# Precision Medicine Successes from the Undiagnosed Diseases Network (UDN)

John A Phillips III, Amy K Robertson, Anna G Bican, Joy D Cogan, Lynette C Rives, Lisa F Germano, Vickie L Hannig, Laura C Fairbrother, Jean P Pfotenhauer, Elly K Brokamp, Patricia Clark Pollock, Thomas A Cassini, Daniel J Pomerantz, Ben A Small, John S Sergent, John H Newman & Rizwan Hamid.

Vanderbilt University Medical Center, Departments of Medicine & Pediatrics, and Division of Genetics & Genomic Medicine

## Abstract

**Aim:** Evaluate how often diagnoses of rare diseases made by UDN evaluations lead to directed therapies. **Methods:** We reviewed the first 6 cases diagnosed by our UDN clinical site to determine the proportion for which improved management options were discovered. Our cohort ranged from 4-48 years. All had previously eluded diagnosis despite extensive clinical assessments & as a result were referred to the UDN. Their age in years (yo), gender and presenting symptoms were the following: 1) 4 yo F with thin, fragile skin; macrocephaly & short stature, 2) 13 yo F with vision loss & hyperlysinemia, 3) 18 yo F with renal disease & pulmonary hypertension, 4) 32 yo F with chronic urticaria, angioedema & recurrent fever, 5) 37 yo F with deafness; sensory and motor neuropathy, & 6) 48 yo M with inflamed nodules of head & neck, & middle cerebral artery obstruction. UDN evaluations began with detailed reviews of all available medical records (clinical, family histories, lab tests, & imaging studies) & OMIM & SimulConsult database searches for key features. Consultations were done by multiple clinical & research specialists before & during CRC admissions. WES or WGS analyses were done on probands & selected relatives in 4/6 cases & analyzed using PhenoDB, Omicia Opal, additional pipelines, phenotype searches of the Vanderbilt BioVU cohort, & structural biology modeling. Co-segregation of candidate variants with case phenotypes was determined. **Results:** In cases 3, 5 & 6 a diagnosis was reached via physical examination, clinical & lab assessments alone. Cases 1, 2 & 4 also required WES/WGS. Corresponding diagnoses were: 1) Severe Progeria due to mosaicism for a *ZMPSTE24* .Leu326fs mutation resulting from uniparental isodisomy, 2) NADK2 Deficiency due to homozygosity for a Met1Val start loss *NADK2* mutation, 3) Systemic Lupus Erythematosus from review of previous renal biopsy EM & ANA titers, 4) PFAPA Syndrome due to *NLRP3* & *IL17A* variants, 5) Riboflavin (B2) Transporter Deficiency (RTD) based on phenotype & poor response to B2 challenge tests & 6) IgG4 Related Disease based on phenotype & review of previous biopsy slides, imaging studies & IgG4 levels. Resulting precise & directed therapies were: 1) Combined statin & bisphosphonate therapy based on reported response of a murine *ZMPSTE24* -/- model, 2) Trial of NADH to correct the NADPH deficiency, 3) Hydroxychloroquine & methotrexate, 4) IL1 antagonist for periodic fever, 5) High dose B2 supplementation resulted in improvement in walking distance & return of touch sensation in lower extremities. Her younger sister with sensory loss of her feet, an audiogram that showed some SNHL & poor B2 challenge test response was also treated with B2 & 6) Rituximab therapy. **Conclusions:** 1) Analysis of clinical, genetic & environmental data by the UDN resulted in diagnosis of cases that had previously been undiagnosed despite thorough evaluations, 2) All of these UDN diagnoses lead to precise & directed therapies, & 3) Our UDN cases demonstrate that RD & UD offer unique opportunities to facilitate research, apply & test principals of precision medicine & offer specific individualized treatment options for patients.

## Aim

To evaluate how often diagnoses of rare diseases made by UDN evaluations lead to directed therapies.

## Methods

- We reviewed our first 8 UDN diagnoses to determine the proportion for which treatment options were discovered.
- UDN evaluations (*ref 1*) included:
  - a) Review of available medical records,
  - b) OMIM/SimulConsult database (*refs 2-3*), searches,
  - c) Consultations by multiple specialists,
  - d) WES/WGS (NGS) on selected cases (using PhenoDB, Omicia Opal, & other pipelines, phenotypic searches of the Vanderbilt BioVU cohort, & structural biology modeling) &
  - e) Co-segregation analysis of NGS candidate variants.
- The proportion of UDN evaluations that required NGS for diagnosis & that lead to directed therapies was determined.

## Results

- In 5/8 (62%) of cases (1, 2, 4, 7 & 8) diagnoses required physical exam, clinical & lab tests & NGS (**Table & Example Case1**).
- In 3/8 (38%) of cases (3, 5 & 6) diagnoses were made on physical exam, clinical & lab tests without NGS (**Table & Example Case 5**).
- In 7/8 (88%) of cases (1-7) the UDN diagnosis led to directed therapy.

## Case Summaries, Diagnoses & Treatments

| Patient Summary | Dx | Gene/clinical | Rx |
|---|---|---|---|
| **1)** 4 yo ♀ Thin, fragile skin, macrocephaly & short stature | Severe Progeria | Mosaic *ZMPSTE24* Leu362fsX18 | Statin + Bisphosphonate |
| **2)** 13 yo ♀ Vision loss & hyperlysinemia | NADK2 Deficiency | Homozygous *NADK2* Met1Val start loss | NADH |
| **3)** 18 yo ♀ Renal disease & pulmonary hypertension | Systemic Lupus Erythematosus | Renal biopsy EM & ANA titers | Hydroxychloroquine & Methotrexate |
| **4)** 32 yo ♀ Chronic urticaria, angioedema & fever | PAPA Syndrome | *NLRP3* Se728Gly *IL17A* Arg123His | IL1 Antagonist |
| **5)** 37 yo ♀ SNHL, sensory & motor neuropathy | Riboflavin (B2) Transporter Def | Phenotype & B2 challenge tests | High Dose B2 |
| **6)** 48 yo ♂ Inflamed nodules head/neck & cerebral artery obstruction | IgG4 Related Disease | Phenotype, biopsy, images & IgG4 levels | Rituximab |
| **7)** 3 yo ♂ Development delay, hypotonia & CNS volume loss | Deficiency GTP Cyclohydrolase | Homozygous *GCH1* Arg235Gln | BH4, L-Dopa, Carbidopa & 5-OH-Tryptophan |
| **8)** 6 yo ♀ Dysmorphic, Dev delay, CHD & dysphasia | Stormorken Syndrome | *De novo STIM1* Arg530Cys | NA (? antibiotics for asplenia) |

## Example + NGS: Case 1

A 4 yr old girl with h/o thin, translucent skin, macrocephaly & short stature (**Table & Fig 1**). NGS showed that she is mosaic (homozygous in 83% & heterozygous in 17% of cells, based on WES reads) for a *ZMPSTE24* Leu326fsX18 mutation resulting from uniparental isodisomy. Since statins & bisphosphonates had been effective in treating a ZMPSTE24 -/- mouse model, she was started on a therapeutic trial of pravastatin & zoledronate (*ref 4*).

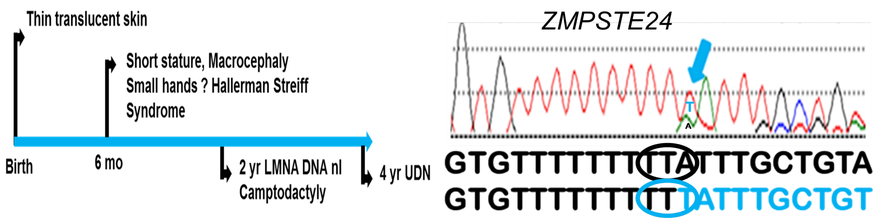
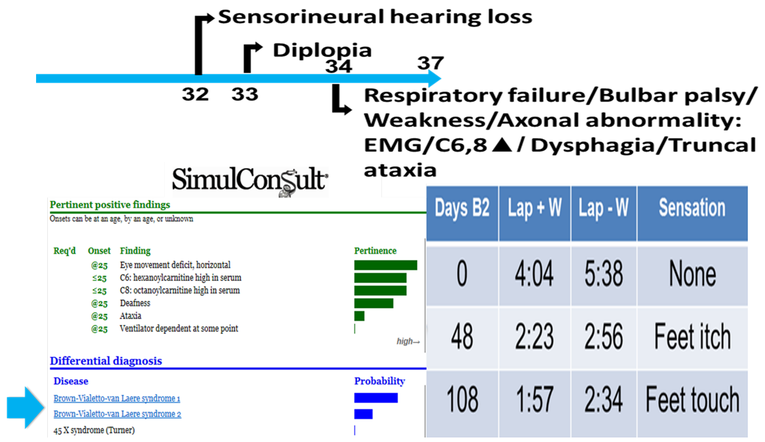



**Fig 1.** Clinical course & Sanger confirmation of normal & mutant (L362fsX18) ZMPSTE24 alleles in case 1.

## Example - NGS: Case 5

A 38 yr old woman with a h/o sensorineural hearing loss, diplopia, ataxia, demyelinating polyneuropathy & respiratory failure (**Table & Fig 2 top**). SimulConsult database search done using her phenotypic features suggested Riboflavin (B2) Transporter Deficiency (OMIM 211530 & 614707) (**Table & Fig 2 bottom**) (ref 3). A B2 challenge test supported this diagnosis & she was treated with high dose B2. She has had subsequent improvement in lap time & return of sensation in her lower extremities.




| Days B2 | Lap + W | Lap - W | Sensation |
|---|---|---|---|
| 0 | 4:04 | 5:38 | None |
| 48 | 2:23 | 2:56 | Feet itch |
| 108 | 1:57 | 2:34 | Feet touch |

**Fig 2.** Clinical course case 5 (top). SimulConsult database search results & improvement in lap time & sensation after B2 Rx (bottom).

## Conclusions

- In 5/8 (62%) of our UDN cases NGS was needed in addition to physical exam, clinical & lab tests to achieve a diagnosis.
- UDN diagnoses led to precise & directed therapies in 88% of our cases.
- UDN cases offer unique opportunities to facilitate research, apply precision medicine & offer specific individualized treatment.

## References

1) UDN https://undiagnosed.hms.harvard.edu & QR code top left
2) SimulConsult www.simulconsult.com
3) OMIM https://www.omim.org
4) Varela et al. Nature Med 14: 767-72, 2008.