Parkinson's Disease in 2023: Updates in Treatments, Research, and the Post-COVID Future.

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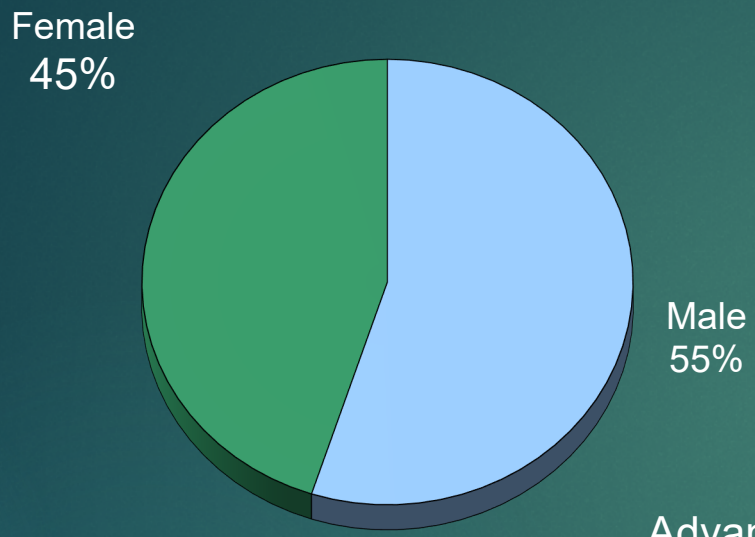
Movement Disorders and Neuromodulation Center

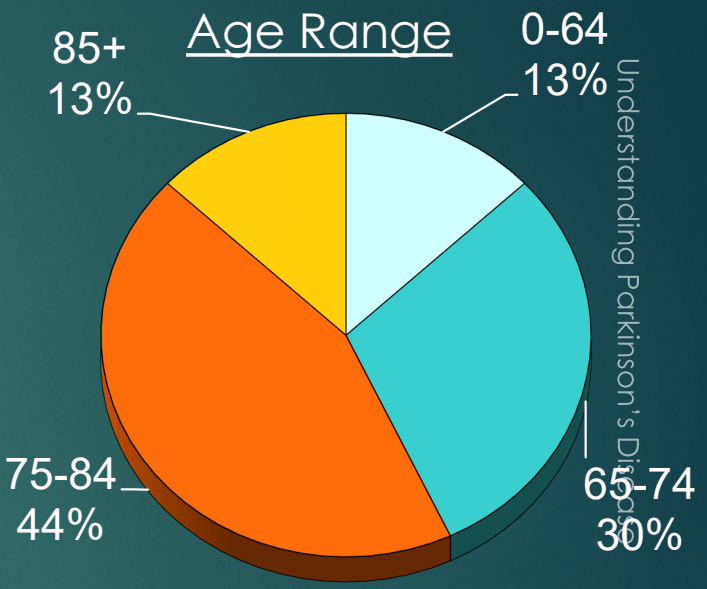
Parkinson's Foundation
CENTER OF EXCELLENCE

Parkinson's Disease Demographics

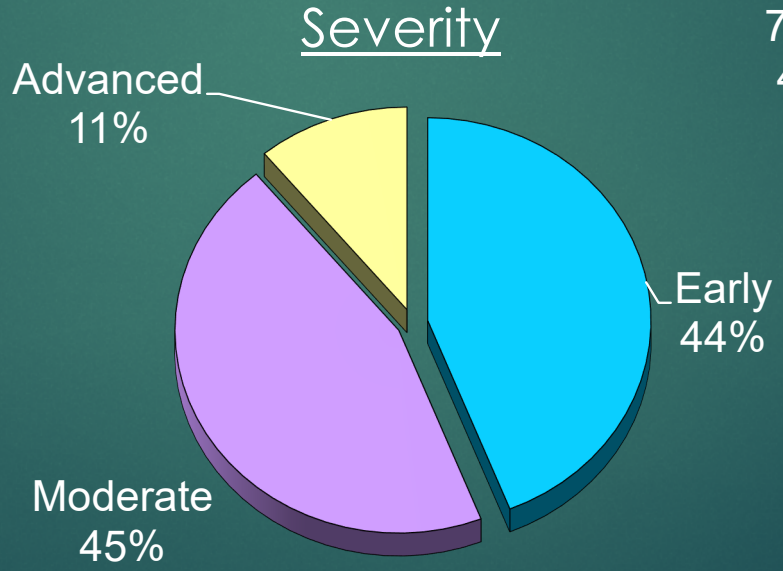
Gender



Age Range



Severity



Parkinson's Disease

Movement Disorder

- A common neurological disease affecting 2% of the population older than 60, average onset age – ~57 years old
- By age 80, 5% of general population shows signs of parkinsonism (5 people per 100)
- Parkinsonism (Stiffness, Slowness, Tremor, Gait Imbalance)
  - Non-Motor Symptoms (Autonomic, Mood, Cognitive, Pain)

10-15% of cases are familial, most cases idiopathic (unknown origin)

- Nature and Nurture: Genetics load the gun, environment pulls the trigger
  - *Hypothesis*: Certain people may have genetic susceptibility to PD, and exposed to environmental factors that trigger the disease

COVID-19 and PD

- Overall, no clear risk factor related to PD and contracting COVID or severity of infection, however:
  - PD patients had longer recovery times
  - PD patients in nursing homes may have increased likelihood of infection
  - If hospitalized with COVID, PD patients faced same hospital complication issues
  - COVID restrictions meant PD patients had to self-advocate and answer all questions when hospitalized

COVID-19 and PD

- Age, frailty, PD disease severity and cognitive impairment were associated with higher mortality in COVID*

  *Same with any type of infection or hospitalization

- Pandemic underscored that social isolation and reduced physical activity led to worse outcomes in patients with PD
  - Anecdotally clinicians reported more cognitive impairment and dementia
- Expansion of telemedicine
  - The good- Much easier for patient and caregiver to check in with MD, address most issues
  - The bad- Rigidity and balance harder to assess via telemedicine
    - Getting out of the house and interacting with the world is beneficial

New Therapeutics for PD

Levodopa inhalation powder (Inbrija®)

- Approved in 2018, adjunct therapy to carbidopa/ levodopa during OFF times
- A breath-activated inhalation device, 2 capsules (42mg)absorbed through the pulmonary tree, taking effect in about 10min, lasting about 1 hour.
- Device can't be pre-loaded, and a person with PD while OFF may find this fine motor manipulation difficult.
- Trials did not test Inbrija in people with asthma or COPD (chronic obstructive pulmonary disease), so safety and benefits in those who live with these conditions is unclear

Subcutaneous Levodopa

New formulation of levodopa — an under-the-skin, continuous daily infusion — is under review by the FDA.

- Phase III trial, 130 subjects with PD infused levodopa vs. oral levodopa for 12 weeks.
- Participants were:
  - Taking at least 400 mg levodopa per day,
  - Had at least 2.5 hours of "off" time each day, and
  - Experienced motor fluctuations.

Subcutaneous Levodopa

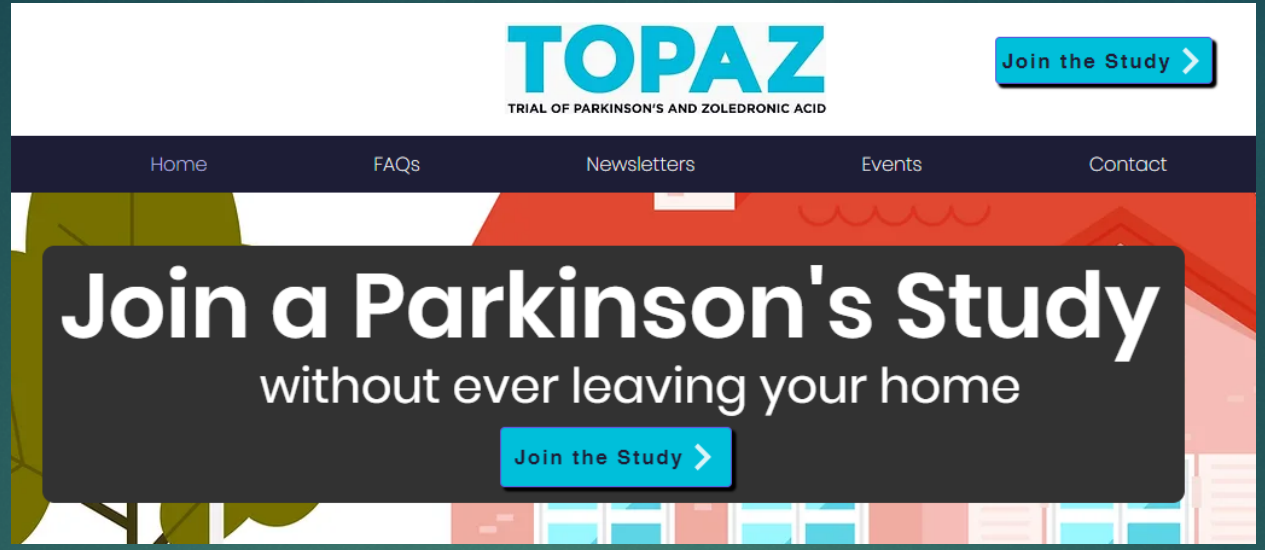
- Those who received infused levodopa reported more "on" time compared to those on oral levodopa.
  - The infusion group had, on average, almost 2 ¾ hours more "on" time per day.
  - Those on oral levodopa experienced an average of about one hour more of "on" time per day.
- The most common side effects of infused levodopa were redness, pain or swelling at the infusion site and involuntary, uncontrolled movement (dyskinesia).
- If approved, this new therapy could be available by mid-2023.

New Research and Treatment Therapies for PD

- TOPAZ
- Genetic Testing
- Deep Brain Stimulation (DBS)
- Stem Cells
- Gene Therapy
- Focused Ultrasound

Research in PD

- **Clinicaltrials.gov**
- 251 Recruiting Studies for Parkinson Disease in USA
  - 150+ observational/non-interventional
  - 23 Phase I
  - 35 Phase II
  - 10 Phase III
  - 3 Phase IV



The goal of the TOPAZ study is to help PD patients avoid fractures that can lead to loss of quality of life and physical function.

The TOPAZ study will test if an FDA-approved medicine called zoledronate can prevent fractures and decrease the risk of death in those:

Inclusion: Aged 60 and over

With Parkinson's Disease or parkinsonism

Who have not had a hip fracture

https://www.topazstudy.org/

- The study is done from your home!
- If eligible for the study, a nurse will come to your home to give you a short exam.
- You'll receive a one-time dose of the study treatment (either zoledronate or a placebo).
- During the study, we will contact you every four months to check if you have had any new fractures.
- Earn $100 upon enrollment and $50 per year during the study.

QUESTIONS?

Call the TOPAZ Study Info Line
1-800-4PD-INFO
[1-800-473-4636]
Monday to Friday

PD GENEration: Mapping the Future of Parkinson's Disease

PD GENEration identifies variants in seven Parkinson's-related genes that include:

1. *GBA*
2. *LRRK2*
3. *PRKN*
4. *SNCA*
5. *PINK1*
6. *PARK7*
7. *VPS35*

Genetic Testing PDGENEration

PD GENEration: Mapping the Future of Parkinson's Disease

~8,000 tests completed, 14% PD genetic link as of 12/22

Why do Genetic testing?

- Tool to uncover biological pathways that cause Parkinson's disease (PD)
- May lead to improved treatments and care.
- Understanding genetic differences can help identify clues about how and why a person's experience with the disease differs from others.
- May qualify for enrollment in certain clinical trials.
- Genetic tests are often not affordable/not covered by health insurance.
- Many genetic tests do not offer genetic counseling, which can help interpret test results.

PD GENEration: Mapping the Future of Parkinson's Disease

Genetic Testing and Genetic Counselors

Genetic counselors help interpret genetic test results and explain the implications of the results for the individual and family members.

PD GENEration study offers genetic counseling in both English and Spanish.

Genetic testing helps estimate the risk of developing PD, but is not a diagnosis, nor does it provide timeline for possibility of developing a disease.

With any genetic test results, it is important to discuss your results with a licensed genetic counselor.

Deep Brain Stimulation (DBS)

DBS Overview

DBS is a safe and effective adjunctive therapy

FDA approved for PD since 2002

Surgical risks are mitigated with experienced surgical centers with interdisciplinary teams

Most insurance carriers provide adequate coverage for DBS

Okun, *Arch* Neurol, 2005

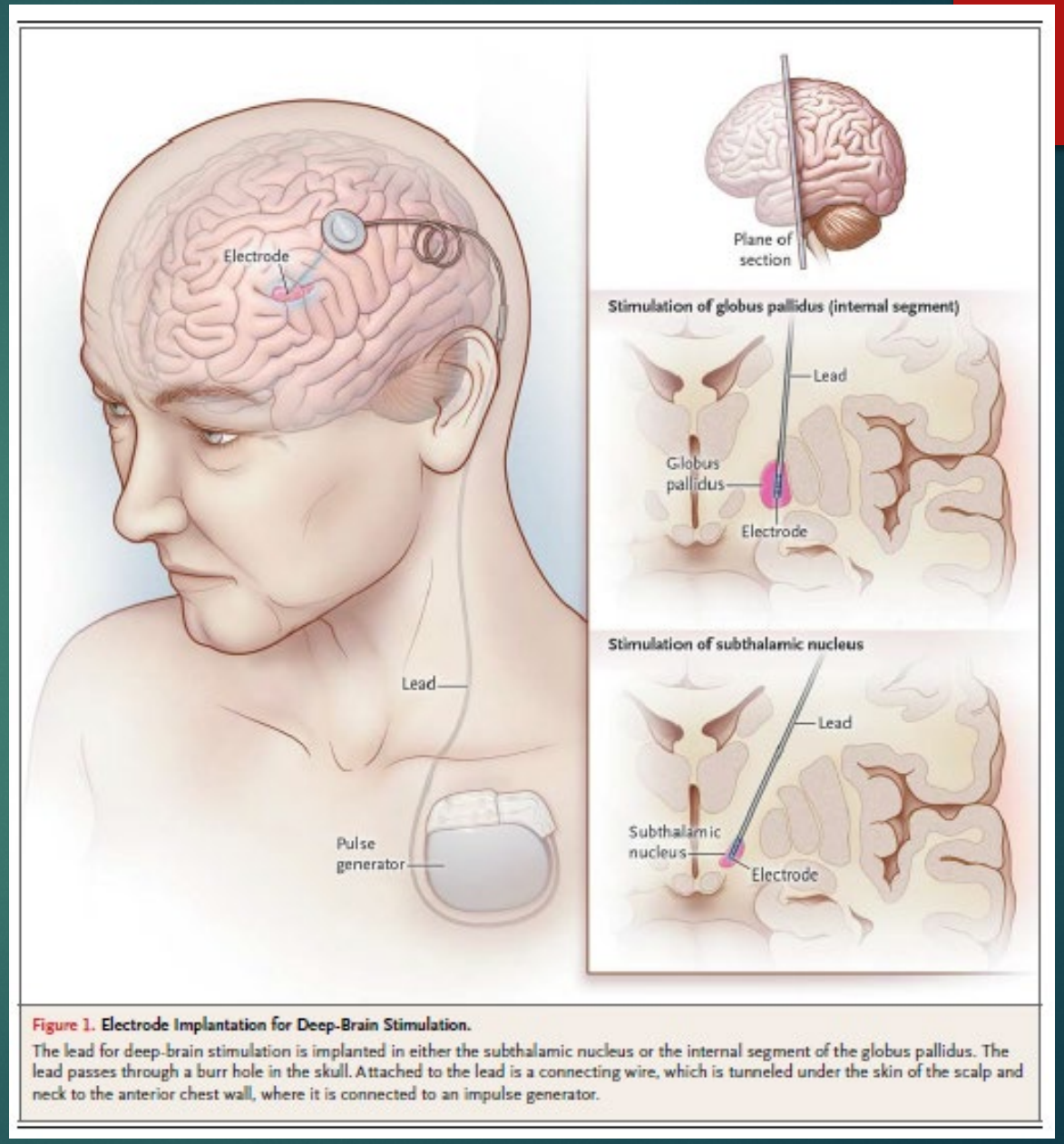
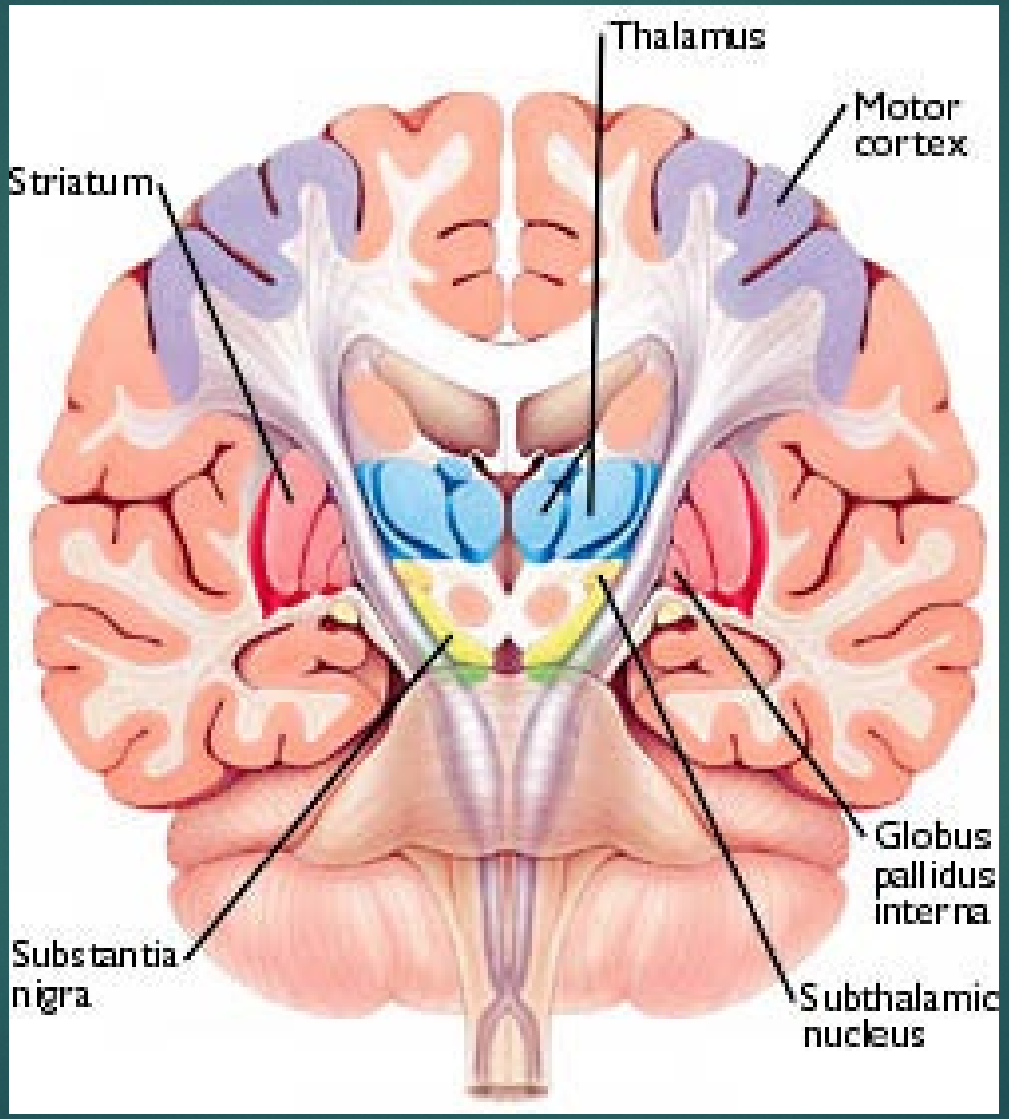


Figure 1. **Electrode Implantation for Deep-Brain Stimulation.**
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.

Where are the DBS leads implanted?



Thalamus = **VIM**
Globus Pallidus = **GPi**
Subthalamic Nucleus =**STN**

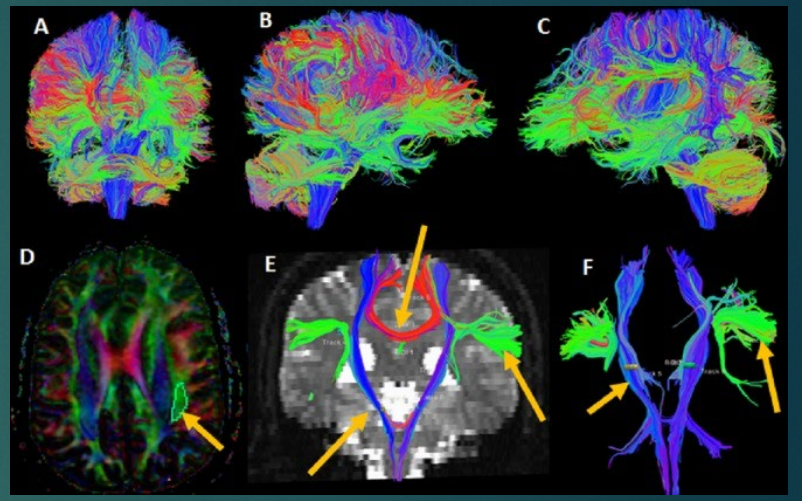
DBS Implantable Systems

Three Components

1. **Implantable Neurostimulator**: Power and software
2. **Extension:** connects stimulator to the lead
3. **Lead:** Implanted in the brain, electrodes in contact with target-network

How does it work? "Neuromodulation"

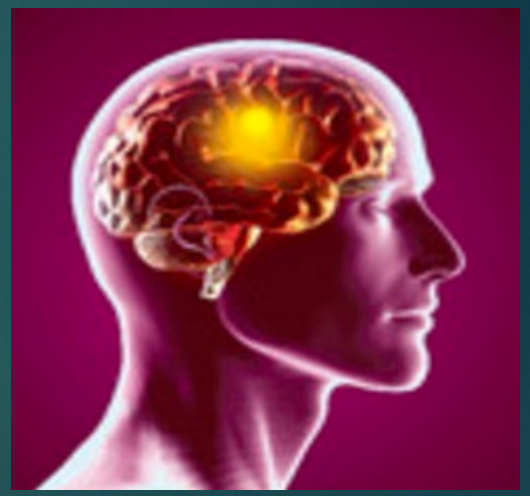
- Mechanism of action still under active investigation
- Abnormal circuits within brain tracts develop from loss of dopamine → motor dysfunction
- Stimulation with low dose electrical current disrupts abnormal brain signals (like brain pacemaker)
- Improves/restores function



Soni N, et al., Diffusion-tensor Imaging and Tractography Application in Pre-operative Planning of Intra-axial Brain Lesions. *Cureus*. 2017;9(10):e1739.

What can DBS Do? Modulates Motor Symptoms

- In general, does only what levodopa (medications) can do for the MOTOR symptoms
- ***Exceptions:*** *tremor and peak dose dyskinesias are often* ***refractory*** *to meds yet respond to DBS*
- Increases the best "on-medication" state by 4-5 hours daily
- Improves motor function by 25-50%
- Raises the ceiling for off-medication times
- Reduction in medication dosing (30-50%)



Marks et al., Editor, 2015, Deep Brain Stimulation Management

Updates and Research in DBS

Rechargeable DBS- Extended device service life lasting ~9-15 years.

Multi-directional leads- Pulses can be turned on/off in 3 directions

Leads- 360°- 120°x3 -120°x3 - 360°

UCSF Closed Loop DBS Study

- Traditional DBS has constant electrical stimulation
- Adaptive DBS has capability to react and adapt stimulation to changes in electrical signals in the brain
- 20 patients with idiopathic PD and motor fluctuations, or medically intractable tremor
  - Unilateral or bilateral devices, connected to a standard quadripolar DBS lead implanted in STN or globus pallidus
  - 4-contact paddle type electrode placed subdurally over sensorimotor cortex.
- Basal ganglia lead will be used for both stimulation and Local Field Potentials (LFPs) recordings, cortical lead will be used only for recording LFPs

Closed Loop DBS Study

- Patients with motor fluctuations cycle between a hypokinetic state (too little movement) and a hyperkinetic state (excessive movement).
- During open-loop DBS, brain state continues to fluctuate between these states and stimulation may induce dyskinesia or inadequately relieve akinesia.
- **Goal-** Maintaining motor function within a normal range away from these two extremes
  - Test stimulation algorithms that utilize presumed markers of both kinetic states.
  - Study neural signals of sleep and test stimulation to support specific sleep stages, to automatically adjust stimulation parameters until abnormal function is minimized.
- Attention to progressive reduction in stimulation currents,
- **Hypothesis-**"Adaptive stimulation" might make the brain progressively less dependent on the device

Stem Cells

Three main types of stem cells:

- **Embryonic stem cells (PSCs):** These cells are pluripotent, meaning they can transform into the many types of cells found in your body. As the name suggests, they're found in embryos.
- **Somatic stem cells:** Also called adult stem cells, these mostly perform repair functions. They can still transform, but not into as many types of specialized cells as embryonic stem cells can.
- **Induced pluripotent stem cells (iPSCs):** These stem cells are made by genetically changing cells that have already matured.

BlueRock Therapeutics LP

Phase 1 (Ph1) enrollment completed 2022

Open-label infusion trial of iPSC dopaminergic neurons in patients with Parkinson's disease (PD)

- Treatment with BRT-DA01, known simply as DA01, involves surgically transplanting dopamine-making nerve cells — derived from human embryonic PSCs — into the putamen.
- The goal is to replace lost cells and provide a regular source of dopamine.
- During surgery, patients are under general anesthesia, and a device that injects fluids into the brain is used to deliver the therapy. After surgery, participants will take immunosuppressants for one year to prevent cell rejection.

Aspen Neuroscience, Inc.

- Developing induced pluripotent stem cell (iPSC)-derived cell therapies, autologous neuron replacement for PD
- Personalized cell replacement eliminates the need for immunosuppressive therapy, utilizes a patient's own skin cell-derived iPSCs to produce replacement dopamine neurons for transplantation back into the same patient.
- Developed from a skin biopsy, each patient's cells will be evaluated for potential effectiveness using proprietary AI-based genomics tools, before being transplanted for clinical use.

Gene Therapy

- Glial cell line-derived neurotrophic factor (GDNF), a protein supports the growth, survival, and differentiation of dopaminergic neurons, which are gradually lost to Parkinson's.
- Uses a disease-modifying adeno-associated virus (AAV2) to deliver the *GDNF* gene to specific brain areas, induces the production and release of the GDNF protein to promote the health and survival of neurons damaged by the disease.
- Intraoperative magnetic resonance imaging (iMRI), delivery directly to targeted areas of the putamen.

Gene Therapy

- Open-label Phase 1b study- safety, tolerability, and effectiveness of four escalating doses of AAV2-GDNF in 25 adults with advanced Parkinson's. Patients given a single surgical infusion of the therapy, followed for five years, Concluded in February 2022.
- Phase 1b trial- safety, tolerability, and effectiveness of GDNF therapy in 12 patients, ages 35 to 75, with early to moderate Parkinson's. Bilateral therapy infusion to the putamen, followed for five years, concludes ~2026
- Randomized, placebo-controlled Phase 1 study in MSA patients

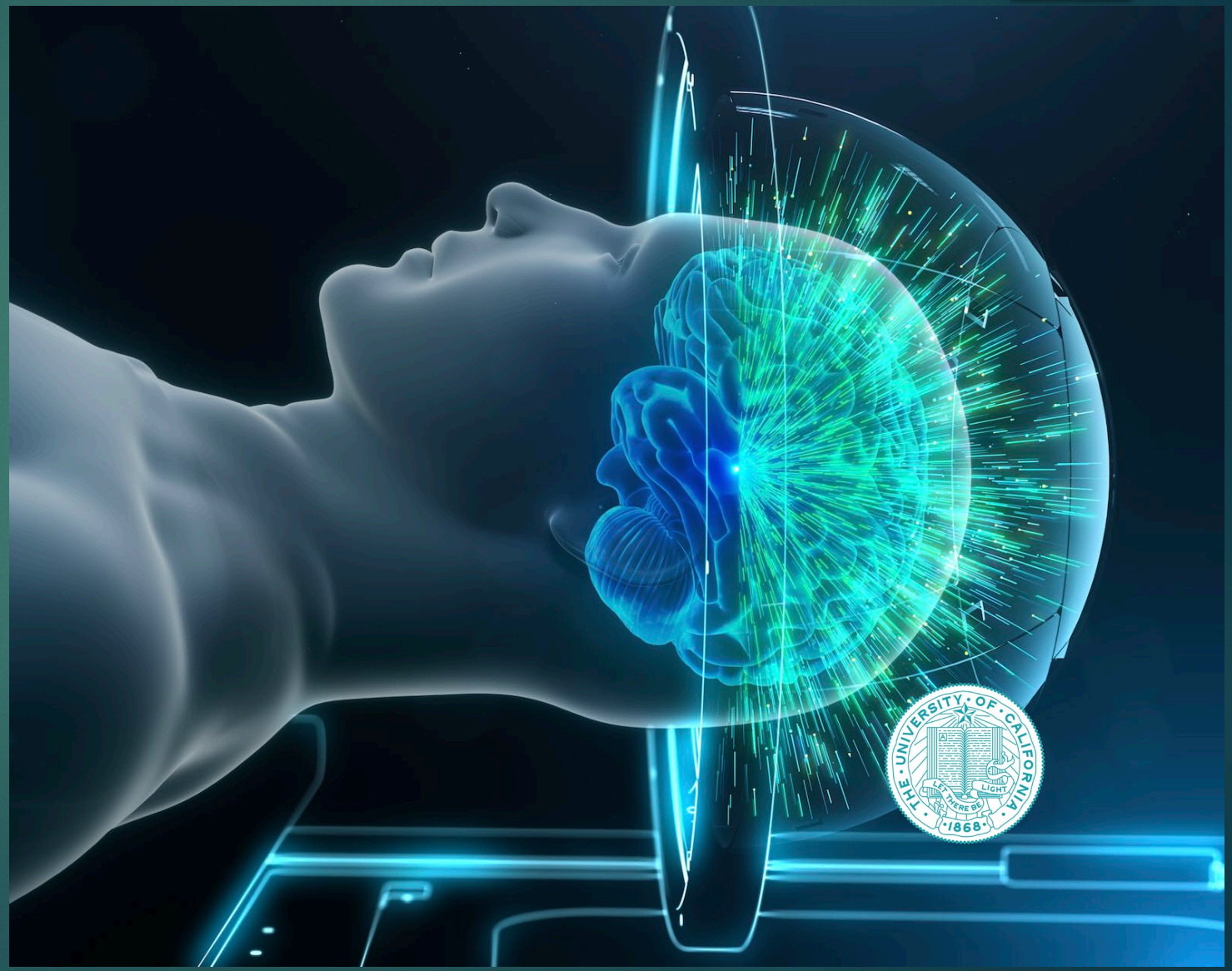
Focused ultrasound

Incision-free, minimally invasive treatment for essential tremor and tremor dominant PD

Research shows tremor can be alleviated by treating a small area of the brain that regulates movement; ventral intermediate (Vim) nucleus of the thalamus.

- Outpatient procedure, high-intensity sound waves, guided by MRI, are focused on the Vim. Waves pass painlessly and safely through skin, bone and brain to reach their target, generates enough heat to burn cells in the Vim without harming surrounding tissue.
- Recovery time is short, and the treatment can significantly reduce tremor, improving the ability to perform daily activities, such as eating, drinking and writing. It does not cure the underlying disease.

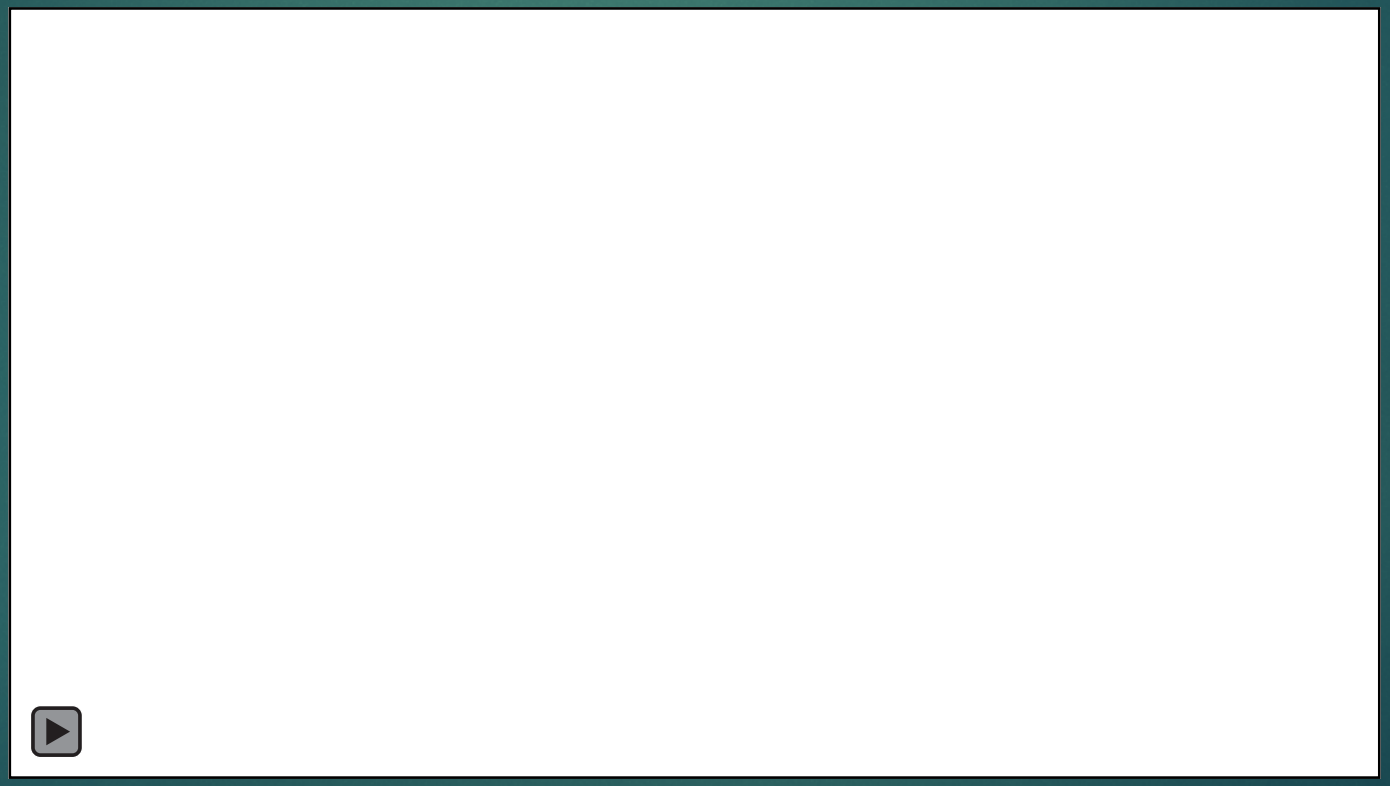
MRI Focused Ultrasound lesion for Tremor or Unilateral PD/GPi target



FDA APPROVED FOR PD DEC 2021

Focused Ultrasound— How it works

Up to 1024 sound waves from a helmet-shaped device are precisely delivered safely through the skull with no incisions.
Only where the sound waves converge, the temperature at the target tissue rises to cause thermal ablation of a small target, about the size of a pea.



Advantages of FUS

- Immediate and durable tremor improvement
- Significant improvement in Quality of Life
- Outpatient, home the same day
- Little to no risk of infection
- No implants, probes or ionizing radiation
- No anesthesia
- **FUS is not adjustable, lesion is fixed. Tremor can/may progress.**

If you are interested in PDGENEration or TOPAZ email me:

Aaron.daley@ucsf.edu

THANK YOU!