

From Endpoints to Impact: **Designing Trials** **that Resonate** **with Patients**

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Introduction

Patient engagement with clinical trials

- Comprehensible mechanism of action
- Safety
- Symptomatic therapies
- Disease modifying therapies (neurodegenerative disorders)
- Gene therapy and therapies targeting genetic causes of disease
- Natural substances – e.g. nutritional supplements, cannabis
- Meaningful endpoints
- Study designs that are sensitive to patient needs
- Communication throughout the course of a trial is critical

Why is Patient Engagement Important?

- Recruitment
- Retention
- Better understanding of the reason for the study
 - May reduce placebo response
- Clinical uptake of the therapy
- Importance of investigator engagement
 - If investigators are enthusiastic and engaged, this may translate to patient engagement

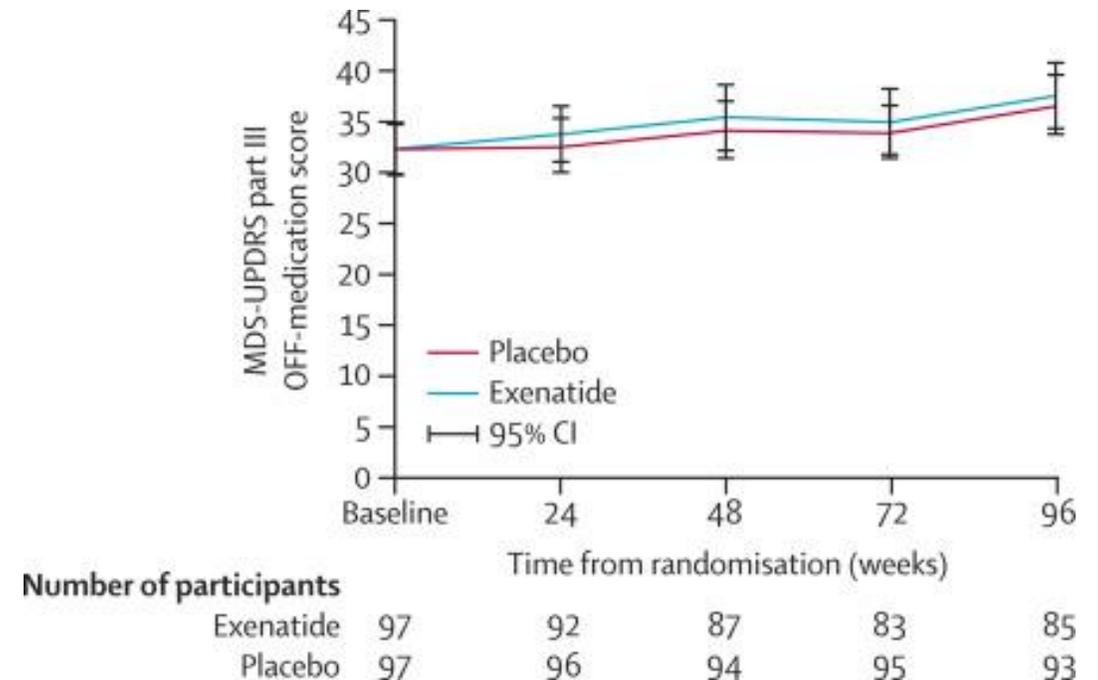
**Investigator and patient
enthusiasm needs to be
supported by sound scientific
rationale.**

GLP-1 Agonists for Neurodegenerative Disorders



- Well-known to the public and widely taken for DM and weight loss
- Multiple small open-label and RCT studies suggested benefit in Parkinson's disease
- Recent RCT in 194 PD patients –
“Our findings suggest that exenatide is safe and well tolerated. We found no evidence to support exenatide as a disease-modifying treatment for people with Parkinson's disease”*
- From the NYT –
“The problem with studying GLP-1s in Parkinson's disease”, Dr. Standaert said, “is that what exenatide is supposed to be doing in the brain is not clear.”

“I wouldn't do another study like this unless you learn what is the target,” Dr. Standaert said.
“What is the biochemistry you are trying to change in the brain? How do these drugs work, anyway?”



Gene Therapy for Parkinson's Disease



Lancet Neurology 10(4):309-319

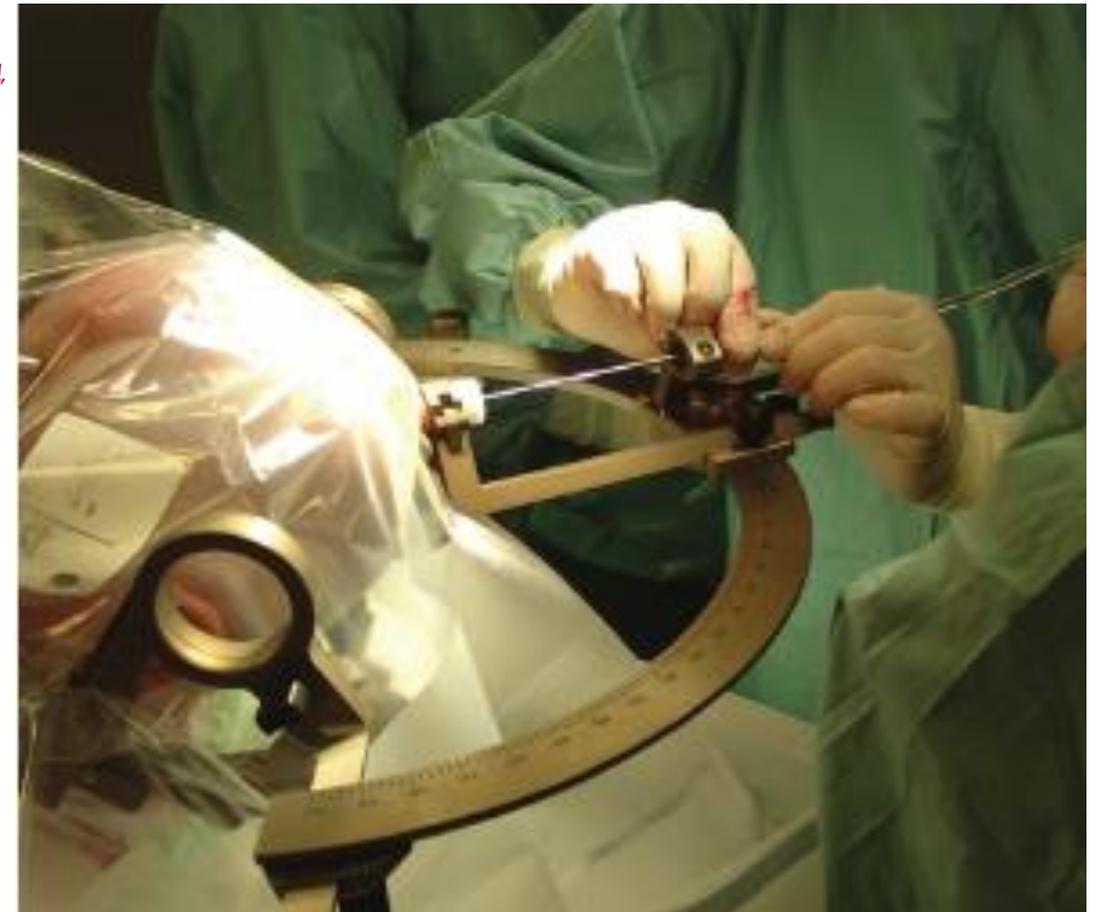
AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial



Peter A LeWitt, Ali R Rezai, Maureen A Leehey, Steven G Ojemann, Alice W Flaherty, Emad N Eskandar, Sandra K Kostyk, Karen Thomas, Atom Sarkar, Mustafa S Siddiqui, Stephen B Tatter, Jason M Schwab, Kathleen L Poston, Jaimie M Henderson, Roger M Kurlan, Irene H Richard, Lori Van Meter, Christine V Sapan, Matthew J During, Michael G Kaplitt*, Andrew Feigin*

Patients very engaged – rapid recruitment, high retention – despite invasive neurosurgical procedure

- 🟢 Strong scientific rationale
- 🟢 Gene therapy
- 🟢 State-of-the-art stereotactic neurosurgical procedure
- 🟢 State-of-the-art imaging outcome measures



Disease Modification

Distinction between symptomatic therapies and disease modifying therapies

- Symptomatic therapies
 - Improve signs, symptoms, function (e.g. levodopa in Parkinson's)
 - May have no effect on pathology/progression
- Disease Modifying
 - Goal is to slow/halt progression
 - May have no effect on signs and symptoms
- Role for both approaches in neurodegenerative disorders
 - Whether a therapy is working symptomatically vs by disease modification may not matter from a drug development perspective
 - But can be critical from a patient engagement perspective

Neurodegenerative Disorders

Disease Modification

Difficult to explain to patients AND physicians

- People expect to have a measurable improvement (clinical or lab) with an effective therapy
 - In clinical trials of potential disease modifying therapies, patients frequently say “I must be on placebo because I see no improvement”
 - Need for reliable biomarkers – e.g. LDL cholesterol for lowering cardiovascular risk – something measurable
- If a therapy slows progression of a neurodegenerative disorder by 25% in a clinical trial this is likely clinically meaningful
 - But patients may not feel better, perform better, or have an improvement in a known reliable biomarker
 - Need to accept results of a trial on faith – they are doing better over time than if they were not taking the therapy
 - Need for reliable and measurable biomarker

Disease Modification in Neurodegenerative Disorders

Biomarkers

nature reviews drug discovery
news 17-May-2023

“NfL makes regulatory debut as neurodegenerative disease biomarker”

- 🌱 “The FDA approved tofersen for amyotrophic lateral sclerosis based on the drug’s ability to lower blood levels of neurofilament light (NfL) — establishing a proof of potential for this neuroscience biomarker that could have implications for other diseases of the brain.”
- 🌱 From FDA – “FDA approved Qalsody (tofersen) to treat patients with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS)” (accelerated approval)
 - “The approval was based on a reduction in plasma neurofilament light (NfL), a blood-based biomarker of axonal (nerve) injury and neurodegeneration”
 - “The findings are reasonably likely to predict a clinical benefit in patients”

Role in Clinical Trials

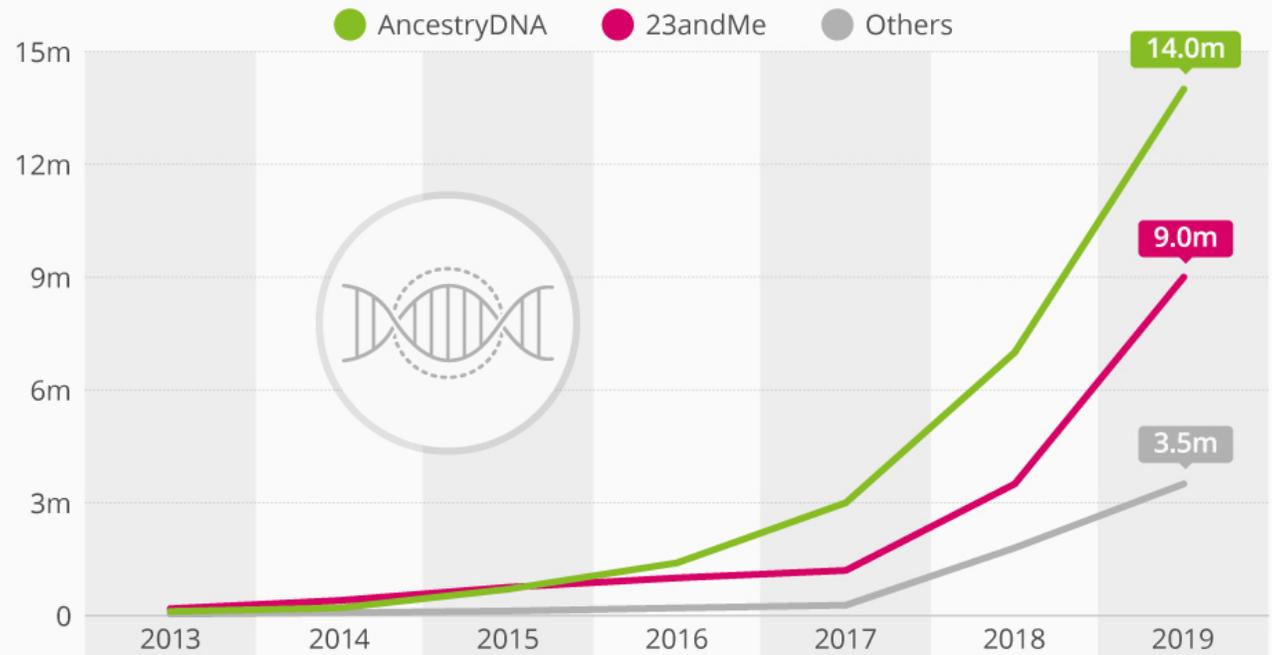
Widespread Genetic Testing

Increasing availability and uptake of genetic testing/screening

- 🌱 Commercial
- 🌱 Clinical
 - AD – e.g. APOE ε4, Presenilin
 - PD – e.g. LRRK2, GBA
 - ALS – e.g. SOD1
 - Many others

Commercial Genetic Testing Is Gaining Momentum

Estimated total number of people tested by consumer genetic companies*



* Direct-to-consumer genetic testing uses DNA samples, such as saliva, to track a person's ancestry; find family members; disclose a limited array of possible health risks; or brief someone on their personal preferences, like a taste for cilantro or wine.

Targeting Genetic Causes of Disease

- Personalized medicine
- Intuitively appealing to patients
 - If I have a gene mutation causing a disease, it is logical that a therapy targeting that mutation might be beneficial



Patient Oriented Endpoints



- Functional scales
 - Ability to stay at work, do ADL's, manage household chores, socialize, exercise, manage finances, etc.
 - Patient reported outcome measures
- Improvement in specific signs and symptoms
 - Important, valuable, and resonate with patients
 - Resonate even more with functional improvement
- Wearables and sensors
- Biomarkers
 - If strongly linked to a functional or symptomatic benefit

Studying Roots and Berries



*Movement
Disorders*

RESEARCH ARTICLE

CLINICAL PRACTICE

Medicinal Cannabis for Parkinson's Disease: Practices, Beliefs, and Attitudes Among Providers at National Parkinson Foundation Centers of Excellence

Danny Bega, MD, MSCI,^{1,*} Tanya Simuni, MD,¹ Michael S. Okun, MD,² Xinguang Chen, MD, PhD,³ Peter Schmidt, PhD⁴

- Survey of movement disorders neurologists
- 16 potential effects of cannabis queried
- 12 effects respondents who indicated both “improve” and “worsen”
- 80% had patients using cannabis



Rho's Leadership in Food Allergy



SCIENTIFIC UNDERSTANDING OF IgE-MEDIATED FOOD ALLERGY



7 Medical Breakthroughs
That Gave Us Hope in 2024

The New York Times

*Drug Drastically Reduces Children's
Reactions to Traces of Food Allergens*



Notable Articles of 2024



*Omalizumab for the Treatment of Multiple
Food Allergies*" - awardee for the 2025 Top 10
Clinical Research Achievement Awards



FDA NEWS RELEASE

FDA Approves First Medication to Help Reduce
Allergic Reactions to Multiple Foods After
Accidental Exposure

Putting the Pieces Together



THERAPIES THAT RESONATE WITH PATIENTS

- Understandable targets
- Safe and well-tolerated
- Cutting edge

STRONG CONNECTION WITH STUDY TEAM

- Able to explain trial clearly and answer questions
- Efforts to minimize visits and maximize efficiency
- Engagement with sponsor

OUTCOME MEASURES THAT ARE MEANINGFUL

- Symptomatic vs disease modifying
- Functional/patient-reported outcomes