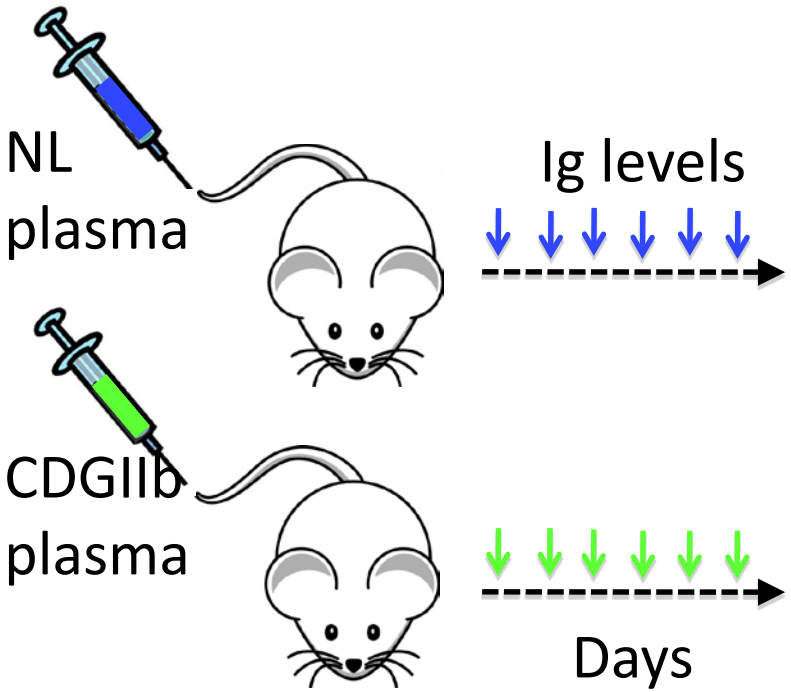
They are the 2nd and 3rd patients in the world with CDG IIb.

CDGIIb Patients

- **Hypogammaglobulinemia**
  - **IgG 142 (504-1465 mg/dL)**
  - **IgA 18 (27-195 mg/dL)**
  - **IgM 25 (24-210 mg/dL)**
- **Why?**
- **IgG, lacking oligosaccharides in patient, is rapidly degraded.**

Hypo/agammaglobulinemia Evaluation: IgG Half-life in RAG1 SCID Mice





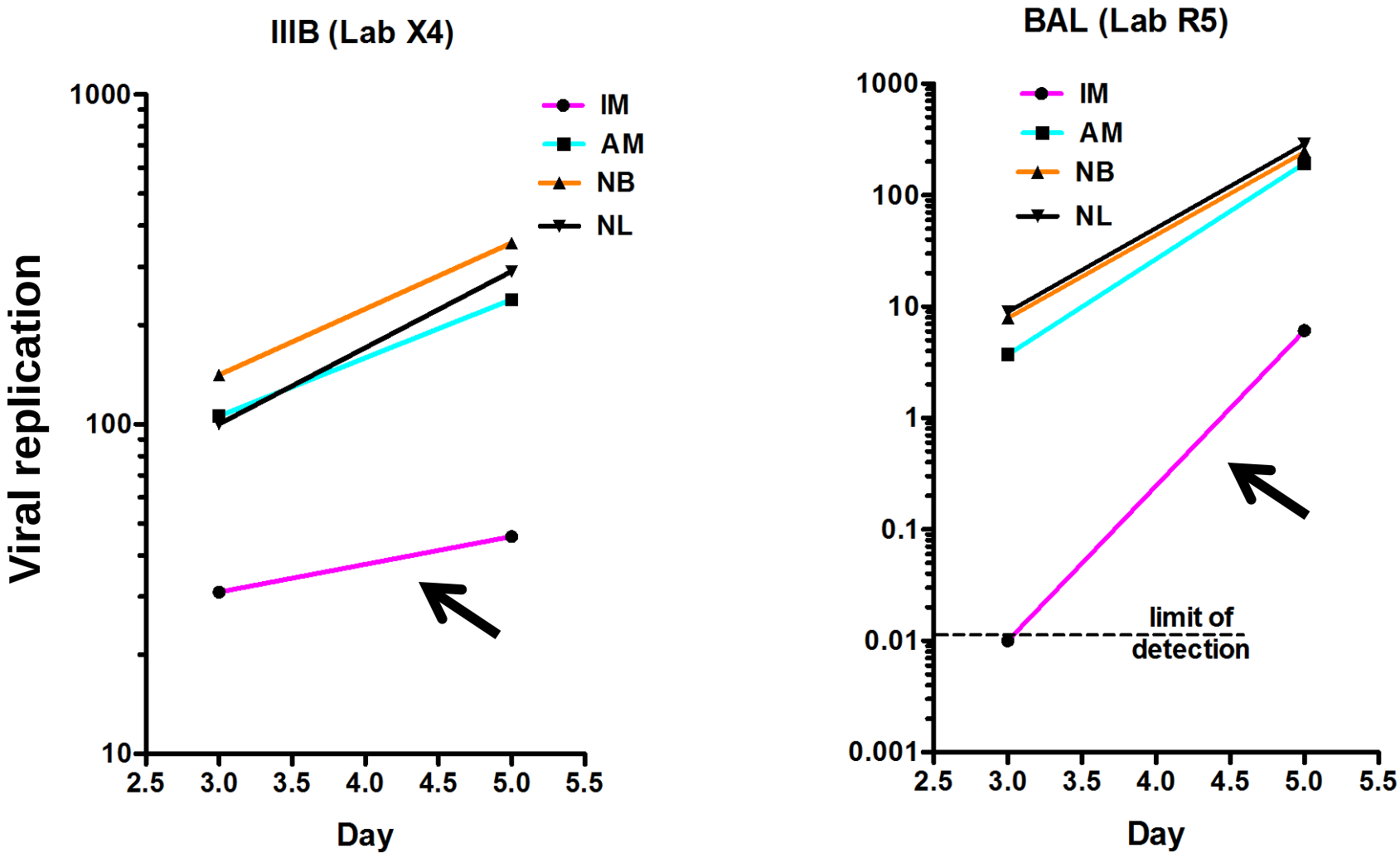
IgG half life: **Control 21 days**
Patient 6 days

Dr. Sergio Rosenzweig

Despite hypogammaglobulinemia, CDGIIb patients do not get infections!

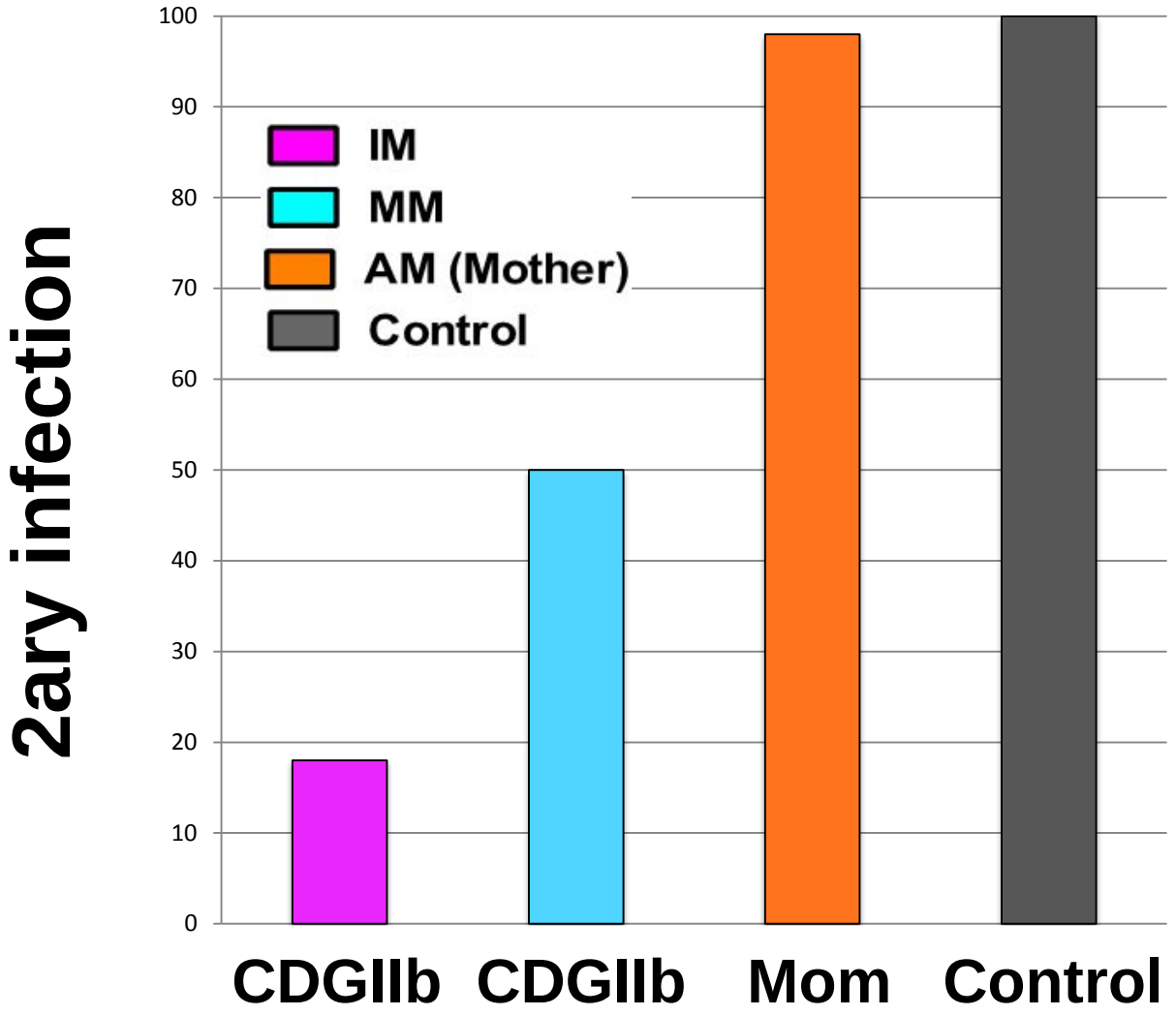
WHY?

CDGIIb cells could be infected with virus, but once infected, they produced much less virus.



Dr. Sergio Rosenzweig

And the virus produced is 50-80% less infective, as gauged by the ability to produce a secondary infection.



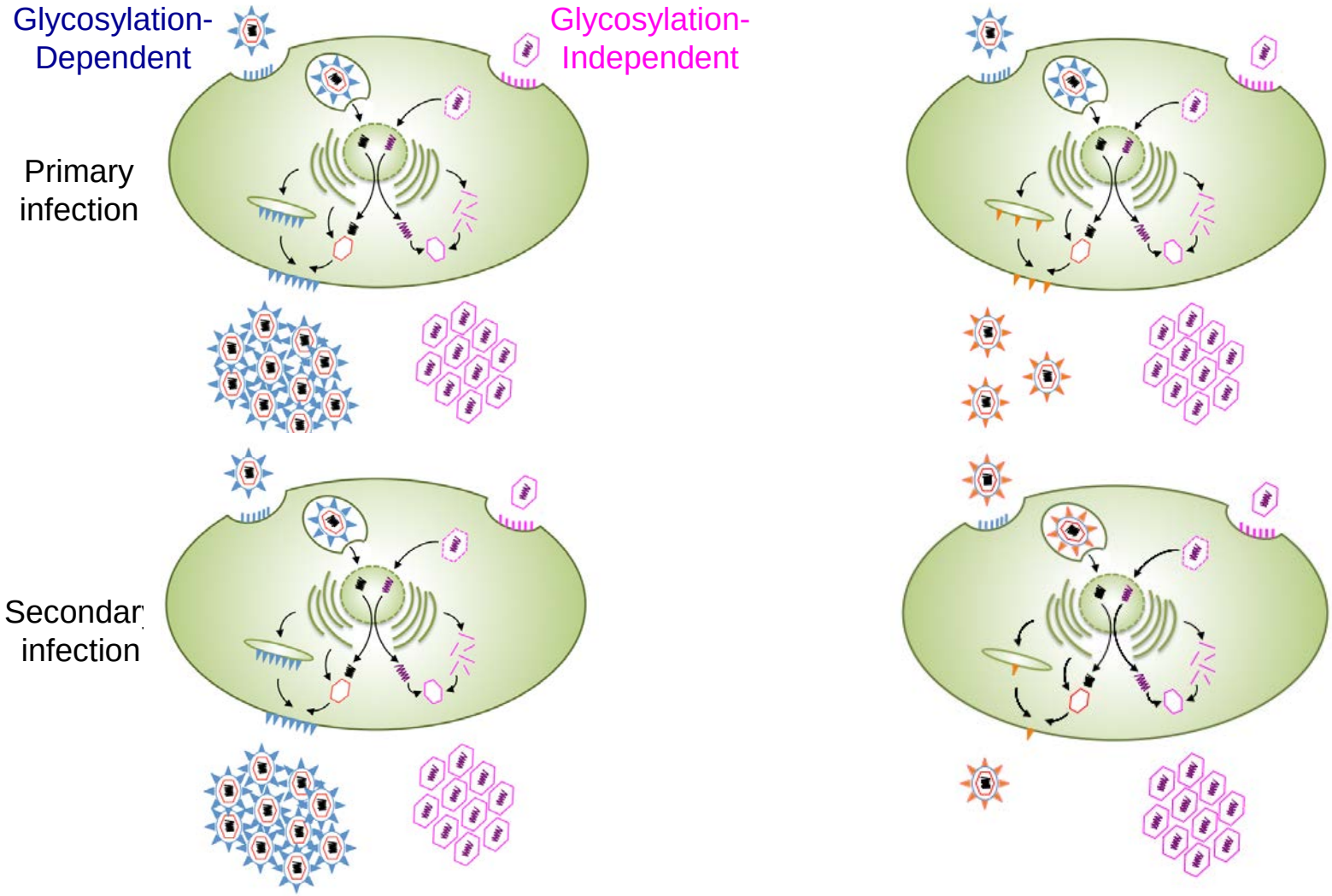
Dr. S. Rosenzweig

Dr. Sergio Rosenzweig

Viral susceptibility model

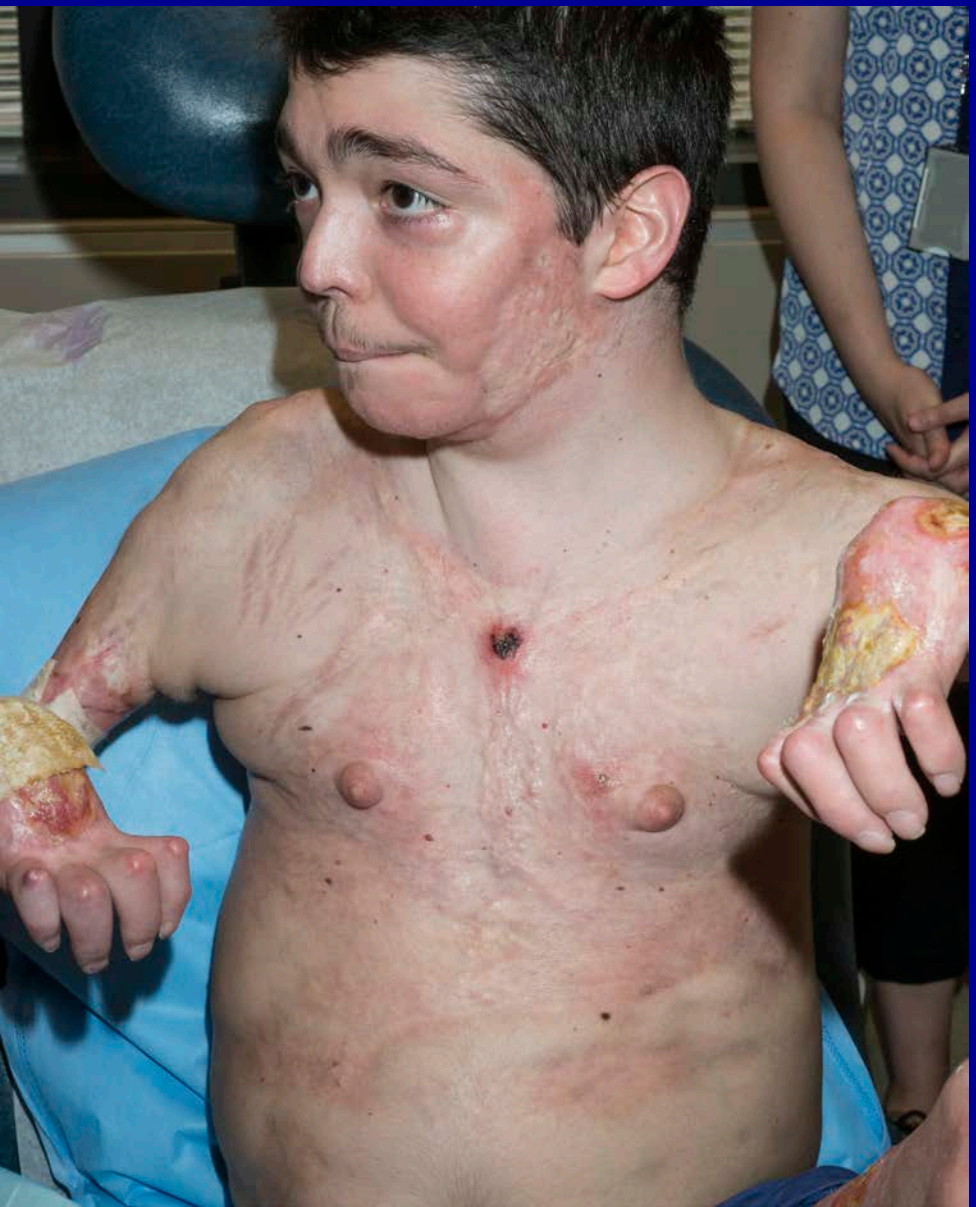
Infections in WT cells

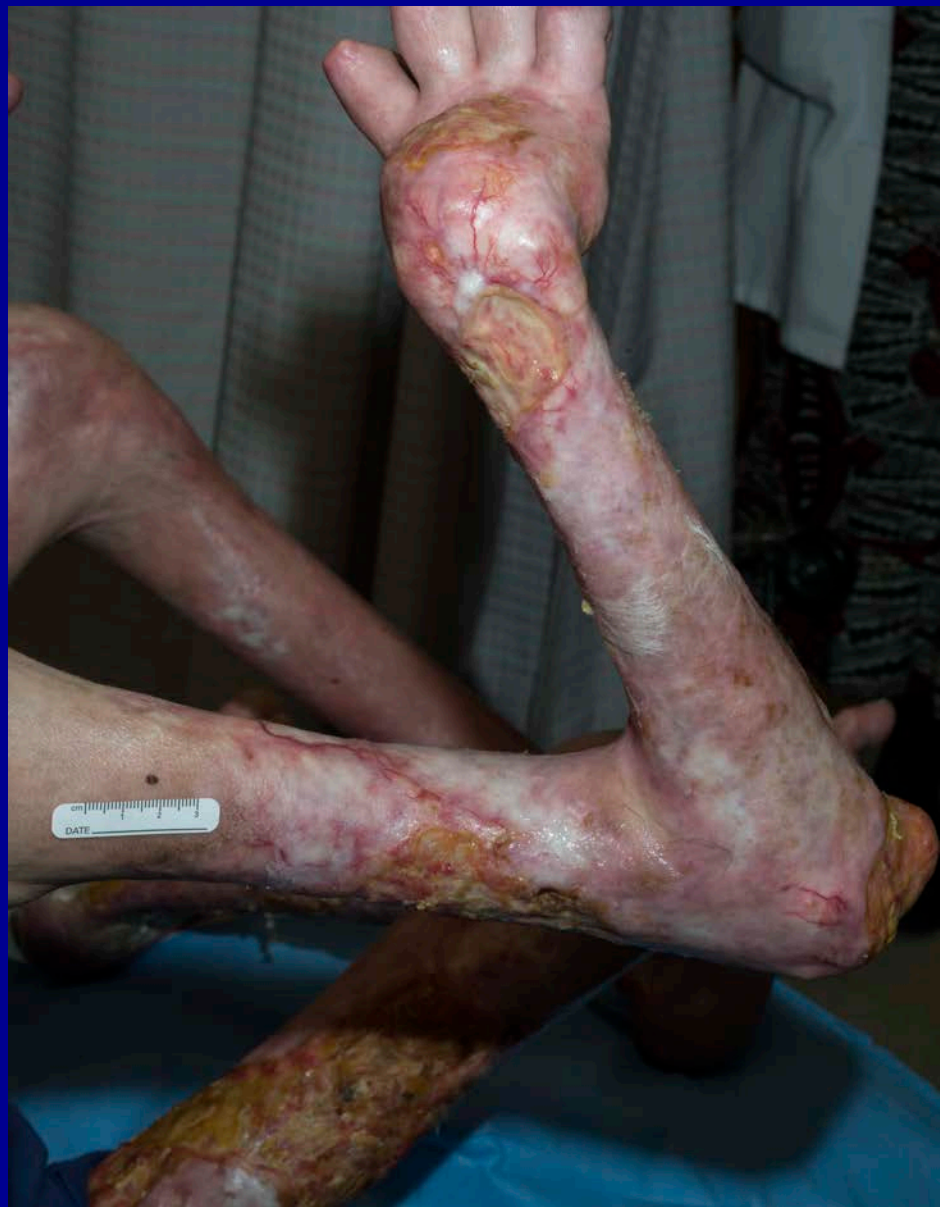
Infections in CDGIIb cells



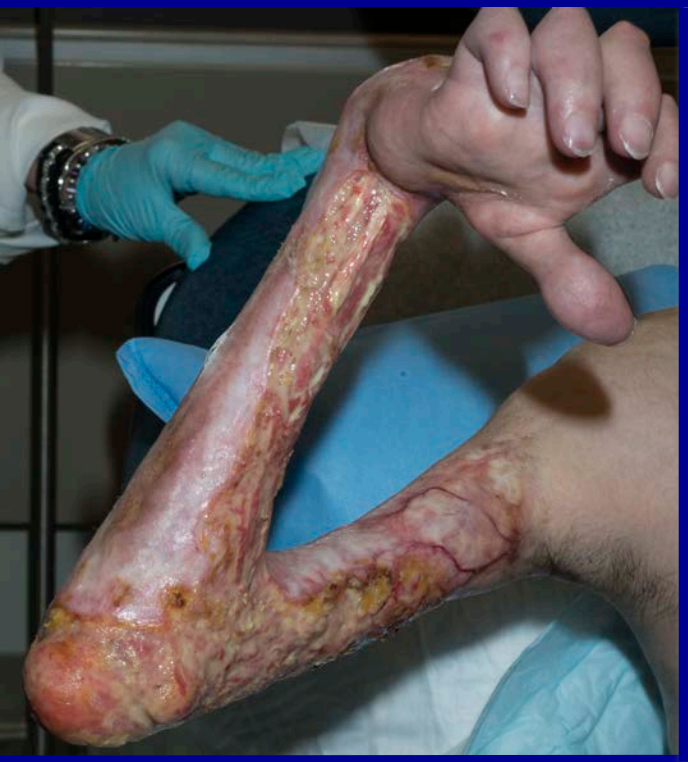
Mysteries/Treatment

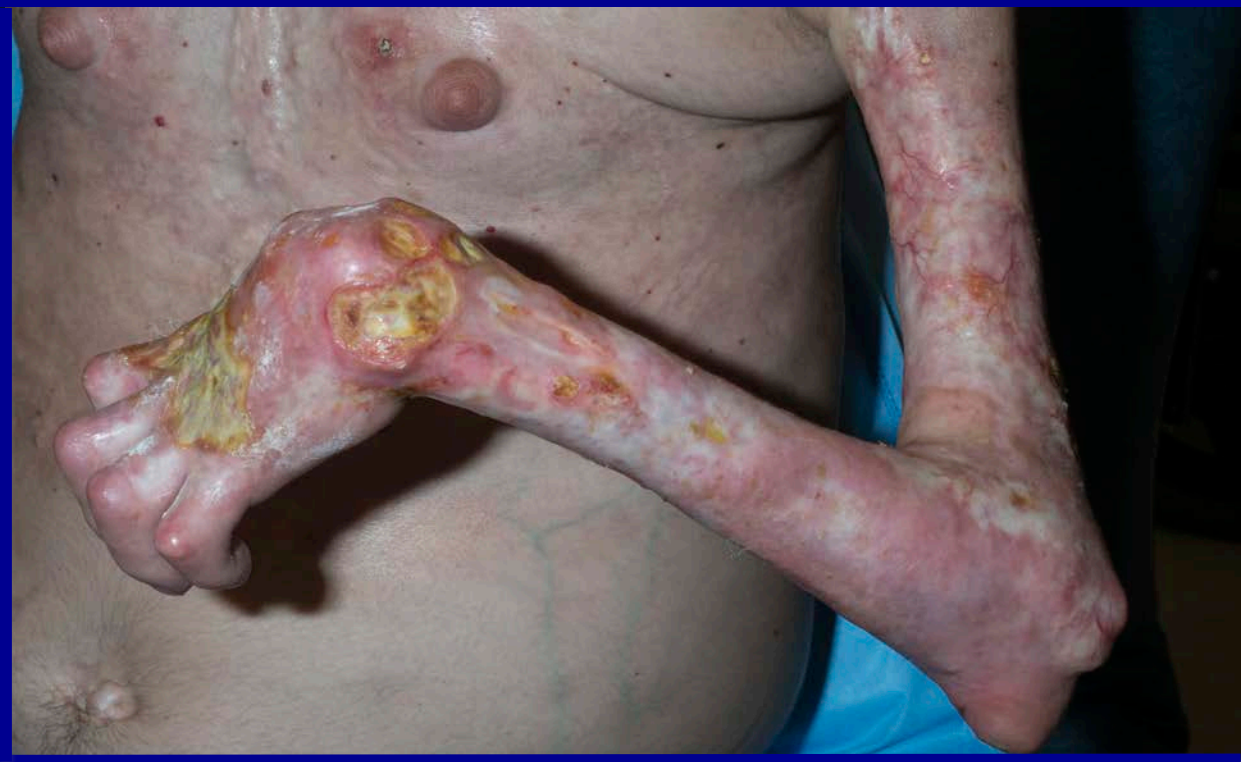
UDP 10237-25 year old man with contractures and skin ulcerations

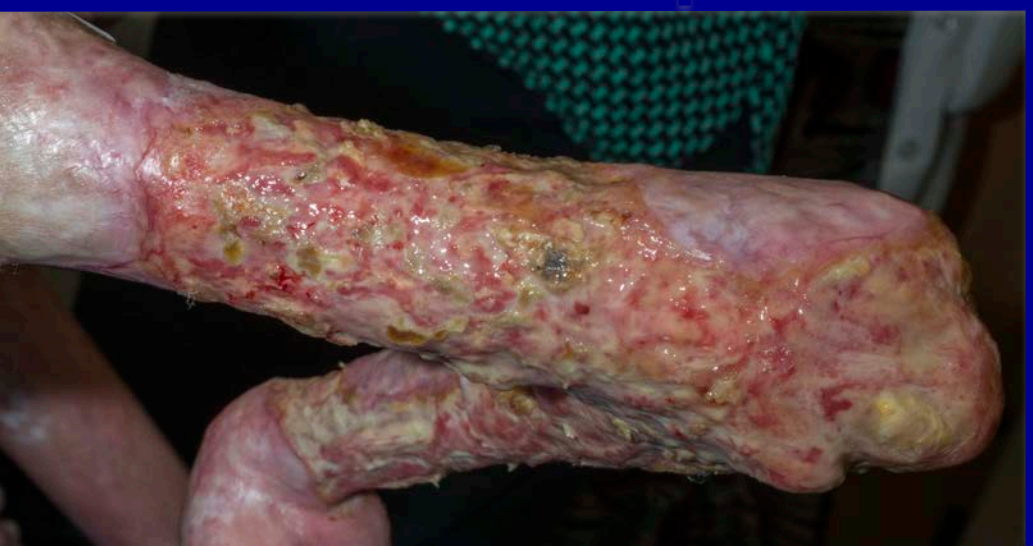


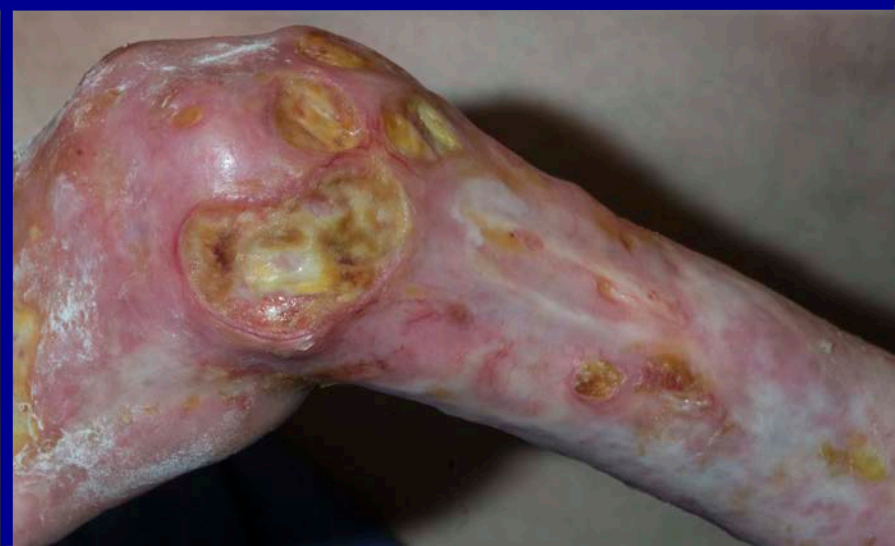


Upper Extremities

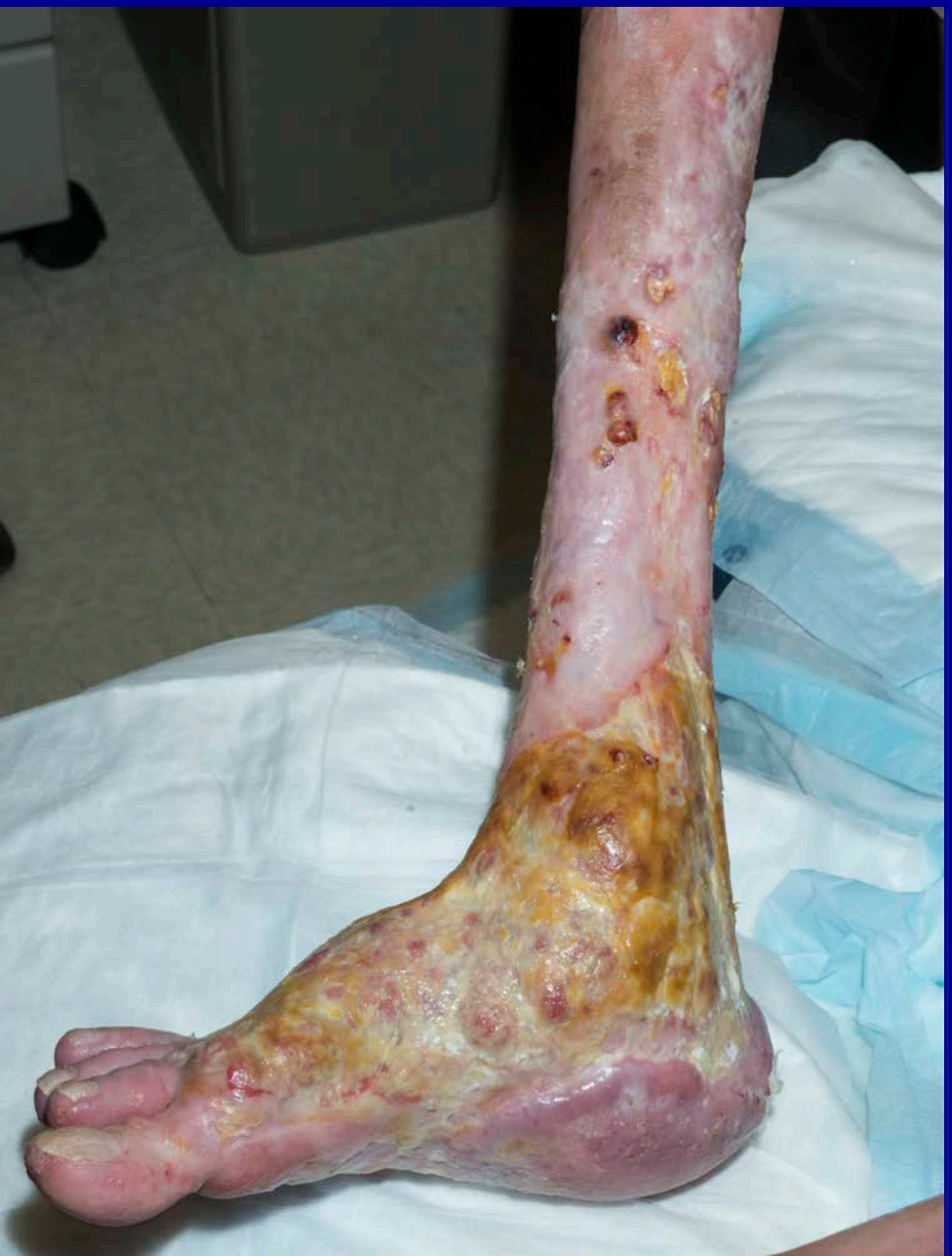


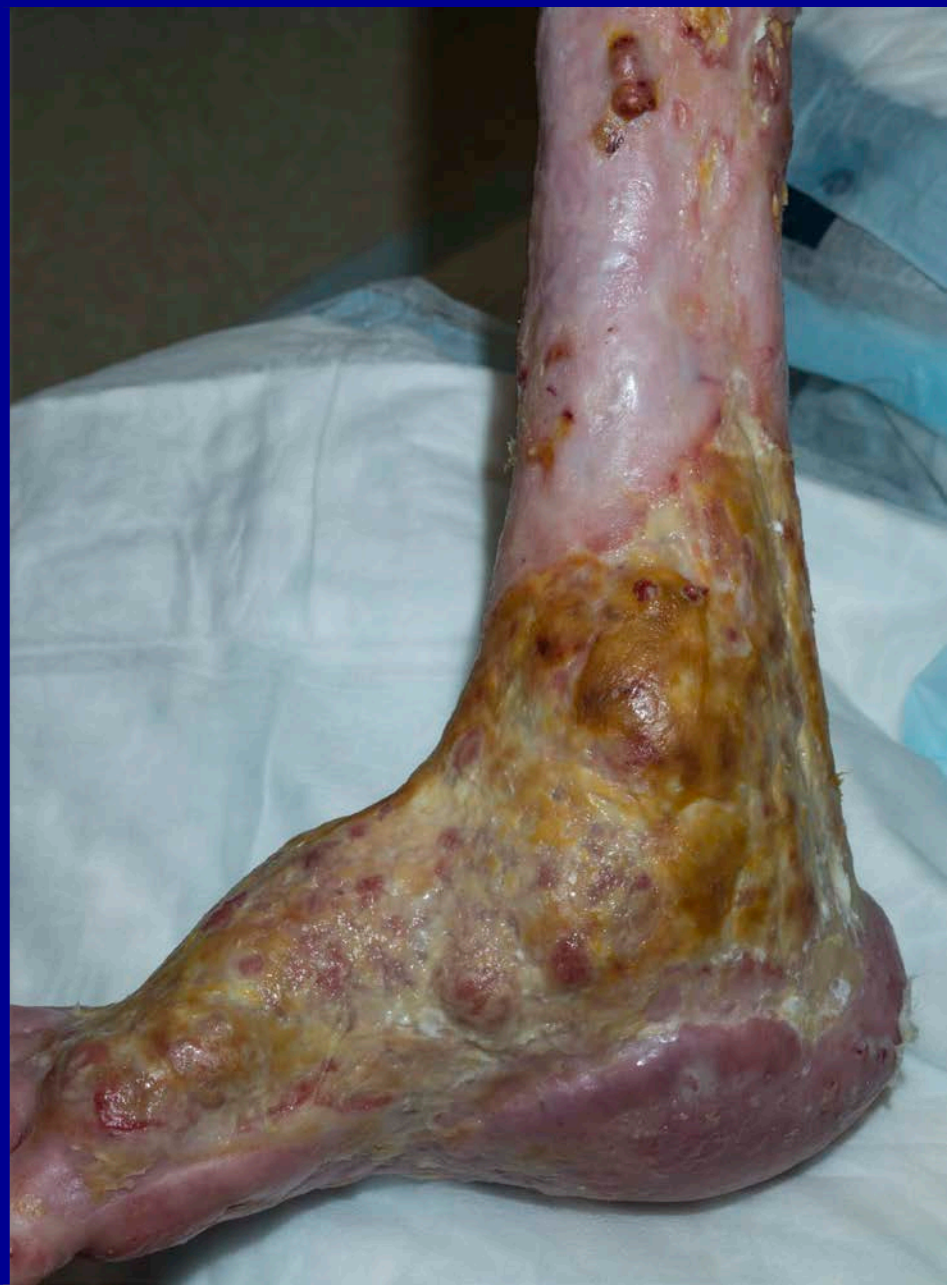




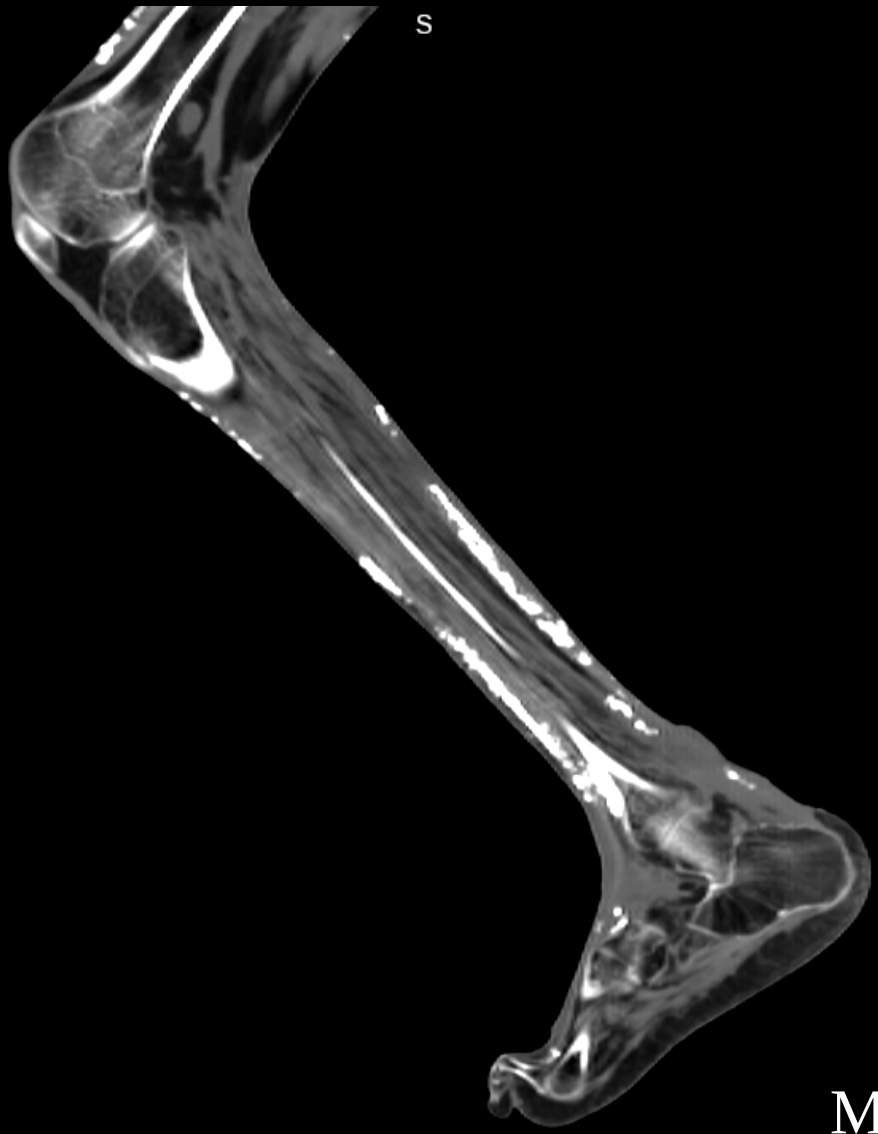


Lower Extremities

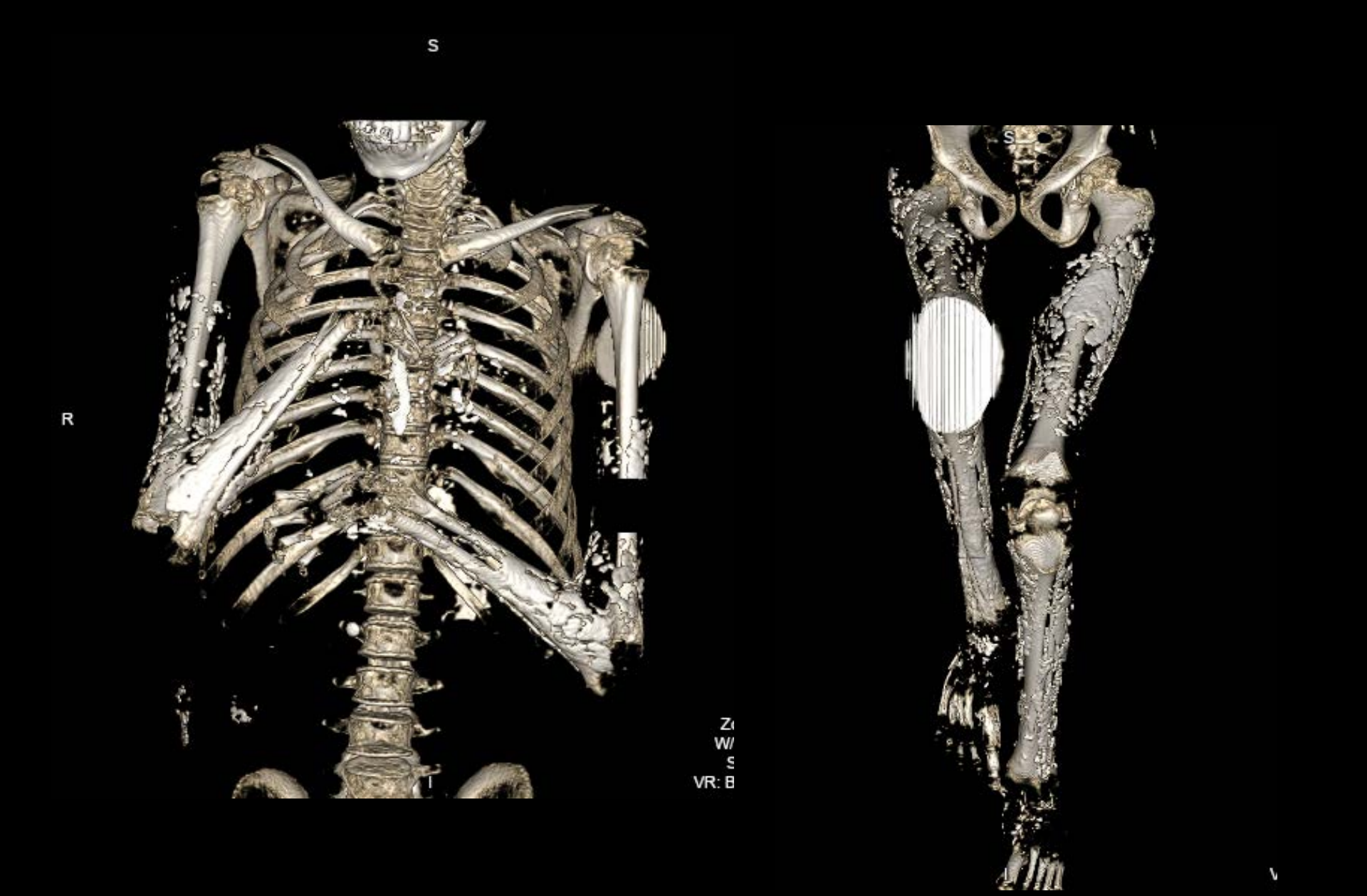




Left lower extremity



Marcus Chen, MD

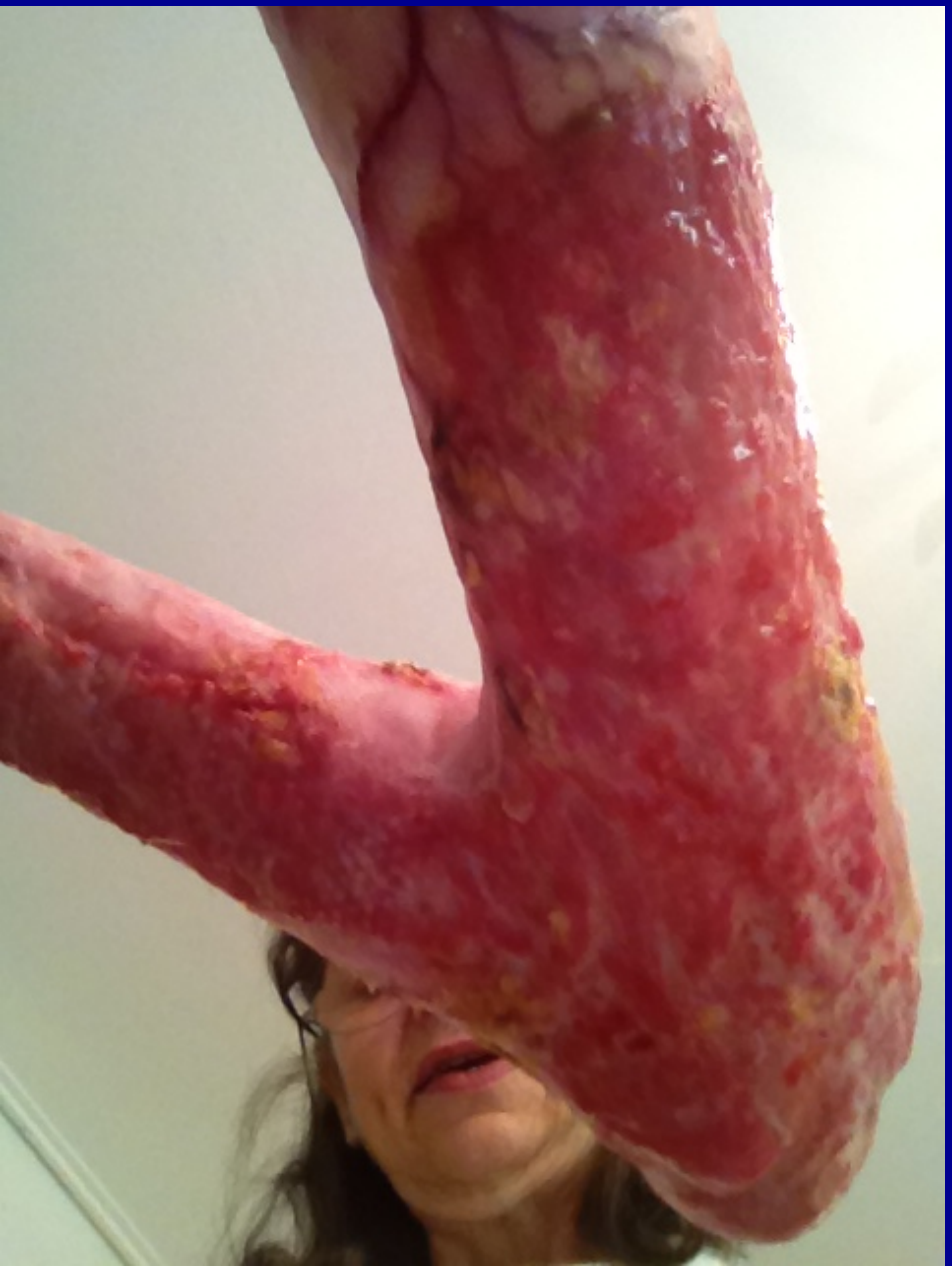


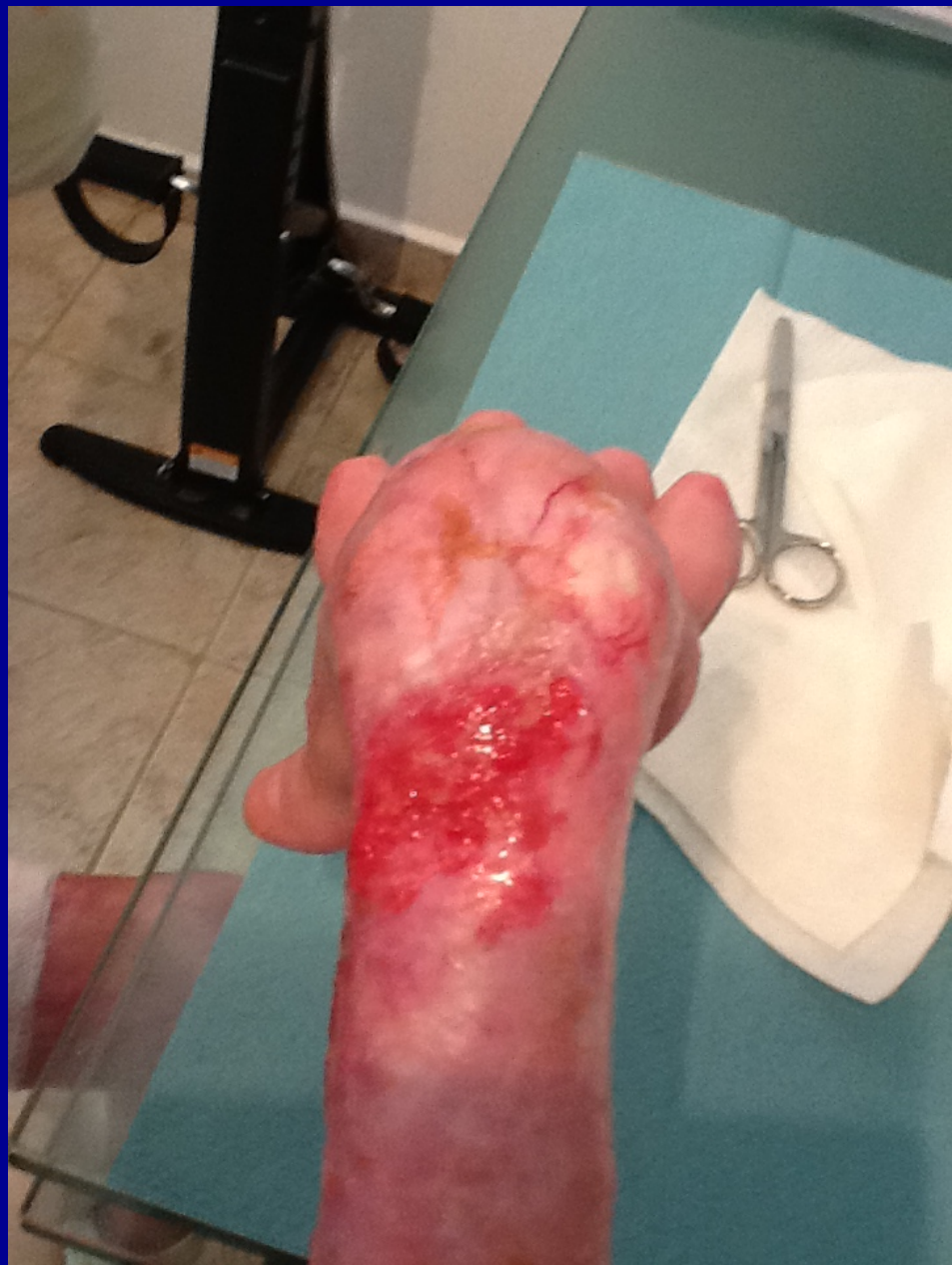
Marcus Chen, MD

UDP 10237

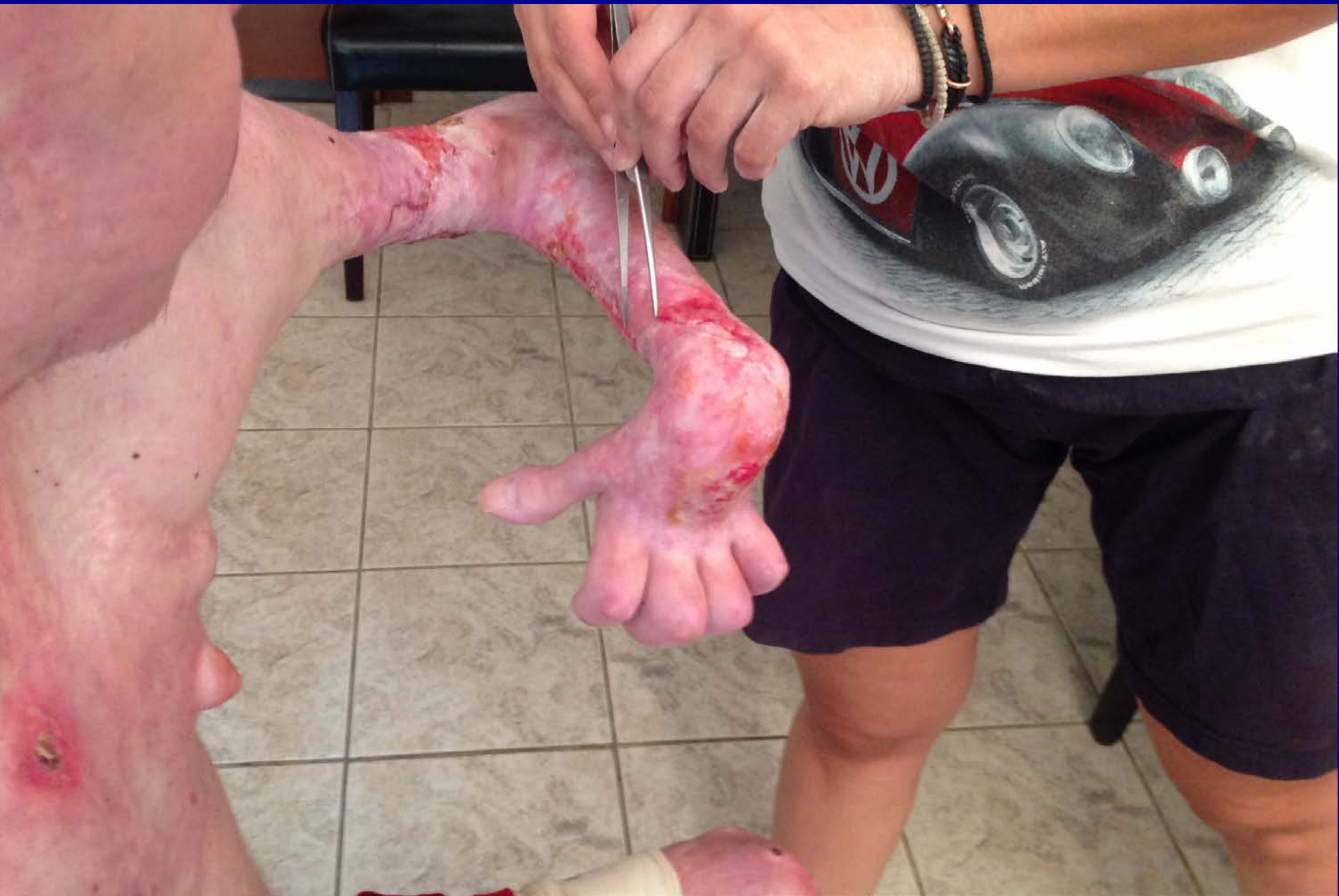
- No diagnosis, but because the calcifications could be stimulating an inflammatory reaction, Dr. Lisa Rider (Rheum) suggested topical sodium thiosulfate.
- The thiosulfate salt of calcium is 250-10,000 times more soluble than the phosphate salt.

Sodium Thiosulfate – July 2014 (1 month)

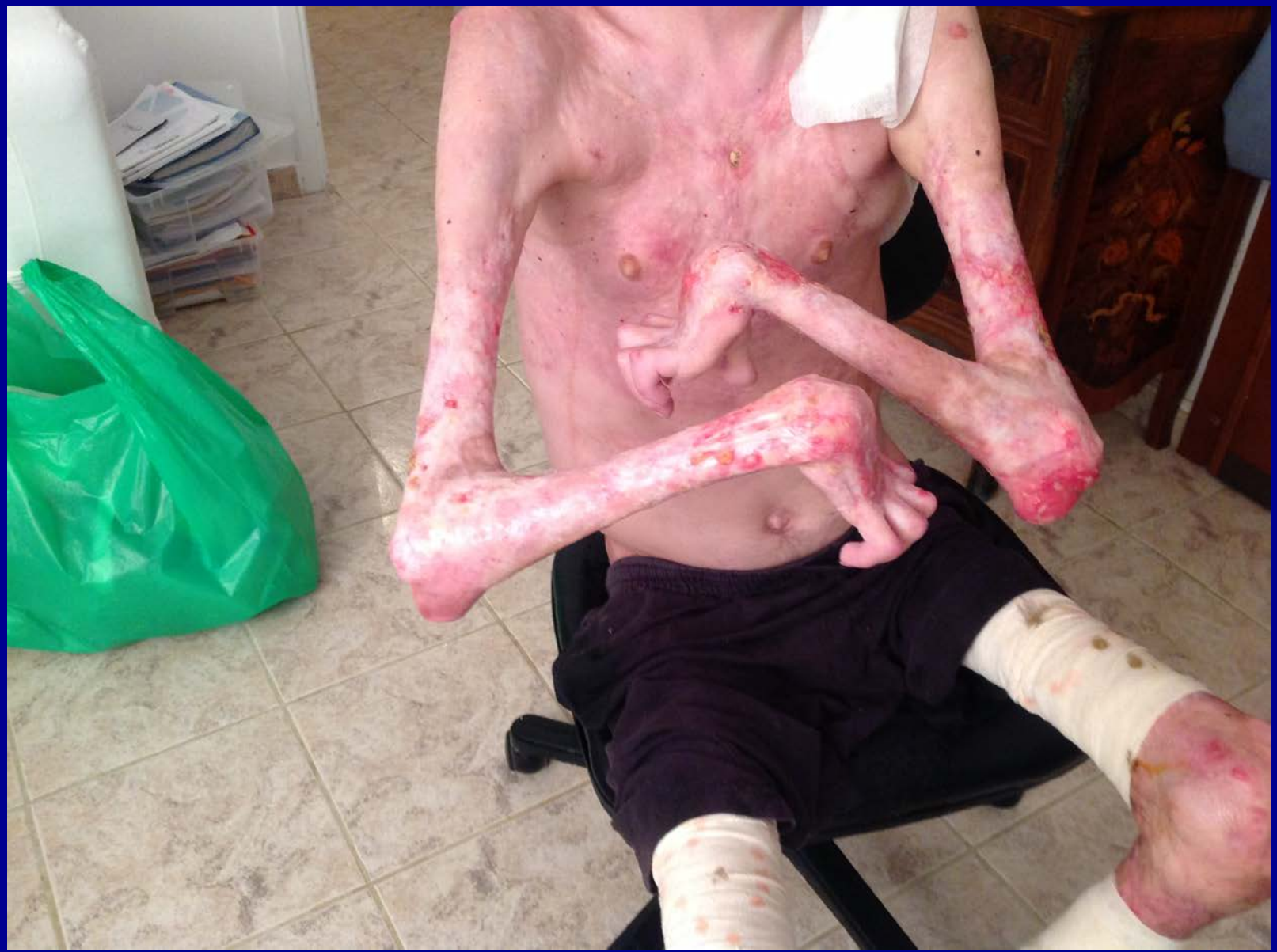




Sodium Thiosulfate – August 2014 (2 months)



Sodium Thiosulfate – October 2014 (4 months)



Diagnoses

Very Very Rare Diagnoses

- Myoclonus epilepsy without renal failure – due to *SCARB2* mutations (5 in world)
- Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) with *MBTPS2* mutations (6 families in world)
- Neurodegeneration with brain iron due to c19orf12 mutations (20 families)
- ALS-Frontotemporal Dementia due to c9orf72 expansion
- Cytosolic PEPCK deficiency due to *PCK1* muts
- *KDCT7* in two sibs with ataxia, Sz (2 families)
- Nephrolithiasis & 24-hydroxylase deficiency (few families)

Very Very Rare Diagnoses

- Congenital Disorder of Glycosylation type 2b (2nd and 3rd cases in world)
- Adducted Thumb-Clubfoot Syndrome & *CHST14* mutations (1st case in U.S.)
- Spinocerebellar ataxia, myoclonic epilepsy & *AFG3L2* muts (1st 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)

Recent Diagnoses

- Spermine synthetase mutations with developmental delays (Snyder-Robinson)
- XP with dementia due to ERCC1 mutation
- Delays and seizures due to PIGT mutations and GPI anchor deficiency
- Stargardt syndrome, Pelger-Huet anomaly, and others with chromosome 1 isodisomy
- Movement disorder due to *PLA2G6* mutations
- Osteopetrosis due to *LRP5* mutation
- Mowat-Wilson syndrome due to *ZEB2* mut
- Fahr's disease due to *PDGFRB* mutations
- Spasticity & leucodystrophy due to *DARS* mut
- Leucodystrophy due to *AARS2* mut

Recent Diagnoses

- Kohlschutter-Tonz syndrome (Sz, neurological regression) due to *ROGDI* mutations
- Delays, hypotonia, strabismus due to biallelic *UNC80* mutations
- CVID, aplastic anemia due to a *CTLA4* mut
- Myofibrillar myopathy with de novo *BAG3* mut
- X-linked intellectual disability, facial dysmorphisms due to *RLIM* mutation
- Desminopathy
- Fatal Creutzfeldt-Jacob; PrPSc/PrP27-30
- Oculodentodigital Dysplasia due to *GJA1* (connexin 43) mutations
- Chorea, hypomyelination-de novo TUBB4A mut

Some UDP Communications

- **Announcement May 19, 2008 (Dr. Zerhouni)**
  - **90 patient advocacy groups; 25 reporting agencies**
- **Written press coverage**
  - ***Newsweek* article**
  - **Scores of newspaper articles**
  - ***NY Times Magazine, People Magazine (!)***
  - ***Nature* article**
- **Television and Radio**
  - **NBC Nightly News**
  - **Fox Television (Chris Wallace); PBS**
  - **CNN (Dr. Sanjay Gupta)**
  - **ABC Today Show**
  - **60 Minutes**
  - **Discovery**

Political Inquiries

Congress	39
NIH Director	30
Secretary HHS	4
White House	1

Congressional Visits to NIH UDP ~6

Expansion to a UDN

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

Mapping UDP to UDN

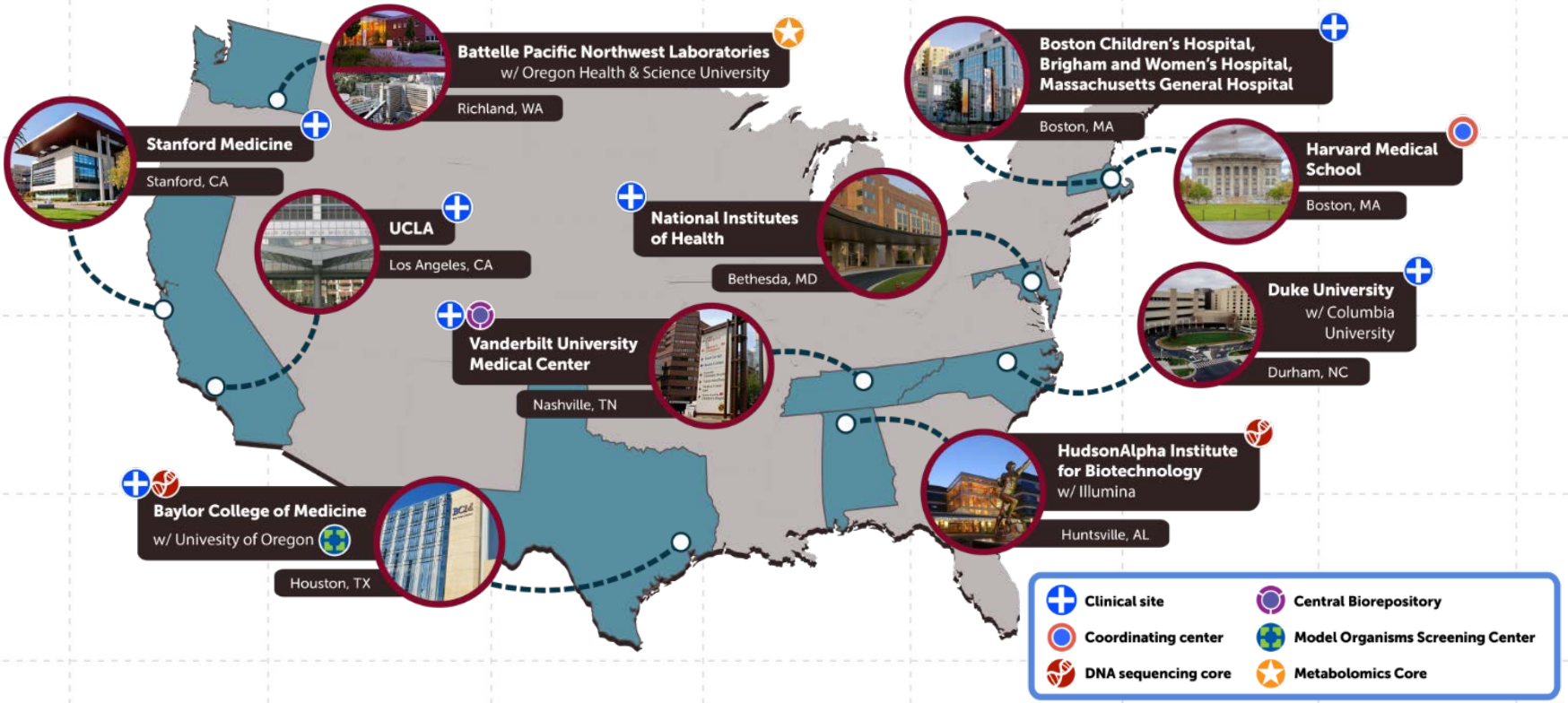
1. Phenotyping -> 7 Clinical Sites

2. Genetics -> 2 Sequencing Cores

1. Functional studies -> Model Organism Screening Core; Gene Function initiatives

Undiagnosed Diseases Network

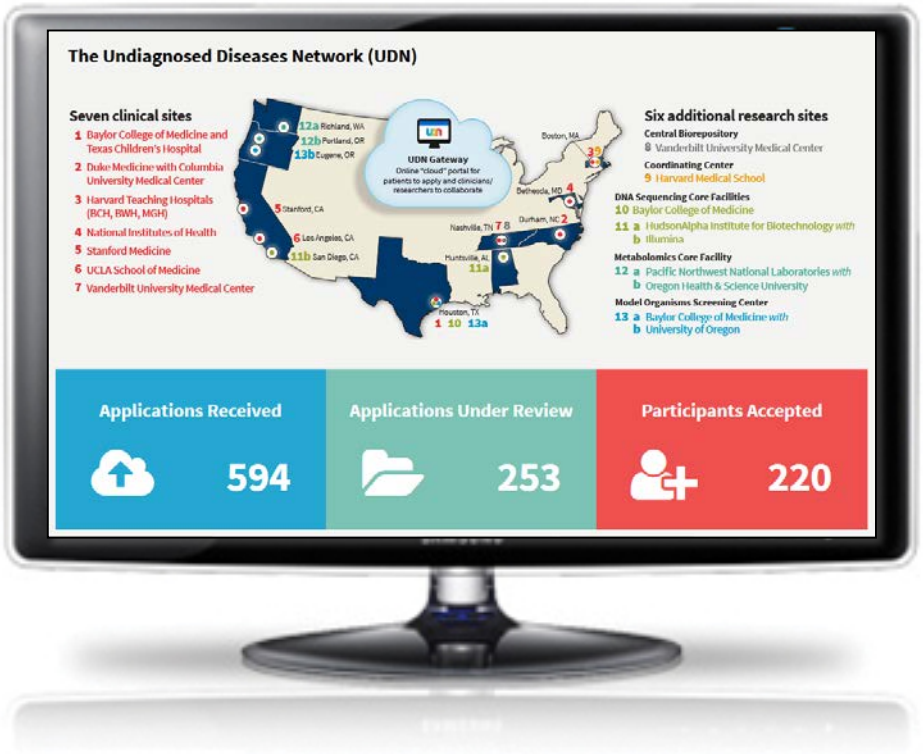
Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository



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.

The UDN Gateway

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



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

Challenges of expanding Intramural UDP -> Extramural centers (UDN)

1. **Financial issues**
   - Billing for clinical vs research
   - Payment for patient travel
   - Ability to examine/study family members
2. **Practical issues**
   - Inpatient vs outpatient; sequence before visit?
   - Availability of diverse specialists
   - Time for consultants to discuss case together
3. **Research issues**
   - Need to expand the capacity to investigate the pathophysiology of new diseases
   - Federal/medical center data sharing

Progress – Toward Diagnosis

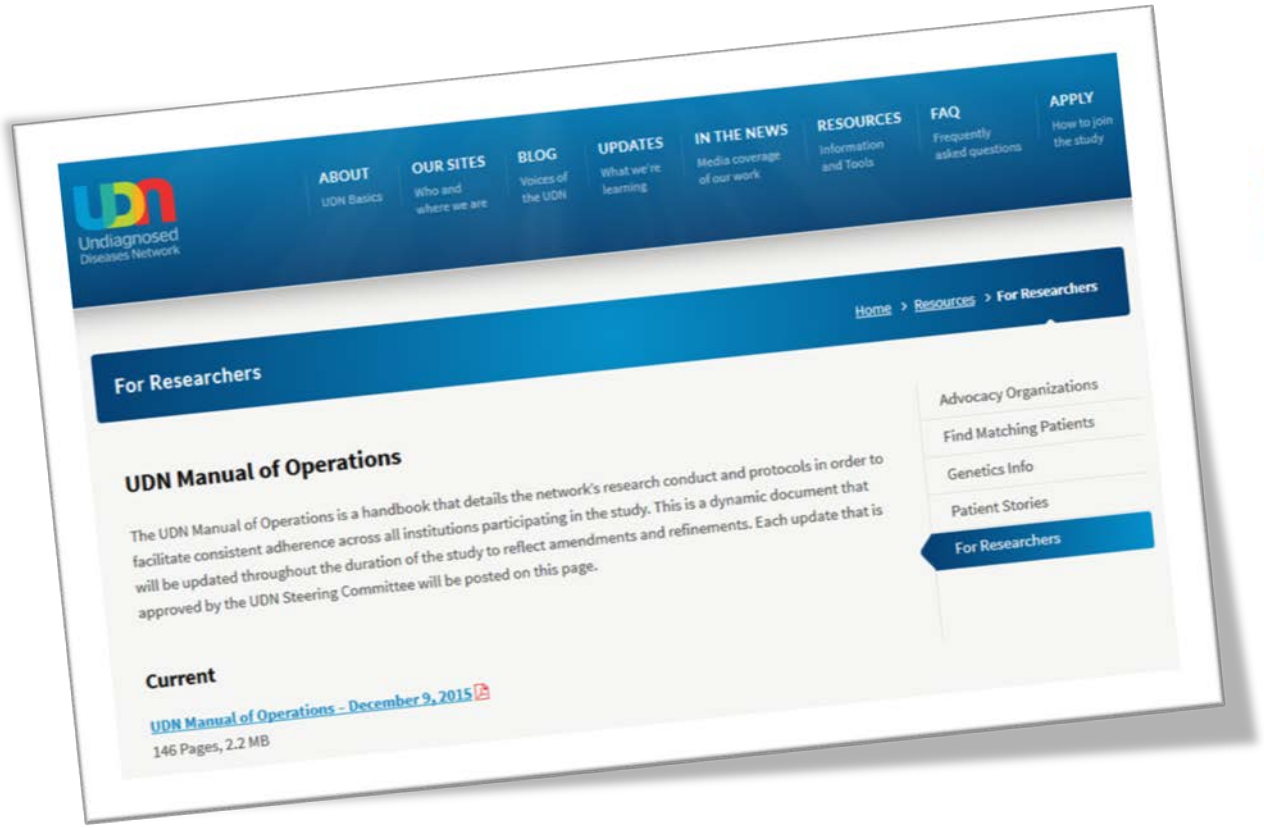
- Applications 611
- Accepted 220
- Evaluated 40
- Diagnosed 11
- Exomes sent 189
- Genomes 135
- Model Organism Genes 52
- Metabolomics Starting
- Collaborations: UCLA & Baylor; Duke

As of May 1, 2016; UDN opened August 2015

Progress - Toward Sharing

- Coordinating Center collecting data; available to Network, collaborators
- Submission to public databases
- UDN accepting applications for Collaborative Clinical Sites abroad
- Model Organisms Screening Core and Metabolomics Cores are discussing cases with clinicians
- International Undiagnosed Diseases Network

UDN Data Sharing and Outreach



dbGaP
GENOTYPES and PHENOTYPES

Phenome Central

Matchmaker Exchange

Manual of Operations Available!

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

Undiagnosed Diseases Network International(UDNI): White Paper for Global Actions to Meet Patient Needs

Domenica Taruscio[a], Stephen C. Groft[b], Helene Cederroth[c], Béla Melegh[d], Paul Lasko[e], Kenjiro Kosaki[f], Gareth Baynam[g], Alexa McCray[h], William A. Gahl[i]

Molecular Genetics and Metabolism 116:223-5, 2015.

Website:

http://www.udninternational.org/

UDNI Meetings - Sharing

1. Meetings

- Rome September 2014
- Budapest – June 2015
- Vienna – February 2016
- Tokyo – November 2016
- Common Fund + Wilhelm Foundation

2. UDPs Operating

- Western Australia
- Japan
- Vienna
- Italy

New United States UDPs

- UDN has stimulated other groups to start UDPs.
- Sequencing but no research testing.
- Other sites look to UDN for collaborations, sharing, MOO.
- Sites include:
  - U. Alabama-Birmingham
  - Emory
  - Mayo
  - U. Utah

Issues for the UDN

1. Billing
2. Sequence before or after seeing patient
3. How to disseminate information
4. Sustainability of UDN model
5. Central support vs. Local support

Sustainability/Dissemination of the UDN

- **FY18-22: Request Common Fund support; plan for future support.**
- **FY23-> : No Common Fund support.**
  - **Extramural portion of UDN**
    - **NCATS? CTSAs? Central NIH Database?**
    - **Independent medical center support? Philanthropy?**
  - **Intramural**
    - **Supported by Clinical Center, consortium of ICs?**
      - **Reduced volume of new patients**
      - **Follow-up for previous patients**
      - **Disseminate new disease patients to ICs**
      - **Maintain UDPICs database**