

Biomarkers to Breakthroughs: Drug Development in the Era of Alpha-Synuclein Imaging

A White Paper on the Emerging PET Tracer Landscape in
Parkinson's Disease and Related Synucleinopathies



THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

October 2026

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Executive Summary

- + Alpha-synuclein (aSyn) positron emission tomography (PET) imaging has reached an important inflection point, with multiple tracers now demonstrating disease-associated signals in human studies across Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA).
- + On June 10 and 11, 2026, The Michael J. Fox Foundation for Parkinson's Research (MJFF) convened over 100 participants across academia and industry in London, UK, to review progress in aSyn imaging.
- + Seven independent research groups reported human imaging data across nine tracer programs showing signals in regions of the brain consistent with known aSyn pathology, including the substantia nigra, putamen, brainstem and amygdala.
- + The strongest current evidence exists in MSA, where aSyn tracer retention is generally higher and more regionally distinct than in PD. Early findings support further evaluation of aSyn PET for differential diagnosis, longitudinal monitoring and pharmacodynamic assessment.
- + In PD, preliminary evidence is encouraging, despite small cohorts, heterogeneous findings and uncertainty regarding tracer sensitivity across disease stages and aSyn conformations.
- + Across all aSyn PET, major scientific challenges remain, including low target density, conformational heterogeneity, off-target binding, radiometabolites, uncertain quantification methods and reference regions, limited neuropathological validation and interpretation of longitudinal change.
- + No aSyn PET tracer is currently ready for broad use in clinical trials, but several credible candidates now have a practical route to validation.
- + MJFF is committed to advancing a diverse pipeline of tracer candidates through transparent, fit-for-purpose validation while building the scientific, operational and regulatory infrastructure needed to integrate validated tracers rapidly into therapeutic trials. This could ultimately support diagnosis and treatment development across PD and other neurodegenerative disorders.

Priority Actions •



Advance a diverse pipeline of promising tracers using clear criteria for progression



Establish reproducibility and the ability to detect change over time



Confirm that human PET signals reflect relevant aSyn biology



Standardize production, imaging and analysis for multi-center trials



1 Current State of the Field

Alpha-synuclein (aSyn) positron emission tomography (PET) imaging has entered a new phase of development. After years of tracer discovery and pre-clinical evaluation, multiple independent programs now show promising disease-associated signals in human studies across Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Although further validation is needed, these findings provide early evidence of disease-associated PET signals consistent with aggregated aSyn in the living brain.

Why does aSyn imaging matter?

There is currently no validated method for directly measuring aggregated aSyn in the living brain. Longitudinal aSyn PET may help characterize the molecular natural history of synucleinopathies by measuring changes in regional distribution and the burden of aSyn across disease stages. Such imaging would support investigation of variation between individuals, proposed disease subtypes (including brain-first and body-first trajectories) and treatment-related biological effect.¹⁻³

For patients and families, this could provide greater clarity about the underlying disease biology and, by improving the evaluation of disease-modifying therapies, support the development of effective new treatments.

On June 10 and 11, 2026, The Michael J. Fox Foundation for Parkinson's Research (MJFF) convened over 100 participants from academia, industry, clinical research, molecular imaging, neuropathology, advocacy and funding

organizations to review emerging data and identify priorities for advancing the field.

Meeting participants emphasized the potentially transformative role of aSyn imaging in therapeutic development, drawing parallels with amyloid and tau PET in Alzheimer's disease (AD) research.

Why is it taking so long?

Aggregated aSyn is largely intracellular and much less abundant than amyloid plaques are in AD, particularly in PD. A successful tracer must therefore cross the blood-brain-barrier and reach intracellular aSyn, then bind with high affinity and produce little nonspecific background signal.^{4,5}

In PD, aSyn accumulation may initially involve small brainstem, midbrain and olfactory structures before extending to limbic and cortical regions. Detecting these low-abundance signals may require PET with high sensitivity and spatial resolution.

The structure, cellular location and regional distribution of aSyn differ across Lewy body diseases and MSA, and may change with disease progression. The expected signal therefore depends on the disease, population and stage.^{4,5}

Amyloid and tau co-pathologies can complicate signal interpretation. Binding to these proteins does not make a tracer unsuitable, but could influence context of use.^{4,5} Further studies combining aSyn, amyloid and tau PET will help distinguish signals associated with each pathology.

How ready is the field?

Multiple independent groups now report human imaging data. While no tracer has yet demonstrated the characteristics needed for broad use in clinical research, meeting participants emphasized the emergence of several independent human datasets as a pivotal shift.



2 Key Scientific Advances

Overview Of The aSyn Tracer Landscape

Seven independent research groups presented early human PET data from nine carbon-11 (^{11}C) or fluorine-18 (^{18}F) tracers. The clearest signals were reported in MSA, including early evidence of regional change over six to 14 months.

In PD and DLB, several tracers showed increased retention in neuropathologically relevant regions, including the substantia nigra, brainstem, putamen, pallidum, amygdala, olfactory structures and cortex. However, patient-control overlap and interpatient variability were common.

The findings support the transformative potential of aSyn imaging, but do not yet establish diagnostic accuracy, sensitivity to disease progression, or treatment responsiveness. Tracer programs are at different stages of development. ACI-12589 currently has the most developed clinical evidence in MSA, while several tracers have

shown encouraging but preliminary signals in PD and DLB. Others remain at an early first-in-human stage. Direct ranking is not yet possible due to different populations and methods.

Key Themes •

- + MSA currently provides the clearest proof-of-concept.
- + Disease-associated signals are increasingly evident in PD and DLB.
- + Early evidence of longitudinal change is beginning to emerge.

Most data presented were preliminary and some were unpublished.

^{18}F ACI-12589 – Presented by Kirsten Scott, AC Immune

Background

ACI-12589 has been evaluated extensively in MSA. Data presented included 13 patients with cerebellar-type MSA (MSA-C) and 10 with hereditary ataxia, plus 15 patients with MSA Parkinsonian (MSA-P) and 20 with PD. One patient with MSA-P underwent pre-mortem PET followed by post-mortem neuropathological assessment.

Key findings

Cerebellar white matter retention distinguished MSA-C from hereditary ataxia, while posterior

putaminal retention distinguished MSA-P from PD in the study cohorts. No reliable disease-associated signal was detected in PD. Regional changes of up to approximately 30 percent over nine months were reported in early longitudinal analyses.

Further validation

Larger studies are needed to confirm longitudinal performance and distinguish changes in aSyn pathology from the effects of neurodegeneration and atrophy in MSA.

Background

ACI-15916 is a higher-affinity, second-generation tracer developed to extend the ACI-12589 program. Initial human imaging included five healthy controls (HCs) and nine patients across PD, DLB, Parkinson's disease dementia (PDD) and MSA.

Key findings

Compared with ACI-12589, ACI-15916 showed increased retention in the substantia nigra in patients with Lewy body diseases, as well as expected regional signals in MSA. However, these

findings are based on a very small first-in-human study and signals in the substantia nigra are confounded by off-target binding to neuromelanin.

Further validation

ACI-15916 showed modestly improved affinity over ACI-12589, but affinity for PD-associated aSyn may remain insufficient for reliable detection in PD. Larger studies are needed to confirm performance in PD, DLB and PDD, replicate cortical findings and characterize venous sinus and choroid plexus retention.

Background

MODAG-009 is a ¹⁸F tracer developed from the same program as [¹¹C]MODAG-005, which demonstrated aSyn binding in pre-clinical studies and early human imaging in PD and MSA.⁶ MODAG-009 has reported higher affinity and selectivity and has now been evaluated in more than 20 individuals across several diagnostic groups.

Key findings

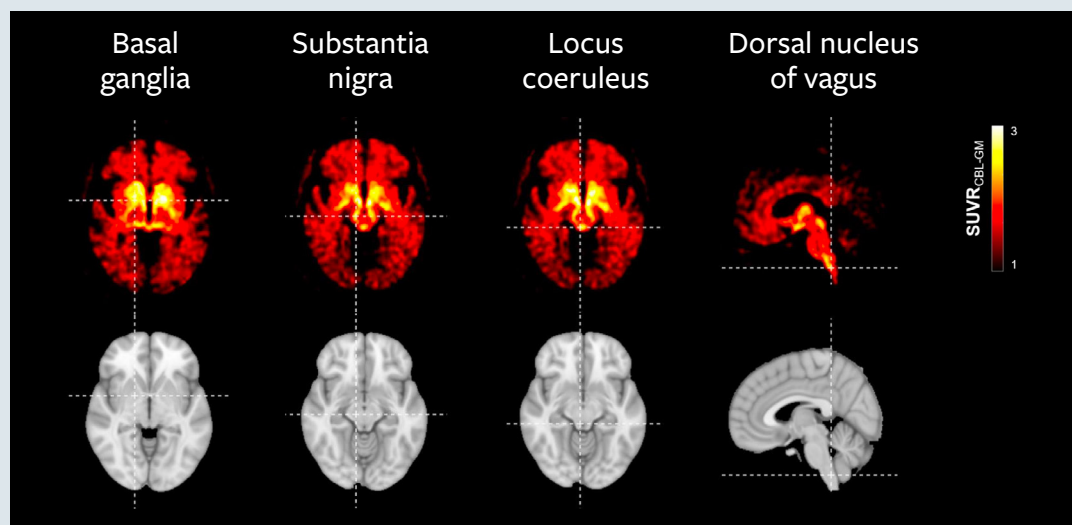
Retention was observed in the basal ganglia and substantia nigra in PD (**Figure 1**), with

brainstem and cerebellar white matter signals in MSA. DLB cases showed amygdala, basal ganglia, substantia nigra and cortical retention. In four DLB cases with amyloid and tau co-pathology, MODAG-009 retention showed little spatial association with either pathology.

Further validation

Phase I studies are underway. Larger cohorts, test-retest studies, quantitative validation and longitudinal imaging are needed to confirm selectivity and reliability. Additional HCs are also needed to better understand results.

Figure 1: [¹⁸F]MODAG-009: High-resolution imaging in PD



PD, n=2. These preliminary anatomical findings require confirmation in larger studies.
Abbreviations:
PD: Parkinson's disease;
SUVR: standardized uptake value ratio.

[¹⁸F]Co5-05

– Presented by Makoto Higuchi, National Institutes for Quantum Science and Technology, Japan

Background

Co5-05 has been evaluated in patients with PD and DLB,⁷ and more recently in two patients carrying the SNCA A53T mutation or an SNCA duplication.

Key findings

Co5-05 has shown small increases in midbrain retention in patients with PD and DLB.⁷ The two genetic cases also showed retention in the substantia nigra, consistent with the earlier

findings in sporadic PD and DLB. Unexpected retention was also observed in the inferior temporal cortex, with little spatial overlap with tau PET.

Further validation

White matter background and the unexplained inferior temporal signal require further study. Although small signals were observed in PD, potential off-target binding to tau and other targets make results difficult to interpret.

[¹⁸F]SPAL-T-06

– Presented by Makoto Higuchi, National Institutes for Quantum Science and Technology, Japan

Background

SPAL-T-06 is structurally related to Co5-05 but has mainly been evaluated in MSA. Human imaging included two patients with MSA-P, one with MSA-C and one HC, with follow-up imaging in individual patients.⁸

Key findings

Retention was observed in the putamen in MSA-P and in the pons, middle cerebellar

peduncles and cerebellar white matter in MSA-C.⁸ Small regional increases were observed over 6 to 7 months.

Further validation

The findings are based on very small numbers. Larger studies are needed to establish test-retest performance, longitudinal change and reproducibility across sites.

[¹⁸F]FD4

– Presented by Roger Gunn, XingImaging

Background

FD4 was evaluated in an initial Huashan (China) dataset including five HCs, eight patients with PD, 12 with MSA and one with rapid eye movement sleep behavior disorder (RBD). The Chinese program has since expanded to nine HCs, more than 80 patients with PD, 45 with MSA and 12 with RBD. A smaller U.S. study included three HCs, three patients with PD and three with RBD.

Key findings

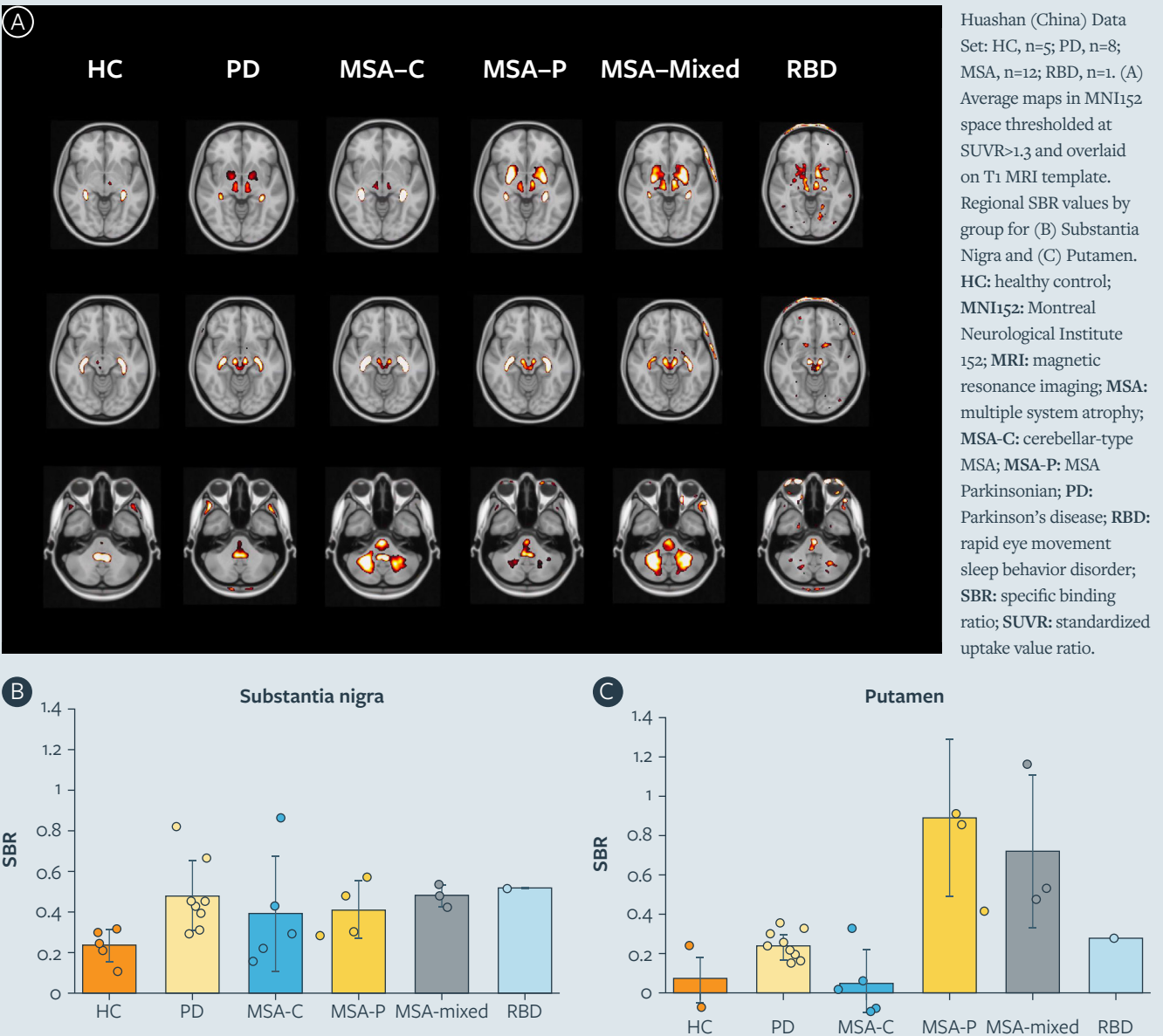
In the Huashan cohort, substantia nigra retention was slightly higher across PD, MSA

and RBD than in controls, but groups overlapped substantially. Clearer retention in the putamen was reported in PD and MSA-P, while MSA-C showed increased retention in the cerebellum (**Figure 2**). The U.S. study did not show increased binding in PD or RBD versus HCs, though data collection is ongoing.

Further validation

The underlying reason for the inconsistent results remains unclear. Potential differences in radiochemistry, tracer formulation or study populations require investigation in order to better understand conflicting results.

Figure 2: [^{18}F]FD4: Brain retention patterns across PD, MSA and RBD



[^{11}C]SYo8 and [^{18}F]SYo8F – Presented by Stephen Gomperts, Massachusetts General Hospital

Background

SYo8 has been evaluated in seven patients with PD, seven HCs, four patients with DLB and three patients with MSA-C. Pre-clinical studies reported greater than 70-fold selectivity for PD over AD tissue.

Key findings

Group-level retention was increased in PD and DLB in relevant brain regions, including the striatum and brainstem, but patient and HC values overlapped. MSA-C showed no detectable region-specific

retention, consistent with possible differential binding across aSyn conformations.

Further validation

Signals in the cerebral venous sinuses and choroid plexus, likely related to radiometabolites, may interfere with measurement. In pre-clinical studies, the ^{18}F -labeled molecule, SYo8F, has shown higher affinity and an improved off-target profile. Its longer radioactive half-life may ultimately support wider distribution and multi-center studies.

Background

M503-1619 was evaluated in a multi-center study of 18 patients with PD and 13 HCs. Pre-clinical studies reported higher affinity for PD tissue than for AD tissue and preferential binding to Lewy bodies over MSA pathology.⁹

Key findings

Twelve of 18 patients with PD exceeded an exploratory retention threshold, compared with one of 13 HCs. Increased retention was observed in the pallidum, thalamus, midbrain and other relevant regions, while six patients with PD

showed retention similar to HCs. An exploratory association with motor severity was observed, but this was largely driven by one patient and requires confirmation in a larger cohort.

Further validation

Interference from a radioactive by-product of M503-1619 meant that analysis was limited to imaging from 20 to 30 minutes after injection. The short half-life of ¹¹C also limits distribution beyond centers with local production. A redesigned tracer has been developed to address this limitation, with first-in-human testing planned.

[¹⁸F]MK-0947 – Presented by Eric Hostetler, Merck

Background

MK-0947 is a second-generation ¹⁸F tracer developed after [¹¹C]MK-7337 demonstrated off-target retention limitations. Initial human imaging included seven patients with PD and three older HCs.

Key findings

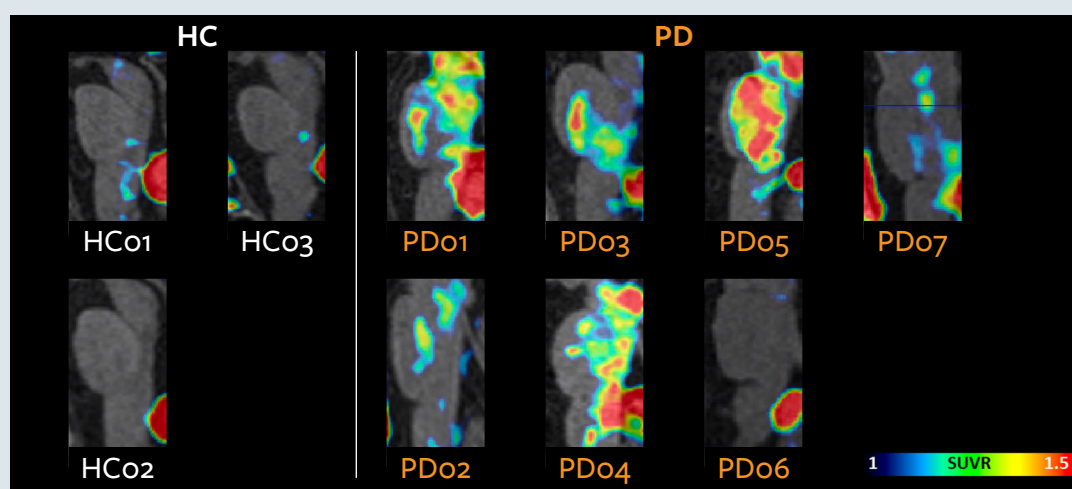
MK-0947 showed increased retention in PD across the brainstem, pons, putamen, pallidum, cerebellar white matter and midbrain, including the substantia nigra (**Figure 3**). Striatal asymmetry was broadly consistent

with clinical symptoms or dopaminergic imaging, although retention varied among patients. Unexplained off-target binding in the frontal cortex may limit use of this tracer in some regions of the brain.

Further validation

Larger cohorts are needed to confirm patient-control separation and reproducibility. Choroid plexus retention may interfere with measurements in nearby regions, while high-resolution PET is being evaluated to improve detection in small brainstem structures.¹⁰

Figure 3: [¹⁸F]MK-0947: Higher brainstem retention in PD versus HCs



PD, n=7; HC, n=3. Parametric [¹⁸F]MK-0947 SUVR images of the brainstem acquired 90 to 120 minutes after injection, using the occipital cortex as the reference region. Images are co-registered with MRI. Abbreviations: HC: healthy control; MRI: magnetic resonance imaging; PD: Parkinson's disease; SUVR: standardized uptake value ratio.

3 Remaining Challenges

Considerable progress has been achieved, but several key scientific and technical questions remain before aSyn imaging can be routinely deployed in clinical trials. Tracers must detect low-abundance, largely intracellular aSyn while accounting for differences in protein conformation, off-target binding and tracer metabolites. Measuring small brain structures affected by atrophy and neuronal loss also requires PET with sufficient sensitivity and spatial resolution, although newer high-resolution brain PET systems such as NeuroEXPLORER may improve visualization of these regions.¹⁰ Studies must also establish

reproducibility, biological validity and sensitivity to detect change. Longitudinal findings will require careful interpretation as changes in retention may reflect aSyn accumulation or reduction, loss of binding sites or tissue degeneration.

Many of these questions are now being addressed through ongoing human imaging studies in patients with PD and related synucleinopathies. The focus is increasingly shifting from proof-of-feasibility to validation, standardization and implementation.

Attendees at the meeting identified minimum evidence requirements for clinical advancement and several areas in which data must be standardized across tracer programs (**Table 1**).

Table 1: Minimum Tracer Qualifications and Challenges

	Minimum qualification for clinical advancement	Data standardization challenges
Signal validity	Retention in biologically relevant regions, with adequate selectivity and characterization of off-target signals and metabolites	Patient groups, regions of interest and outcome measures are defined differently across studies
Quantification	Validated imaging window, reference region and analytical approach	Acquisition, image processing and reporting methods vary across tracer programs
Reliability	Acceptable test-retest performance and sensitivity to longitudinal or treatment-related change	Differences among sites, scanners and populations may affect consistency of measurement
Biological validity	Evidence that PET signals reflect relevant aSyn biology in well-characterized living participants, including those with known aSyn-SAA status, with post-mortem confirmation where possible	PET findings are not yet consistently aligned with aSyn-SAA, other imaging and biofluid biomarkers, or neuropathology
Clinical trial readiness	Acceptable safety, reliable tracer supply and operational feasibility	Production, distribution, scanner calibration and quality control are not yet standardized for multi-center use

Abbreviations: aSyn: alpha-synuclein; PET: positron emission tomography; SAA: seed amplification assay.

4 Integration into Clinical Research

Well-characterized observational cohorts provide an opportunity to address the remaining evidence gaps and evaluate leading tracers as exploratory biomarkers while validation continues.¹

In prodromal cohorts such as isolated RBD, aSyn PET could identify and stage detectable brain pathology, helping to characterize early disease and inform future trial enrichment.

Researchers should continue to share data transparently as evidence on existing and emerging tracers evolves.

Longitudinal aSyn PET and multimodal imaging could map changes in regional aSyn pathology, investigate disease heterogeneity and proposed progression patterns and clarify relationships with amyloid and tau co-pathology. Pairing aSyn PET with seed amplification assays (SAA) and other biomarkers could combine molecular evidence of aSyn pathology with regional localization and support biological staging and trial enrichment. Multi-center use will also require standardized tracer production and distribution, harmonized scanning and analysis and consistent quality control.



How Can Neuroimaging Complement Other Biomarkers?

aSyn PET could complement other biomarkers by providing information on the location and regional distribution of aSyn aggregates. SAAs can indicate the presence of misfolded aSyn, while dopaminergic imaging, magnetic resonance imaging (MRI) and amyloid or tau PET provide information on neuronal function, brain structure and coexisting pathologies.



Parkinson's Precision Medicine Initiative (PPMI)

Meeting participants highlighted PPMI as a powerful accelerator for aSyn PET development.¹¹ With several tracer studies already underway, PPMI could combine extensive biomarker, imaging, genetic and clinical data to rapidly generate evidence for broader clinical validation.

5 Strategic Roadmap

From aSyn Tracer Discovery to Trial-Ready Imaging

MJFF is committed to helping move the field beyond demonstrating that a tracer can enter the brain or distinguish small groups of patients. The priority is to establish that the signal reflects relevant aSyn biology, can be measured reproducibly across populations, time points and sites and can ultimately support dependable decision-making in therapeutic trials. Our strategic roadmap outlines a proposed pathway (see **Table 2**).

Cross-cutting MJFF and field priorities

- + Maintain a diversified tracer portfolio while applying explicit, stage-appropriate decision gates
- + Enable rapid, independent review of emerging human data and prioritize the most promising tracers for larger investment
- + Promote transparent data-sharing and use shared cohorts, methods, reference standards and data to facilitate comparison across tracers
- + Engage regulators and drug developers early to define the evidence required for fit-for-purpose use in clinical trials
- + Build multi-center manufacturing, acquisition, analysis and quality-control infrastructure in parallel with clinical validation

Build Now, Deploy When Ready

MJFF's goal is to prepare the field for clinical use in parallel with tracer validation. By supporting well-characterized cohorts, harmonized methods, regulatory engagement and multi-center infrastructure now, MJFF aims to enable fit-for-purpose tracers to enter therapeutic trials as soon as the evidence supports their use.

North Star

Develop and validate an aSyn PET tracer with sufficient specificity, reproducibility, biological validity and operational scalability for reliable use in multi-center therapeutic trials.

Table 2: Strategic Priorities

1	Build and de-risk the tracer pipeline	
	Key activities Support tracer discovery, optimization, toxicology and pre-clinical testing; define relevant binding sites; compare promising tracers head-to-head when feasible	Evidence needed to advance Selective aSyn binding, favorable brain penetration and washout, minimal off-target binding and suitable kinetics
2	Establish a credible human signal	
	Key activities Conduct first-in-human studies followed by expanded testing across disease stages; include MSA where its higher aSyn burden may strengthen early signal detection; develop quantitative methods and complete safety, dosimetry and test-retest studies	Evidence needed to advance Retention in biologically relevant regions; separation between affected and control groups; acceptable safety; reproducibility; and evidence that uptake varies with disease stage
3	Demonstrate clinical and longitudinal validity	
	Key activities Embed imaging in PPMI and other deeply characterized cohorts; expand across the PD spectrum and other synucleinopathies; assess regional and longitudinal change; pursue pathology-imaging correlation where possible	Evidence needed to advance Replicated group differences, stage-dependent uptake, detectable change over time and a validated analytic approach, including reference region selection
4	Standardize and scale for clinical trials	
	Key activities Establish radiotracer production and distribution across sites; harmonize acquisition and analysis; validate performance across scanners and centers; build a quality-controlled imaging network	Evidence needed to advance Consistent multi-center performance and an operational model that enables reliable use for participant characterization and measurement of treatment-related or longitudinal change
5	Define and evaluate contexts of use	
	Key activities Engage drug developers, regulators, imaging experts and people with PD; prospectively evaluate leading tracers in trial-ready cohorts and appropriate RCT substudies	Evidence needed to advance A pre-specified fit-for-purpose use case, with performance sufficiently reproducible and operationally feasible to support relevant trial decisions

Abbreviations: aSyn: alpha-synuclein, MSA: multiple system atrophy; PD: Parkinson's disease; PET: positron emission tomography; PPMI: Parkinson's Precision Medicine Initiative; RCT: randomized controlled trial.

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Acknowledgments

MJFF would like to thank the meeting co-chairs, presenters and attendees for their valuable contributions to this meeting and report. Writing for this report was funded by MJFF and provided by Noa Chapman and Debbie Nixon, Costello Medical, UK. Graphic design support was provided by Louis Nassé, Costello Medical, UK.

List of Abbreviations

AD: Alzheimer's disease; **aSyn:** alpha-synuclein; **DLB:** dementia with Lewy bodies; **HC:** healthy control; **MJFF:** The Michael J. Fox Foundation for Parkinson's Research; **MNI152:** Montreal Neurological Institute 152; **MRI:** magnetic resonance imaging; **MSA:** multiple system atrophy; **MSA-C:** cerebellar-type MSA; **MSA-P:** MSA Parkinsonian; **PD:** Parkinson's disease; **PDD:** Parkinson's disease dementia; **PET:** positron emission tomography; **PPMI:** Parkinson's Precision Medicine Initiative; **RBD:** rapid eye movement sleep behavior disorder; **RCT:** randomized controlled trial; **SAA:** seed amplification assay; **SBR:** specific binding ratio; **SNCA:** alpha-synuclein gene; **SUVR:** standardized uptake value ratio.



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