where science meets humanity™

Human Genetics

A "human-first" drug discovery pipeline

Sally John, Ph.D., Head of Translational Biology

R&D Day
September 21, 2021

Biogen

Forward-looking statements

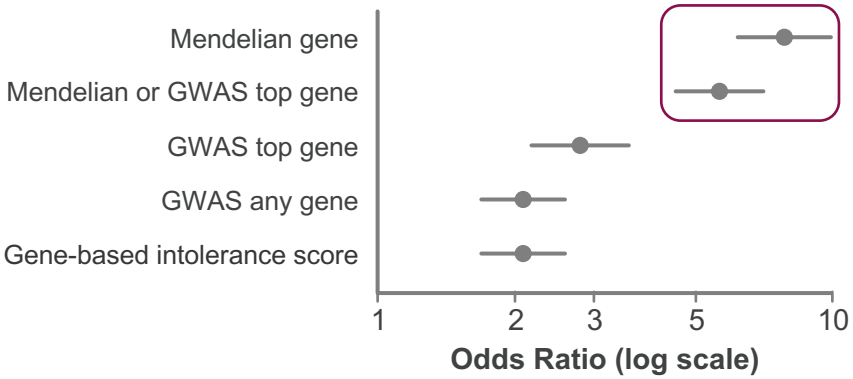
This presentation contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our strategy and plans; potential of, and expectations for, our commercial business and pipeline programs; capital allocation and investment strategy; clinical development programs, clinical trials, and data readouts and presentations; risks and uncertainties associated with drug development and commercialization; regulatory discussions, submissions, filings, and approvals and the timing thereof; the potential benefits, safety, and efficacy of our and our collaboration partners' products and investigational therapies; the anticipated benefits and potential of investments, collaborations, and business development activities; and our future financial and operating results. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "potential," "possible," "prospect," "will," "would," and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our dependence on sales from our products; uncertainty of long-term success in developing, licensing, or acquiring other product candidates or additional indications for existing products; failure to compete effectively due to significant product competition in the markets for our products; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives; difficulties in obtaining and maintaining adequate coverage, pricing, and reimbursement for our products; our dependence on collaborators, joint venture partners, and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; risks associated with current and potential future healthcare reforms; risks related to commercialization of biosimilars; failure to obtain, protect, and enforce our data, intellectual property, and other proprietary rights and the risks and uncertainties relating to intellectual property claims and challenges; the risk that positive results in a clinical trial may not be replicated in subsequent or confirmatory trials or success in early stage clinical trials may not be predictive of results in later stage or large scale clinical trials or trials in other potential indications; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events, restrictions on use with our products, or product liability claims; risks relating to the distribution and sale by third parties of counterfeit or unfit versions of our products; risks relating to the use of social media for our business; risks relating to technology failures or breaches; risks relating to management and key personnel changes, including attracting and retaining key personnel; failure to comply with legal and regulatory requirements; the risks of doing business internationally, including currency exchange rate fluctuations; risks relating to investment in our manufacturing capacity; problems with our manufacturing processes; fluctuations in our effective tax rate; the direct and indirect impacts of the ongoing COVID-19 pandemic on our business, results of operations, and financial condition; fluctuations in our operating results; risks related to investment in properties; the market, interest, and credit risks associated with our investment portfolio; risks relating to share repurchase programs; risks relating to access to capital and credit markets; risks related to indebtedness; change in control provisions in certain of our collaboration agreements; environmental risks; and any other risks and uncertainties that are described in other reports we have filed with the U.S. Securities and Exchange Commission (SEC).

These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

Drug targets with a genetic link to disease are more likely to succeed in the clinic and be approved

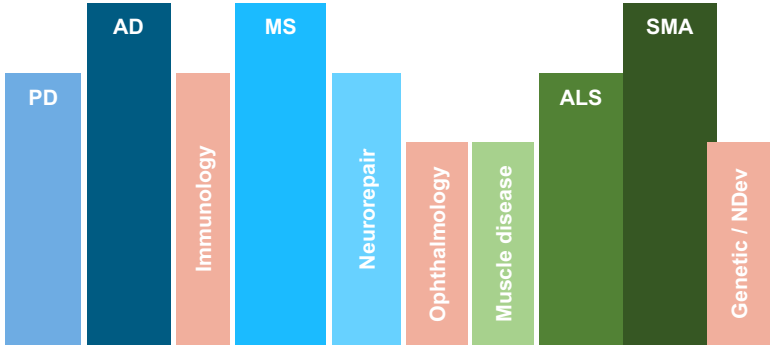
Genetic targets have at least double the probability of success



>1/3 of FDA approvals in 2019 – 2020 are supported by genetics

Nelson et al, Nat Genet, 2015

Biogen's disease areas have a substantial genetic component



- Single causative gene (SMA)
- Rare familial forms of more common disease (AD)
- Complex genetic disease – genetic risk may be estimated via measured polygenic risk score

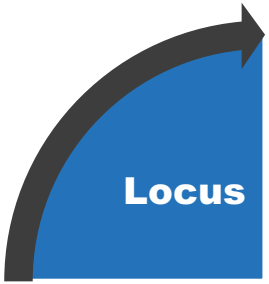
AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; GWAS = genome wide association study; HD = Huntington's disease; MS = multiple sclerosis; Ndev = neurodevelopmental; PD = Parkinson's disease; SMA=spinal muscular atrophy

We have built a neuroscience translational platform that allows us to leverage advances in human genetics and inducible Pluripotent Stem Cell (iPSC) technologies

Genetic Locus Discovery

Genes associated with disease onset, biology progression and protection

FINNGEN biobank uk



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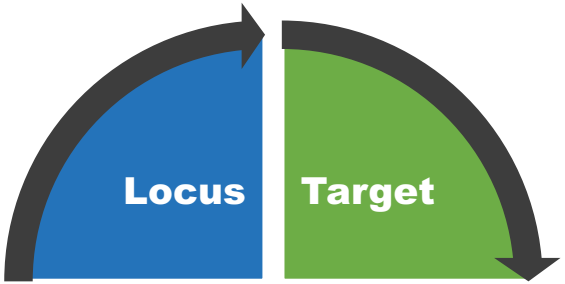
biobank uk
Improving the health of future generations



Causal Genes and Mechanism

Enrich for CNS data in human cohorts and Postmortem tissue

Pharma Proteomics Project

THE SWEDISH BIOFINDER STUDY™

MetaBrain

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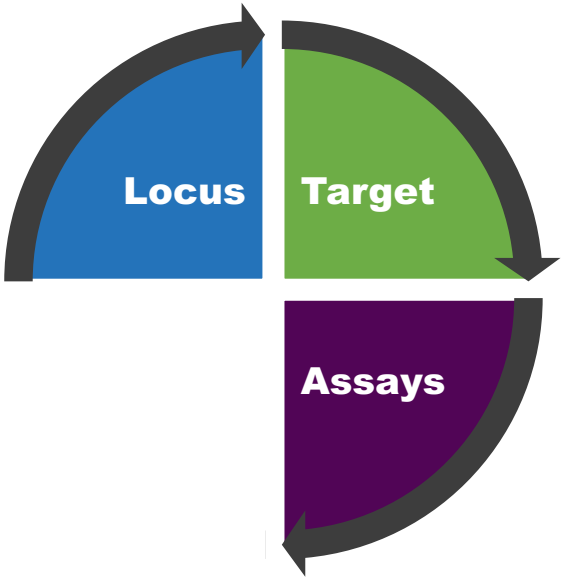

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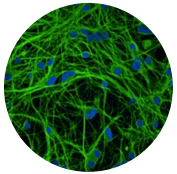
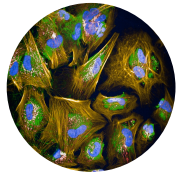
Functional Genomics

Engineering patient mutations into disease relevant human functional assays or in vitro validation





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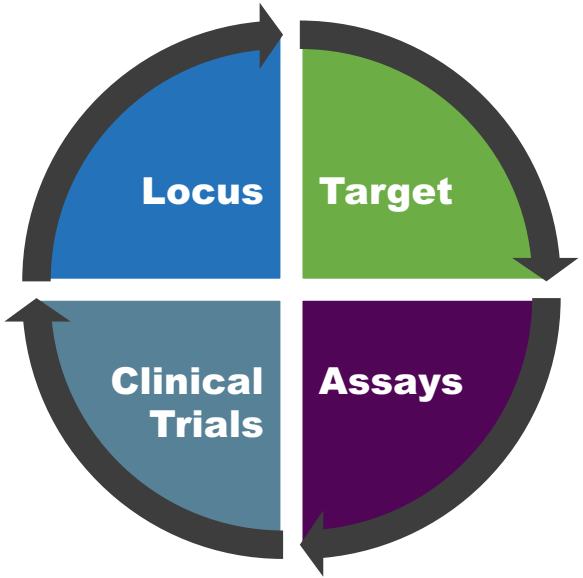


Causal Genes and Mechanism

Enrich for CNS data in human cohorts and Postmortem tissue

Pharma Proteomics Project

THE SWEDISH BIOFINDER STUDY™

MetaBrain

Observations in Humans

Prediction of clinical trial success
Natural History in genetic subgroups
Patient Stratification

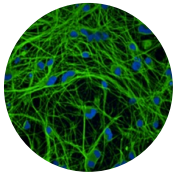
luna DNA

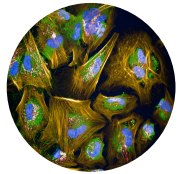
project MinE
Make it yours

MS PATHS

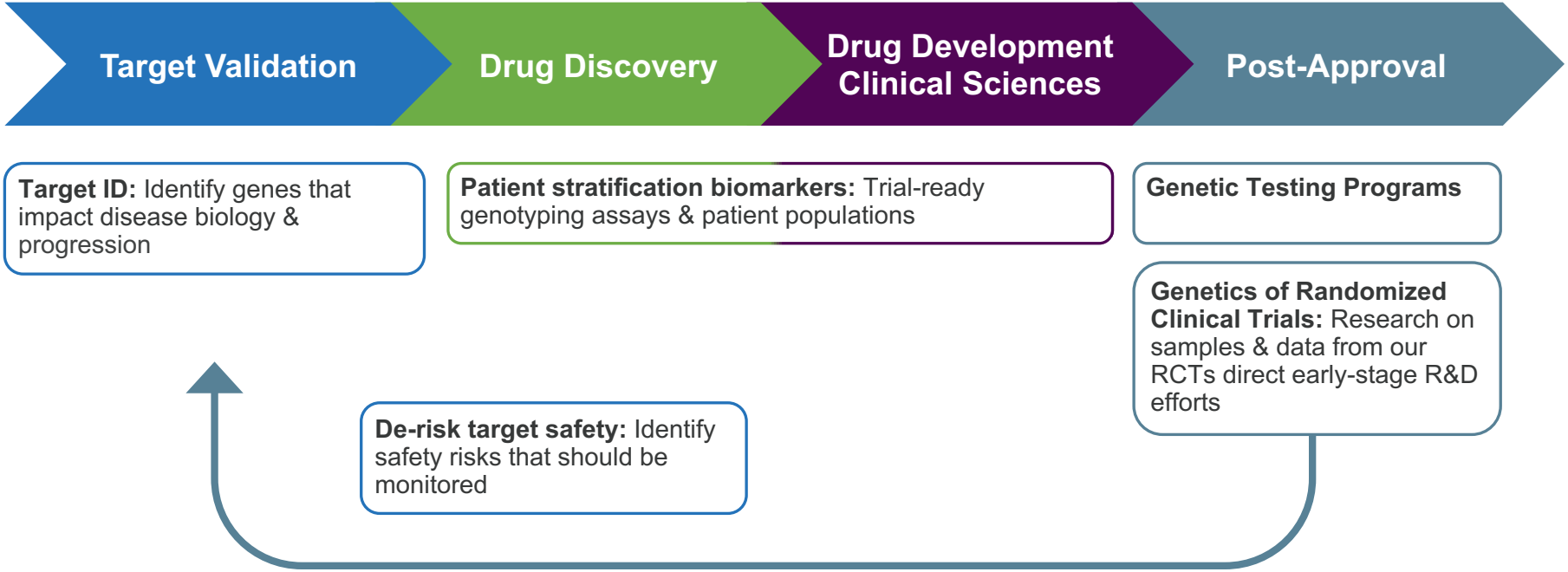
Functional Genomics

Engineering patient mutations into disease relevant human functional assays or in vitro validation





Human genetics helps increase confidence at critical stages of pipeline



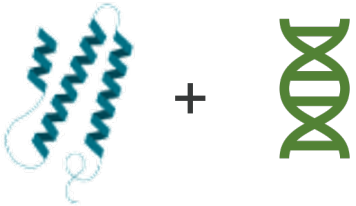
Linking genetics to changes in Cerebral Spinal Fluid (CSF) protein levels to propose new CNS targets

CNS-focused molecular data

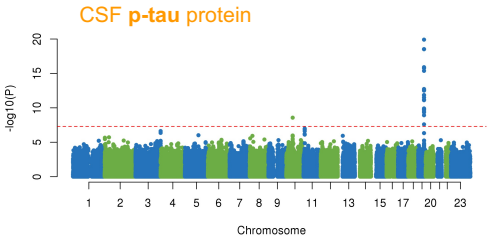
1. Acquire **patient cerebrospinal fluid + plasma (N=1,600)** from Swedish BioFINDER clinics

THE SWEDISH BIOFINDER STUDY™

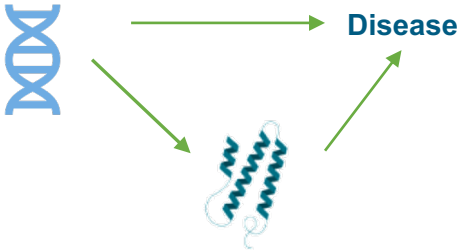
2. Measure **relative concentrations of 400+ proteins**



3. Perform **genome-wide genotyping of** protein concentrations



4. Conduct **Mendelian randomization** to infer causal associations (disease <- gene -> protein)



5. Identify novel **AD, MS and neuropsychiatry targets** with **genetic validation***

Multiple sclerosis	Alzheimer's	Depression	Bipolar & schizophrenia
9 potential drug targets	**9** potential drug targets	**1** potential drug target	**2** potential drug targets

Lui JZ, et al American Society Human Genetics Meeting Abstract 2020

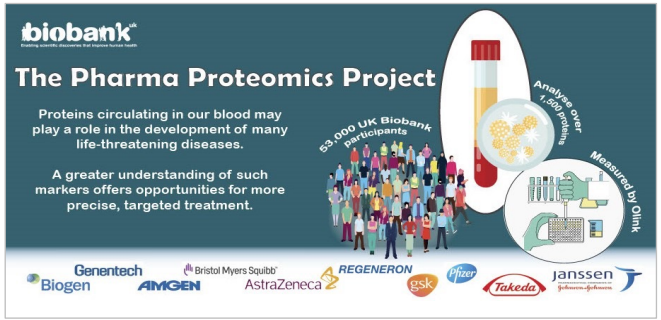
Whelan CD Acta Neuropathol Commun. 2019

AD = Alzheimer's disease; CNS = central nervous system; MS = multiple sclerosis p-tau = phosphorylated tau protein

Large-scale collaborations identify & help de-risk target safety

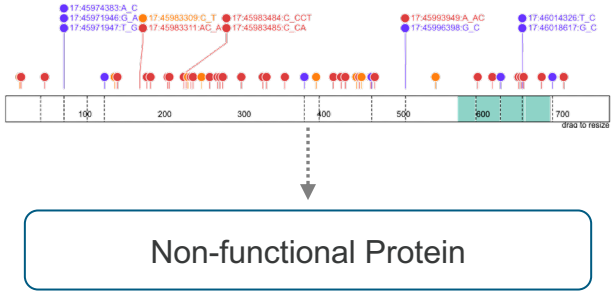
Biogen acts as an architect to shape public resources to support drug discovery

UK Biobank Exome Sequencing Consortium (UKB-ESC)



Linking UK Biobank exomes to phenotypes: MAPT LoF is well-tolerated, increasing confidence in targeting tau

- 40 Predicted loss of function mutations
- 230 Heterozygous carriers
- No obvious safety concerns



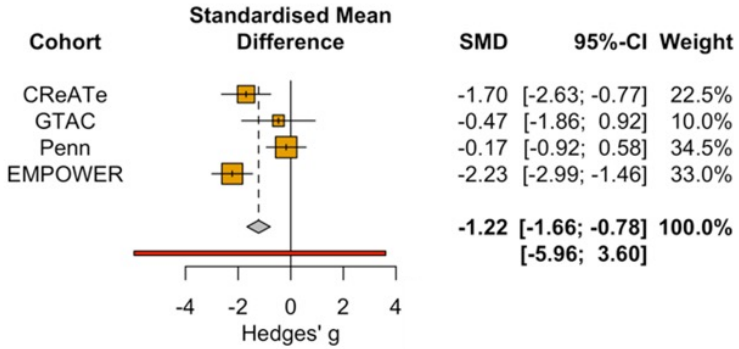
Next step: Plasma tau to be measured in a subset of 53k samples to confirm finding

Szustakowski,. *et al. Nat Genet* **53 2021** Genebass browser: https://genebass.org/

LoF = loss of function; MAPT = microtubule-associated protein tau

Discovery of sporadic ALS progression genetics informs clinical design

Carriers of 30-33 repeat alleles in ATXN2 show faster sALS progression, informing BIIB105 efficacy



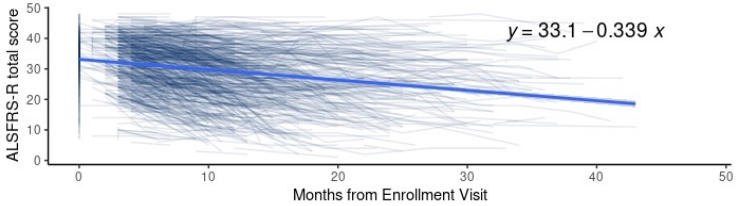
ATXN230-33 carriers have a 1.22/month faster rate of decline on the ALSFRS-R relative to ATXN220-23 carriers

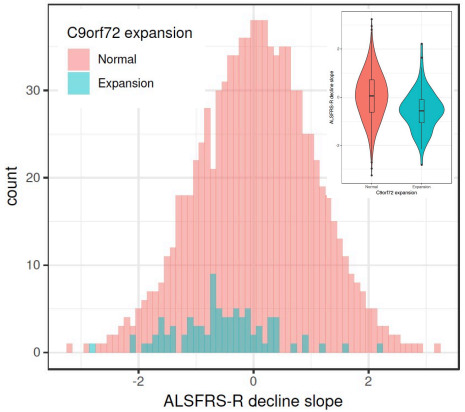
McMillan et al American Academy Neurology Abstract 2020

ALSFRS-R = ALS functional rating scale-revised; ATXN2 = ataxin 2; sALS = sporadic ALS

Analysis of 1300 patients with genome wide data to identify genes

ALSFRS-R score decline over disease course





C9orf72 expansion

Patient identification and confidence in pathogenicity is critical to progression of well-established genetic targets

Identify mutations

INVITAE

EIMFS
Epilepsy of infancy with Migrating Focal Seizures

EOEE
Early-Onset Epilepsy Encephalopathy

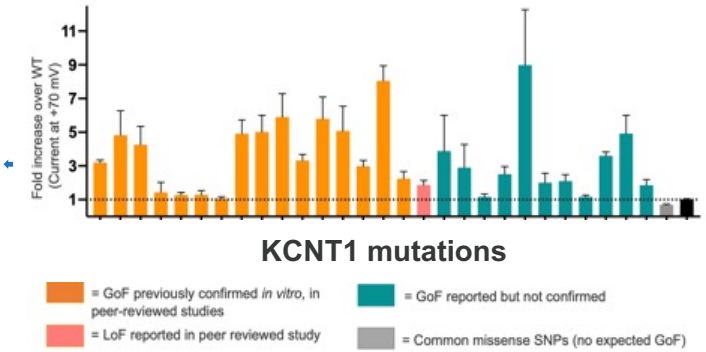
SHE
Sleep-related Hypermotor Epilepsy

290 Genes on Invitae Epilepsy Panel (including *KCNT1*)

Do KCNT1 mutations show evidence of physiological gain-of-function in relevant cell types?

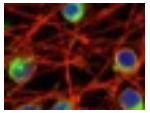
Expression construct generation

Xenopus oocyte expression
- Primary assay for rapid mutation classification
- Well validated in academic literature



CRISPR editing + neuron productions

Engineered mutations in hiPSC derived neurons
- Confirm in human neuronal system for key mutations



Identify patients for clinical trials

Genetic Alliance

luna DNA

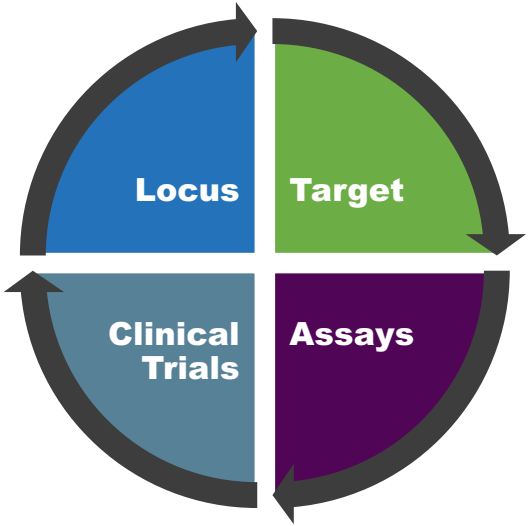
KCNT1 EPILEPSY
HOPE IS ON THE HORIZON

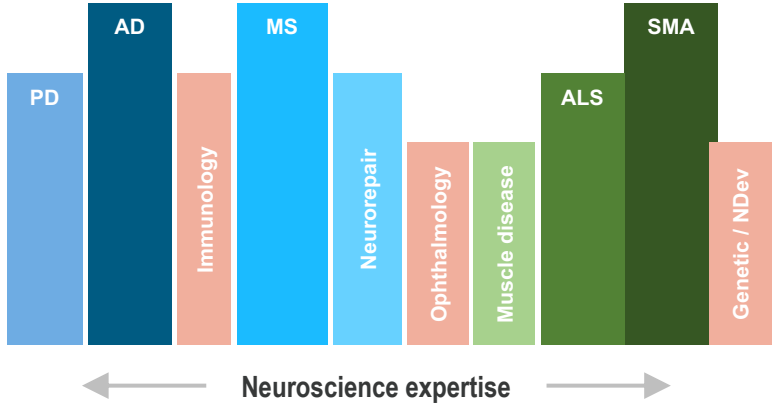
KCNT1 Epilepsy Foundation @KCNT1_Epilepsy · Jul 8

I also want to point out Dr. David Bearden and @biogen innovative approach: Telehealth and in-home assessments, remote video eegs, in-home bio collection...this design removes participation barriers, will yield truer data, and ultimately result in better science.

GoF = gain of function; hiPSC = human induced pluripotent stem cells

We work to be pioneers in translating human genetics to treat, prevent & cure diseases of the CNS





We have improved the quality & probability of success of our R&D pipeline, >75% of our pre-clinical portfolio is supported by human genetics