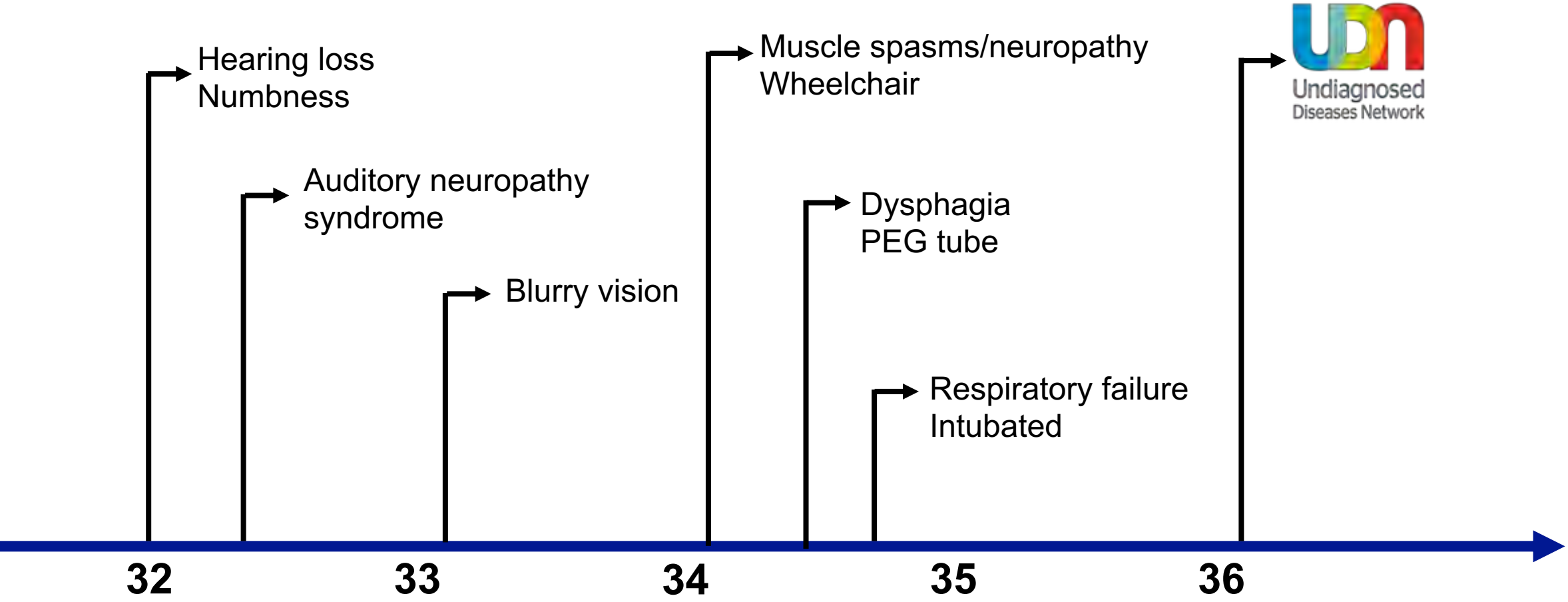
How much more can we explain with genetics?
EHR mining and the undiagnosed patient

Lisa Bastarache

Future of Individualized Medicine, 2019

VANDERBILT UNIVERSITY
MEDICAL CENTER

What is wrong with this patient?



BROWN-VIALETTO-VAN LAERE SYNDROME

HEAD & NECK

Ears

- Hearing loss, sensorineural
- Absent brainstem auditory-evoked responses

Eyes

- Visual loss

RESPIRATORY

- Respiratory insufficiency

MUSCLE, SOFT TISSUES

- Muscle weakness, proximal, distal, and axial, severe
- Neurogenic changes seen on EMG
- Fibrillations

NEUROLOGIC

Central Nervous System

- Cranial nerve palsies
- Loss of independent ambulation

Peripheral Nervous System

- Axonal sensorimotor neuropathy

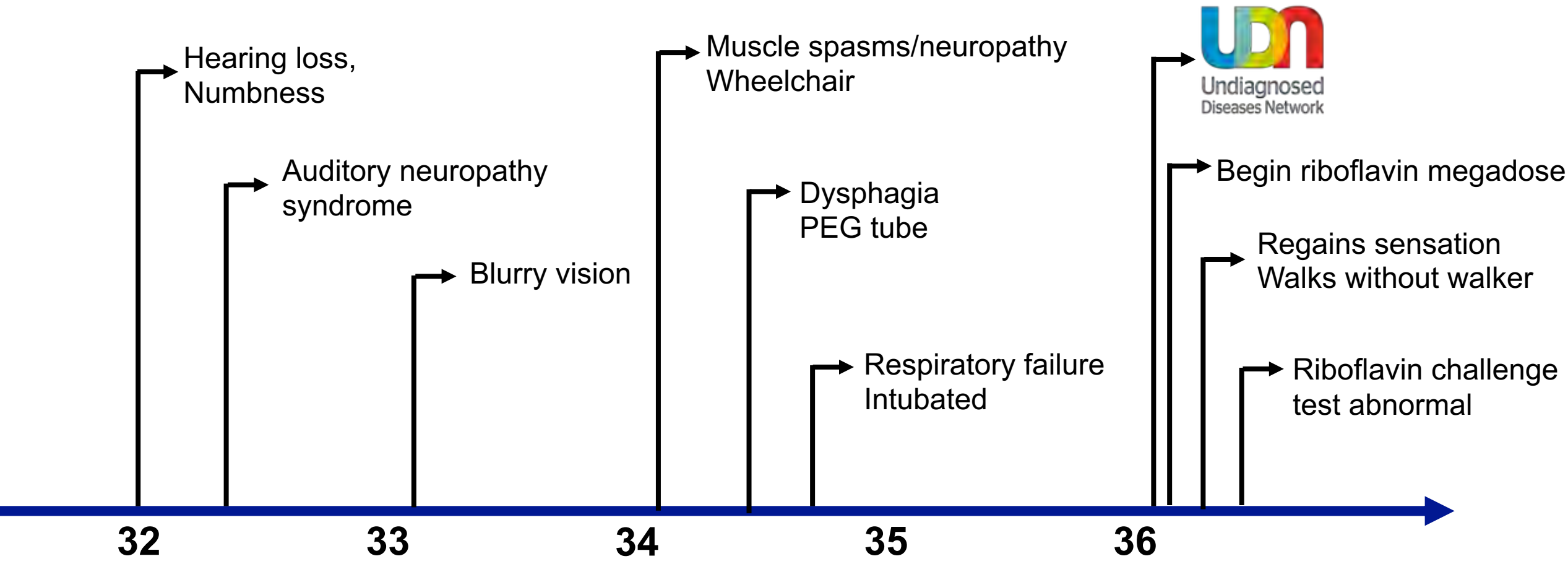
LABORATORY ABNORMALITIES

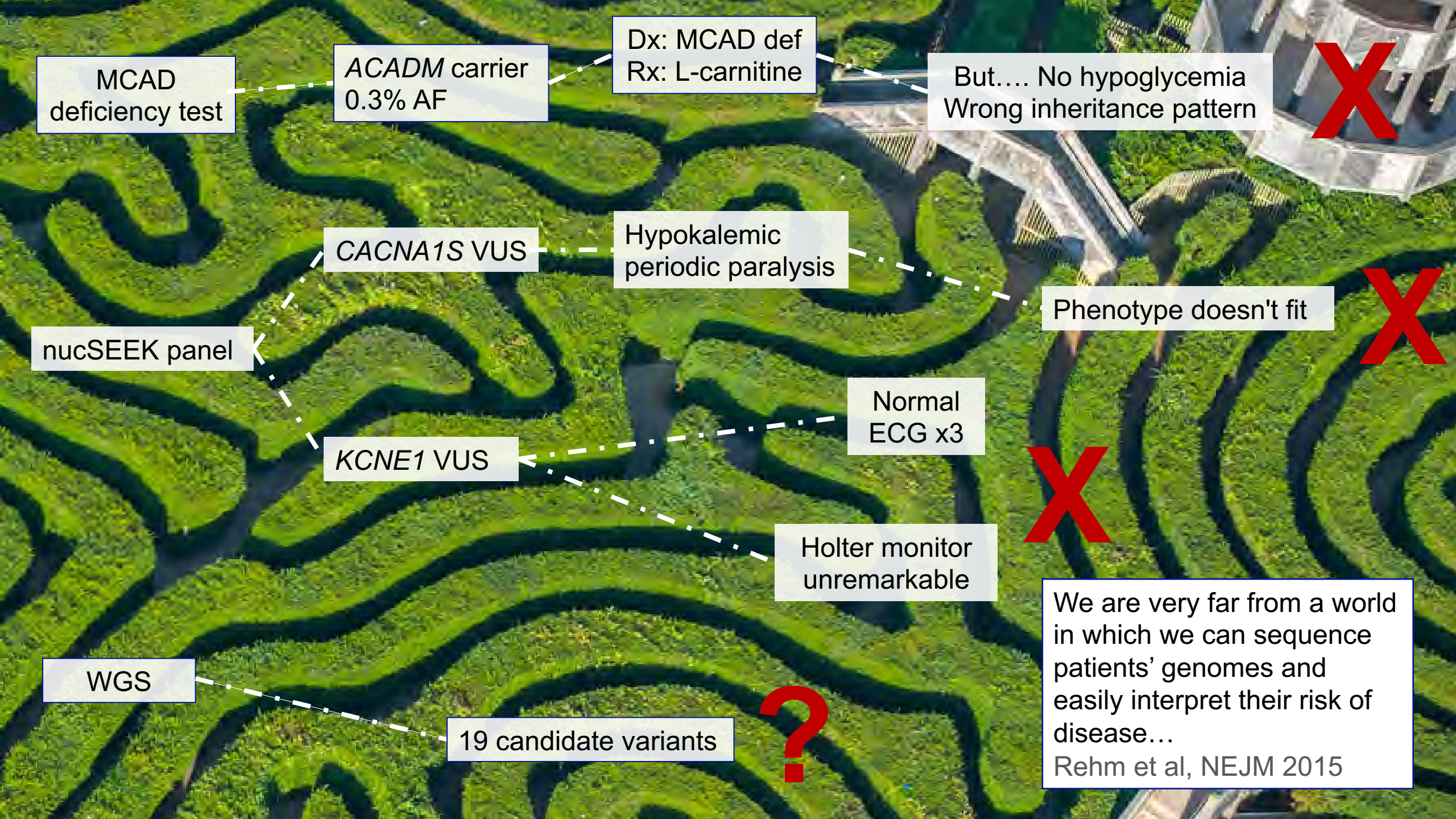
- Abnormal acylcarnitine profiles

SLC52A2 or *SLC52A3*

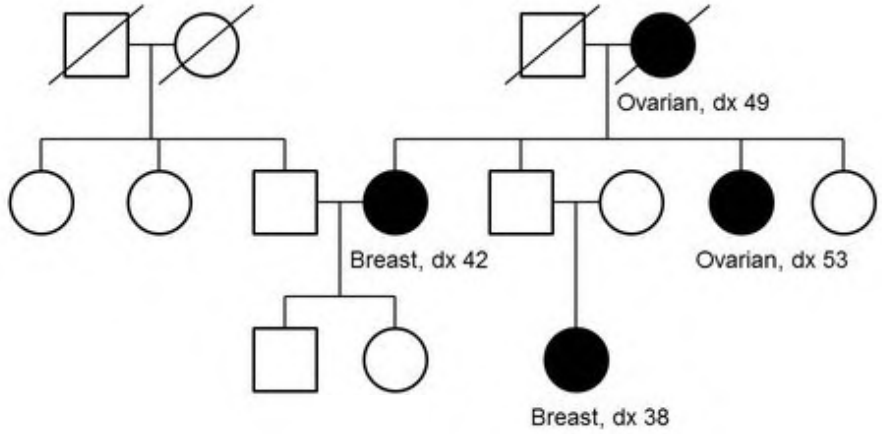
Riboflavin transport deficiency

A diagnosis, the old fashioned way




MCAD deficiency test
ACADM carrier 0.3% AF
Dx: MCAD def
Rx: L-carnitine
But…. No hypoglycemia
Wrong inheritance pattern
X
CACNA1S VUS
Hypokalemic periodic paralysis
Phenotype doesn't fit
X
nucSEEK panel
Normal ECG x3
KCNE1 VUS
X
Holter monitor unremarkable
WGS
19 candidate variants
?
We are very far from a world in which we can sequence patients' genomes and easily interpret their risk of disease…
Rehm et al, NEJM 2015

Why don't we know more?



Why don't we know more?

Phenotype risk score (PheRS)

A method to create Mendelian disease phenotypes

- Uses EHR data (billing codes)
- Enables a population level scan of Mendelian disease variants

MARFAN SYNDROME

HEAD & NECK

Eyes

- Retinal detachment
- Iris hypoplasia

CARDIOVASCULAR

Heart

- Aortic regurgitation

Vascular

- Aortic root dilatation
- Aortic dissection

SKELETAL

Limbs

- Joint hypermobility

CHEST

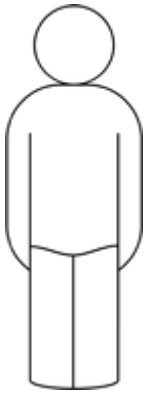
Ribs Sternum Clavicles & Scapulae

- Pectus excavatum

RESPIRATORY

Lung

- Pneumothorax

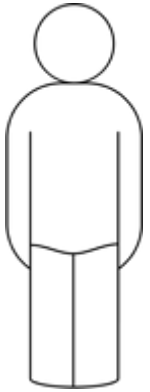


Pectus excavatum

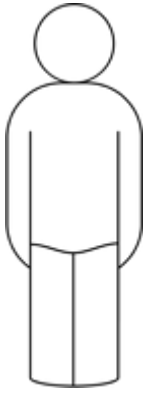
Joint dislocation

Pneumothorax

Retinal detachment



Aortic aneurysm



No Marfan symptoms

MARFAN SYNDROME

HEAD & NECK

Eyes

- Retinal detachment
- Iris hypoplasia

CARDIOVASCULAR

Heart

- Aortic regurgitation

Vascular

- Aortic root dilatation
- Aortic dissection

SKELETAL

Limbs

- Joint hypermobility

CHEST

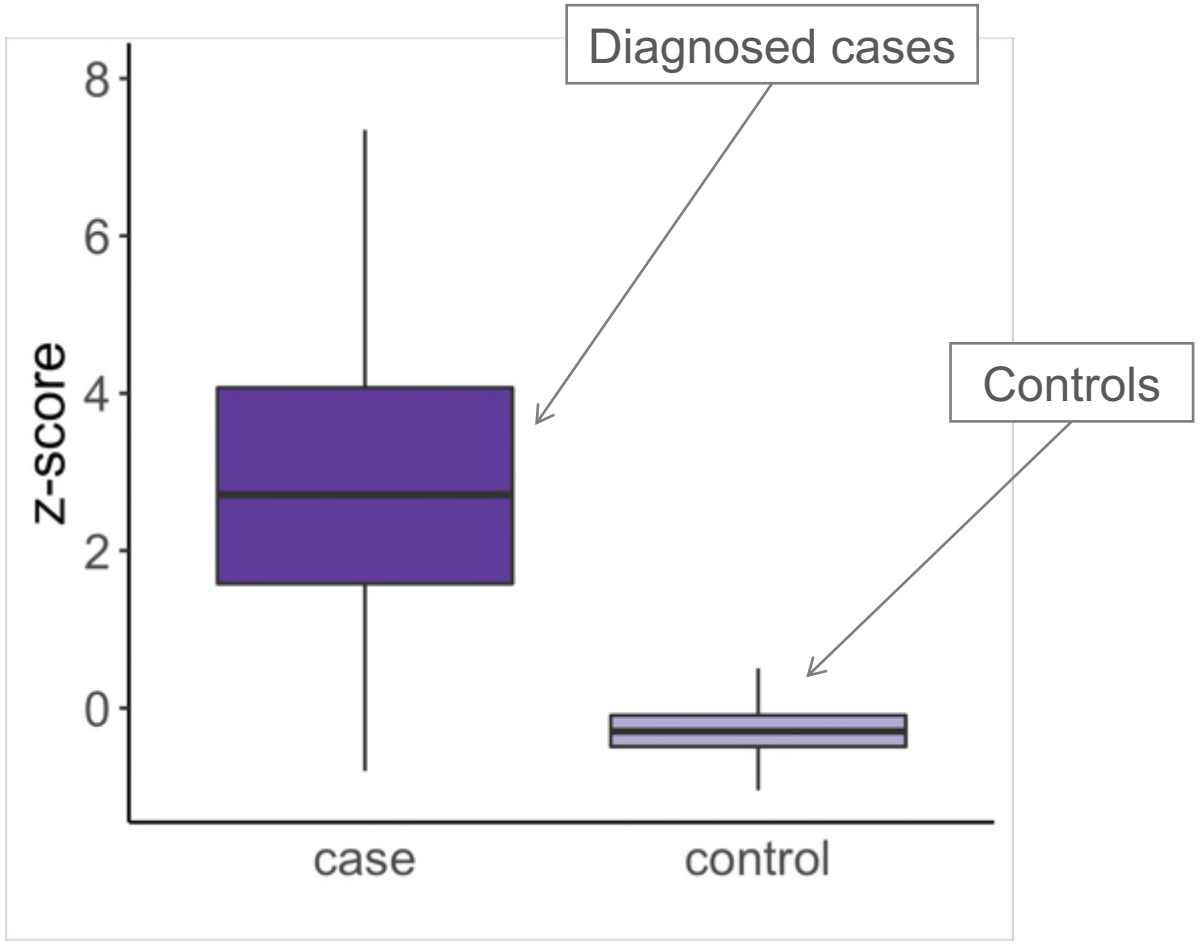
Ribs Sternum Clavicles & Scapulae

- Pectus excavatum

RESPIRATORY

Lung

- Pneumothorax



You can differentiate individuals diagnosed with Marfan syndrome using ***only the features*** of the disease

RESEARCH ARTICLE

HUMAN GENOMICS

Phenotype risk scores identify patients with unrecognized Mendelian disease patterns

Gene	Variant	rsID	HOM/ HET	Associated Mendelian Disease	OMIM Reported Inheritance	Phenotype categories in PheRS	Beta	P	ClinVar	HGMD	ACMG
CFTR	c.1624G>T p.Gly542Ter	rs113993959	1/27	Cystic fibrosis	AR		1.39	2.9×10^{-8}	P	Y	P
CHRNA4	c.1448G>A p.Arg483Gln	rs55855125	1/21	Nocturnal frontal lobe epilepsy, 1	AD		0.58	9.0×10^{-8}	U		U
DGKE	c.966G>A p.Trp322Ter	rs138924861	1/14	Nephrotic syndrome, type 7	AR		1.31	2.8×10^{-7}	LP	Y	LP→P
SUOX	c.226G>T p.Arg76Ser	rs202085145	0/24	Sulfocysteinuria	AR		0.82	1.7×10^{-6}	U		U→P
CFTR	c.1657C>T p.Arg553Ter	rs74597325	0/12	Cystic fibrosis	AR		1.81	2.1×10^{-6}	P	Y	P
KIF1B	c.2021C>T p.Thr674Ile	rs41274468	0/21	Charcot-Marie-Tooth disease, 2A1	AD		0.79	5.3×10^{-6}			U
VWF	c.5851A>G p.Thr1951Ala	rs144072210	0/21	Von Willebrand disease	AR*		0.53	8.6×10^{-6}		Y	U
KIF1A	c.2676C>T p.Ala993=	rs116297894	1/25	Spastic paraplegia-30	AR		0.84	1.3×10^{-5}	LB		LB→U
F10	c.872G>A p.Arg291Gln	rs149212700	0/15	Factor X deficiency	AR*		0.62	1.9×10^{-5}			U
HFE	c.502G>C p.Glu168Gln	rs146519482	0/40	Hemochromatosis	AR		1.08	4.0×10^{-5}	U	Y	U
TG	c.229G>A p.Gly77Ser	rs142698837	0/69	Thyroid dyshormonogenesis	AR		0.26	6.0×10^{-5}		Y	U→P
SH2B3	c.1183G>A p.Glu395Lys	rs148636776	0/22	Familial erythrocytosis, 1	AD		1.48	6.1×10^{-5}			U→P
SPTBN2	c.7109G>A p.Arg2370His	rs145522851	0/11	Spinocerebellar ataxia	AR*		0.75	9.0×10^{-5}			U→LP
FAN1	c.1520G>A p.Arg507His	rs150393409	0/434	Interstitial nephritis, karyomegalic	AR		0.15	9.9×10^{-5}			LB→U
PANK2	c.1561G>A p.Gly521Arg	rs137852959	0/26	HARP syndrome	AR		0.58	1.1×10^{-4}	P	Y	P
SH2B3	c.1183G>A p.Glu395Lys	rs148636776	0/22	Essential thrombocythemia	AD		0.33	1.4×10^{-4}			U→P
AGXT	c.883G>A p.Ala295Thr	rs13408961	1/35	Primary hyperoxaluria, type I	AR		0.82	1.7×10^{-4}	U/LB		LB→U
PLCG2	c.751A>G p.Ile251Val	rs190840748	0/10	Familial cold autoinflammatory syn. 3	AD		0.70	1.9×10^{-4}			U

Neoplastic
Endocrine/Metabolic/Blood
Nervous/Psychiatric/Sensory
Circulatory/Respiratory
Digestive/Genitourinary
Musculoskeletal/Dermatologic
Other symptoms/Injuries

Tested
6644 variant/disease pairs

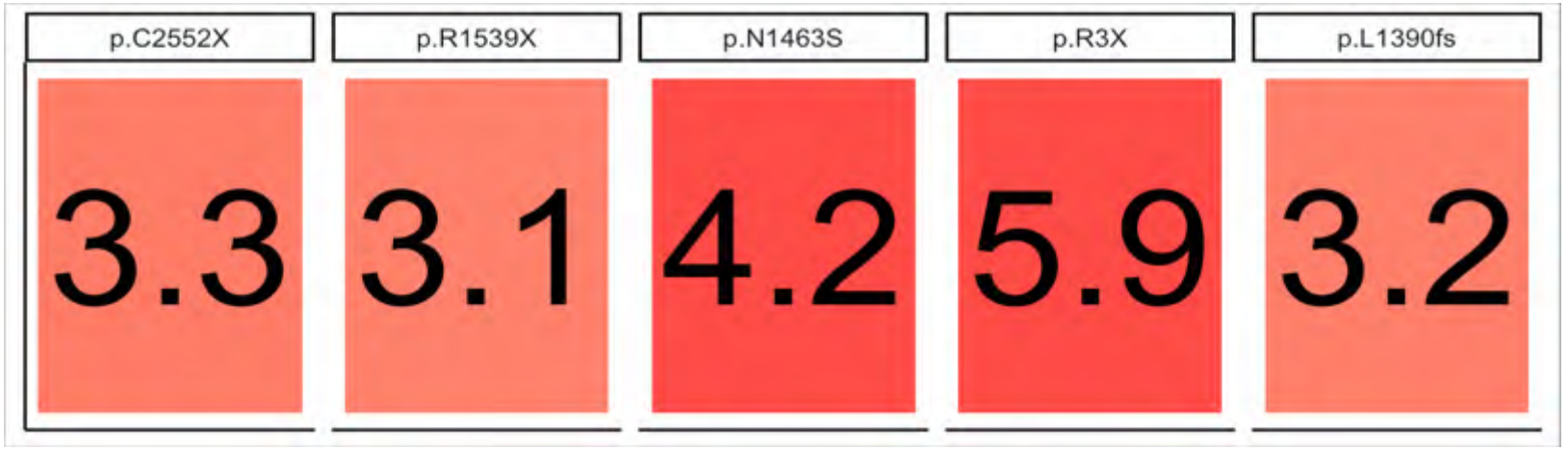
Found
18 significant associations

Do patients with X variant have a higher PheRS?

eMERGEseq

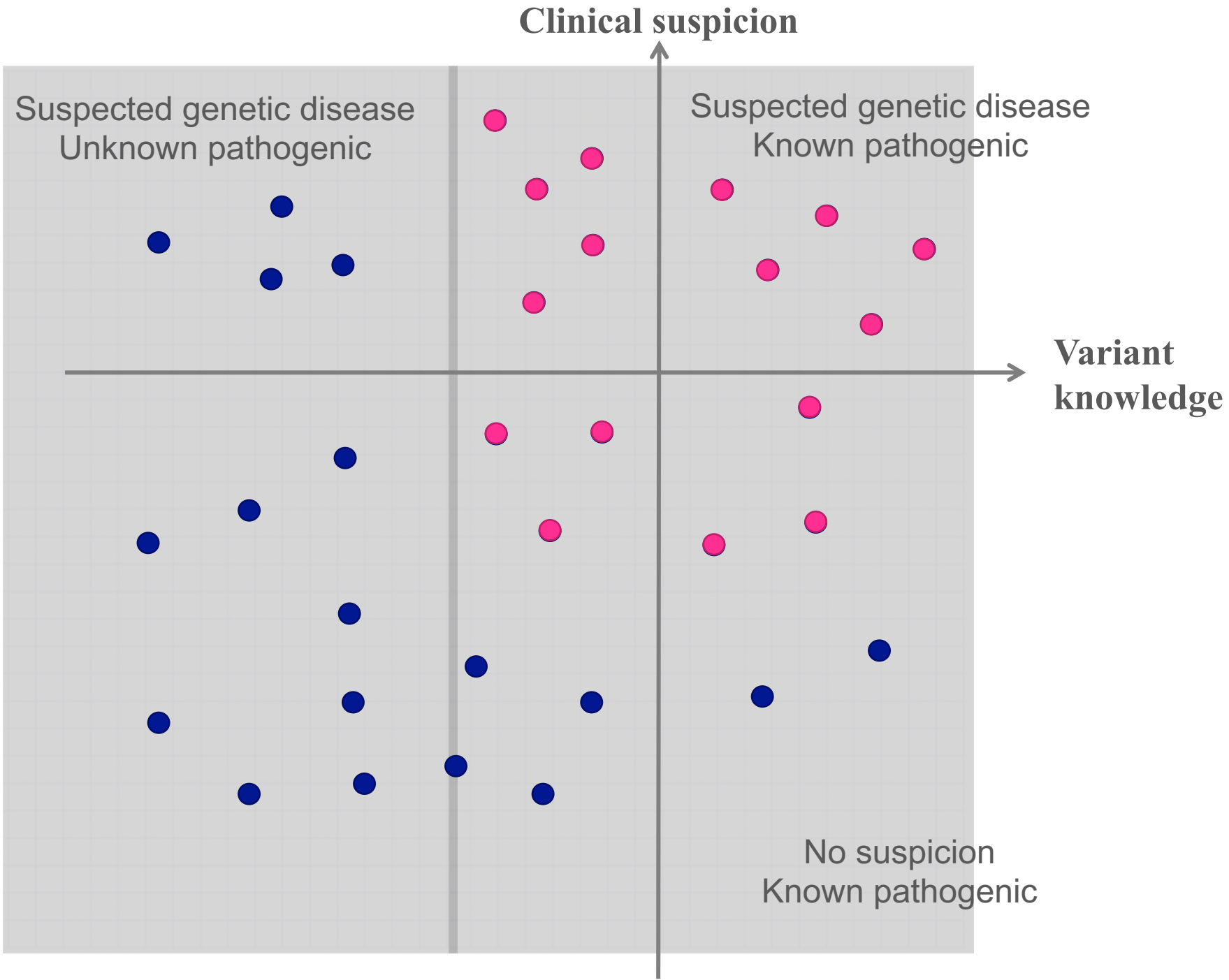
- 15,000 patients sequenced for 109 genes
- 9 clinical sites
- Demographics, billing codes, sequence

High-throughput *FBN1* variant readout



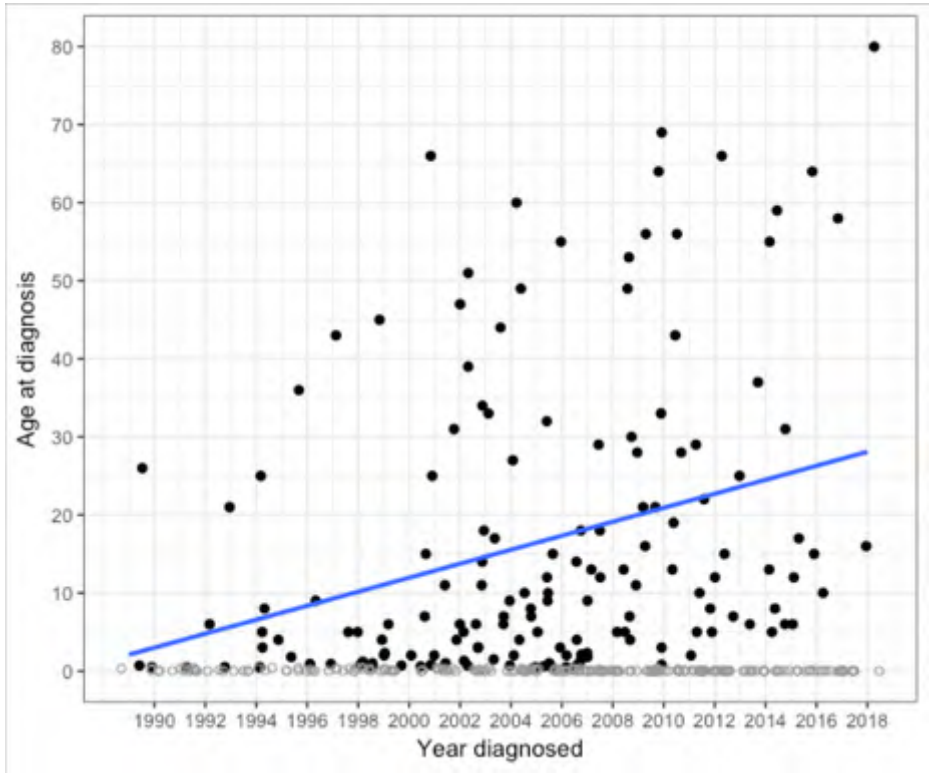
Variants of Uncertain Significance

Two reasons patients remain undiagnosed

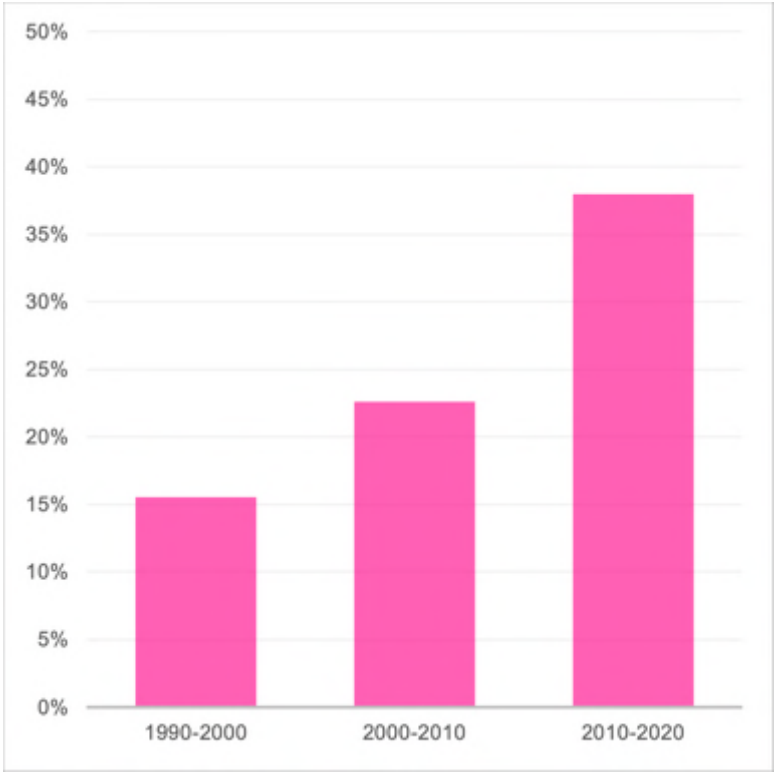


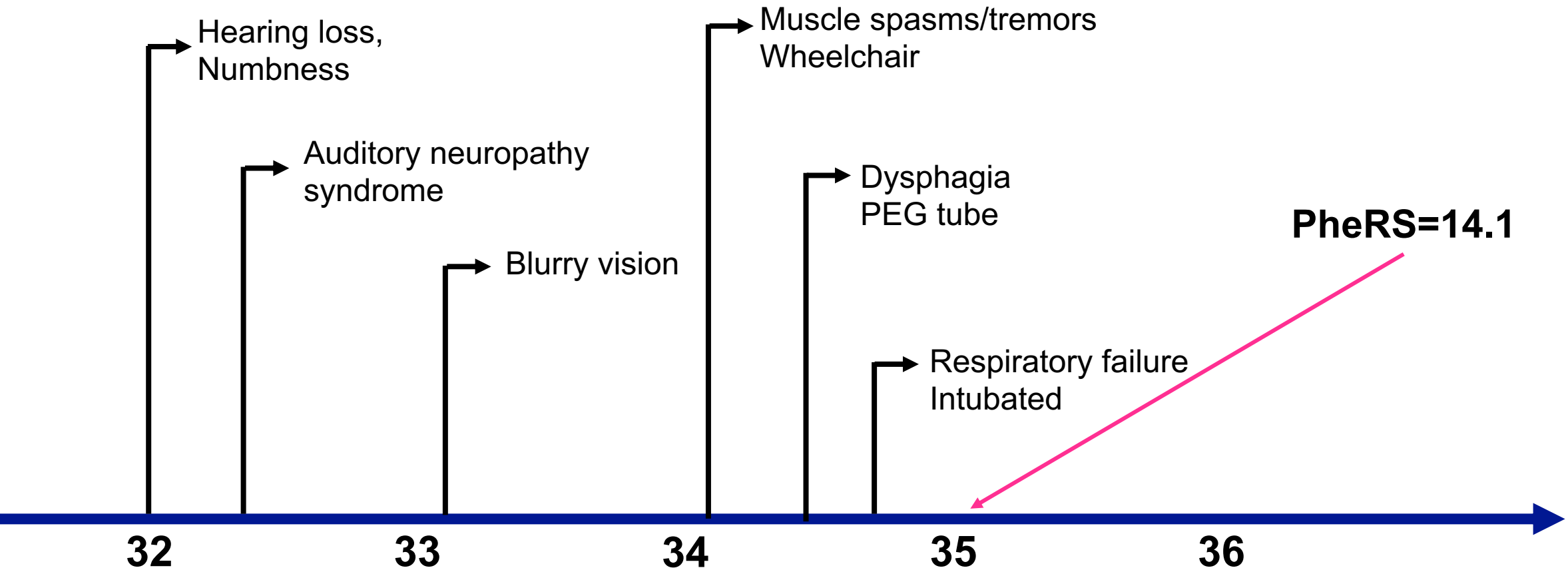
Making a Cystic Fibrosis diagnosis, not just for pediatricians anymore

Age of CF diagnosis is increasing!



Atypical CF diagnosis by decade




Hearing loss,
Numbness
Auditory neuropathy
syndrome
Blurry vision
Muscle spasms/tremors
Wheelchair
Dysphagia
PEG tube
Respiratory failure
Intubated
PheRS=14.1
32
33
34
35
36

Josh Denny

Dan Roden

Nancy Cox

Leigh Anne Tang

Andrea Ramirez

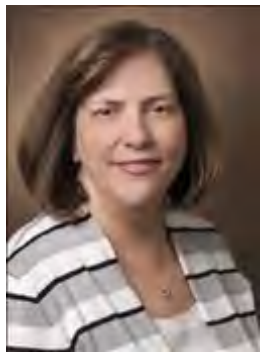
Randy Miller

Jonathan Mosley

Julie Bastarache

Sara Van Driest

Rizwan Hamid



Joy Cogan

John Newman

Doug Ruderfer

Wei-Qi Wei

Mike Noto

Jake Hughey

John Phillips

VANDERBILT UNIVERSITY MEDICAL CENTER

Undiagnosed Diseases Network

emerge network