Mass General Brigham

Multiple System Atrophy: Overview & Current Research

Patient Education Series

Mission MSA

Improving quality of life and bringing hope to those affected by MSA through care, support, community, education, and research

Meet Our Team

Parkinson's + Ataxia + Multiple System Atrophy (PAMSA) Multidisciplinary Clinic

- Neurology
- Urology
- Physical Therapy
- Speech Therapy
- Social Work
- Research

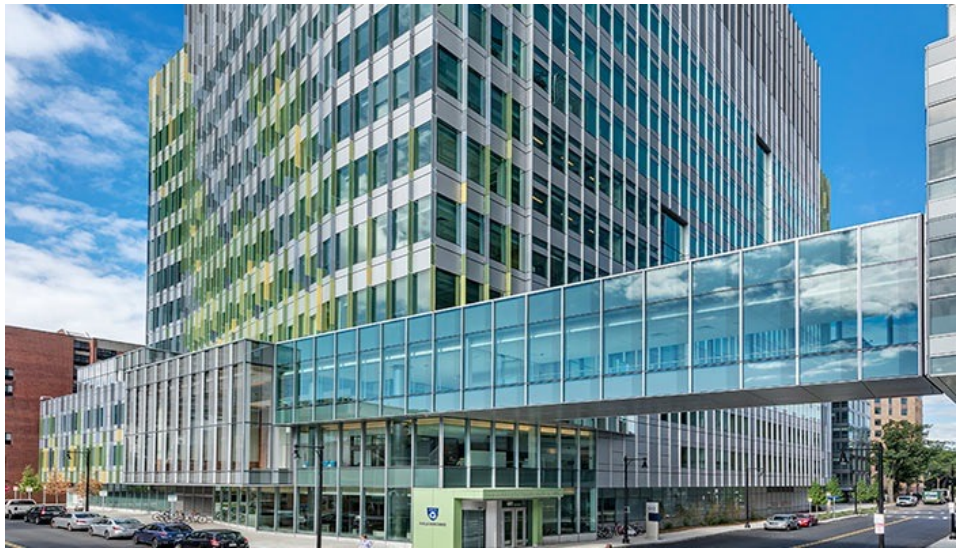
About Our Co-Directors

Vikram Khurana, MD, PhD is Chief of the Division of Movement Disorders at Brigham and Women's Hospital and Co-Director of the Mission MSA Center of Excellence. His clinical and research interests focus on synucleinopathies including Parkinson's disease (PD), multiple system atrophy, and related dementias and ataxias. Dr. Khurana led some of the first studies to identify and reverse pathologies in human stem cells derived from PD patients while undergoing his postdoctoral training. His current research continues to bring stem-cell technologies toward personalized and precise diagnostics and therapeutics for neurodegenerative disorders.

Barbara Changizi, MD is Director of Clinical Operations and Co-Director of the Mission MSA Center of Excellence. She is also Co-Director of the Mass General Brigham Fellowship Program, a training program for neurologists interested in becoming experts in parkinsonian disorders. She is an expert in treating Parkinson's disease and parkinsonian syndromes including multiple system atrophy and progressive supranuclear palsy, as well as ataxia syndromes. She is familiar with comprehensive care of complex MSA patients, including management of orthostatic hypotension, dementia, depression, dystonia, and parkinsonism. She is involved in industry-supported clinical trials for MSA, and supports the Khurana Lab and MyTrial program with clinical expertise.

WELCOME TO THE FIRST OF OUR QUARTERLY LECTURE SERIES ON MSA!

- Every 3 to 4 months we will educate on topics related to MSA
- This conference will discuss
  - CLINICAL FEATURES OF MSA
  - TREATMENTS OF MSA
  - CLINICAL TRIALS
  - RESEARCH



Multiple system atrophy (MSA)

- MSA is a rare neurodegenerative disorder which involves (1) autonomic, (2) cerebellar, and (3) parkinsonism symptoms
  - Lots of body systems, hence the name!

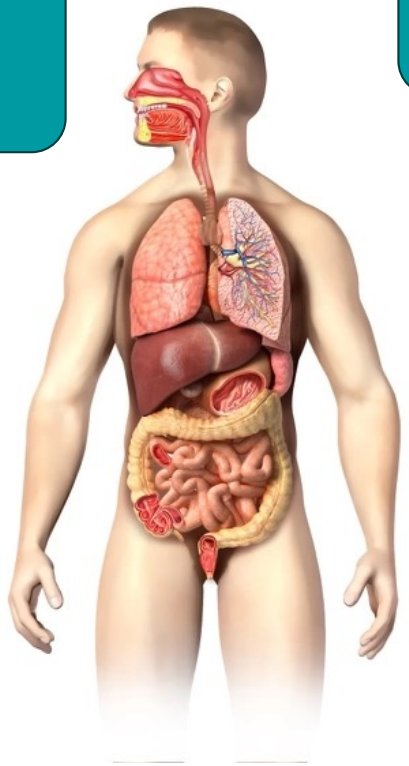
- “Atypical parkinsonian disorder” as it has overlapping features with Parkinson disease

- “Synucleinopathy,” meaning the disease is associated with aggregation of an abnormal protein called synuclein in cells of the nervous system

Dysautonomia: impairment of the nervous system that manages unconscious processes

Orthostatic hypotension

Anhidrosis, or lack of sweating



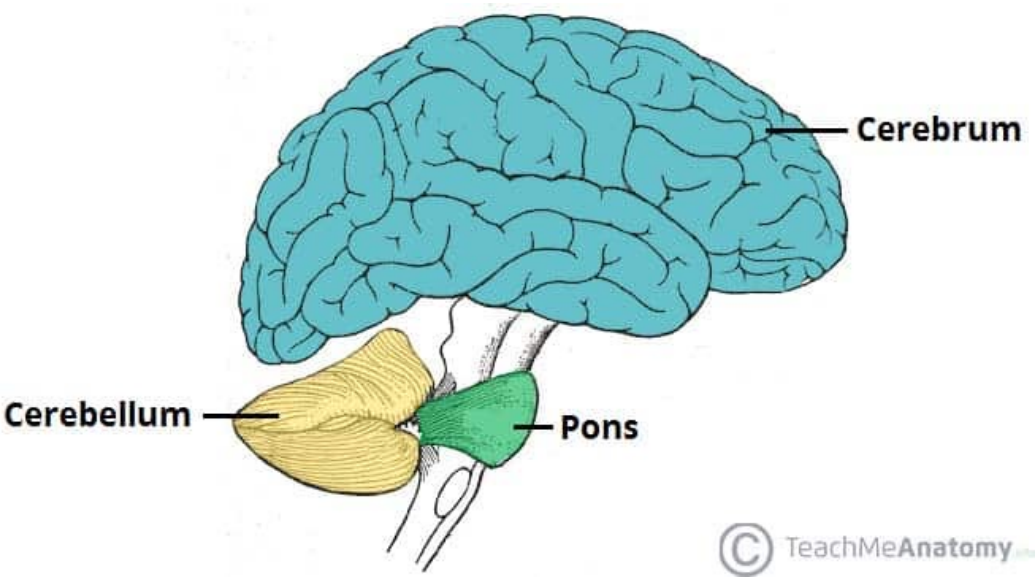
Constipation

Urinary dysfunction

- Retention, urgency, frequency, incontinence

Erectile dysfunction

Cerebellar involvement



- Ataxia, or incoordination
  - Gait ataxia
  - Limb ataxia
- Speech impairment, or “dysarthria”
  - Gait ataxia
  - Limb ataxia
- Eye movement problems

Parkinsonism

- Bradykinesia, or slowness
  - Shuffling walk
  - Soft voice
  - Reduced blinking
  - Problems with rapid movements or dexterity
  - Drooling
- Rigidity, or muscle stiffness
- Tremor
  - Differs from Parkinson's disease

How do you know it's not Parkinson disease?

- Levodopa responsiveness
  - In Parkinson disease (PD), there is dopamine deficiency in the brain due to cells in the substantia nigra dying off. This leads to slowness, stiffness, and tremor
  - We prescribe levodopa, which is a precursor of dopamine. This is converted to dopamine in the brain
  - In PD, patients have marked improvement in motor symptoms from levodopa.
  - In MSA, there is lack of sustained benefit from levodopa.

- Dysautonomia, including changes in skin coloration and breathing patterns, is more prominent and may occur earlier in MSA, compared to PD.

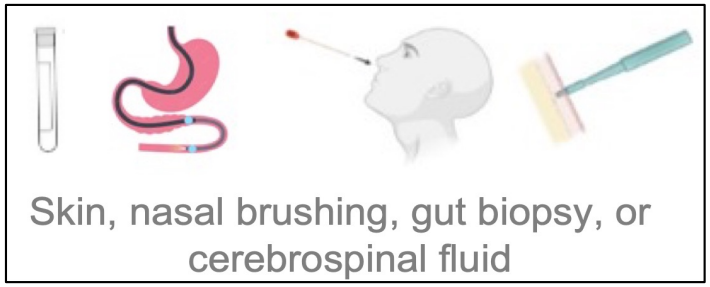
- Loss of smell is less common in MSA than PD, but early impairment of speech and swallowing is more common in MSA.

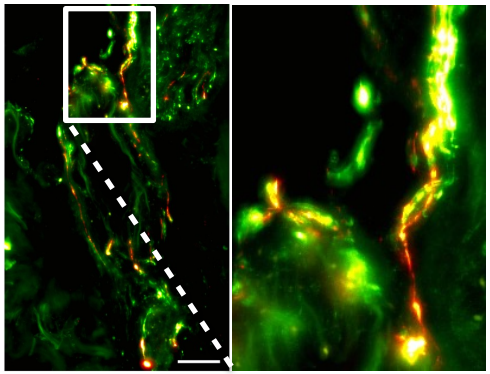
- PD does not cause ataxia

How do you know it's not Parkinson disease?

- Both PD and MSA involve clumping of the protein called "alpha-synuclein" in the brain. The alpha-synuclein clumps into different shapes in each of these diseases, and this change can be detected now in the skin, spinal fluid or nasal brushings.

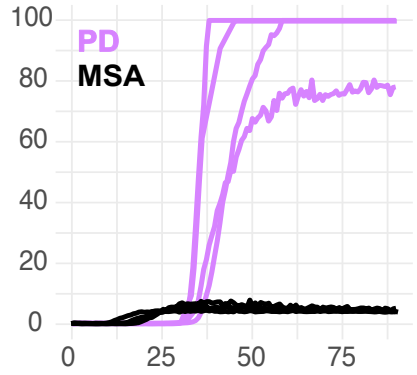
- New skin and spinal fluid tests make is possible to distinguish Parkinson's from MSA but these are in an early stage and not fully validated.
  - Visualizing alpha-synuclein in the skin (immunofluorescence; CND SynOne Test)
  - Identifying the abnormal alpha-synuclein shape in the spinal fluid (Amprion SAAmplify) or skin (Khurana lab research)





Skin biopsy

Nerves marked in green; alpha-synuclein in red



Seeded amplification Test

REM Sleep Behavior Disorder

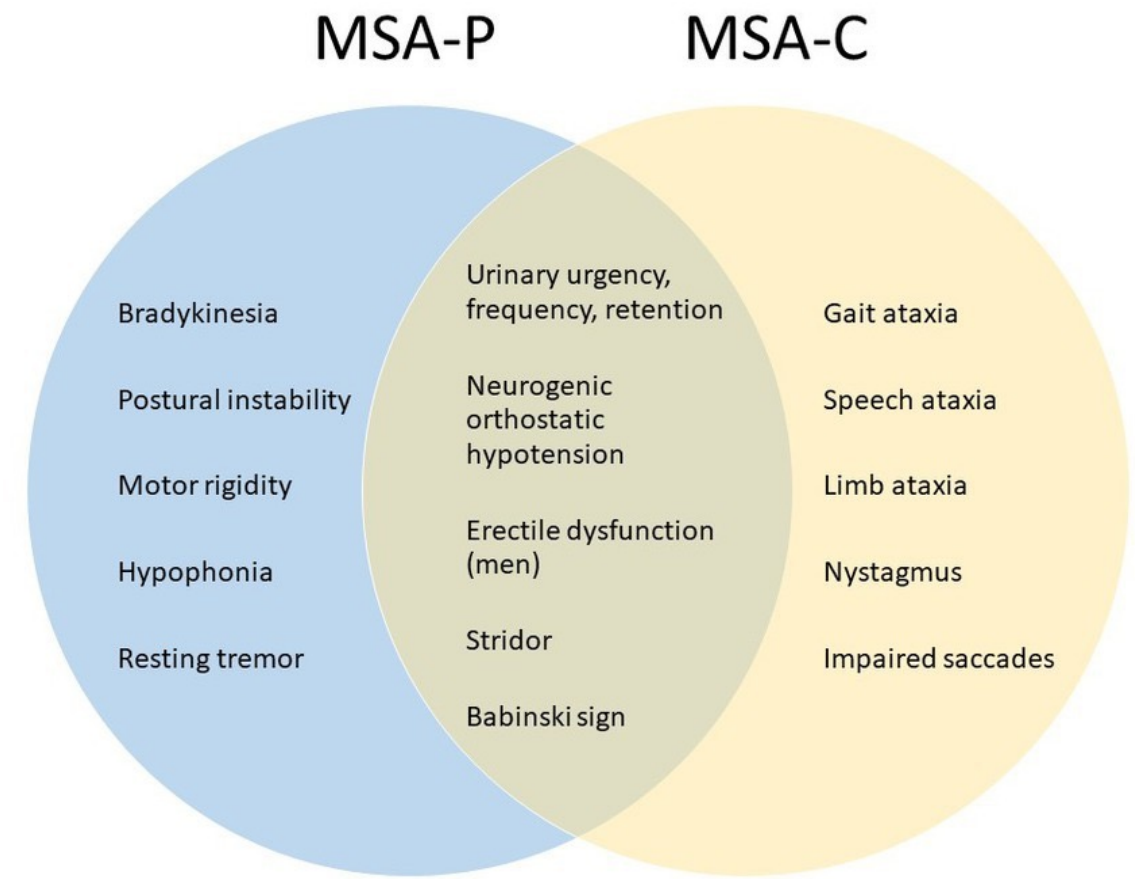
- 2/3 of MSA patients have Rapid Eye Movement (REM) Sleep Behavior Disorder, or RBD
- May be prodromal; may present decades before clinical motor symptoms emerge
- REM sleep should have muscle atony, meaning the temporary paralysis of most skeletal muscles; this prevents people from acting out their dreams
- In RBD, patients act out their dreams and may talk or should out, thrash about, punch, or fall out of bed
- RBD tends to decrease in severity over the course of MSA

Sleep-related breathing disorders

- Stridor
  - 15 to 40% of patients with MSA
  - Laryngospasm with impaired vocal cord abduction
  - Result is a high-pitched sound as air vibrates through narrowed vocal folds
  - Sounds like loud snoring, but NEED TO BE EVALUATED BY OTOLARYNGOLOGY **ASAP**
- Obstructive sleep apnea
- Central sleep apnea

LISTEN TO STRIDOR BY PUSHING BLUE KEY

Two subtypes of MSA, depending on which symptoms predominate at time of diagnosis



Goolla M, Cheshire W, Ross OA, Kondru N. Diagnosing multiple system atrophy: current clinical guidance and emerging molecular biomarkers. Front Neurol.28 September 2023. Sec Autonomic disorders vol 14.

Treatment of MSA is best done in multidisciplinary settings!

- Involves a multidisciplinary team as this is a multi-system disease!
- Movement specialists to treat parkinsonism and coordinate care
- Physical therapists to help balance and coordination
- Speech therapists to improve dysarthria, evaluate swallowing
- Urologists to treat bladder impairment
- Autonomic specialists to treat dysautonomia including orthostatic hypotension
- Social worker to provide counseling and help navigating living situation, resources, transportation, health care proxies, etc.
- Research team to enable clinical trial participation

There is no cure or protective treatment for MSA at this time

Treatment of motor symptoms

- Parkinsonism (slowness, rigidity, tremor) is treated with levodopa
  - A poor or unsustained response is typical, but this is still worth a try!
  - Carbidopa/levodopa = Sinemet IR, Sinemet CR, Rytary
    - Levodopa is always given with a peripheral decarboxylase inhibitor called carbidopa to facilitate longevity and uptake by the brain
    - Three or four times daily dosing typically
  - We tend to avoid dopamine agonists such as ropinirole and pramipexole as these aggravate orthostatic hypotension and sleep disorders in MSA, and are less potent than levodopa
  - No role for deep brain stimulation (DBS) in MSA
- Ataxia unfortunately has no effective medications
  - Physical therapy
  - Speech therapy

Orthostatic hypotension: sudden drop in BP with sitting or standing, leading to lightheadedness

Treatment	Mechanism of action	Side effects/comments
Fludrocortisone	First-line	Monitor salt and water retention, hypokalemia
Midodrine	Can be used prn or scheduled	Supine and rebound hypertension, may need a rescue such as clonidine
Droxidopa	Improvement at doses of 100 to 600 mg 3x daily	Does not cause supine hypertension

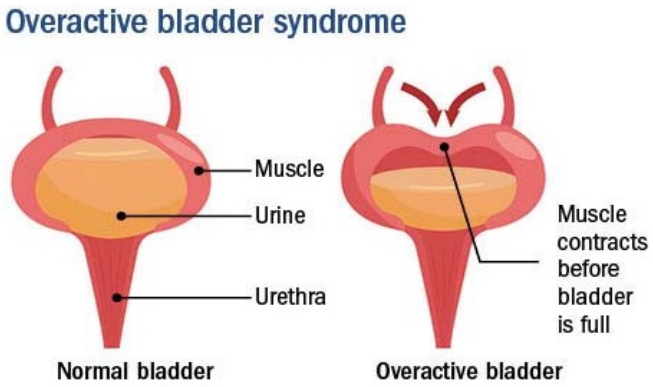
Image courtesy of https://www.neurolab360.com/blog/navigating-orthostatic-hypotension

Constipation (bowel movement < 3 per week)

Treatment	Mechanism of action	Side effects/comments
Polyethylene glycol (Miralax)	1 tbsp daily in clear liquid	Can be used daily, side effects are nausea, bloating, diarrhea
Lubiprostone (Amitiza)	Increases intestinal fluid secretion to increase motility in the intestine (Chloride channel activator) Probably clinically useful Taken with food and water 2 x daily	Side effects are nausea, diarrhea, headache, bloating
Linaclotide (Linzess)	Stimulates guanylate cyclase C receptors, also increases fluid in the intestines	
Increase water intake		
Prunes, fruits with skins		
“Rancho recipe”	1 cup applesauce, 1 cup oat bran or heat bran, 1 cup prune juice	

Urinary dysfunction: urgency, frequency, nocturia

Drug for overactive bladder	Mechanism of action	Side effects/comments
Miragebron	selective agonist of Beta3 adrenergic receptors	Well tolerated Expensive Risk of urinary retention
Oxybutynin	Competitive acetylcholine antagonist at muscarinic receptors, relaxes bladder smooth muscle	Anticholinergic side effects (constipation, cognitive impairment)
Botulinum toxin to the detrusor muscle	Refer to urology	
Bladder stimulators	Refer to urology	



Clinical trials

ONO-2808

Just closed enrollment
Multi center, phase 2, double-blind, placebo-controlled, parallel group study
ONO-2808 may improve symptoms as well as slow progression of disease in MSA

TEVA TOPAS trial for TEV-56286

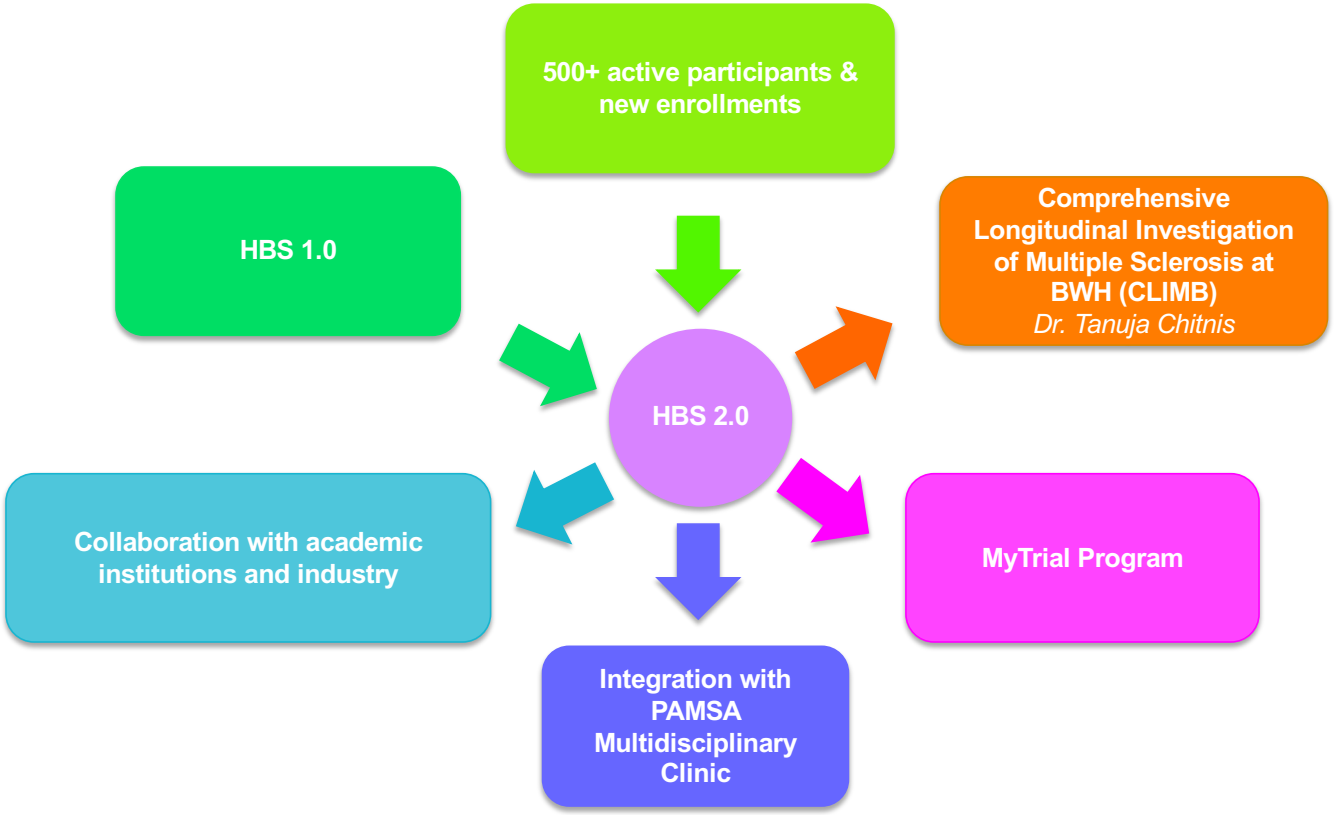
Multi center, phase 2, placebo-controlled, parallel group study
TEV-56286 may treat symptoms of MSA as well as slow progression of disease
About to enroll in early 2025! Our site visit from the sponsor is in December 2025… stay tuned!

Ongoing discussions with Lundbeck and Yoda

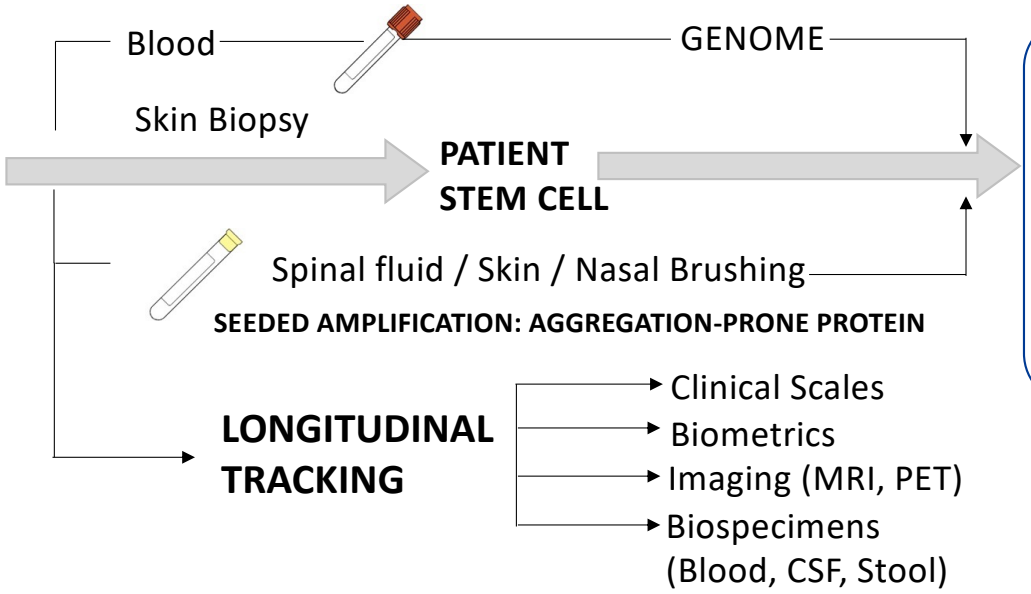
MyTrial: GLP-1 agonists, Nasal Foralumab

Research at BWH:
The Harvard Biomarkers Study (HBS 2.0)

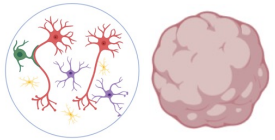
- HBS has tracked thousands of patients and healthy subjects for more than 15 years.
- Tens of thousands of biospecimens from these subjects are banked at Brigham and Women's Hospital.
- HBS is a key way in which we longitudinally track our patients and triage them into appropriate clinical trials, including our own MyTrial Program.
- Spinal fluid, also called CSF is a critical biomarker.



Research at BWH:
The Harvard Biomarkers Study (HBS 2.0) & MyTrial

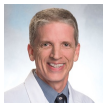


PERSONALIZED SCREENING



Parallel drug & diagnostics testing in the dish through single-patient and pooled-cohort screening

We can do trials in patients and "in the dish" at the same time…



Geoff Young
BWH

Tarun Singhal
BWH

Anoopum Gupta MGH

Laurie Cox
BWH

Howard Weiner
BWH

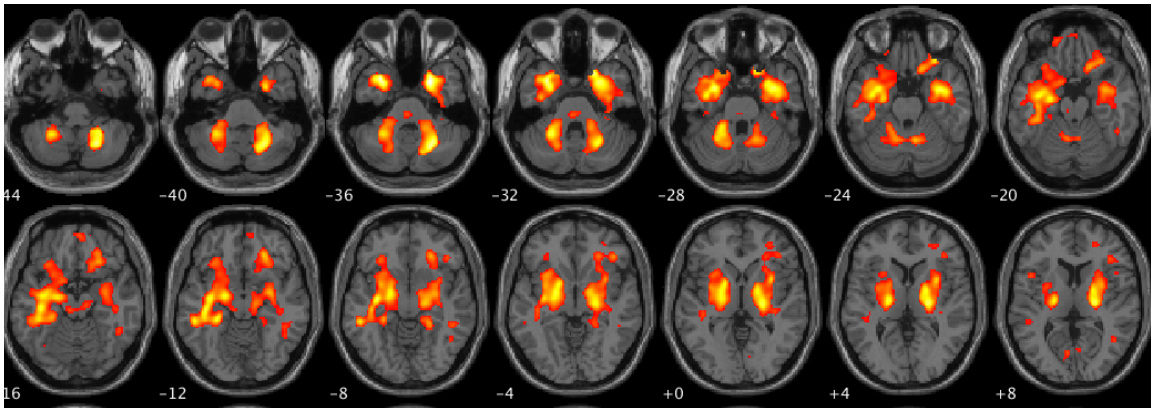
What does a visit with HBS look like?

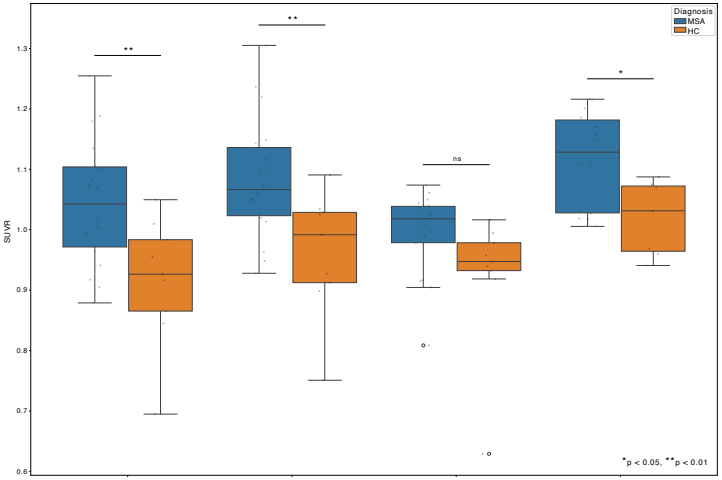
- Annual; aligned with your visits to BWH
- Enrollment visit – 45 minutes; follow-up visits – 30 minutes
- Each visit includes a blood draw, motor exam, cognitive exam, and at-home questionnaire.

- Spinal fluid (also called CSF) is one of the most important aspects of HBS collection. While it is optional, it is one of the best ways we can identify disease processes, inform on the best clinical trial, *and* measure whether a drug is hitting the proper target.

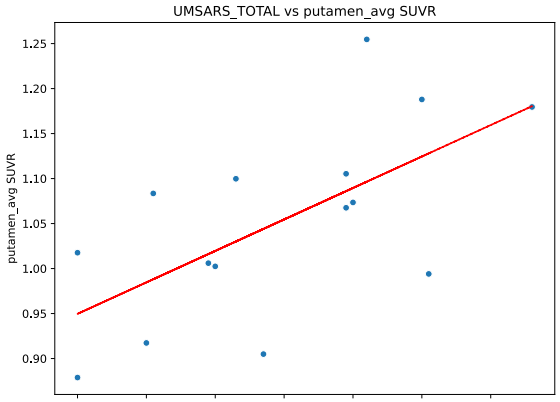
- MyTrial patients have HBS visits twice annually in addition to…
  - additional blood testing (our CLIMB blood/immune and stool/microbiome collection)
  - biometric testing including video-oculography, at-home computer tasks, and accelerometry

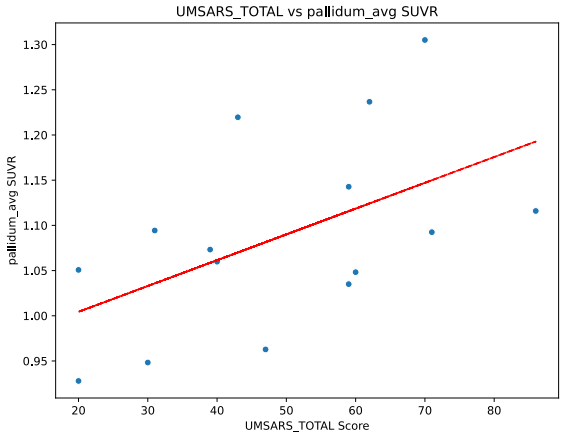
One key marker is brain inflammation





Putamen Pallidum Hippocampus CBW

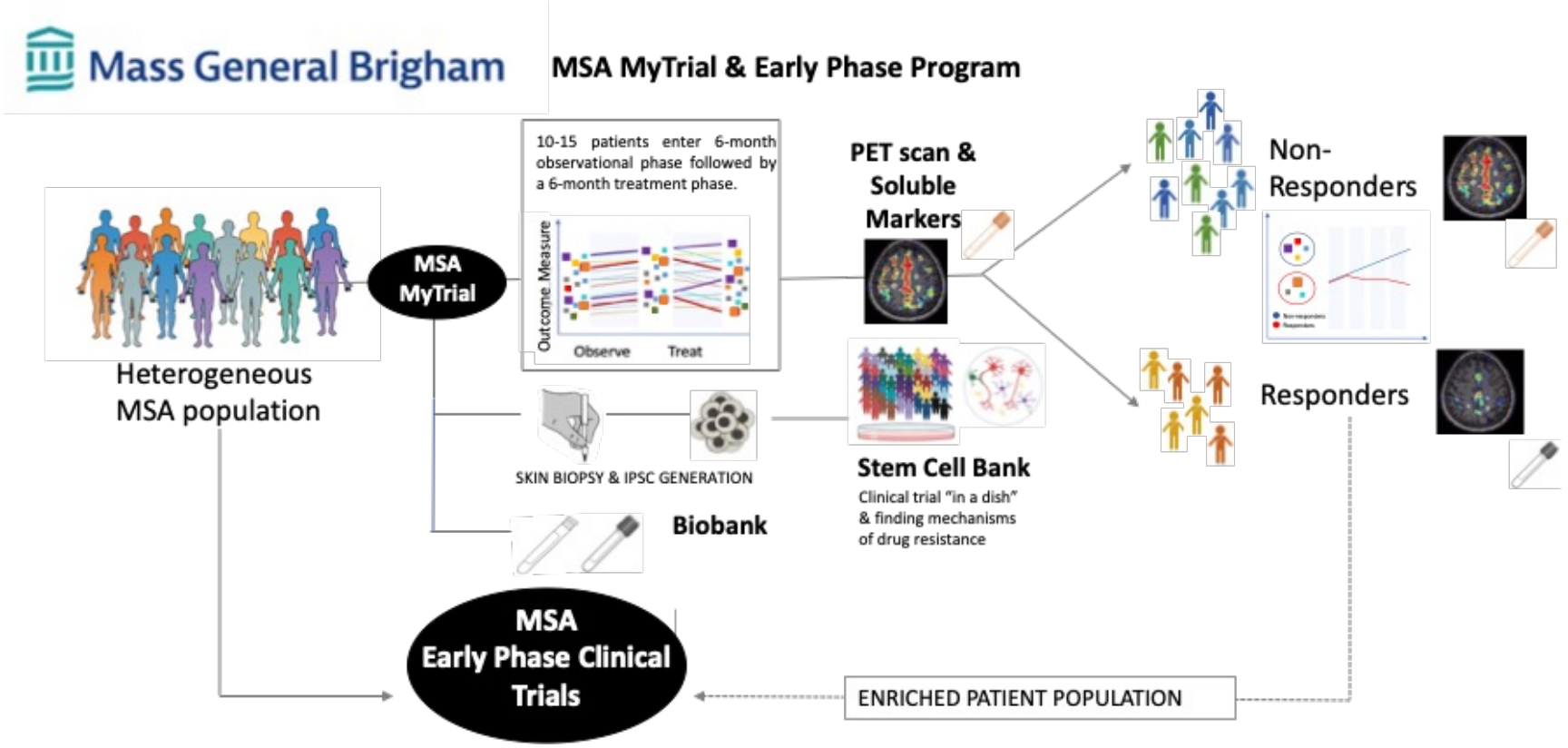




Clinical MSA diagnosis (N = 18)
Age-matched controls (N = 9)

The more severe the disease, the higher the brain inflammation

Our Approach

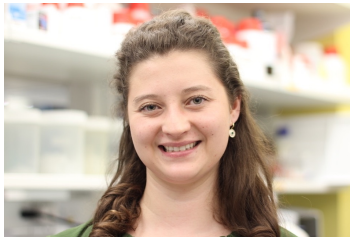


Get In Touch

- Contact Information: BWHMovementResearch@bwh.harvard.edu
- Study Managers: Dr. Daniel El Kodsi (HBS) & Dr. Diego Rodriguez (MyTrial)
- Study Coordinators: Olivia Laun, Breelyn Gilbert, Anya Gemos, and Shreya Rai









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Thank you!