MEIRAGTx

AAV-GAD R&D Day

December 13, 2019

Forward-Looking Statements

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Welcome Remarks and MeiraGTx Overview

Zandy Forbes, Ph.D.

President and CEO

MeiraGTx

Today's Agenda

Introduction and Welcome Remarks
Zandy Forbes, Ph.D.
President and CEO, MeiraGTx

Parkinson's Disease: Clinical Perspective
Ali Rezai, M.D.
West Virginia University

Parkinson's Disease: Patient Perspective
Jamie Eberling, Ph.D.
Michael J. Fox Foundation for Parkinson's Research

Parkinson's Disease: Health Economics Perspective
Jalpa A. Doshi, Ph.D.
University of Pennsylvania

AAV-GAD: Strategy for Functional Improvement
Matthew During, M.D. Ph.D.
Head of R&D, MeiraGTx

AAV-GAD: Clinical Data
Michael Kaplitt, M.D. Ph.D.
Weill Cornell Medical College and MeriaGTx SAB

Q&A Panel

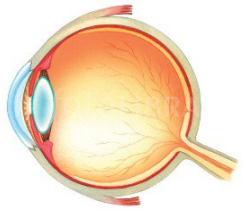
A Vertically Integrated, Clinical Stage Gene Therapy Company

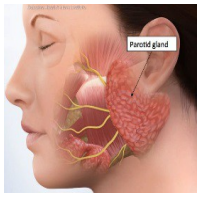
Developing a new pharmaceutical modality designed for the cost effective treatment of a broad range of serious disorders

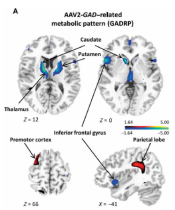
Diversified Pipeline of Gene Therapy Candidates

6 ongoing clinical programs:

- Inherited retinal diseases
- Salivary gland
- Parkinson's Disease



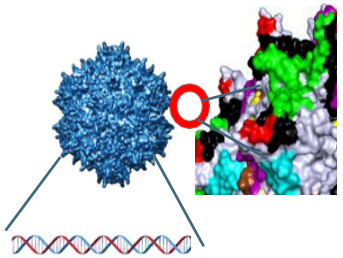


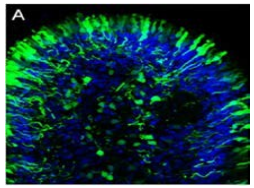


Platform of Core Viral Vector Engineering Capabilities

Viral vector design platform:

promoters, capsid, transgene optimization, ITRs, immunogenicity





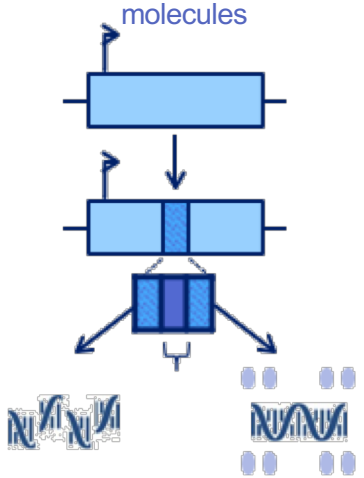
Manufacturing Capacity & Know-How

Flexible and **scalable cGMP manufacturing facility** with capacity for commercial supply for our programs.

Process Development Platform

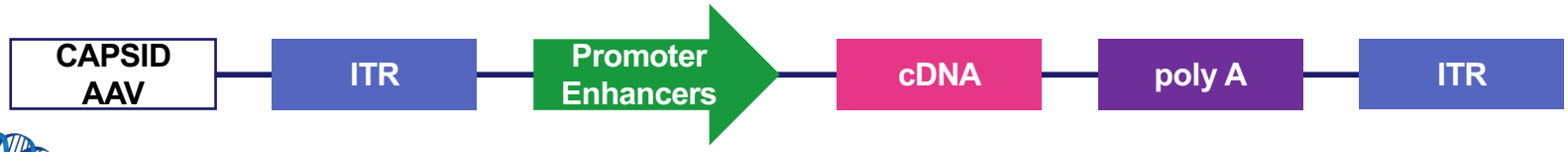
Next Generation Gene Therapy Riboswitch-Based Gene Regulation

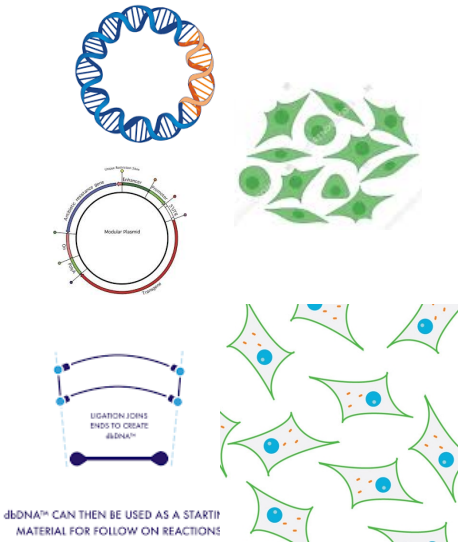
Proprietary technology that may allow for innovative gene therapy treatments whose **expression can be turned on and off** with small molecules

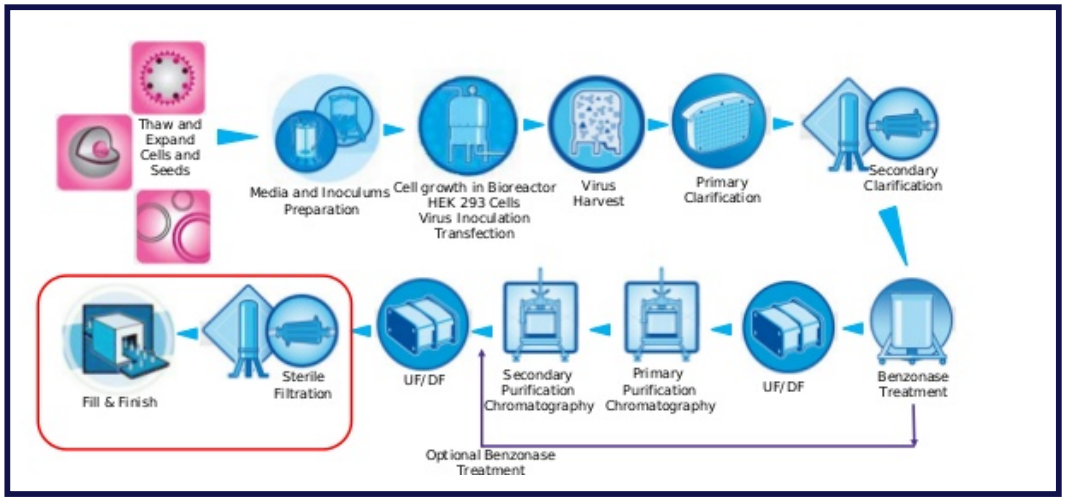


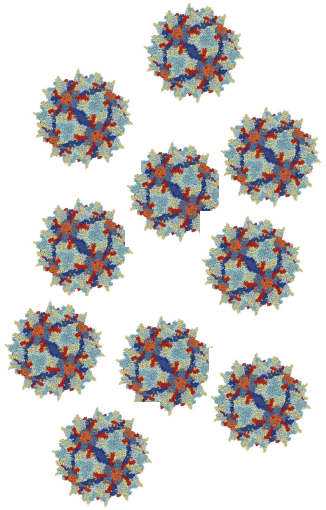
Modular Approach Brings Development Synergies

- Vector development is modular
- Toolkit can be broadly applied across therapeutic areas
- Synergistic drug development
- Fast time to IND: as little as 18-24 months from idea to IND
- Truncated development timelines
- Timeframes are short and potential enormous









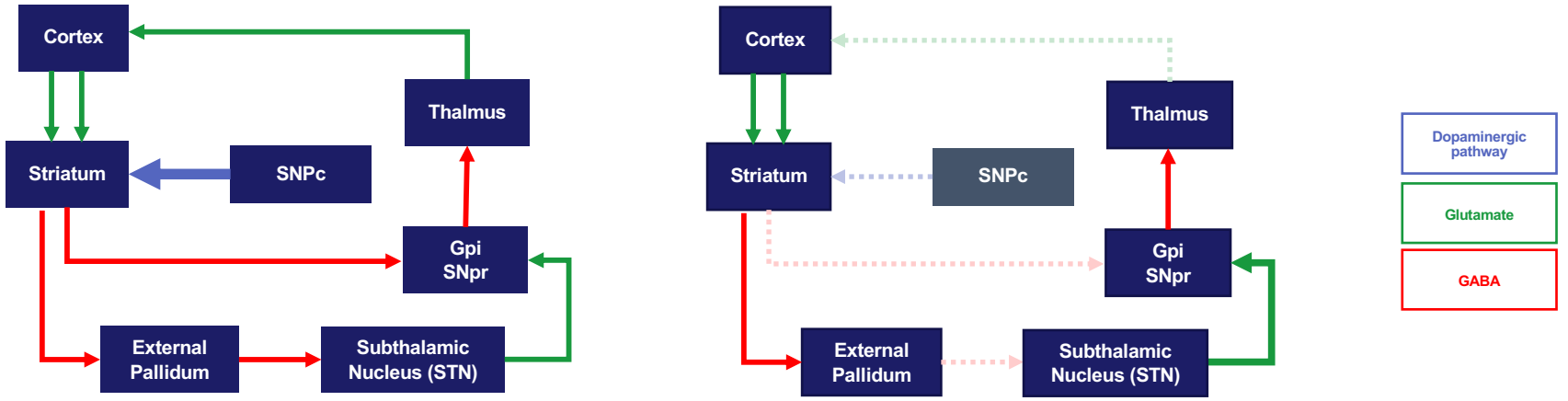
- Manufacturing synergies across multiple products
- Current process under development – purity, potency, starting materials, assay validation

Broad Clinical Pipeline

Product	Indication	Preclinical	Phase 1/2	Details
Ocular				
AAV-RPE65	RPE65-Deficiency	RPDD, Orphan Drug		
AAV-CNGB3*	Achromatopsia (CNGB3)	RPDD, PRIME, Fast Track, Orphan Drug		janssen
AAV-RPGR*	X-linked RP (RPGR)	Fast Track, Orphan Drug		janssen
AAV-CNGA3*	Achromatopsia (CNGA3)	RPDD, Orphan Drug		janssen
AAV-AIPL1	LCA4 (AIPL1)	Orphan U.S. & EU		EU Compassionate Use under Specials License
A006	Wet AMD (anti-VEGFR2)			
Neurodegenerative Disease				
AAV-GAD	Parkinson's Disease (GAD)			
Salivary Gland				
AAV-AQP1	Xerostomia (hAQP1)	Orphan Drug		
AAV-AQP1	Sjögren's Syndrome (hAQP1)			

*Co-development program with Janssen Pharmaceuticals pursuant to a collaboration agreement.

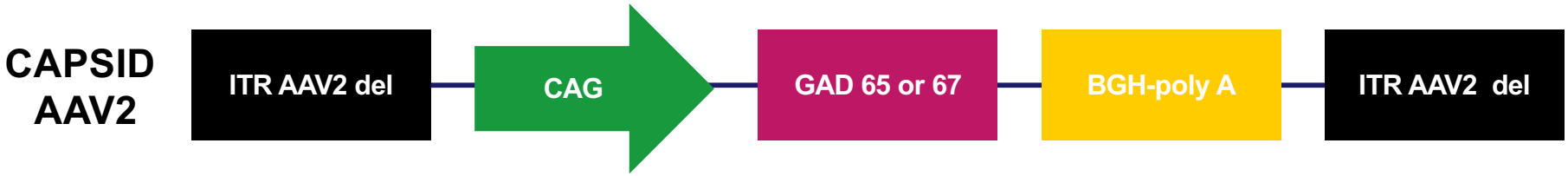
AAV-GAD for Parkinson's Disease



AAV-GAD gene therapy to rebalance STN excitation and inhibition

Glutamic Acid Decarboxylase converts glutamate (excitatory neurotransmitter) into GABA (inhibitory neurotransmitter)

- Delivered directly into the STN, bypassing circuitry disrupted by dopamine loss
- AAV-GAD converts some STN neurons to inhibitory phenotype
  - Reduce STN activity
  - Normalize neuronal firing
  - Normalize basal ganglia outflow to the motor cortex



Expression cassette

Clinical Perspective: Treating Parkinson's Disease

Ali Rezai, M.D.
Executive Chair, Rockefeller Neuroscience Institute; Vice President of Neuroscience; and Professor of Neuroscience

West Virginia University School of Medicine

Parkinson's Disease Overview

Progressive neurodegenerative disease characterized by degeneration of dopaminergic neurons involved in motor control

- ~1M U.S. patients
- >6M patients globally

In majority of patients, unknown cause

Chronic, progressive and debilitating disease affecting motor function

- Rest tremor, rigidity and bradykinesia of limbs and body
- Postural instability

Progression and treatment complications cause wide spectrum of other symptoms

- Dyskinesias, dementia, abnormal speech, depression, sleep disturbance, psychosis, impulse and behavioral disorders

Dorsey ER. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):939–953.
Marras C. Prevalence of Parkinson's disease across North America. npj Parkinson's Disease. 2018; 4:21.
Lewin Group Report on "Economic Burden and Future Impact of Parkinson's Disease" 2019.

Diagnosis and Early-Stage Disease

Patients

- **Typical age of onset: 55-65**

- **Age is strongest risk factor for PD: nearly exponential increase in incidence between ages 55 and 79**
  - Most PD patients are older than 65
  - Early-onset PD may be diagnosed at age 40 or younger

- **Diagnosed based on presence of bradykinesia, rest tremor and rigidity**
  - Goal of current treatment is to control these primary motor symptoms

First-line Treatment

- **Levodopa, an oral drug from which dopamine is synthesized in the brain**
  - Oral levodopa compensates for loss of dopamine

In early stage patients (0-3 years after diagnosis), levodopa is highly effective at controlling primary motor symptoms

Rizek P. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016;188(16):1157–1165.
Driver JA. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology. 2009;72(5):432–438.

Disease Progression

- High doses and frequent dosing of levodopa are necessary to control motor symptoms (3-6x per day is common)
- Because PD is a progressive disease, doses and dosing frequency must be increased over time to maintain control
- The long-term use of high doses of levodopa is associated with motor complications that impact QoL, including motor fluctuations and dyskinesia
- Moderate and advanced PD patients often prescribed adjunctive dopaminergic therapy to control motor complications after ~3-5 years of levodopa

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- While PD primarily manifests as a movement disorder, it is also associated with **nonmotor symptoms**, including:
  - Cognitive impairment, speech/swallowing problems, instability/balance problems, psychosis and dementia

Rizek P. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016;188(16):1157–1165.

Standard of Care Therapeutics

Current Anti-Parkinsonian Drugs

Levodopa	Dopamine agonists	Enzyme inhibitors (COMT/MAO-B)
At diagnosis and for remainder of life	~3-5 years after diagnosis	~3-5 years after diagnosis

- Replace depleted dopamine
- Reduce symptoms of disease progression

- None provide satisfactory relief to advanced patients
- Tolerability issues
- Uncontrolled motor fluctuations
- Increased doses required
- Dopamine overproduction/dyskinesias

Standard of Care Neuromodulation

Deep Brain Stimulation

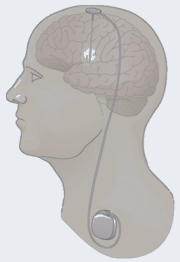
Surgically based adjunctive therapy

Only FDA approved neurosurgical therapy for late stage patients

Effective but highly underutilized

Indication

- When insufficient relief from best medical therapy



Contraindications

- Dementia
- Active psychiatric disorders
- Structural abnormalities
- Unable to tolerate general anesthesia

Surgical procedure

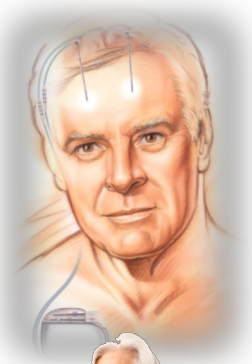
- Two stage surgical procedure: bilateral brain implant followed by lead extension and pulse generator placement under general anesthesia

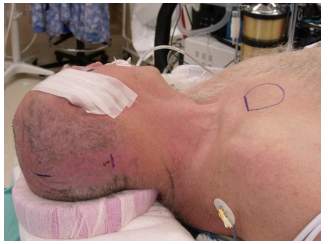
Programming & maintenance

- Repeated post-surgery programming sessions over several months at an expert center
- Frequent maintenance over patient's life cycle
  - Adjustments for disease progression
  - Battery replacements

Deep Brain Stimulation (DBS)

- **Surgery stage 1:** brain lead implantation
- **Surgery stage 2:** battery and programmable chip implantation in chest—Pulse generators under anesthesia
- Battery Devices are adjusted by movement disorder neurologists
- Patient need to recharge the system weekly





Deep Brain Stimulation (DBS)

DBS OFF **DBS ON**

DBS Highly Effective but Underutilized

Clinically highly effective[1,2]

- 25-35% improvement in UPDRS part 3 (“off” medication motor scores)
- Average of 2-4hrs of increased ON time per day
- Reduction in dyskinesia

SAEs in 56% of STN-DBS patients in large, randomized U.S. study[3]

- 24% CNS related
- 10% Device related

Speech complications

- Approx. 15% of patients receiving STN-DBS experience significantly deteriorating speech one year after treatment[4]

1. Weaver FM. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63–73.
2. Deuschl G. A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. N Engl J Med. 2006; 355:896-908.
3. Follet KA. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010; 3;362(22):2077-91.
4. Tripoliti E. Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology. 2011; 76 (1) 80-86.

DBS Highly Effective but Underutilized (continued)

A large number of PD patients have symptoms refractory to medication adjustments and potentially responsive to DBS

- Wearing off – 40-60% by 6 years after therapy initiation[1]
- Levodopa-induced dyskinesia (LID) – 40% by 6 years after therapy initiation[2]
- Motor fluctuations – 40% by 6 years of treatment[2]

Dementia absent from 70% of patients when motor complications present[3]
Yet… Only 1-2% of PD patients undergo DBS

- Even when a special tool was used to pre-select the best DBS candidates, less than 30% accepted and completed the DBS referral[4]

1. Ouma S. The Risk Factors for the Wearing-off Phenomenon in Parkinson's Disease in Japan: A Cross-sectional, Multicenter Study. Int Med. 2017; 56. 1961-1966.
2. Ahlskog JE. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov. Disord. 2001; 16: 448-458.
3. Svenningson P. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012; 11(8):697-707.
4. Dinkelbach L. How to improve patient education on deep brain stimulation in Parkinson's disease: the CARE Monitor study. BMC Neurol. 2017; 17, 36.

Medical Needs of Parkinson's Disease Patients Today

Progressive disease → Increasing doses → Medication complications

- Motor symptoms are well-controlled with levodopa for the first few years after diagnosis
- Current treatments only address the symptoms of disease, they do not modify or delay the progressive nature of PD

New therapeutic options should:

✓ Control primary motor symptoms

✓ Reduce LID/ increase ON time without dyskinesia

✓ Not contribute to dopaminergic drug related AEs (dizziness, confusion, hallucinations)

✓ Not increase already high pill burden, which impacts QoL for both patients and caregivers

✓ Not cause sufficient AEs to limit treatment acceptance

✓ Have a low burden of optimization and maintenance to improve access to therapy

DBS experience: 2600 patients over 22 years

NYU, Cleveland Clinic, Ohio State University, West Virginia University Rockefeller Neuroscience

DBS is effective, but still limited in penetration after 20 years

- **Neurologists not comfortable with implant and life long management of device and complications vs. medications**
- **Patient and family considerations**
  - Do not want an implant in their bodies
  - Multiple surgeries and anesthesia and cost
  - Hardware related complications
    - Infection, breakage, short and open circuit
  - Life long maintenance and additional cost
    - Additional surgeries to replace batteries
    - Battery recharging
    - Visits to physician offices
    - Limitation of life style and subsequent medical care
      - MRI, metal detectors, a pacemaker

Gene Therapy Solution for Advanced Parkinson's Disease

A gene therapy solution would be welcome as an option for neurologists, patients and families

- One shot procedure
  - Less surgery and anesthesia
  - No implant related complications
- Similar benefits as DBS
- No lifelong maintenance and management of implant
- Reduced life long physician visit and costs

The Patient Perspective:
Challenges Related to Disease Progression

Jamie Eberling, Ph.D.

Director, Research Programs

Michael J. Fox Foundation for Parkinson's Research

Overview

MJFF's Patient Engagement Vision

Bridging the gap between science and patients to get better treatments faster

- In addition to providing **$80M+ in grants** each year and supporting research through other resources such as access to **data, biosamples, tools, and recruitment** materials, MJFF also has a strong patient engagement strategy

End-to-end Clinical Development Solutions

- **PwP-identified bothersome problems** drive R&D
- Better designed trials with **outcome measures that matter to patients**
- **Efficient trials** that recruit on time with retention to power analyses
- Regulators informed of **patient preferences** for decision making

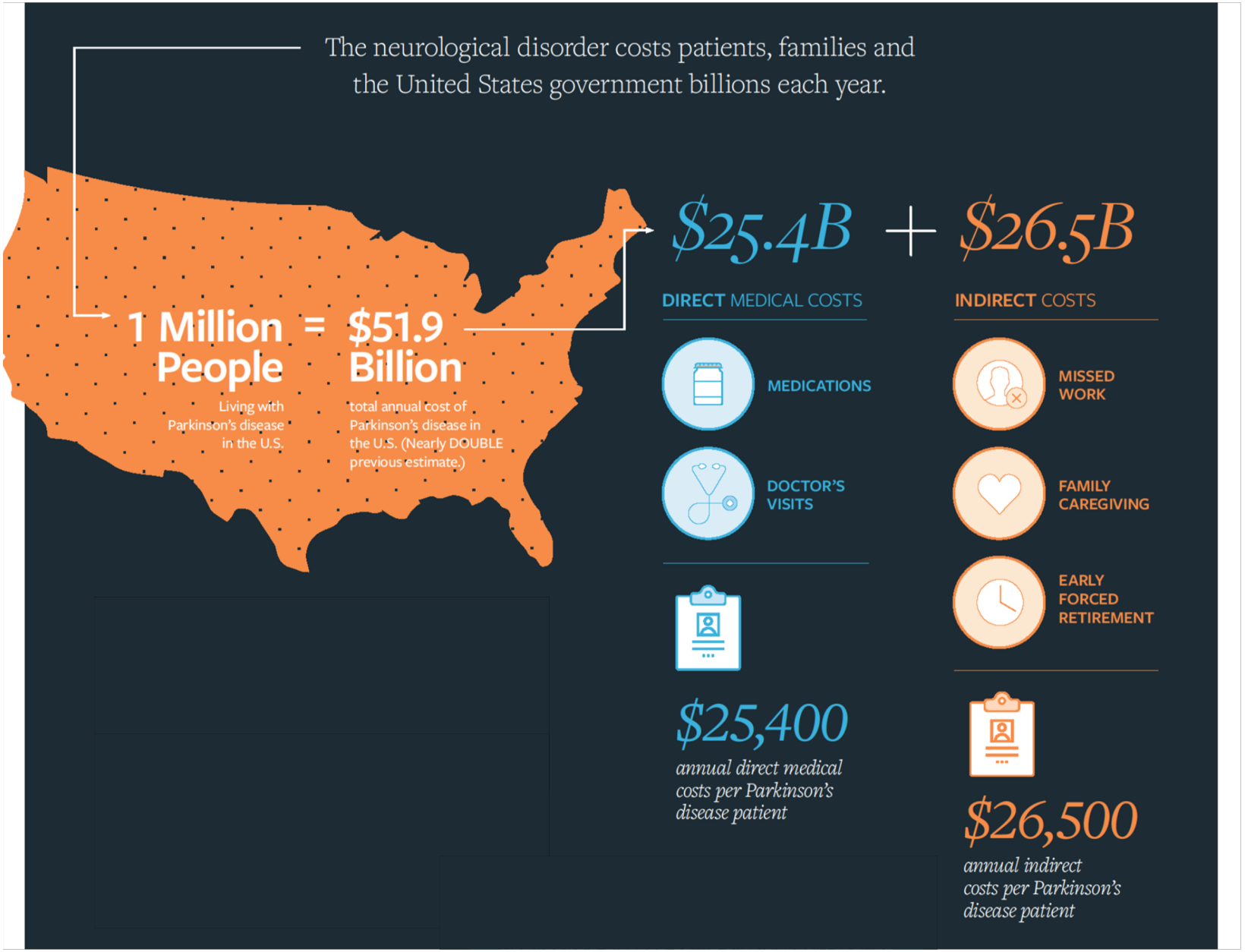
Education to Action

- Patients and families equipped to **optimize their Parkinson's care**
- Increased awareness and **participation in research**
- **Advocacy** for research funding and access to care

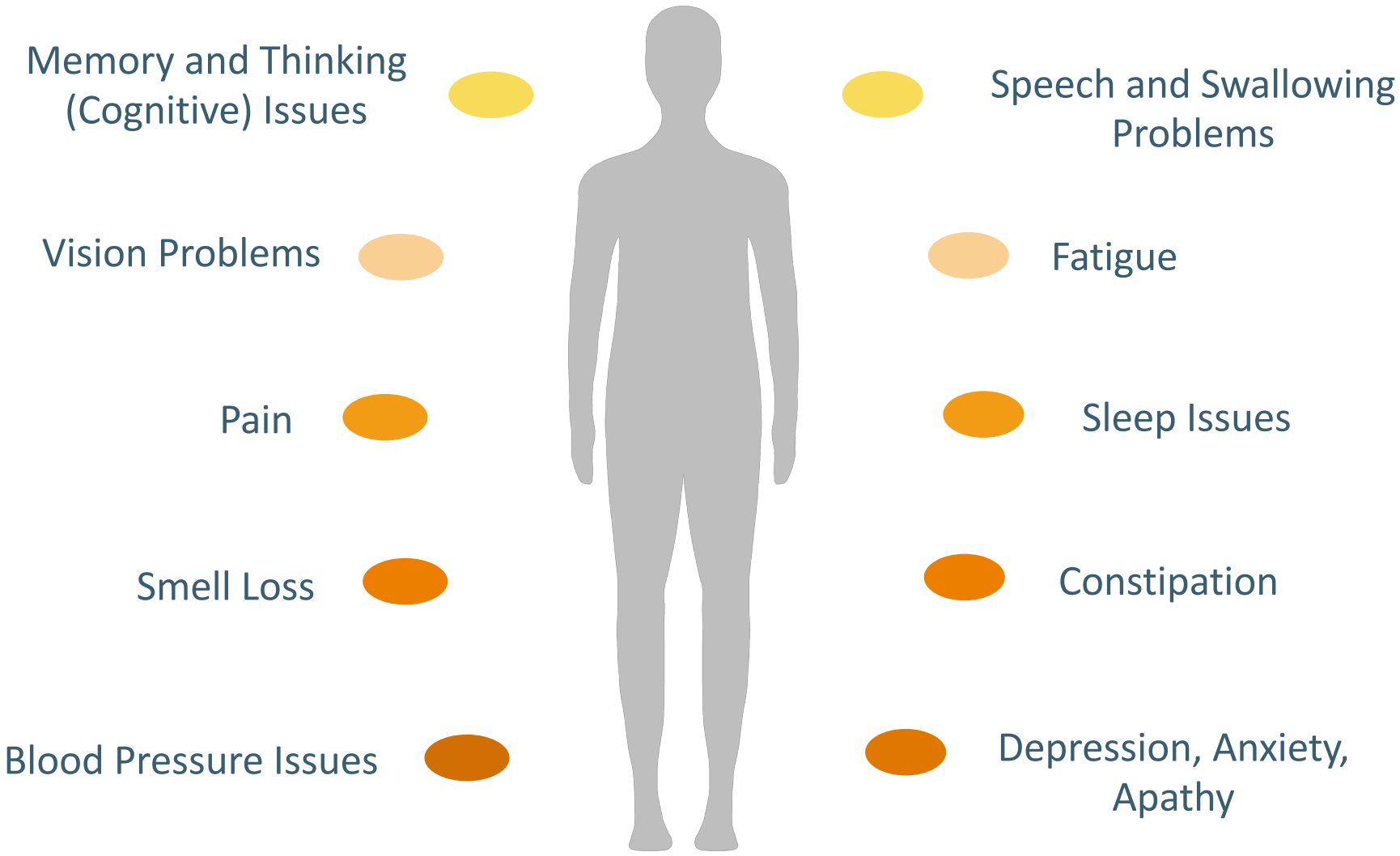
Improved Communication

- Patients **empowered to discuss symptoms and treatment options** with HCPs
- **HCPs have deeper understanding** of patient experiences and communication

Parkinson's Disease in the U.S.



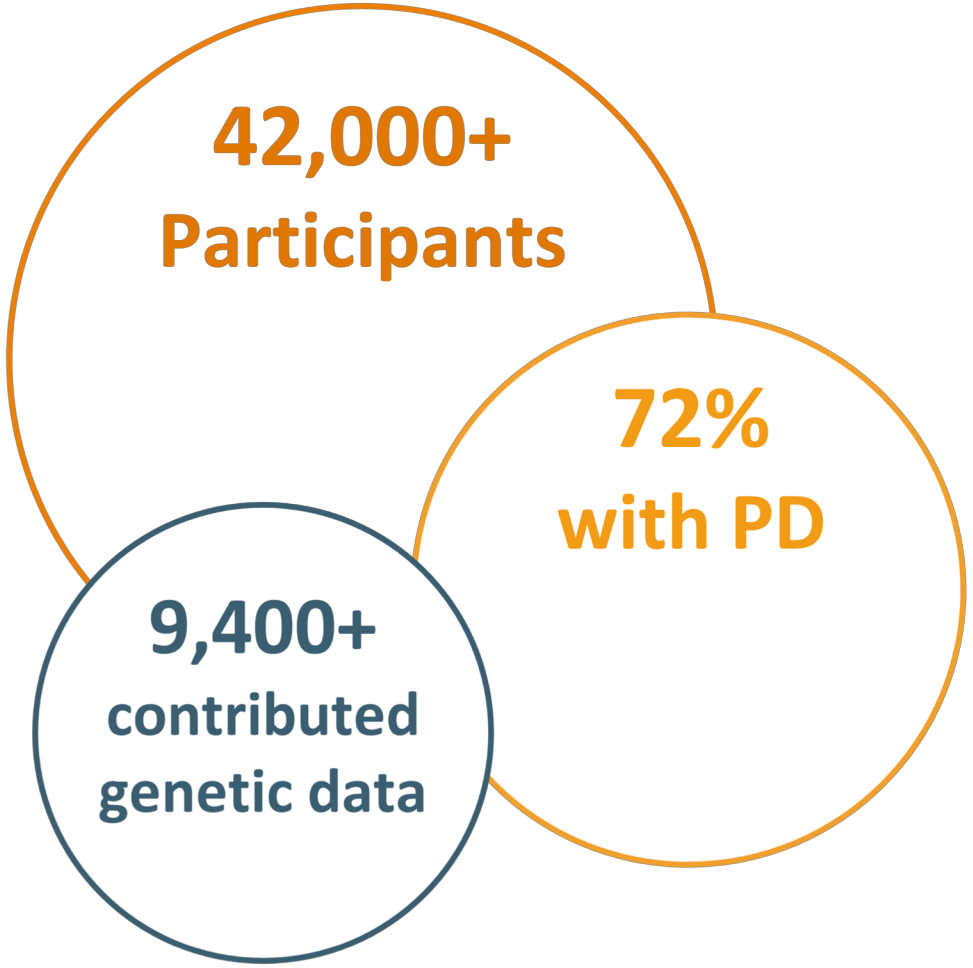
Yang G. Economic Burden and Future Impact of Parkinson's Disease. Lewin Group Report (2019)


Memory and Thinking (Cognitive) Issues
Speech and Swallowing Problems
Vision Problems
Fatigue
Pain
Sleep Issues
Smell Loss
Constipation
Blood Pressure Issues
Depression, Anxiety, Apathy

Disease Progression

FOX INSIGHT

in collaboration with 23andMe®



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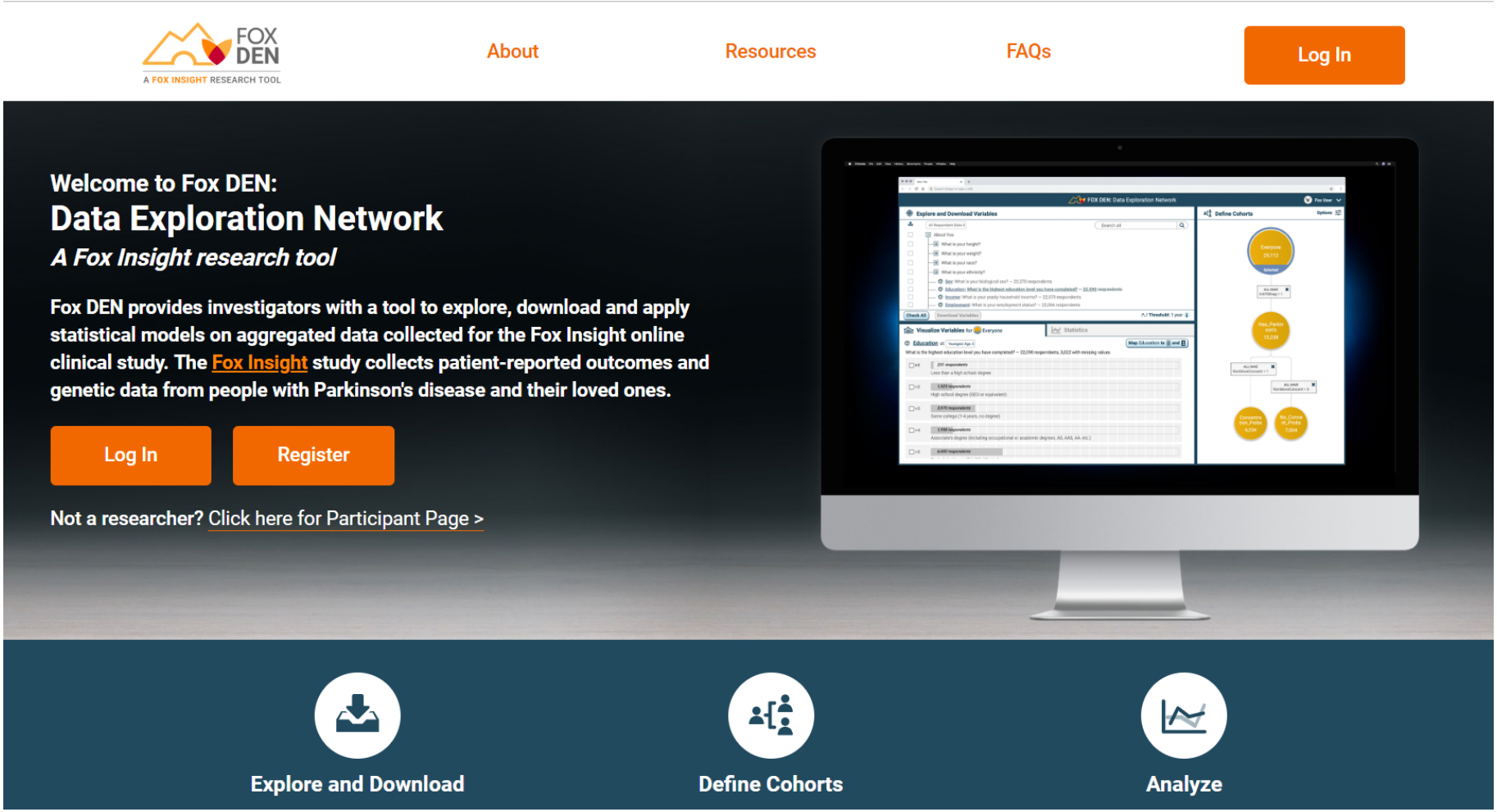
FOX DEN
A FOX INSIGHT RESEARCH TOOL
About
Resources
FAQs
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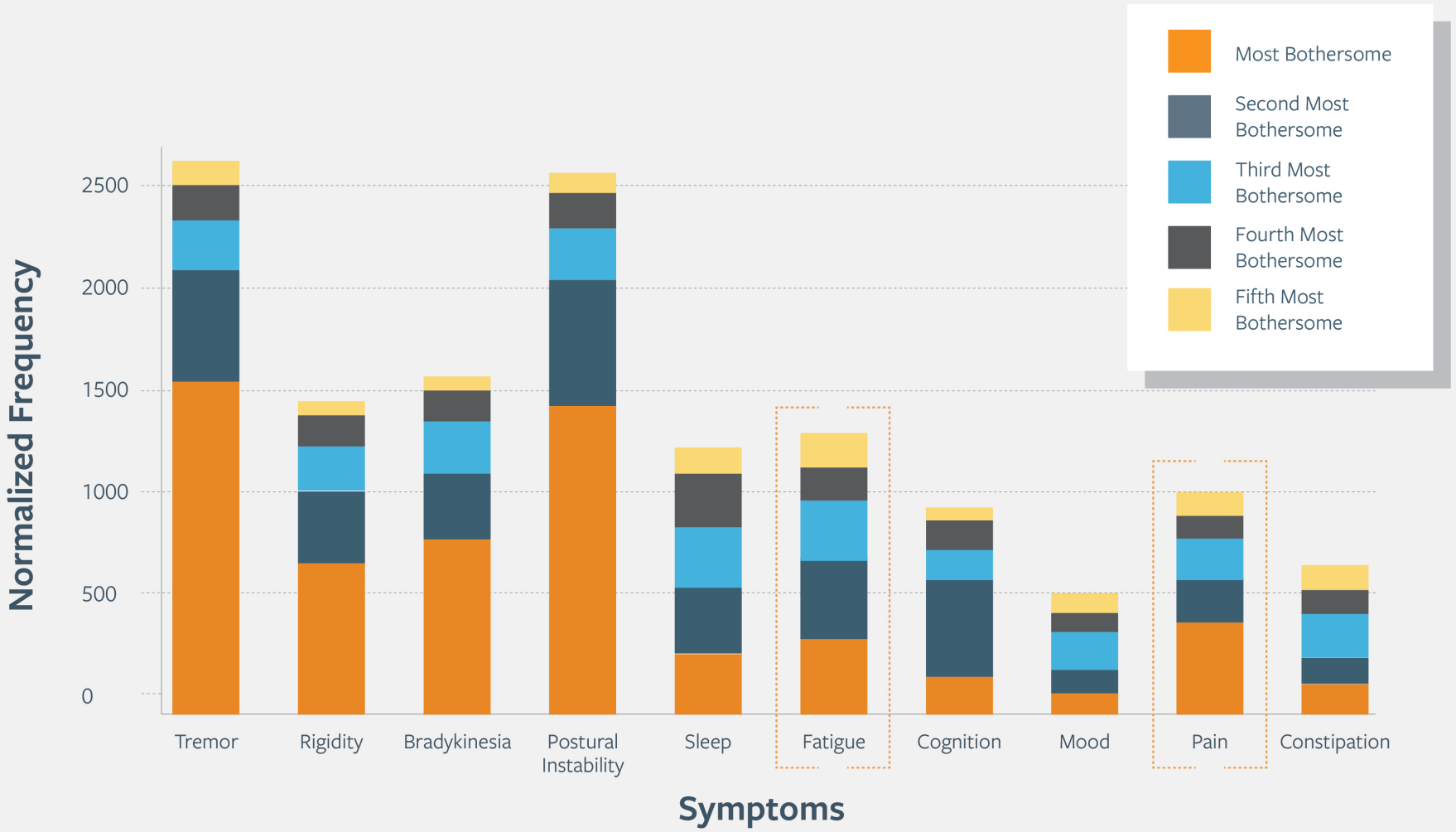
Welcome to Fox DEN:
Data Exploration Network
A Fox Insight research tool
Fox DEN provides investigators with a tool to explore, download and apply statistical models on aggregated data collected for the Fox Insight online clinical study. The Fox Insight study collects patient-reported outcomes and genetic data from people with Parkinson's disease and their loved ones.
Log In
Register
Not a researcher? Click here for Participant Page >
Explore and Download
Define Cohorts
Analyze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Normalized Frequency
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500
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Tremor
Rigidity
Bradykinesia
Postural Instability
Sleep
Fatigue
Cognition
Mood
Pain
Constipation
Symptoms

Parkinson's 360

A glimpse into the life of a patient

- Some individuals will live with Parkinson's disease for several decades or more
- PD can be managed, but as the disease progresses current treatments often become less effective

https://www.michaeljfox.org/parkinsons-360

Health Economics Perspective:
Burden and Unmet Need in Parkinson's Disease

Jalpa Doshi, Ph.D.

Professor of Medicine
Director, Economic Evaluations Unit, Center for Evidence-based Practice
Director, Value-based Insurance Design Initiatives, Center for Health Incentives and Behavioral Economics
Senior Fellow, Leonard Davis Institute of Health Economics

University of Pennsylvania

Economic Burden of Parkinson's Disease

Total economic burden of PD in the United States in 2017: $51.9 billion[1]

- **Direct medical costs: $25.4 billion**
- **Indirect and non-medical costs: $26.5 billion**
  - ~$20B attributable to persons with PD
  - ~$6.6B attributable to unpaid care partners
  - **Indirect costs: $14.2 billion**
    - Premature death-related future earnings loss; reduced employment; labor market productivity losses; social productivity losses in volunteer work
  - **Non-medical costs: $7.5 billion**
    - Paid daily non-medical care; home modifications; motor vehicle modification; other expenses like transportation costs
  - **Disability income: $4.8 billion**

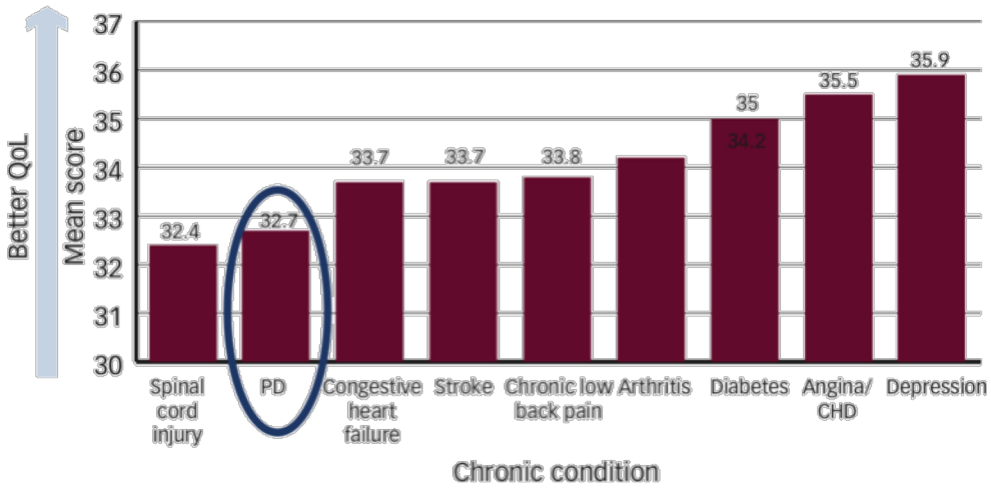
- **Disease progression and motor symptoms associated with major increase in costs among persons with PD[2,3]**

1. Yang G. Economic Burden and Future Impact of Parkinson's Disease. Lewin Group Report (2019)
2. Kaltenboeck A. Direct costs and survival of medicare beneficiaries with early and advanced Parkinson's disease. Parkinsonism and Related Disorders. 2012; 18(4):321-6.
3. Dodel RC. Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics. 2001;19(10):1013-38.

Quality of Life Burden of Parkinson's Disease

- **Parkinson's disease has a severely negative impact on the quality of life (QoL) of patients and their caregivers[1]**

- **Disease progression and motor symptoms associated with poorer QoL[1,2]**
  - 66% of persons with PD polled reported that their QoL was "directly related to or worse than expected from my motor symptoms"[3]



Gage et al. (2003) *J Neurol Neurosurg Psychiatry*

1. Stocchi F. Quality Of Life In Parkinson's Disease – Patient, Clinical And Research Perspectives. European Neurological *Review*, 2014;9(1):12–8
2. Dodel RC. Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics. 2001;19(10):1013-38.
3. Wicks P. Innovations in e-health. *Qual Life Res*. 2014;23(1):195–203.

Cost-effectiveness of Treatments for PD Motor Symptoms

Cost-effectiveness modeling studies have shown that several medication-based treatments and deep brain stimulation (DBS) surgery generally offer good value but…

Major barriers remain in the real-world setting for persons with PD to truly realize the value of these treatments

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- Medication-based treatments
  - Need to be taken on a life-long basis and require ongoing adherence and out-of-pocket costs
- DBS Surgery
  - High rates of follow-up procedures and complications in real-world setting
  - Regular monitoring and follow-up procedures required after surgery impose additional burden and potentially limit access to DBS for PD patients with lack of social support and/or lack of proximity to an expert center

Non-Adherence to Anti-Parkinsonian Medications is a Major Issue in the Real-World Setting

- **Numerous factors exacerbate medication non-adherence in Parkinson's disease[1]**
  - Drugs such as levodopa often taken 3 to 4 times daily, with advanced PD patients taking up to 6 to 10 doses per day
  - Polypharmacy is exceedingly common in PD
  - Depression and cognitive impairment, both common features of PD, are independent risk factors for non-adherence
  - Cumulative out-of-pocket costs for medications can be high and a well-known barrier to adherence

- **Adherence to high levodopa equivalent doses (LED) is very poor among advanced PD patients[2]**
  - Only 5%, 20%, and 56% of patients adherent to LEDs of >1000 mg/day, >800 mg/day, and >500 mg/day, respectively

1. Fleisher JE. Medication nonadherence in Parkinson's disease. Curr Neurol Neurosci Rep. 2013; 13(10):382.
2. Dahodwala. Medication adherence and discontinuation in a national cohort of Medicare beneficiaries with Advanced Parkinson's Disease. Neurology. 2019; 92 (15 Supplement)

DBS Associated with High Rates of Follow-up Procedures and Complications in the Real-World Setting

DBS frequently associated with additional surgical procedures:

- Real-world analysis shows that 15% of the 28,179 DBS procedures performed between 2004-2013 in Medicare patients were for revision or removal of intracranial stimulator electrodes[1]

Real-world U.S. study of veterans with PD undergoing DBS over 5 years showed[2]:

- High rates of follow-up procedures and complications
  - 59% had the electrodes and generator implanted during separate admissions
  - 52% of DBS patients had follow-up DBS procedures
  - Over 45% had complications after follow-up procedures

1. Rolston JD. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: Analysis of multiple databases. Parkinsonism Relat Disord. 2016; 33: 72–77
2. Stroupe KT. Healthcare Utilization and Costs for Patients With Parkinson's Disease After Deep Brain Stimulation. Movement Disorders Clinical Practice. 2019; 6(5): 369–378.

Key Takeaways

- **Economic and quality of life burden of PD is enormous for persons with PD and their caregivers**

- **Large unmet medical need exists to better manage motor symptoms as PD progresses:**
  - High rates of non-adherence to high dose anti-Parkinsonian medications and high rates of DBS follow-up procedures and complications
  - Regular monitoring and programming required after DBS surgery potentially limit access to many PD patients

---

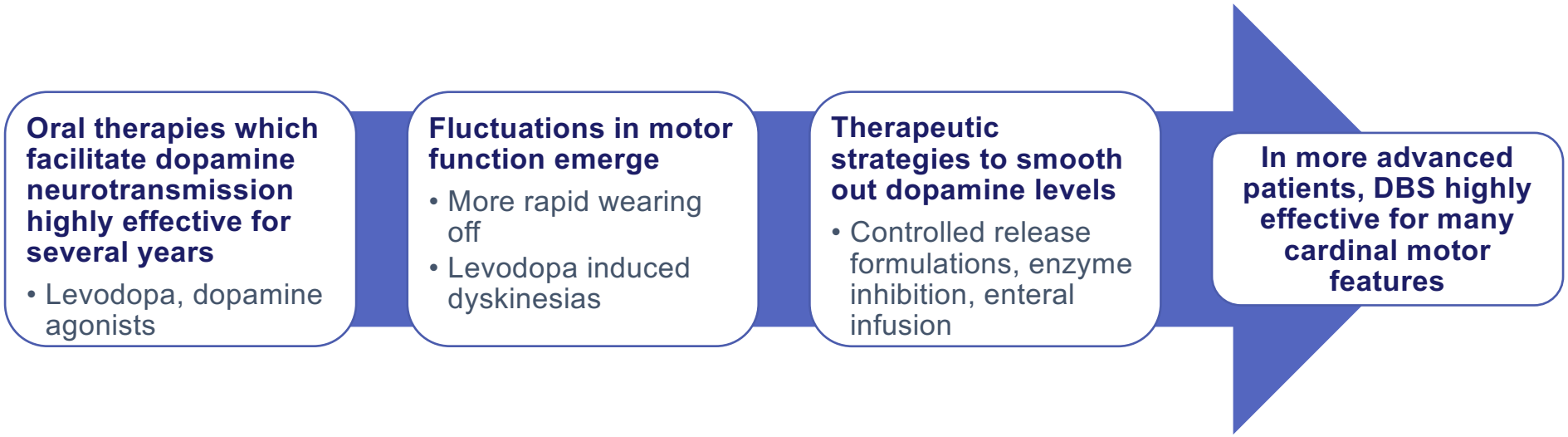
New therapeutic options that reduce these burdens and address unmet needs of patients have the potential to offer high value to persons with PD, their caregivers, payers, and society

AAV-GAD Gene Therapy for the Treatment of Parkinson's Disease

Matthew During, M.D. Ph.D.
Head of R&D

MeiraGTx

Rationale to Go Beyond a Dopamine Strategy When Levodopa and Equivalents Fail



Physiological dopamine release in the putamen is synaptic and regulated

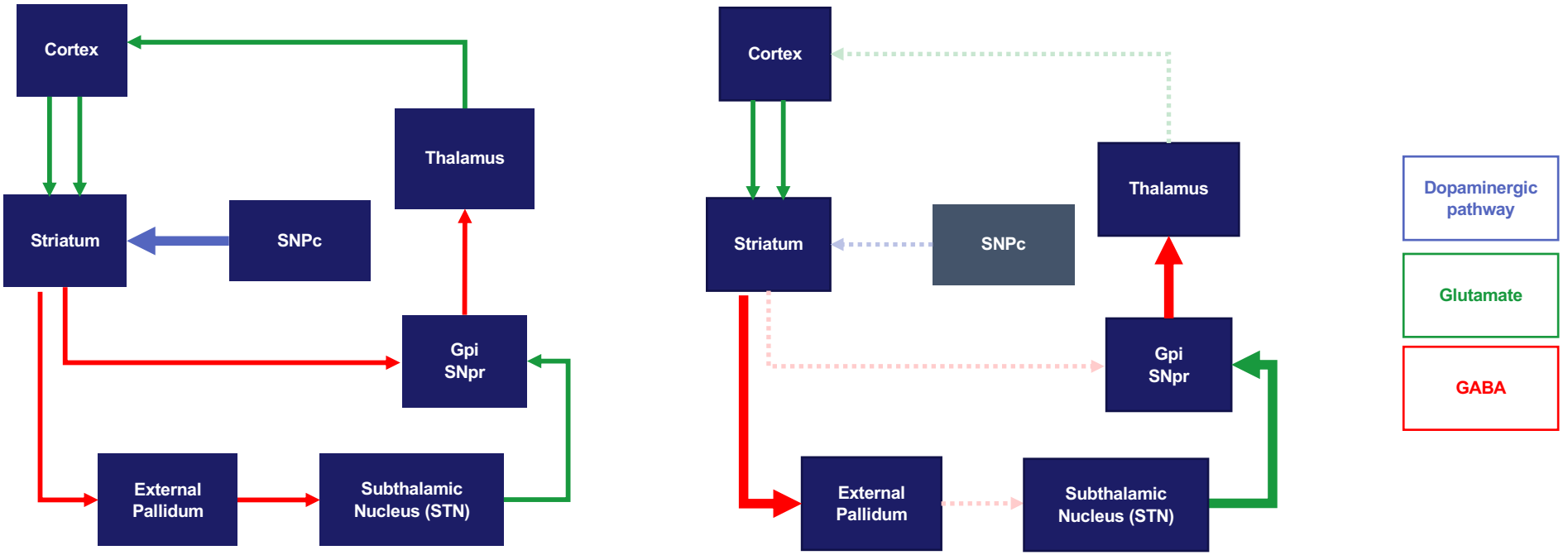
- Dopamine neurons show tonic and burst firing
- Dopamine from cell transplants or dopamine synthetic enzyme gene transfer leads to non-physiological release
- Biological strategies to directly deliver dopamine into the putamen/caudate have been unsuccessful in past blinded controlled studies
  - Severe, disabling and difficult to treat dyskinesias have resulted from such approaches
- Pharmacological treatment with levodopa and DA agonists leads to changes in receptor function which make a dopamine strategy as the disease advances challenging

History of Blinded Surgical Trials in Parkinson's Disease Suggests Need for an Alternative Approach

2001	Randomized, double-blind study of putaminal fetal cell transplantation fails to meet primary endpoint
2003	Second randomized, blinded fetal cell transplantation study fails
2004	Phase 2 randomized, blinded trial of intraputaminal GDNF infusion fails to meet primary endpoint
2008	Phase 2b randomized, blinded trial of Spheramine (retinal pigment epithelial cells) transplantation fails to meet primary endpoint
2008	Phase 2 randomized, blinded trial of CERE-120 (AAV-neurturin) fails to demonstrate any appreciable difference between groups
2013	Phase 2B randomized, blinded trial of CERE-120 (delivered both intra-putamen and intra-nigral) fails to meet primary endpoint
2019	Randomized, blinded trial of intraputaminal GDNF using CED showed no difference with sham during 9 month blind and no difference between 9 & 18 months in open-label extension despite increased F-dopa on PET

Activation of STN in Parkinson's Disease

- Dysregulation of basal ganglia signaling in PD with substantia nigra pars compacta (SNPc) degeneration
- Reduced GABA inhibitory input results in persistent activation of the STN
- The STN acts through the major basal ganglia output nuclei to put a brake on the thalamus
- AAV-GAD to the STN relieves this brake, enabling restoration of thalamic and cortical activity to improve motor function



Autoregulatory Control of Basal Ganglia Output to Restore Motor Function

Strategy: bypass dopamine, act directly downstream with an autoregulatory inhibitory gene therapy approach to the STN

- AAV mediated transfer of the inhibitory gene, GAD
- Directs transduced neurons to synthesize GABA
  - Increase intracellular levels of GABA in the STN

Restore basal ganglia output to the thalamus and cortex

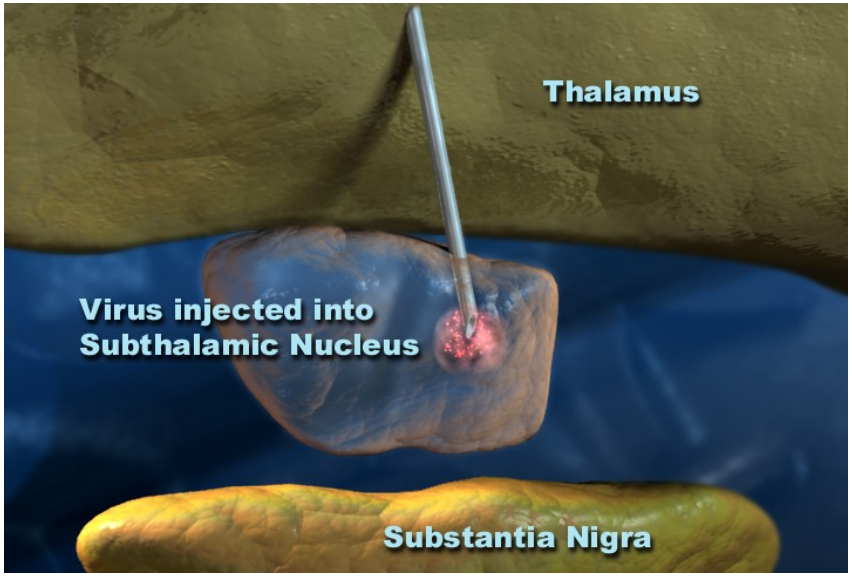
- Upon increased neuronal firing, GABA released and acts postsynaptically to dampen hyperexcitability
- Neurons expressing GAD transgene contain $GABA_A$ autoreceptors
  - GABA release inhibited by increase in extracellular GABA leading to negative feedback and autoregulation

Luo J. Subthalamic GAD Gene Therapy in a Parkinson's Disease Rat Model. Science. 2002; 298:425-429.

Strategy for Functional Improvement

Bypass dopamine, improve STN output

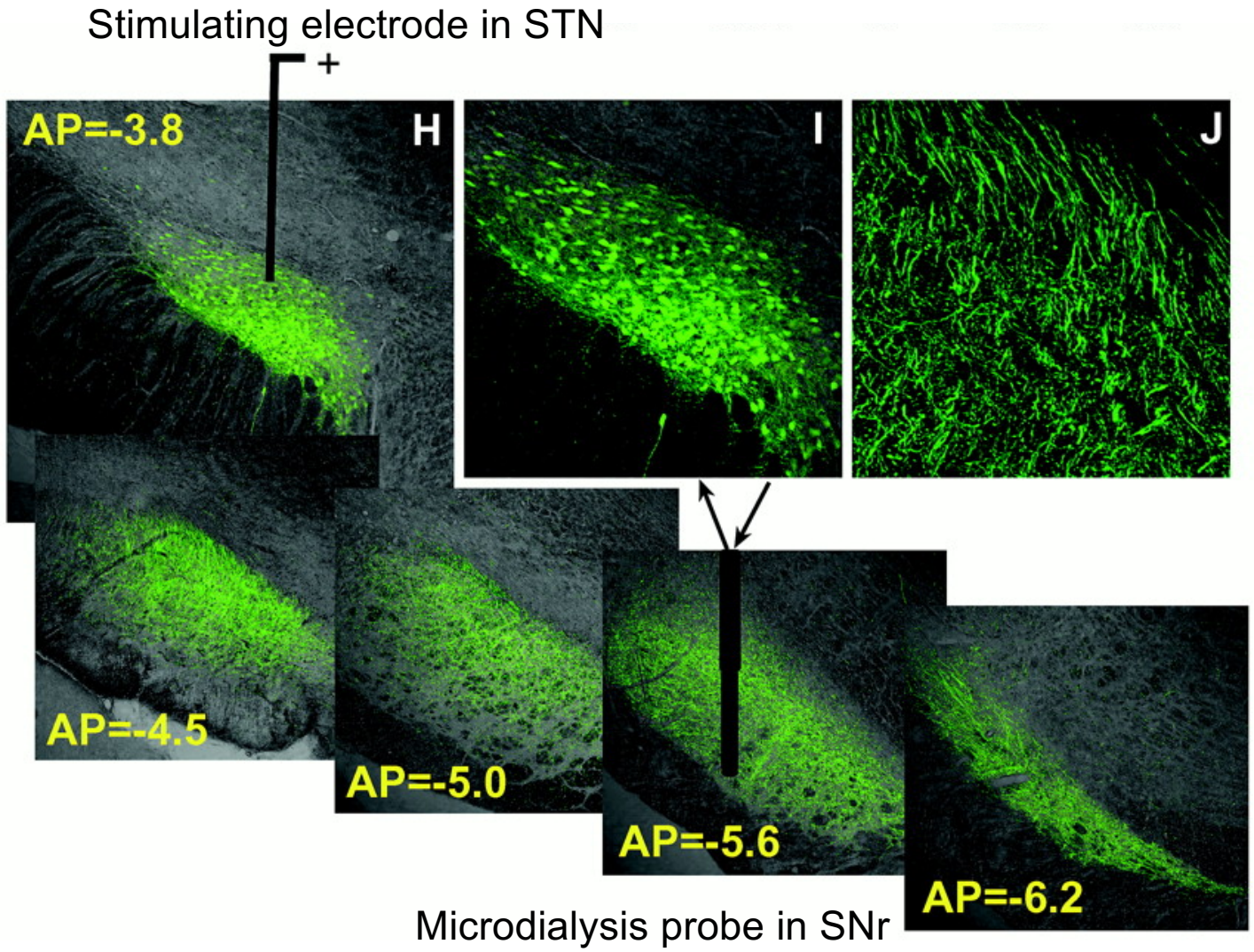
- GAD is the rate-limiting enzyme in synthesis of GABA
- $GABA_A$ agonist (muscimol) direct infusion into STN of the human Parkinsonian brain reduces firing and improves core PD symptoms[1]
- STN DBS is the most effective therapy for advanced PD but is severely underutilized due to complications of hardware, adverse off-target effects of stimulation and complicated, lengthy programming requirements
- STN AAV-GAD improves motor function and normalizes motor circuits in rodent and primate PD models[2,3]



Deliver GAD (glutamic acid decarboxylase) gene to STN to increase production of GABA locally only where increased GABA is desired

1. Levy R. Lidocaine and muscimol microinjections in subthalamic nucleus reverse parkinsonian symptoms. Brain . 2001; 124:2105-2118.
2. Luo J. Subthalamic GAD Gene Therapy in a Parkinson's Disease Rat Model. Science. 2002; 298:425-429.
3. Emborg ME. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J Cereb Blood Flow Metab. 2007; 27:501-509

Effect of STN AAV-GAD on SNr GABA release



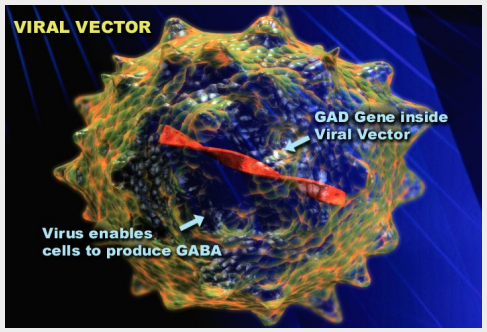
Luo J. Subthalamic GAD Gene Therapy in a Parkinson's Disease Rat Model. Science. 2002; 298:425-429.

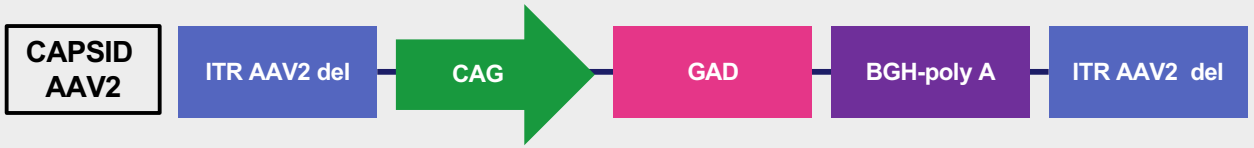
AAV-GAD for Parkinson's Disease

AAV-GAD gene therapy rebalances excitation and inhibition in key nuclei

Glutamic Acid Decarboxylase converts glutamate (excitatory neurotransmitter) into GABA (inhibitory neurotransmitter)

- Delivered directly into the STN, bypassing circuitry disrupted by dopamine loss
- AAV-GAD converts some STN neurons to inhibitory phenotype
  - Reduces abnormal STN activity
  - Restores GABAergic transmission to multiple key basal ganglia structures
  - Restores normal basal ganglia outflow to the motor cortex



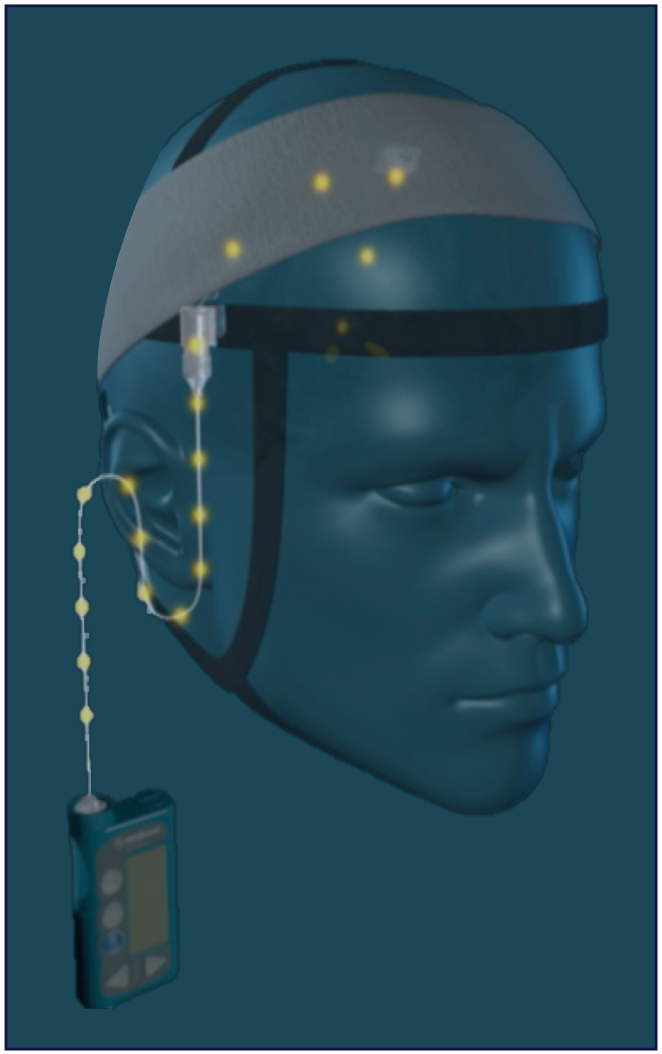


Technology Platform Overview

Simpler and safer alternative to current surgical methods (standard of care)

- ✓ Under local anesthesia
- ✓ Novel catheter infusion system permits bedside infusion and bedside removal out of operating room
- ✓ No hardware left behind
- ✓ Minimal hospital stay

MeiraGTx has rights to infusion system



AAV-GAD Background and Rationale

	AAV-GAD	DBS	Dopaminergic Gene Therapy	Growth Factor Gene Therapy
Brain target based upon effective surgical therapies	✓	✓	✗	✗
Standard surgical technique easily adopted with minimal training	✓	✓	✗	✗
Brief operative time (reduce cost, improve turnover for surgeons)	✓	✗	✗	✗
No need for further specialized follow-up (anyone can refer)	✓	✗	✓	✓
No implanted hardware (no hardware-related risks)	✓	✗	✓	✓
No need for general anesthesia	✓	✗	✗	✗
Potential for autoregulation based upon circuit activity	✓	✗	✗	✗
Potential for disease modification alone or with dual gene therapy	✓	✗	✗	✓

AAV-GAD Target Patient Population

Moderate to advanced idiopathic Parkinson's patients	Age range 25 – 90+ years	Motor fluctuations and dyskinesias despite optimal oral therapy	Contraindications: dementia, untreatable depression, major stroke
Patients not eligible for general anesthesia can still be treated	Available to patients residing in areas far from surgical centers	No indwelling hardware	No speech and cognition AEs observed in clinical trials to date

Differentiation vs. DBS

Clinical Development of AAV-GAD

Michael Kaplitt, M.D. Ph.D.

Professor of Neurological Surgery
Vice Chair for Research, Department of Neurological Surgery

Weill Cornell Medical College

SAB Member, MeiraGTx

Taking AAV-GAD into the Clinic: Surgical Procedure

Subthalamic Nucleus

- Most popular DBS target worldwide
- Well established methods for identification and targeting in routine clinical practice
- Small structure (4x4x5mm) easily covered by small volume of AAV-GAD

Catheter Placement

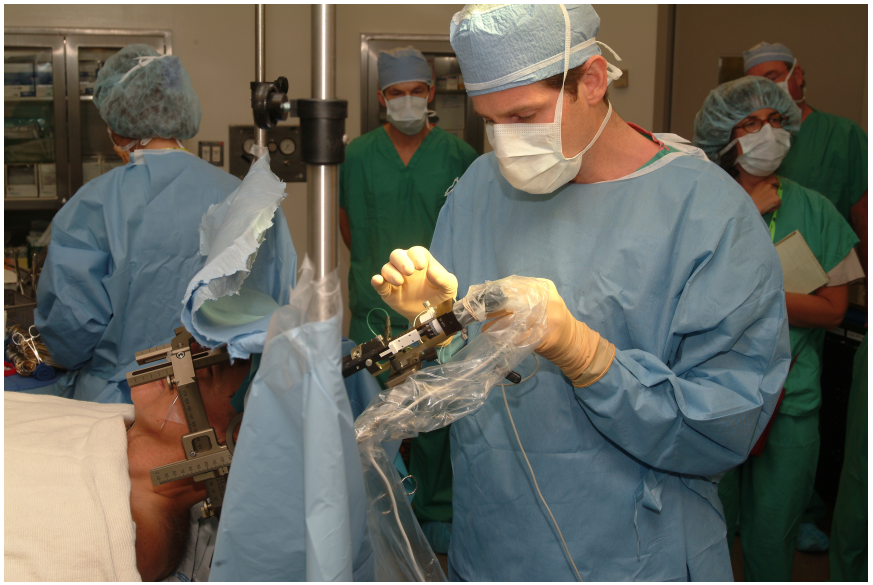
- Catheter insertion nearly identical to STN DBS
  - Any practitioner currently inserting STN DBS capable of performing AAV-GAD surgery with minimal training
- Standard surgical equipment, no need for intraoperative imaging

Surgical Procedure

- Brief operative time (2 hours for bilateral insertion)
- Infusion performed in recovery
- Catheter removed at bedside; no need to return to OR

Phase 1 Study of AAV-GAD STN Gene Therapy

- ✓ Unilateral STN AAV-GAD was safe and well tolerated
- ✓ No evidence of induction immune response or effect on outcome of pre-immunity in two patients
- ✓ Significant improvement in both “off” and “on” UPDRS largely limited to hemibody opposite treated hemisphere
- ✓ Effects seen starting at 3 months (trend at 1 month) and stable to one year
- ✓ No decline in neuropsych scores or other non-motor parameters

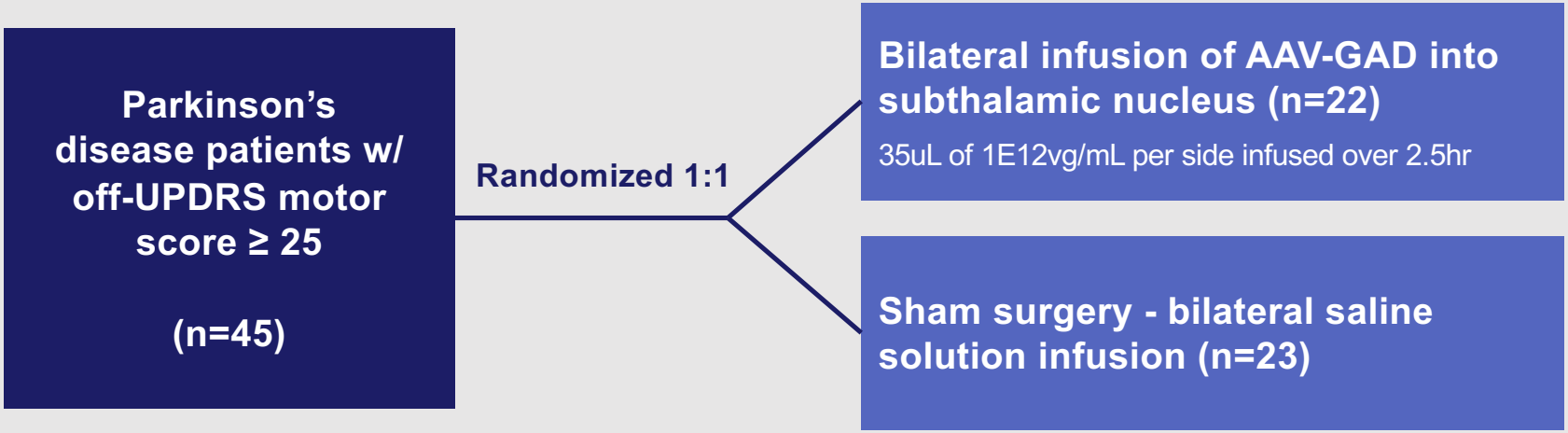


Articles

Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial

Kaplitt MG. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007;369:2097-2105

Randomized, Double-Blind, Sham-Surgery Controlled Phase 2 Trial of AAV-GAD



LeWitt PA. AAV2-GAD gene therapy for advanced Parkinson's Disease: a double-blind, sham-surgery controlled, randomized trial. *Lancet Neurology.* 2011; 10(4):309-19.

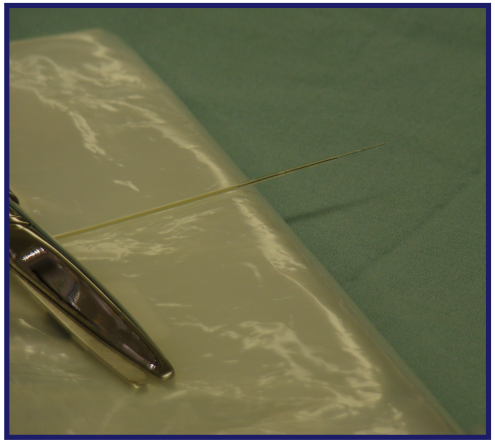
Study Design Detail

Patients selected by both clinical criteria and FDG-PET

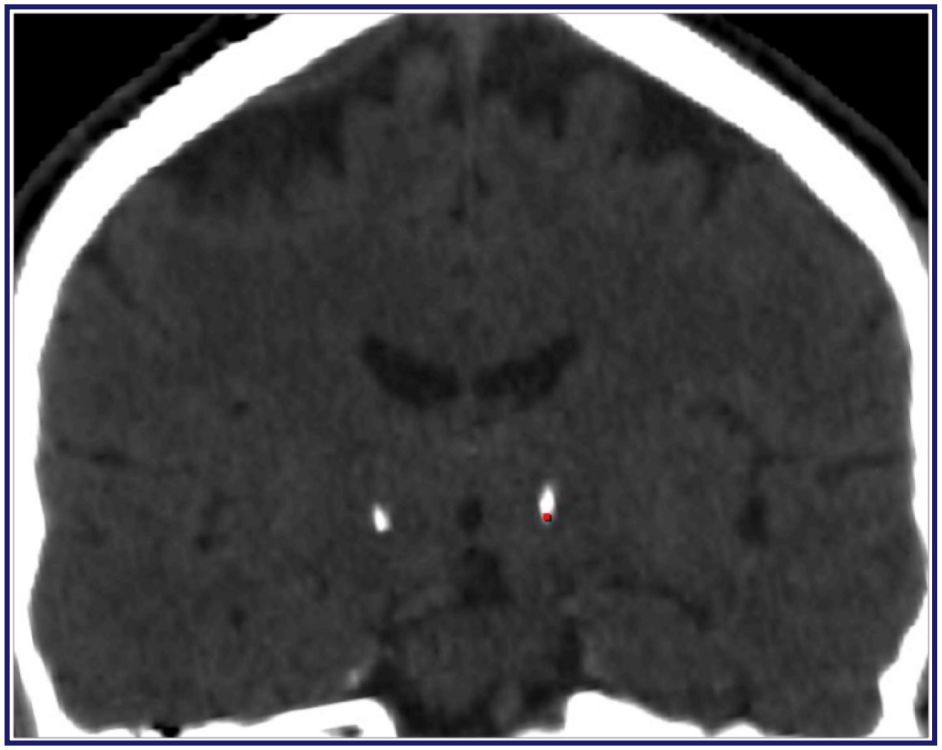
AAV-GAD	• Frame; Standard awake MER (microelectrode recording) mapping • Bilateral STN infusion of 3.5x1010vg/STN in 35 µl of buffer
Sham	• Frame; Partial-thickness burr hole; Sham awake MER mapping • Bilateral infusion of 35µl PBS into burr hole

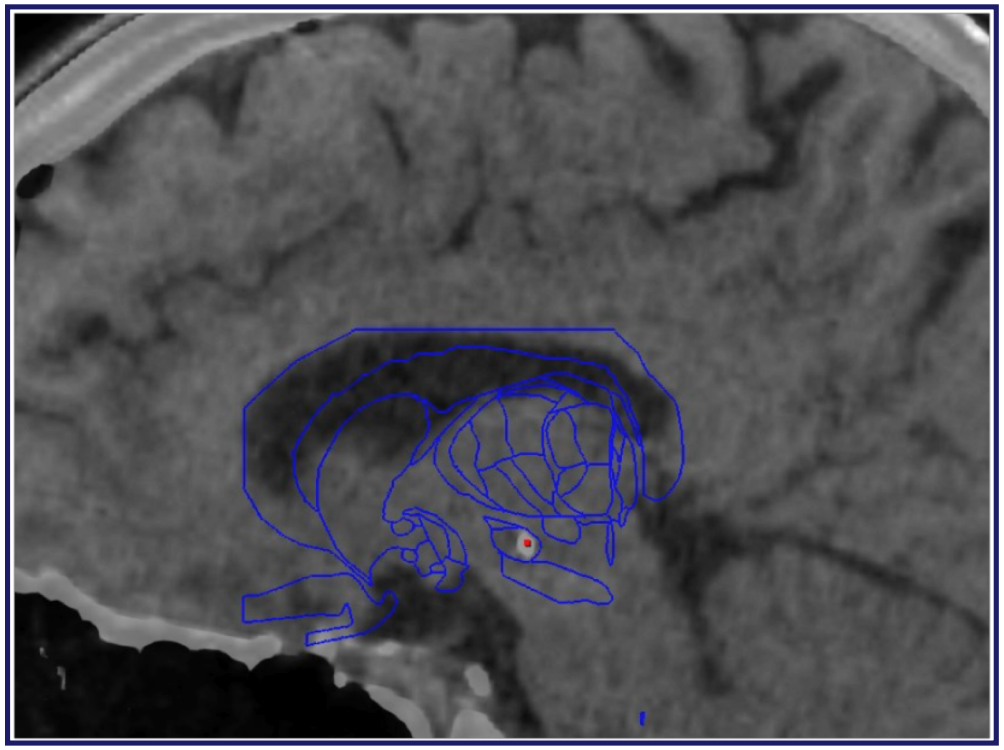
All received CT before and after catheter removal

- **Per protocol, prior to breaking blind, efficacy analysis group excluded data from patients with catheter tips outside the pre-defined target zone and/or infusion failures (prior to breaking blind, per protocol)**
  - Final number for efficacy analysis group: AAV-GAD=16 (exclusions from 22 randomized include: mistargeting 2, infusion failure 1, both 3), Sham=21 (exclusions from 23 randomized include infusion failure in 2)
- **Following completion of randomized study, design flaw in locking mechanism found to be cause of catheter failures**
  - Simple fix completed and tested in sham crossover subjects with no device failures in 14 bilateral treatments (28 catheter insertions/infusions)



Blinded Catheter Tip Localization





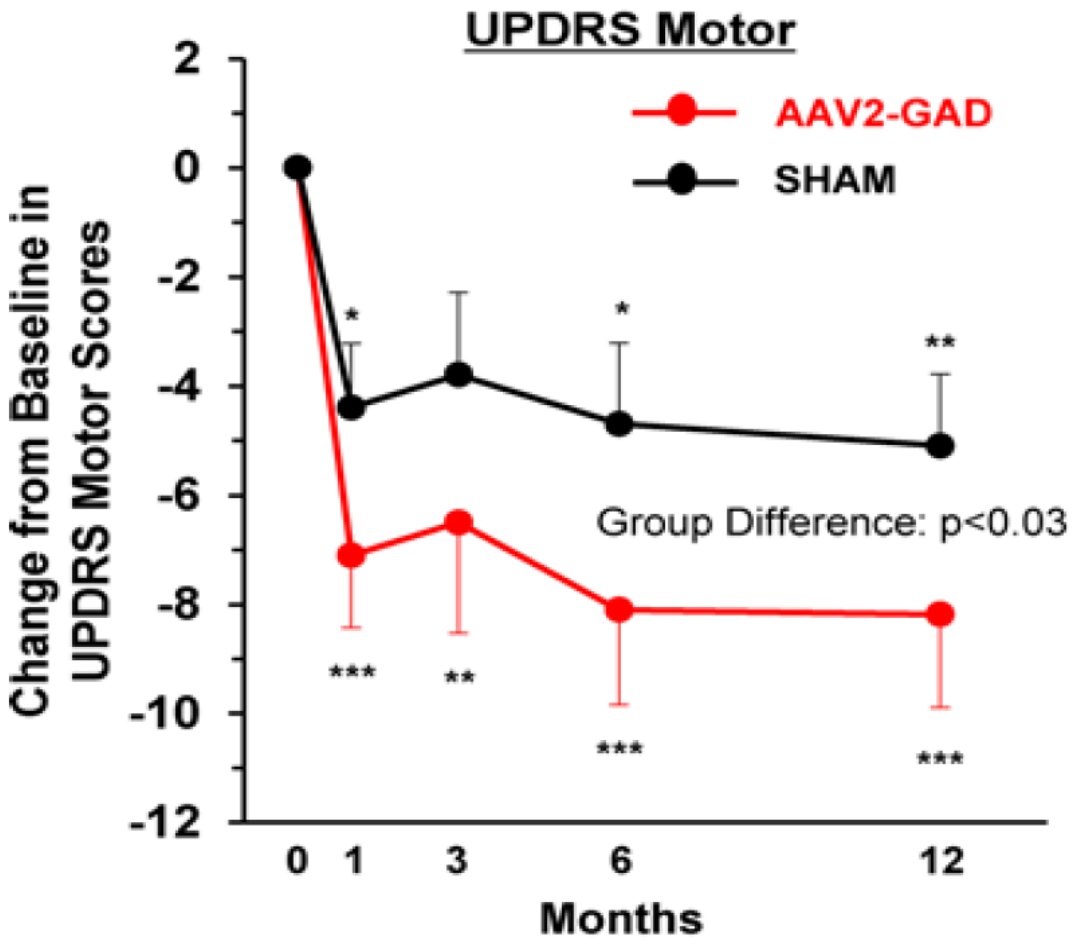
Target Area Relative to Mid-Commissural Point (MCP):

- X=9-14mm lateral Y=2mm anterior-5mm posterior Z=1mm dorsal-7mm ventral

Standard DBS tip coordinates in postero-ventral STN:

- X=12mm lateral Y=3.5mm posterior Z=4mm ventral

Primary Outcome Measure: Change in UPDRS Part 3 (Motor Score)

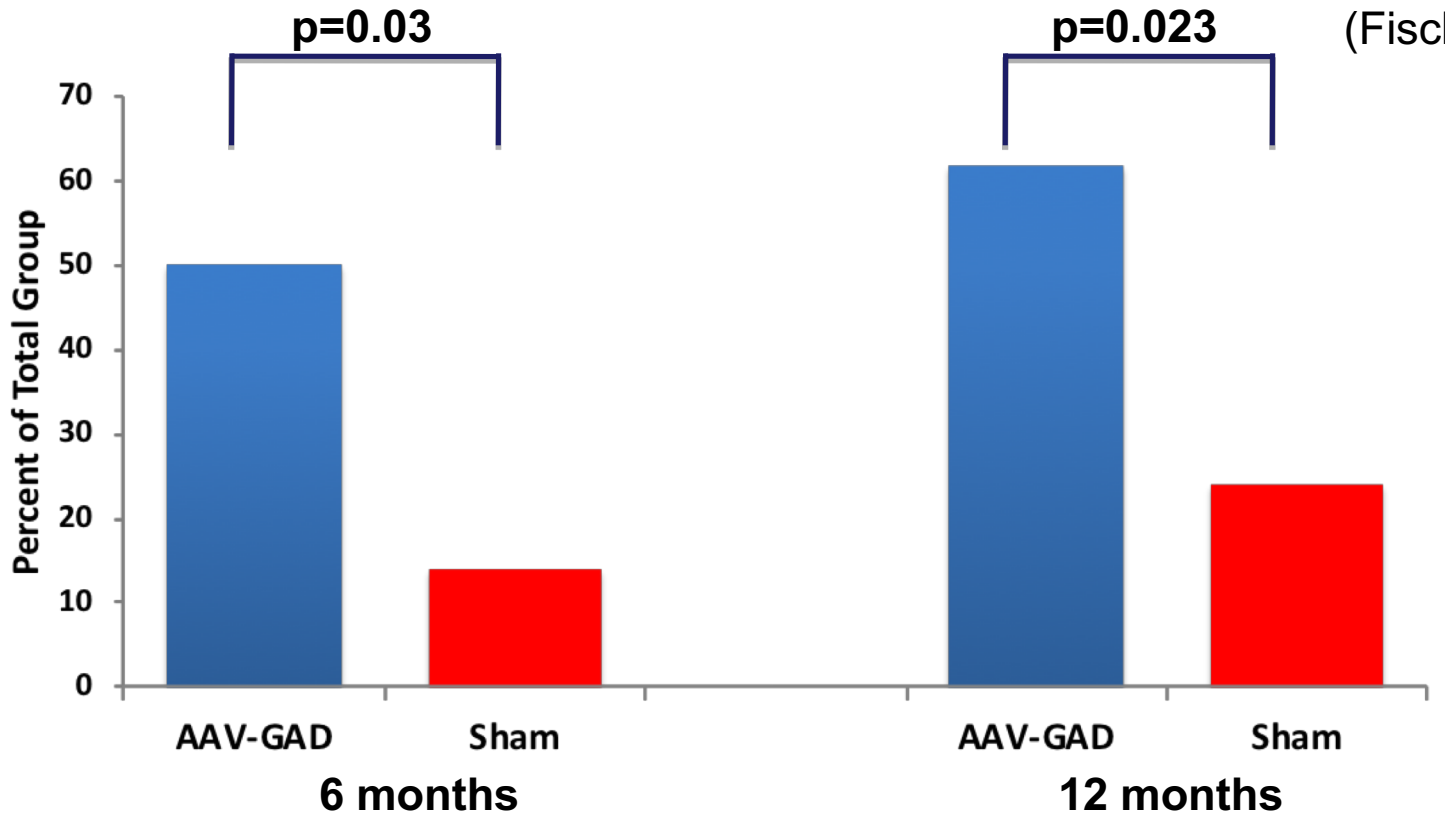


Greater improvements observed in the AAV-*GAD* treatment group over all follow-up time points

Group effect: $p < 0.03$; 2 × 5 RMANOVA; *$p < 0.05$, **$P < 0.01$, ***$p < 0.001$, post-hoc Bonferroni tests relative to baseline

Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133

UPDRS Part 3 Clinically Meaningful Responder Rate



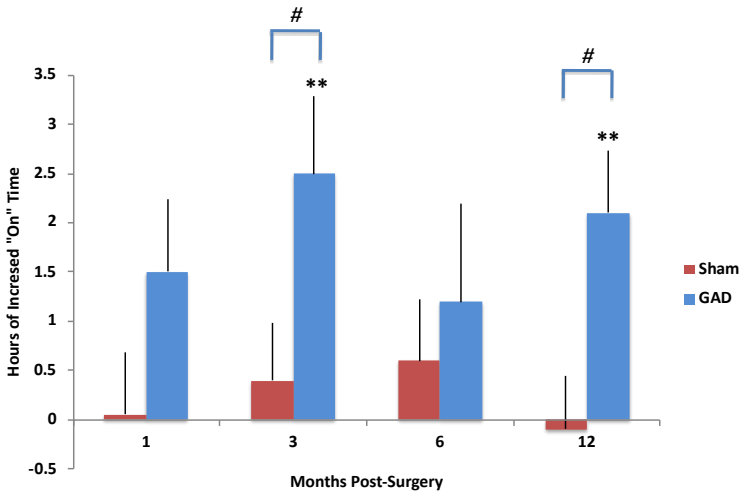
Clinically meaningful response[1]

- ≥9 point reduction in UPDRS Part 3 "off" scores
- Approximately 25% improvement in UPDRS Part 3 "off" scores
- Well above moderate clinically important difference (4.5-6.7 points) and close to large clinically important difference (10.7-10.8 points)[2]

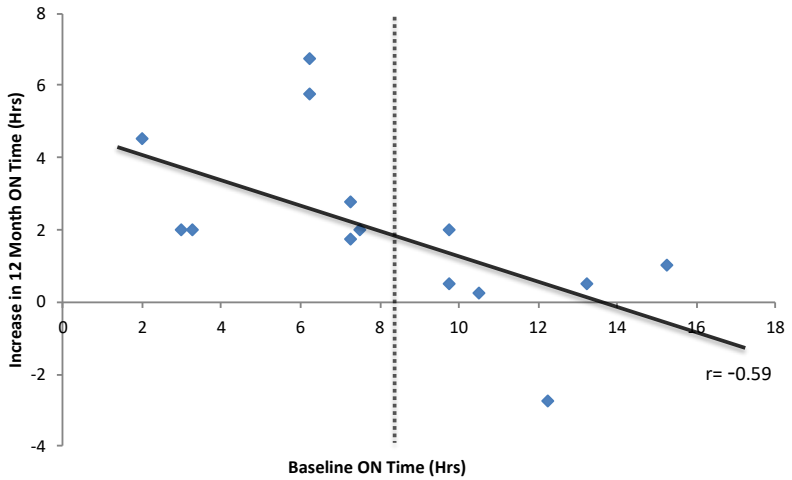
1. Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133
2. Shulman LM. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol. 2010; 67(1):64-70

Increased ON Time Without Dyskinesia

A. Increased ON time w/o dyskinesias following AAV-GAD

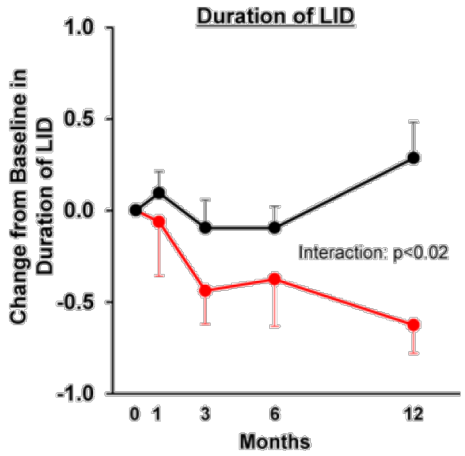


B. Correlation between lower baseline ON time (worse) & increased ON time w/o dyskinesias 12 mo after AAV-GAD



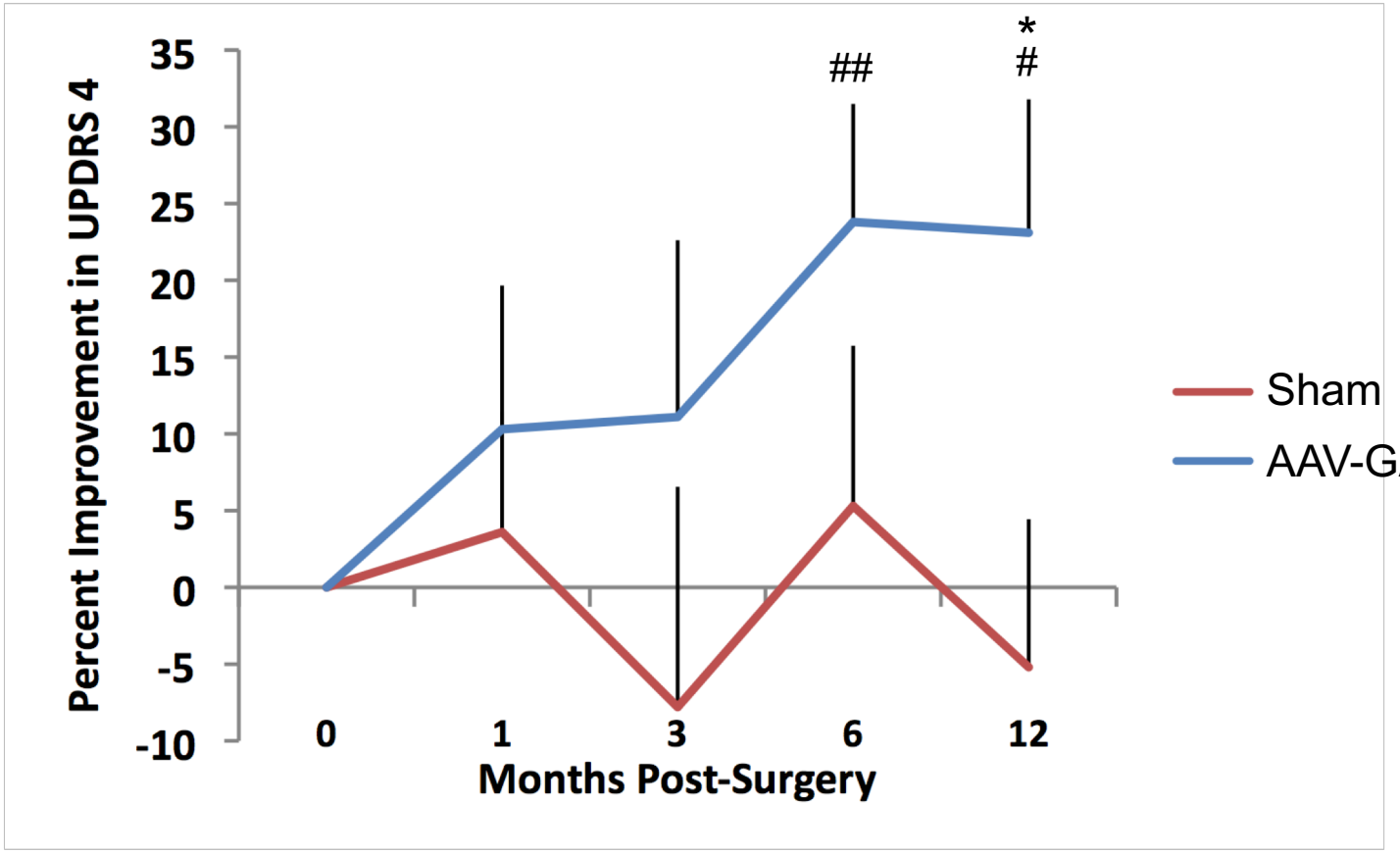
Overall change in ON time GAD vs. sham p=0.044 (ANOVA)

C. Reduction in dyskinesia duration following AAV-GAD



Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133

Improvement in Medication Complications (UPDRS Part 4) Following AAV-GAD

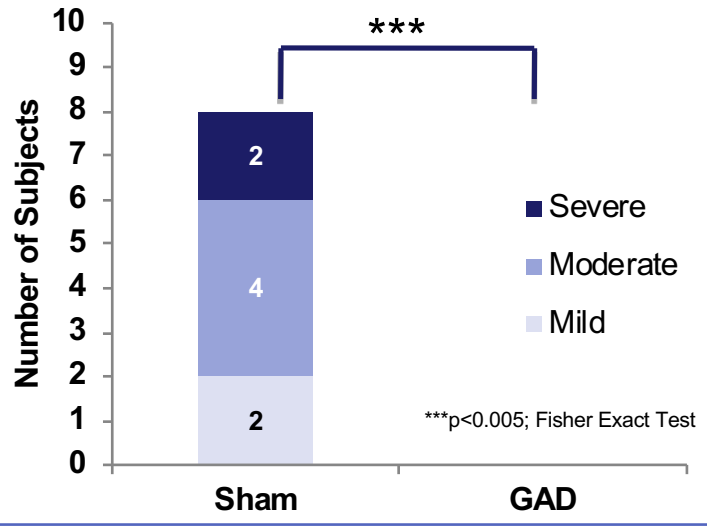


UPDRS Part 4 is a composite score of dyskinesias, on/off fluctuations, dystonia, insomnia and other complications

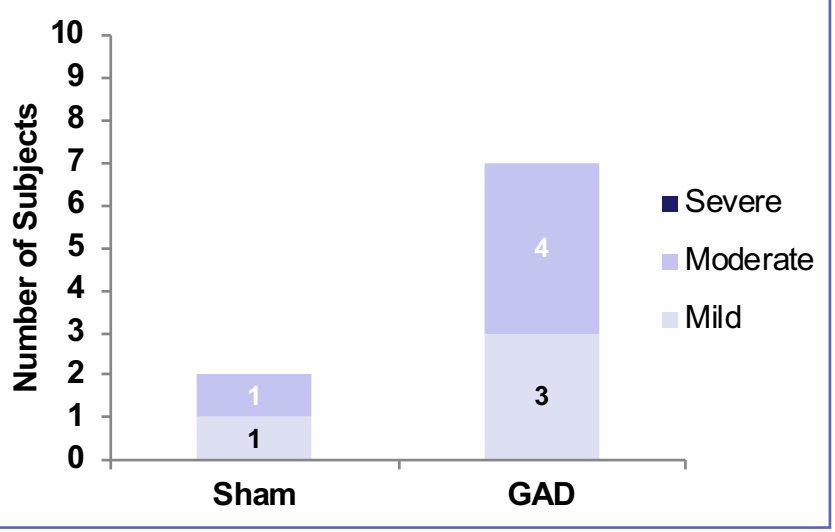
*p<0.05 vs. sham (t-test)
#p<0.05 vs. baseline (t-test)
##p<0.01 vs. baseline (t-test)

Adverse Events Over 12 Months (20% or Greater Frequency)

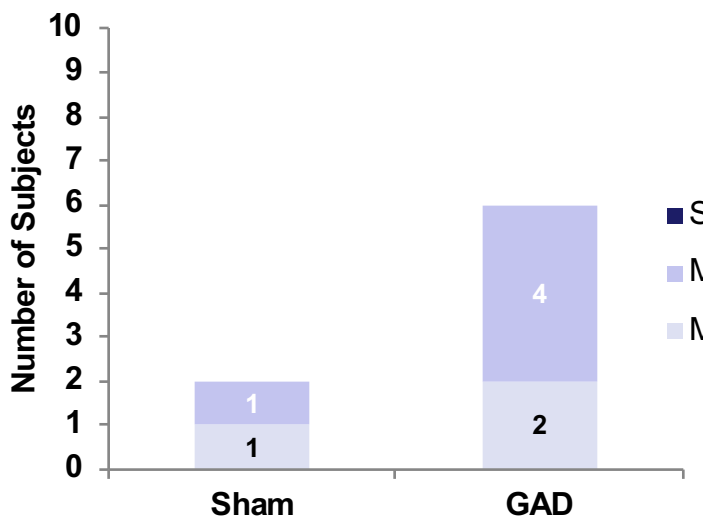
Worsening of Parkinson's Disease



Headache



Nausea



Serious Adverse Events*
(Number of Subjects)

	Sham	GAD
Intestinal obstruction		1
Accidental drug overdose		1
Prostatitis		1
Delusion, Hallucination Parkinson's Disease worse	1	

*All SAEs occurred 4-12 months post-surgery and all resolved

AAV-GAD was Well Tolerated and Achieved Primary Endpoint

Phase 2 randomized, double-blind multi-center trial

- ✓ Met primary outcome measure - UPDRS 3 improvement vs. sham at 6 months
- ✓ Significantly greater responder rate in treated compared with sham
- ✓ Secondary outcome measures also improved including ON time across one year (no change in shams at any time point)
- ✓ Significant reduction in medication complications at 6 and 12 months (UPDRS 4) with no change in sham at any point
- ✓ No adverse events related to the gene therapy
- ✓ **No difference in neuropsychological, speech and depression ratings**


Articles

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

JCI insight

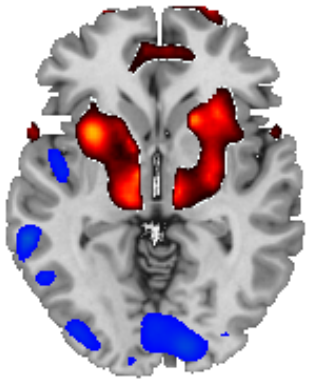
CLINICAL MEDICINE

Long-term follow-up of a randomized AAV2-*GAD* gene therapy trial for Parkinson's disease

FDG-PET Analyses

Fluorodeoxyglucose positron emission tomography (FDG-PET)

- **Neurons metabolize glucose proportionate to their level of activity**

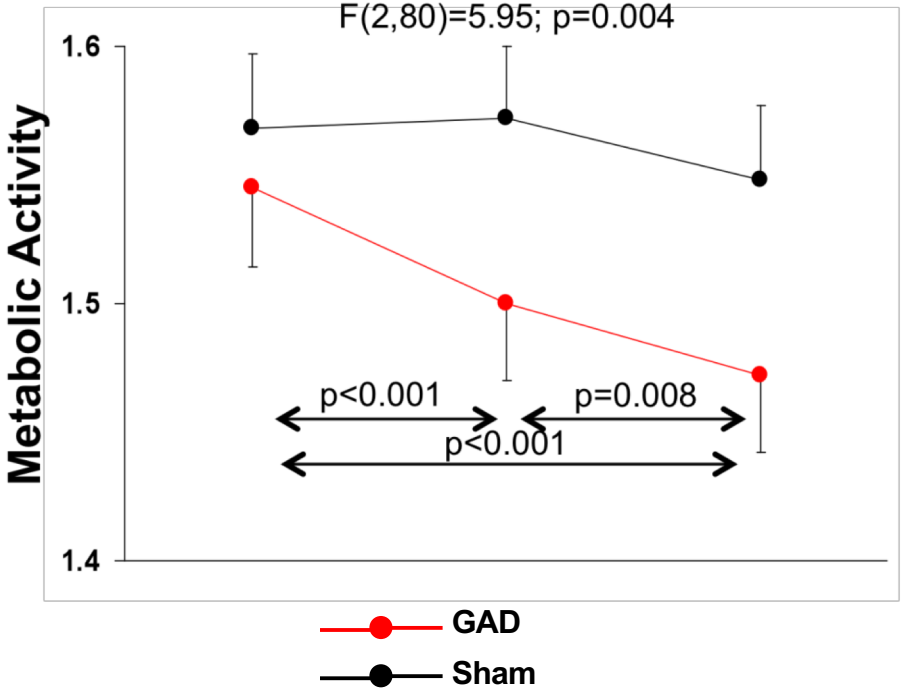


- **FDG-PET measures regional metabolism of radioactive glucose to determine changes in activity**
  - Most mitochondria are in axons projecting into a brain region so FDG-PET mostly reflects changes in afferent projections into a brain region

- **FDG-PET can be utilized to evaluate brain physiology in multiple ways:**
  - Measure changes in specific brain regions of interest
  - Determine interactions between brain regions during disease progression
  - Determine interactions between brain regions as a biomarker of response to therapy

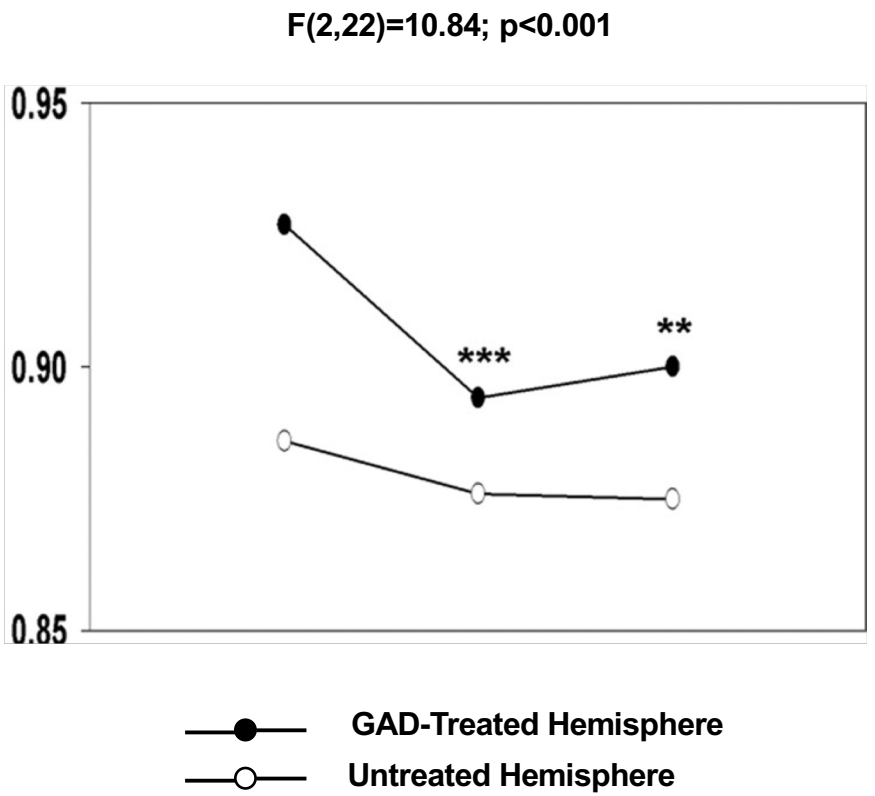
Improvement in Thalamic Metabolism by FDG PET

Phase 2



Niethammer M. Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease. JCI Insight. 2017; 2(7):e90133

Phase 1



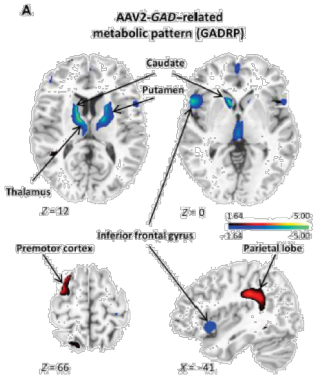
**p<0.005 relative to baseline

***p<0.001 relative to baseline

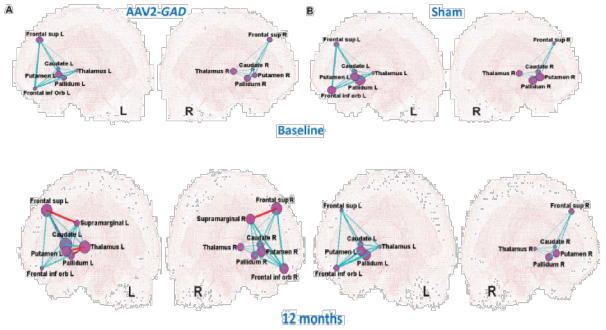
Feigin A. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. Proc Natl Acad Sci U S A. 2007; 104(49): 19559–19564.

Functional Imaging – GAD Related Pattern (GADRP)

- **AAV-GAD recipients developed unique treatment-dependent polysynaptic brain circuit (GAD related pattern, GADRP)**
- **Statistically significant correlation between improvement in UPDRS motor ratings and GADRP expression (p< 0.009)**
- **This treatment-induced brain circuit is a novel endpoint to isolate true treatment-driven responses from placebo responses**
- **AAV-GAD is the first gene or cell therapy for PD to have an objective imaging biomarker of treatment effect that was significant relative to sham surgery patients and correlated with clinical improvement**



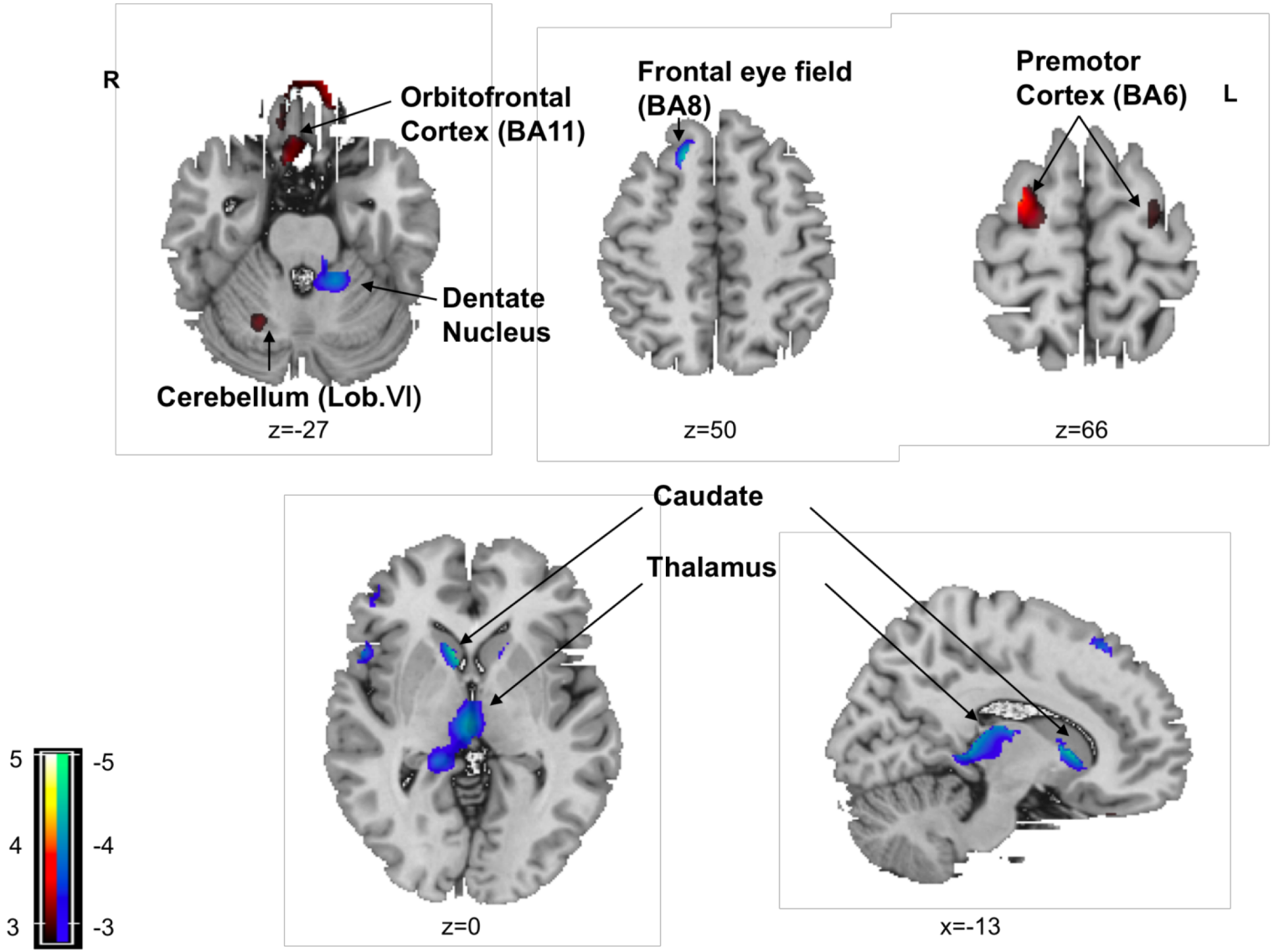
- Decreased metabolic activity in striatum and thalamus
- Increased metabolic activity in premotor cortex



- New polysynaptic pathways connecting STN to motor cortex

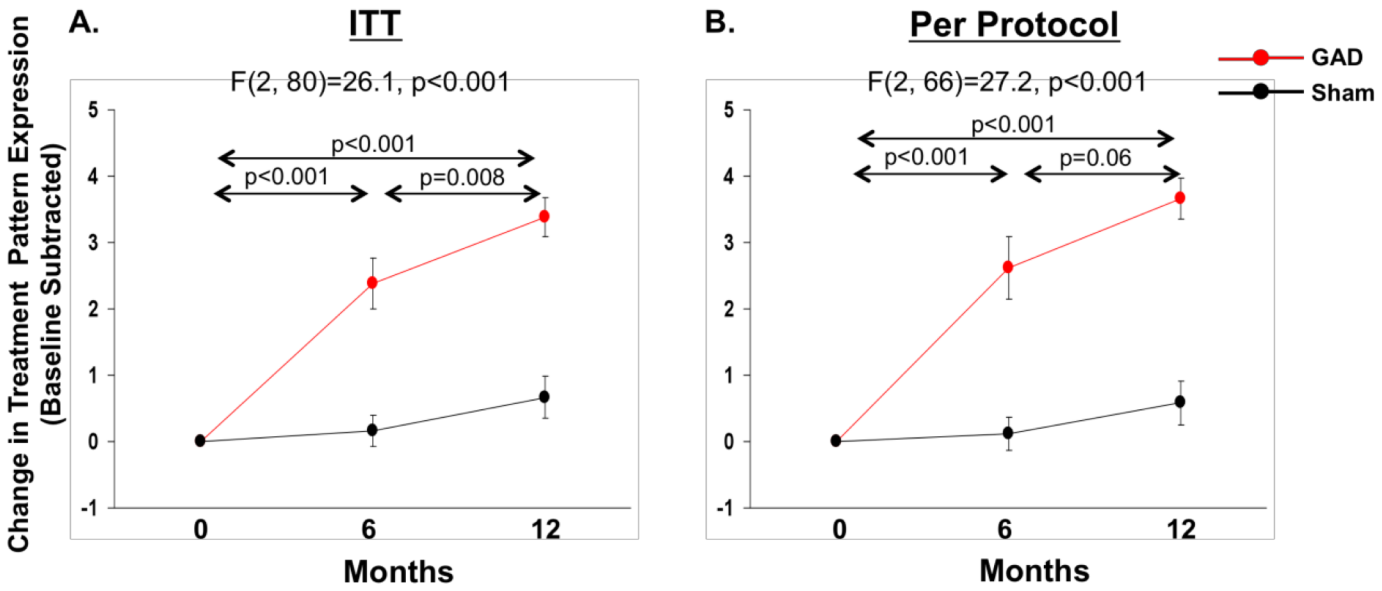
Niethammer M. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. Sci. Trans. Med. 2018; 10(469). pii: eaau0713

Identification of PET Biomarker of Activity: GADRP

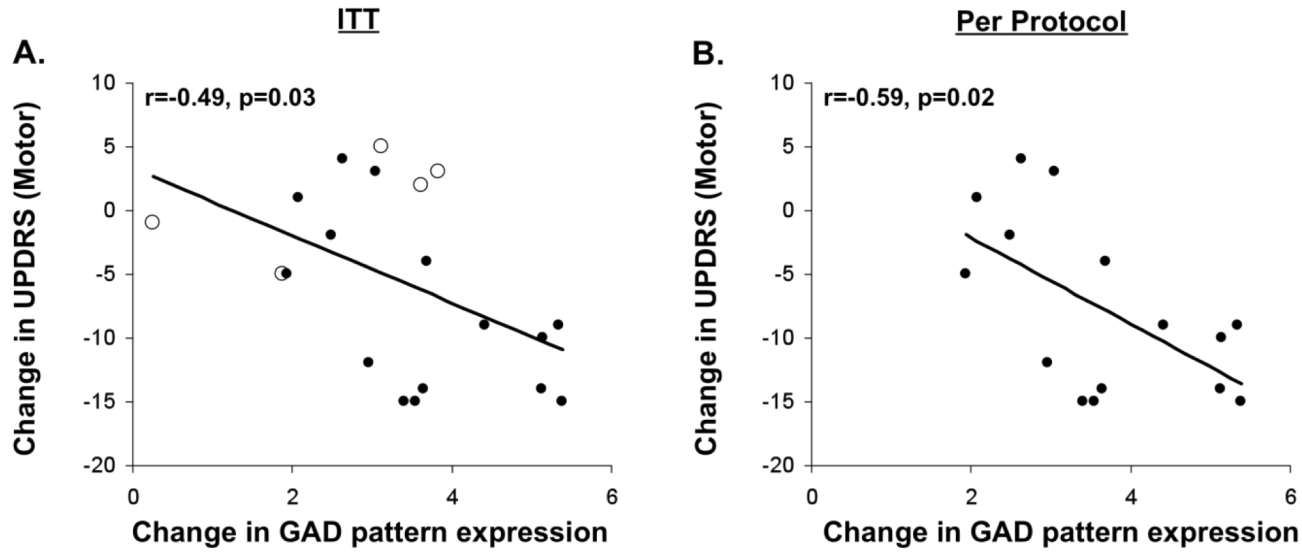


Change in Treatment Pattern Expression & UPDRS (Part 3)

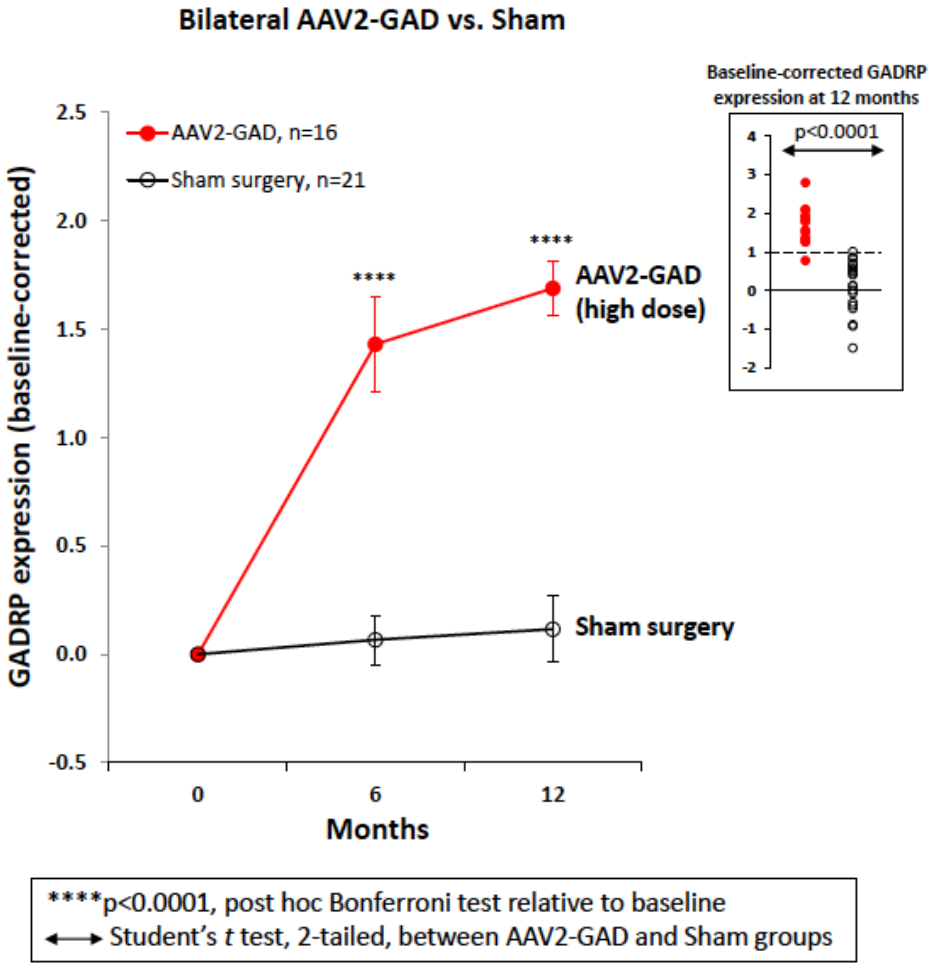
GADRP robust in per protocol and ITT in both blind and open phase

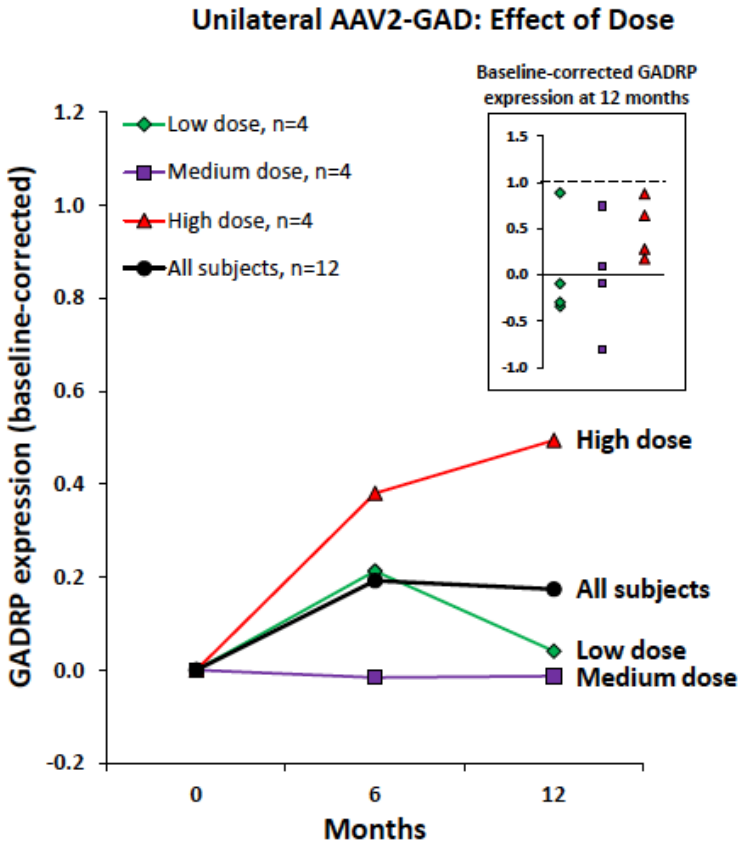


Improvement in PET treatment pattern correlates with clinical outcome



GADRP Present in Phase 1 Subjects and Most Robust at High Dose Used in Phase 2 Study





****p<0.0001, post hoc Bonferroni test relative to baseline
Student's *t* test, 2-tailed, between AAV2-GAD and Sham groups

Niethammer M. Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity. Sci. Trans. Med. 2018; 10(469). pii: eaau0713

Feigin A. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. Proc Natl Acad Sci U S A. 2007; 104(49): 19559–19564.

Kaplitt MG. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007;369:2097-2105

AAV-GAD Clinical Development

Phase 1 unilateral study

- ✓ Safe and well tolerated
- ✓ Significant improvement in UPDRS, improvements limited to hemibody opposite treated hemisphere
- ✓ No speech/cognitive AEs

Randomized, double-blind, sham surgery controlled Phase 2 bilateral study

- ✓ Met primary outcome measure – UPDRS 3 improvement vs. sham at 6 months
- ✓ Significantly greater responder rate vs. sham
- ✓ Improvements in secondary outcome measures including ON time, medication complications, dyskinesias
- ✓ No speech/cognition AEs

Summary of Key AAV-GAD Features

- ✓ **AAV-GAD is the only gene or cell therapy:**
  - To meet primary clinical efficacy endpoint in a randomized, blinded multi-center PD trial
  - With an imaging biomarker supporting efficacy which correlates with clinical outcome
  - With a routine and brief surgical procedure that requires minimal OR time, virtually no special training, no general anesthesia
- ✓ **Improvement in off-medication clinical ratings, ON time without dyskinesia and complications of medical therapy without declines in neuropsychological function or speech**
- ✓ **Consistency in clinical outcomes and imaging from phase 1 to phase 2**
- ✓ **AAV-GAD could be accessible to more patients than current standard of care**
  - Absence of retained hardware
  - No need for specialized post-op care
- ✓ **Non-dopaminergic strategy**
  - AAV-GAD potentially applicable to large patient population not adequately treated with currently available therapies

Q&A Panel

Moderator: Zandy Forbes, Ph.D.

Participants:

- Jalpa Doshi, Ph.D.
- Matthew During, M.D. Ph.D.
- Jamie Eberling, Ph.D.
- Michael Kaplitt, M.D. Ph.D.
- Ali Rezai, M.D.

Audience Q&A