Inside our biobank:
FPN's Peripheral Neuropathy Research Registry

featuring

Ahmet Hoke, MD, PhD & Adam Halper

DATE

Today’s moderator:

Amanda Homscheid
Program Manager
the Foundation *for* Peripheral Neuropathy

PLEASE NOTE

We're recording!

All our webinars get added to our website.

FoundationForPN.org/past-webinars

Questions?

Submit questions anytime in the **questions box.**

We will answer as many as we can.

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Check your email for how-to.

Today’s experts:

Ahmet Höke
MD, PhD
Neurologist
Professor of Neurology and Neuroscience
Johns Hopkins

Adam Halper
Head of Product Innovation
Elevance Health
FPN board member

the FOUNDATION for PERIPHERAL NEUROPATHY®

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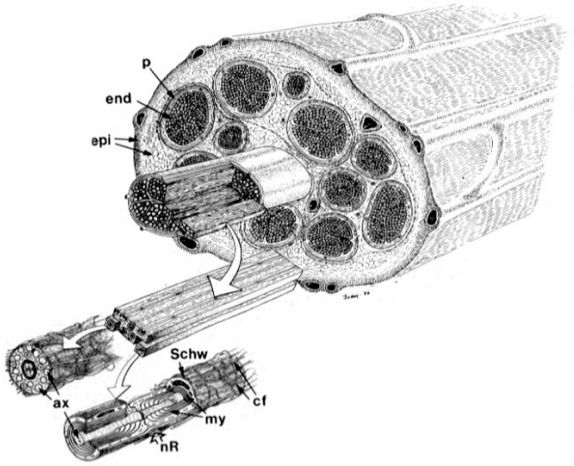
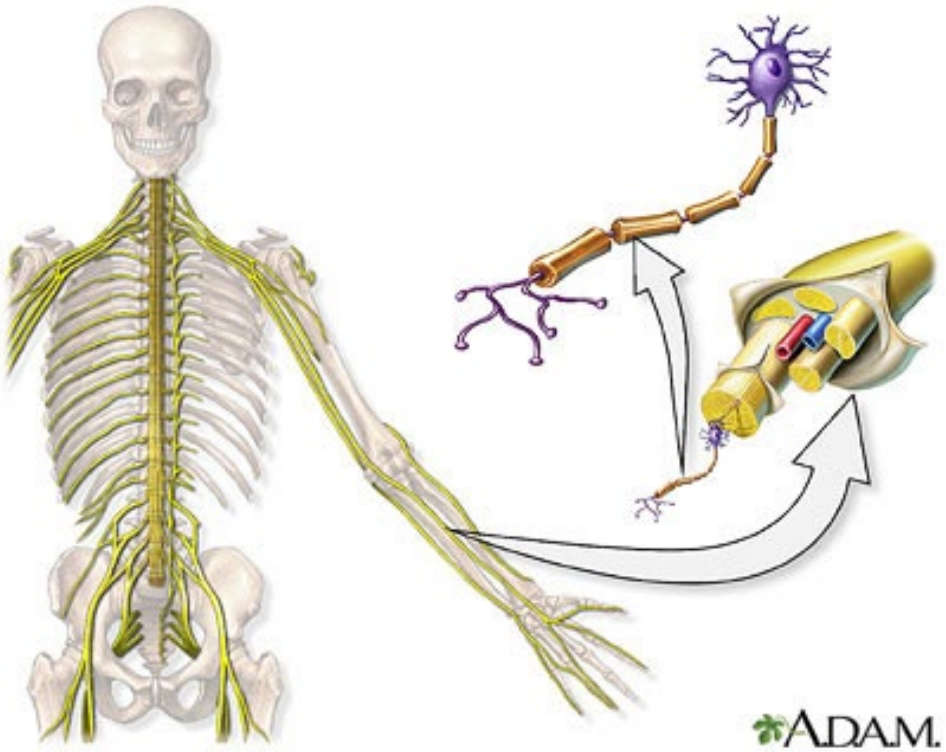
Peripheral Neuropathy Research Registry

Peripheral Neuropathy

- Disease of peripheral nerves
  - Motor
  - Sensory – large
  - Sensory – small
  - Autonomic

- Axon
- Myelin



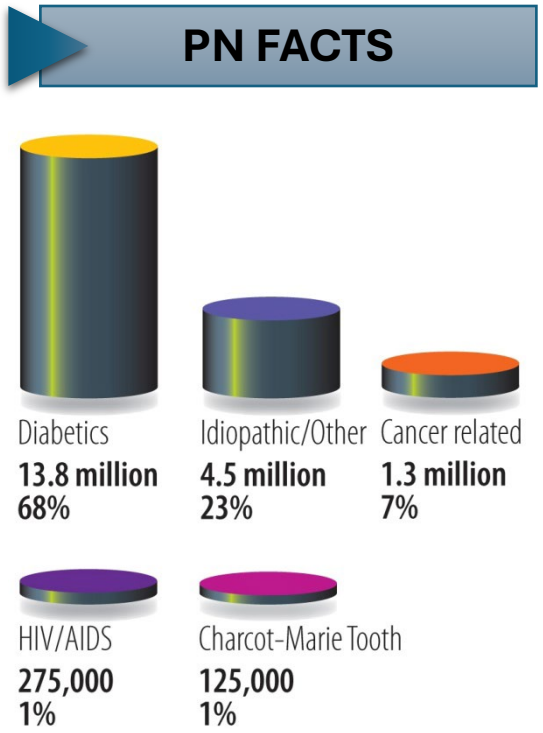


Impact of Peripheral Neuropathy

Over 20 million Americans suffer from all forms of PN;

1 out of every 15 people you know!

- There are 100 identified types of PN
- No cures
- Difficult to treat & can be unresponsive to available therapies
- Causes of Idiopathic PN are unknown
- 30-40% of cancer patients treated with chemotherapy have PN
- 60%- 70% of all diabetics are living with PN
- 33% of all HIV/AIDs patients have PN
- Federal funding for PN research is **< $0.30** for every American
- Overall benefit of existing drugs is 30-40% pain reduction in less than 50% of patients



What unites different types of neuropathy?

- Dysfunction of the peripheral nerves with failure to repair completely.
- Lack of scientific understanding of the processes of nerve injury, repair and regeneration.
- Lack of effective treatments across the many types of neuropathy.

NIH Neuropathy Facts

- From 2005-2009, the NIH “had committed” US$100-115 million each year to neuropathy research with no recent change in that actual dollar amount. Thus, NIH funding is falling at about 3%/year in real dollars.
- Many NIH neuropathy clinical trials have marginal value and fail frequently.
- Monies for disease at NIH are allocated by the squeaky wheel theory.

Neuropathy Facts

- There are at least 30,000,000 in the US with neuropathy.
- There are more people with neuropathy in the US than most of the “big name” neurologic diseases combined.
- We are spending about US$3/year/person with neuropathy on research!

Neuropathy Facts

- As a result of the low funding, young people are not drawn to the field.
- Research has slowed dramatically and in fact most is done ex-US.
- Slow research means few gains, lack of pharma interest, and no drug development.

We need to change this!

"Unfortunately, there's no cure—there's not even a race for a cure."

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Research in PN

PNRR: Peripheral Neuropathy Research Registry

Johns Hopkins University, School of Medicine, Baltimore

Northwestern University, School of Medicine, Chicago

Mount Sinai Medical Center, New York

University of Kansas, School of Medicine, Kansas City

University of Utah, School of Medicine, Salt Lake City

University of Michigan, School of Medicine, Ann Arbor

Washington University, School of Medicine, St Louis

University of North Carolina, School of Medicine, Chapel Hill

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PNRR

- Idiopathic PN
- Diabetic PN
- HIV-associated PN
- Chemotherapy Induced PN

- Careful history and exam
- Questionnaire
- NCS, skin biopsy and labs
- Biobanking: Blood for future genetics and biomarker studies

701	1610	151	185	63
Diabetes samples	Idiopathic samples	HIV / AIDS samples	Chemo induced samples	Mean age

2,647 subjects

as of August 2025

PNRR related projects

- Publications: 10
- Abstracts and Poster presentations: >20

- Ongoing projects:
  - Academic – 14
  - Industry – 4

- Grants: submitted - 1

Incidence of Na_v Channel Variants

- 457 DNA samples (278 idiopathic, 179 diabetic) were made available to **Bristol-Myers Squibb** for next generation sequencing (NGS) together with data
- Objective was to investigate the incidence of nonsynonymous missense variants in SCN9A ($Na_v1.7$), SCN10A ($Na_v1.8$) and SCN11A ($Na_v1.9$) as potential factor cause of neuropathic pain
- Low yield in Na_v mutations in analyzed samples led to the conclusion that other factors must determine why some patients develop neuropathic pain while others do not
- Citation:

Wadhawan S, Pant S, Golhar R, Kirov S, Thompson J, Jacobsen L, Qureshi I, Ajroud-Driss S, Freeman R, Simpson DM, Smith AG, Hoke A, Bristow LJ. Na_V channel variants in patients with painful and nonpainful peripheral neuropathy. Neurol Genet. **2017** Dec 15;3(6):e207. doi: 10.1212/NXG.0000000000000207. PMID: 29264398; PMCID: PMC5732007.

PNRR – a prospective cohort

- Description of the Peripheral Neuropathy Research Registry (PNRR) database and biorepository
- Manuscript prepared by Johns Hopkins University
- Citation:

Thomas S, Ajroud-Driss S, Dimachkie MM, Gibbons C, Freeman R, Simpson DM, Singleton JR, Smith AG; PNRR Study Group; Höke A. Peripheral Neuropathy Research Registry: A prospective cohort. J Peripher Nerv Syst. **2019** Mar;24(1):39-47. doi: 10.1111/jns.12301. Epub 2019 Jan 29. PMID: 30629307.

Benefits of exercise

- Primary objective was to investigate if exercise is effectively reducing neuropathic pain intensities in patients with painful idiopathic PN
- Data analysis / manuscript by Johns Hopkins University. Only JHU data records were utilized
- Citation:

Stewart S, Thomas S, Van Doormaal PT, Höke A. Relation of exercise and pain in patients with idiopathic distal axonal polyneuropathies. J Peripher Nerv Syst. **2020** Dec;25(4):388-394. doi: 10.1111/jns.12415. Epub 2020 Oct 13. PMID: 33025680.

Vitamin B6 Levels in PN

- Investigation if elevated blood Vitamin B6 level can cause or contribute to PN
- Research showed that elevated Vitamin B6 level (as caused by supplements) do not influence PN severity
- Data analysis done by Johns Hopkins University; utilizing all records with Vitamin B6 level recorded
- Citation:

Stewart SL, Thomas S, Höke E, Simpson D, Singleton JR, Höke A. Vitamin B6 levels do not correlate with severity of neuropathy in chronic idiopathic axonal polyneuropathy. J Peripher Nerv Syst. **2022** Mar;27(1):31-37. doi: 10.1111/jns.12480. Epub 2021 Dec 29. PMID: 34931740.

Biomarker for Neuropathic Pain

- Omics study to search for a potential biomarker for neuropathic pain. Metabolomics, lipidomics and proteomics were performed on 60 PNRR samples. Proteomics was performed on a verification cohort of another 60 samples.
- Twelve proteins were identified with reasonable discriminatory power to differentiate between painful and painless idiopathic PN
- Study done by Johns Hopkins University
- Citation:

van Doormaal PTC, Thomas S, Ajroud-Driss S, Cole RN, DeVine LR, Dimachkie MM, Geisler S, Freeman R, Simpson DM, Singleton JR, Smith AG, Stino A; PNRR Study Group; Höke A. Plasma proteomic analysis on neuropathic pain in idiopathic peripheral neuropathy patients. J Peripher Nerv Syst. **2024** Mar;29(1):88-96. doi: 10.1111/jns.12606. Epub 2023 Dec 1. PMID: 37989721.

Vitamin D levels and PN

- Evaluation if vitamin D levels influence PN severity or phenotype
- Vitamin D deficiency does not contribute to PN severity
- Study done by Johns Hopkins University
- Citation:

Morrison AH, Hoke M, Thomas S, Chaudhry V, Polydefkis M; PNRR Study Group; Höke A. Vitamin D levels do not correlate with severity of idiopathic peripheral neuropathy. J Peripher Nerv Syst. **2024** Dec;29(4):393-399. doi: 10.1111/jns.12670. Epub 2024 Nov 6. PMID: 39506207.

Role of DM and MetSyn in PN

- Determine the association between diabetes and metabolic syndrome with pain, neuropathy severity, and fiber type involvement in individuals with PN
- Diabetes was associated with pain and PN severity. Increased metabolic syndrome burden was associated with pain, neuropathy severity, and mixed fiber type involvement
- University of Cincinnati, University of Michigan, Johns Hopkins
- Citation:

Davalos L, Callaghan BC, Muthukumar L, Thomas S, Reynolds EL, Smith AG, Singleton JR, Höke A, Ajroud-Driss S, Dimachkie MM, Geisler S, Simpson DM; PNRR Study Group; Stino AM. The Impact of Diabetes and Metabolic Syndrome Burden on Pain, Neuropathy Severity and Fiber Type. Ann Clin Transl Neurol. **2025** Jul;12(7):1408-1417. doi: 10.1002/acn3.70072. Epub 2025 May 19. PMID: 40386990; PMCID: PMC12257117.

Genomics in PNRR cohort

- Initial white paper describing different methods of genomics analysis, including methodology developed by Washington University to analyze PNRR cohort samples
- Washington University at St. Louis and Johns Hopkins
- Citation:

Choi J, Tang Z, Dong W, Ulibarri J, Mehinovic E, Thomas S, Höke A, Jin SC. Unleashing the Power of Multiomics: Unraveling the Molecular Landscape of Peripheral Neuropathy. Ann Clin Transl Neurol. **2025** Apr;12(4):674-685. doi: 10.1002/acn3.70019. Epub 2025 Mar 24. PMID: 40126913; PMCID: PMC12040521.

RFC1 AAGGG Repeat Expansions

- Whole genome sequencing of DNA from 798 participants enrolled in PNRR at Johns Hopkins
- Increased frequency of monoallelic expansions in IPN compared to controls (13.2% versus 2.5%), and biallelic expansions in 2.8% of cohort
- Washington University at St. Louis, Johns Hopkins University and University of Michigan
- Under revision at Annals of Neurology, but also available:

Tang Z, Ovunc SS, Mehinovic E, Thomas S, Ulibarri J, Li Z, Baldridge D, Cruchaga C, Johnson M, Milbrandt J, Callaghan B; PNRR Study Group; Höke A, Todd PK, Jin SC. Heterozygous and Homozygous *RFC1 AAGGG* Repeat Expansions are Common in Idiopathic Peripheral Neuropathy. medRxiv [Preprint]. **2025** Apr 23:2025.04.18.25325809. doi: 10.1101/2025.04.18.25325809. PMID: 40313272; PMCID: PMC12045428.

Neurofilaments in Idiopathic PN

- Evaluate Neurofilaments as a potential biomarker for disease severity and activity in idiopathic PN
- Utilizing 296 plasma samples from PNRR patients enrolled at Johns Hopkins
- Citation

Thomas S, Khan M, Sari MC, Hu X, Lewis A, Lobana J, Mukherjee-Clavin B, Moghekar A, Morrison BM, Sumner C, Xie S, Höke A. Neurofilament Light Chain Levels in a Large Idiopathic Peripheral Neuropathy Cohort. J Peripher Nerv Syst. **2025** Sep;30(3):e70050. doi: 10.1111/jns.70050. PMID: 40799056.

Ongoing Data Analysis Projects – not yet published

Phenotypic Description of RCF1 expansion cohort

- **Brian Callaghan, University of Michigan**
- Phenotypic comparison of patients with biallelic or monoallelic RFC1 expansions as identified in WGS performed by WashU
- Analysis did not show significant differences between general cohort and monoallelic RCF1 expansions, but more severe phenotypes in those with biallelic expansions
- Manuscript written, and submission for publication is imminent

Metabolomics in DPN – in search of biomarker for neuropathic pain

- **Daniella Menichella, Northwestern University**
- Received 60 plasma and serum samples from patients with painful and non-painful diabetic neuropathy
- Pilot study to search for metabolic biomarker for neuropathic pain.
- The study was negative. Dr. Menichella is not planning to publish

Genetic Modifiers in Oxaliplatin- Induced CIPN

- **Andrea Cortese, UCL London**
- Whole Genome Sequencing of DNA from patients with Oxaliplatin-Induced CIPN, including 17 PNRR
- Purpose is to check if there are genetic modifies that determine the severity of CIPN – or in other words if there are genetic variants in the genome that determine why some patients get severe CIPN, while others don’t
- Results were presented at PNS; publication in preparation

Clinical Features of CIPN

- **Stephanie Geisler, Washington University**
- Initial data analysis is done, comparing CIPN with DPN cohort
- Key information in regard to overall dosage of chemotherapy received and duration and control of DM is not available for over 50% of the records. Thus, advanced data analysis correcting for PN duration etc. cannot be completed and will be difficult to publish this work (in current state)

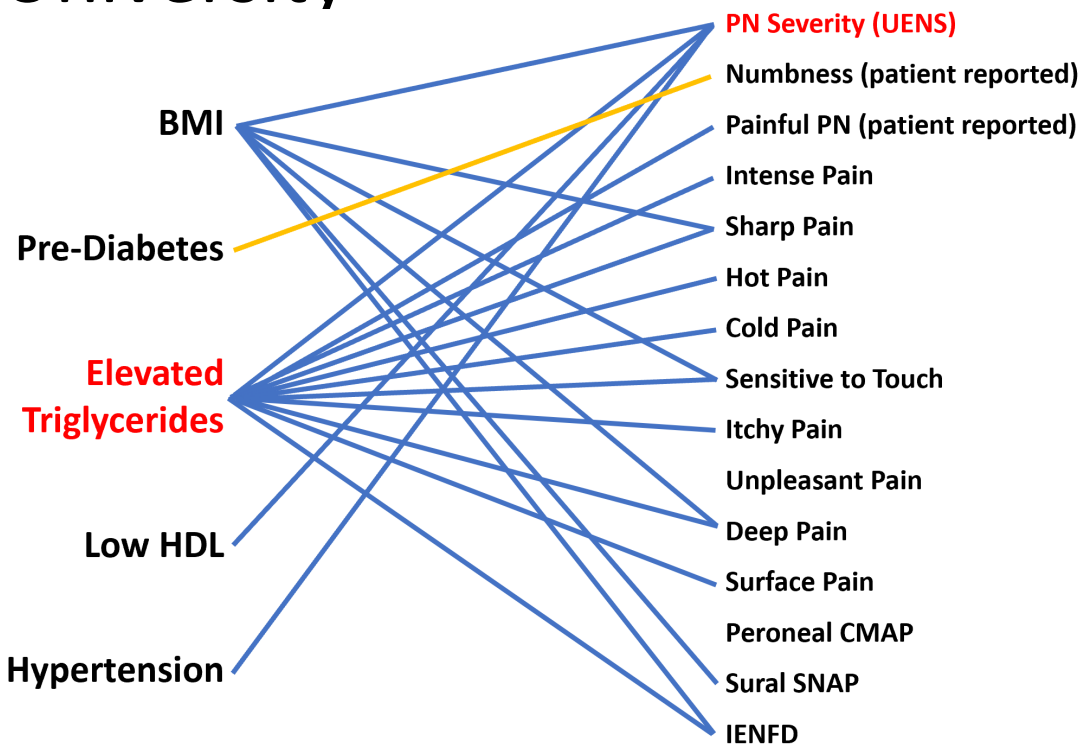
Genetic Modifiers in DPN + CIPN

- **David Bennett, Cambridge; Michael Coleman, Oxford; Mary Reilly, UCL; and Ahmet Hoke, Johns Hopkins**

- WGS of provided DNA samples underway
- Project is looking for additional participants (N not large enough at this time) before data analysis will start in earnest

Prediabetes vs Metabolic Syndrome

- Metabolic Syndrome as cause of PN and contributing to disease severity in those with mild hyperglycemia
- Johns Hopkins University



Hyperlipidemia as cause of PN

- Mice on HFD with hyperlipidemia in form of elevated cholesterol and triglycerides developed SFN, even in the absence of hyperglycemia. When doing proteomics, several therapeutic candidates were identified
- Request to receive blood samples from patients with skin biopsy tissues stored at Johns Hopkins Skin lab to check if same pattern is observed in humans
- Simone DiGiovanni, Imperial College London and Ahmet Hoke, Johns Hopkins

Proteomics in RCF1 cohort

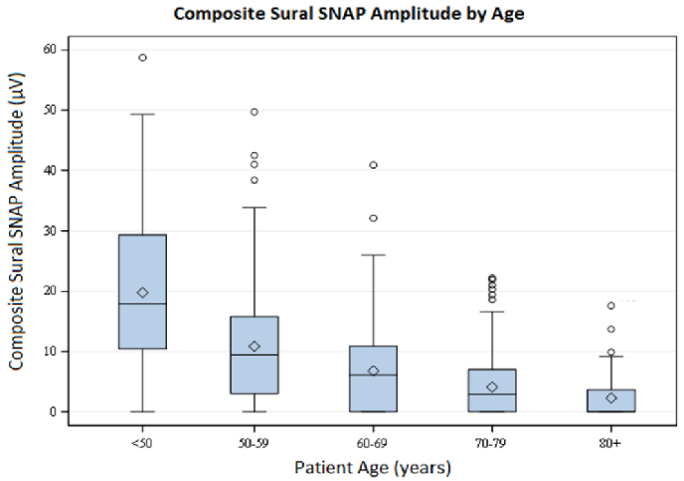
- It is planned to perform proteomics for the RCF1-genomics cohort, to cross-reference if any abnormalities can be observed in those with RCF1 expansions
- Peter Jin, Washington University and Ahmet Hoke, Johns Hopkins

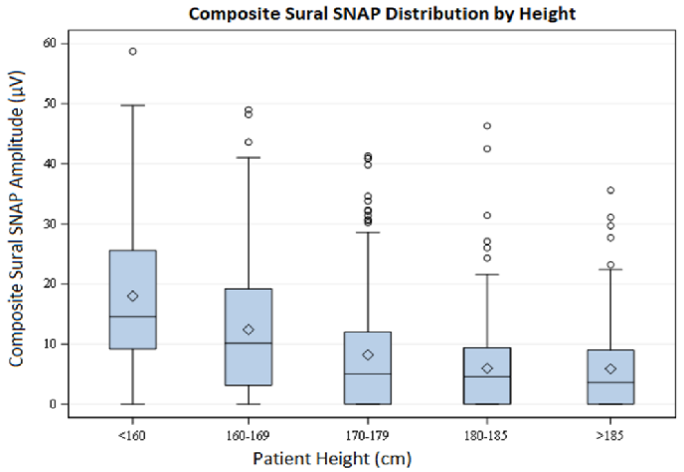
Genomics in DM type 2 and CIPN

- Genomics of patients with DM type 2 and CIPN, in particular evaluating those with extreme phenotypes to search for mechanisms to prevent Wallerian degeneration
- DNA of 205 PNRR participants were shipped to UCL for WGS in 2022
- Mary Reilly, UCL and Haddad Saif, UCL

Achilles tendon reflex and sural SNAP abnormalities in older and taller PN patients

- Results presented at NMSG, manuscript drafted
- Kansas University, Johns Hopkins, University of Michigan





Hypothyroidism and PN

- Evaluation if hypothyroidism is contributing to PN progression and severity
- Initial data analysis is done, showing that controlled hypothyroidism is not contributing to PN progression
- Currently evaluating if patients with abnormal high TSH levels have higher PN severity scores
- Kansas University, Johns Hopkins, University of Michigan

Ulnar and Median Nerve Entrapments in PNRR cohort

- Data analysis of median and ulnar nerve conduction data to evaluate if PN increases risk of nerve entrapments
- Presence of hyperglycemia in form of DM increases prevalence of median entrapment at the wrist; presence of metabolic syndrome increases risk of ulnar entrapment at the elbow
- Results presented at PNS 2025; manuscript drafted and currently in review

Pharma interests

- 1 completed (first paper from BMS)
- 4 ongoing studies
  - Analysis of longitudinal data in diabetic PN (Vertex Pharmaceuticals)
  - Medication use in DPN with longitudinal data (Averitas Ph.)
  - Wallerian degeneration pathway validation in 120 samples from patient with idiopathic, diabetic and chemotherapy induced polyneuropathy (Scripps Institute)
  - Anti-AAV antibody assay (Sangamo Ph.)

Future

- We need to think big!
  - Creating iPSC lines
    - Target validation, mechanism of disease investigations
  - Generating WGS, and large scale –omics datasets (proteomics, lipidomics, metabolomics, epigenomics etc.)
    - Using AI/ML to investigate disease mechanisms and identify therapeutic targets
  - Make these research resources publicly available
- This is the largest dataset of PN and need to grow it.
  - ALS field already has 1000 iPSCs and >5000 WGS now working on generating 10,000 WGS with iPSCs

A patient's perspective

- A personal neuropathy journey
- Why the biobank is important to patients
- About biobank enrollment
- The future of PN research

Thanks for joining us!

ANY QUESTIONS?!

HOW WAS IT?

Let us know!
Take our short **survey** after the webinar

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