The Coalition Against Major Diseases: Dopamine Transporter Neuroimaging as an Enrichment Biomarker To Enable Parkinson's Disease Clinical Trials

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Background

- The Coalition Against Major Diseases (CAMD) was formed by the Critical Path Institute in response to FDA's Critical Path Initiative (Romero et al., 2010, 2011). The CAMD PD Biomarkers Team plans to seek regulatory qualification of biomarkers to support effective drug development in PD.
- Reduced levels of dopamine transporter (DAT) in the putamen more so than in the caudate by SPECT neuroimaging correlate with known Parkinson's disease (PD) pathology and functional impairment.
- Patients identified as SWEDD (Scans Without Evidence of Dopaminergic Deficit) have clinical signs and symptoms of suspected PD, however their DAT scans on SPECT imaging are indistinguishable from those of aged-matched controls and represent a reliable indicator that presynaptic dopaminergic deficits are absent.

Objectives

To qualify reductions in DAT levels assessed by SPECT as an enrichment biomarker for clinical trials in early onset PD.

Methods

- We assessed the % of SWEDDS patients in several PD trials, including ELLDOPA, PRECEPT, and REAL-PET (all de novo), CALMPD (start of dopaminergic therapy) and GP11485 (treated with stable response).
- A literature review was conducted to identify observational and clinical studies of first diagnosed PD patients that utilized DAT imaging with longitudinal follow up, blinded imaging assessments, relevant statistics, and defined ligands (DaTscan^{TM} [^{123}I Ioflupane or FP-CIT] or β-CIT).
- Four studies were identified that fulfilled the criteria and each study was further analyzed to define DAT imaging's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), calculated with 95% confidence intervals (Clopper and Pearson method, Clopper and Pearson, 1934).
- Nine separate comparisons of DAT imaging in patients with PD vs. essential tremor, or vascular, drug-induced, or other secondary Parkinsonisms, were evaluated with visual or quantitative interpretation of DAT images vs. the "gold standard" clinical diagnosis by movement disorder experts.
- To understand the relationship between the results from the different studies and to give an estimate of an overall level of sensitivity and specificity, a meta-analysis was performed taking a single comparison from each study (it would not be possible to use multiple comparisons from the same study).

Results

Fig. 1: DAT Imaging illustrating reduced uptake in PD patients

^{123}I-DaTScan
Healthy control | Parkinson's Disease | MRI+SPECT: PD

Table 1: Conditions distinguishable by SPECT imaging

Movement disorders without striatal dopaminergic deficit (separable by SPECT)	Movement disorders with striatal dopaminergic deficit (inseparable by SPECT)
Vascular PS	Corticobasilar Degeneration
Drug induced	Multiple System Atrophy
Psychogenic	Lewy Body Dementia
Essential Tremor	Progressive Supranuclear Palsy
Idiopathic Dystonia	Rare genetic motor disease
Atypical tremors	Toxin-induced parkinsonism
Alzheimer's disease	Post-encephalitic parkinsonism
Dystonic tremor	Huntington's disease
Wilson's Disease	Post traumatic encephalopathy

Fig. 2: SWEDD (Scans Without Evidence of Dopaminergic Deficit) in PD Trials

Study	Stage –PD	Dur DX at Baseline (mo)	% SWEDD
Elldopa-CIT	Denovo	6	21/142 (14%)
PRECEPT	Denovo	8	91/799 (12%)
REAL-PET	Denovo	9	21/186 (11%)
Calm-CIT	Start of DA Rx	18	3/82 (5%)
GPI1485	Treated Stable responder	23	3/212 (1.4%)

Fig. 3: % SWEDDS in PD trials

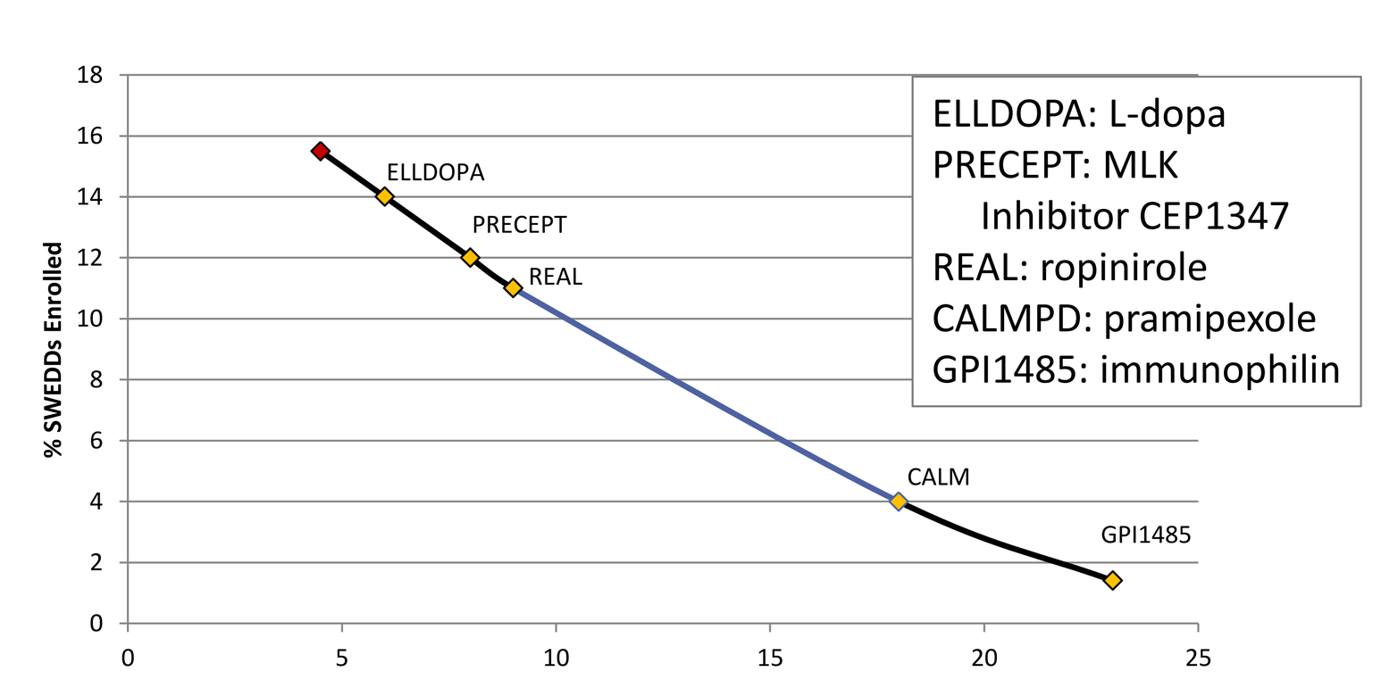


Fig. 2 and 3: SWEDD rates in PD clinical trials as factor of stage of illness and duration of PD diagnosis

A higher incidence of SWEDDs is observed as the duration since PD diagnosis decreases.

Results

Fig 4

Sensitivity & Specificity Of Different Studies Excluding Vlaar PD v APS

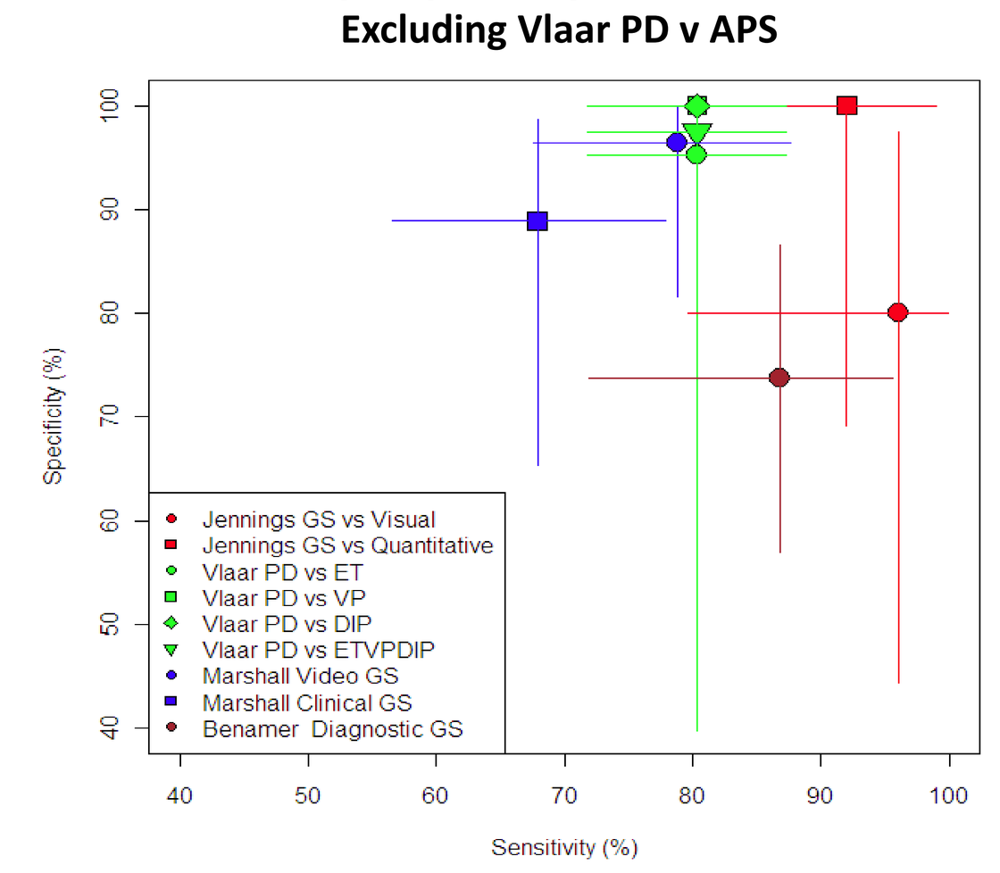


Fig 5

Meta-Analysis Of Sensitivity & Specificity Of Different Studies

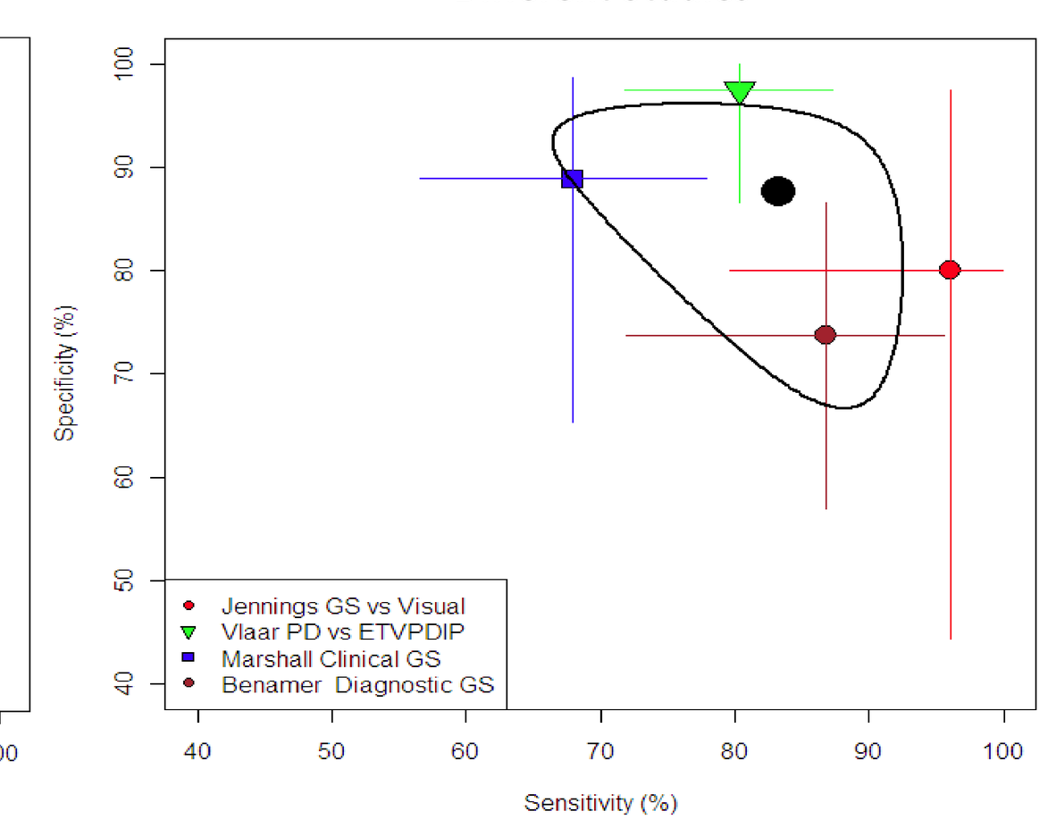
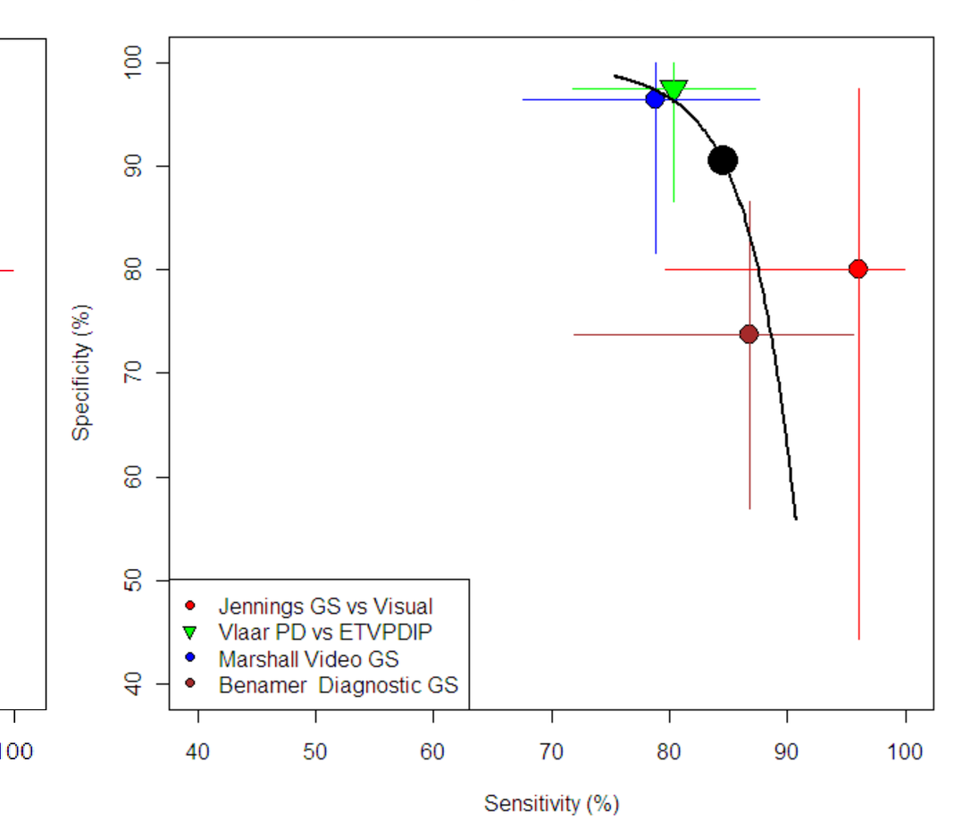


Fig 6

Meta-Analysis Of Sensitivity & Specificity Of Different Studies



Figs. 4-6: Graphic representations of sensitivity-specificity analyses

- The overall estimate of sensitivity and specificity is shown as the large point and the shape is a 95% confidence interval for the combined sensitivity-specificity. Note that in Fig. 5, the 95% confidence interval for the combined sensitivity-specificity is an ellipse, whilst with the different selection of comparisons in Fig. 6 this has collapsed to a line. This is underestimating the true uncertainty and is an artifact due to performing the analysis on a limited number of comparisons.
- These examples showed a significant level of heterogeneity between the studies; i.e., the differences between the studies were greater than may be expected by chance alone. However given the differences in study design such as the length of follow up time, this may not be surprising.

Table 2: Characteristics of the DAT neuroimaging biomarker supportive studies

Author/Yr /Country	Population:PS/NC /Other (define)	Study design	Population definition	Exclusions	PD drugs allowed	Follow-up time	Clinical outcome measure	Gold Standard	Sample size w/SPECT & f/u data	Ligand: FP CIT/B-CIT	Image interp: Visual	Image interp: semi-quantitative	Stat Comparison	Inter-reader reliability	Control population
Benamer, 2003 Europe	PD/NC/Tremor	Prospective, blinded controlled	UK Brain Bank step 1 & UPDRS maximum 16	PSP, MSA, stroke, & amphetamine drugs, hyperthyroid	Yes	3-mo blinded assessment	UK Brain bank step 1 (PD; ET)	MDE: Movement Disorders expert	14 healthy; 38 with PD; 24 uncertain PD or ET	FP-CIT	Visual: normal, abnormal grade 1,2,3	Semi Quant with ROI templates	3-mo comparison: clin features vs. presence of dopamine loss by Chi Sq.	None reported	11/14 from Benamer et al Mov Disorder 2000;15:503-510
Marshall, 2009 Europe	PS/-/ET	Prospective, blinded controlled	PS including PD UK Brain Bank step 3, MSA, PSP (criteria defined), ET	stroke, dementia, injury, amphetamine-like drugs, hyperthyroid	Yes	3-yr blinded assessment	UK Brain back criteria step 1 (PD) & Findley Koller criteria (ET)	MDE	At time=36 mo: Probable PD=66; Possible PD=5 Non-PD=28	FP-CIT	Visual: normal, abnormal (grade 1,2,3), other		3 assessments over 3 yr of patients with ET or PD	Three raters. Cohen's kappa high=0.94 0.97	Patients served as their own controls in prospective design
Vlaar, 2008 Europe	PS/-/Non-PS	Prospective, blinded controlled	Uncertain diagnosis, tertiary unit	Clear Dx of PD	Yes	3-33 mo, Mean 18 Mo	Published criteria: PD, PSP, MSA, ET, DLB	MDE	248 total: 127 PD; 27 APS 27 (17 MSA, 8 PSP, 2 DLBD) 2 unclear PD or APS, 22 ET; 5 DIP;	FP-CIT	No	Semi-Quan	FP-CIT & IBZM to gold standard clin DX		Used separately to generate normal baseline for subsequent measurement
Jennings, 2004 US	PS/-/Non-PS	Prospective, blinded controlled	Uncertain Dx. BL: classified as PS Positive or Negative	None stated	Not stated	6 mo	MDE: PS positive or Negative	MDE blind to Scan	35	Beta CIT	Yes: Positive or Negative	Yes 80% below separately measured age corrected controls	BL Scan to Gold standard DX	Vis: k=0.49 Quan: k=0.47	Separately analyzed for quantitative norms

Table 3: Statistical parameters of DAT neuroimaging biomarker supportive studies

Study	Sensitivity (Upper, Lower)	Specificity (Upper, Lower)	PPV (Upper, Lower)	NPV (Upper, Lower)
Jennings GS vs Visual	0.96 (0.80, 1)	0.80 (0.44, 0.97)	0.92 (0.75, 0.99)	0.89 (0.52, 1)
Jennings GS vs Quantitative	0.92 (0.74, 0.99)	1 (0.69, 1)	1 (0.85, 1)	0.83 (0.52, 0.98)
Vlaar PD vs ET	0.80 (0.72, 0.87)	0.95 (0.76, 1)	0.99 (0.94, 1)	0.48 (0.32, 0.64)
Vlaar PD vs VP	0.80 (0.72, 0.87)	1 (0.77, 1)	1 (0.96, 1)	0.39 (0.23, 0.57)
Vlaar PD vs DIP	0.80 (0.72, 0.87)	1 (0.40, 1)	1 (0.96, 1)	0.15 (0.04, 0.35)
Vlaar PD vs APS	0.80 (0.72, 0.87)	0.24 (0.07, 0.50)	0.87 (0.79, 0.93)	0.15 (0.04, 0.35)
Vlaar PD vs ETVPDIP	0.80 (0.72, 0.87)	0.97 (0.87, 1)	0.99 (0.94, 1)	0.63 (0.50, 0.75)
Marshall Video GS	0.79 (0.68, 0.88)	0.96 (0.82, 1)	0.98 (0.91, 1)	0.64 (0.48, 0.78)
Marshall Clinical GS	0.68 (0.57, 0.78)	0.89 (0.65, 0.99)	0.96 (0.88, 1)	0.38 (0.24, 0.54)
Benamer Diagnostic GS	0.87 (0.72, 0.96)	0.74 (0.57, 0.87)	0.77 (0.61, 0.88)	0.85 (0.68, 0.95)

Discussion

- Statistical parameters of DAT neuroimaging identified patients with PD and other primary parkinsonian syndromes and supported a robust and stable method for discriminating PD from essential tremor, and from cases of vascular, drug-induced, or other secondary parkinsonisms, that may have scans without evidence of dopamine deficiency (SWEDDs).
- Sensitivity ranged from 68-96% and specificity from 74-100% (with one outlier).
- Limitations: Differences in the study design (e.g. length of follow-up) and neurobiology likely contributed to this heterogeneity.

Conclusions

- These analyses suggest that in suspected PD patients, reduced levels of DAT assessed by SPECT can discriminate PD from essential tremor and certain secondary parkinsonisms without nigrostriatal degeneration.
- Such data support the use of DAT imaging to enable identification of a target patient population for enrichment of clinical trials with idiopathic PD patients.

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Disclosures

Dr. Gordon received personal compensation as an employee of Boehringer Ingelheim; Dr. Comery received personal compensation as an employee of Pfizer, Inc; Dr. Grachev received personal compensation as an employee of GE Healthcare; Dr. Grosset received personal compensation from Civitas, Inc, and Vectura Group PLC as a consultant; Dr. Harbron received personal compensation as an employee of AstraZeneca R&D; Dr. Kuoppamäki received personal compensation as an employee of Orion Pharma; Dr. Marek received personal compensation as an employee of Molecular NeuroImaging, LLC; Dr. Lindstedt received personal compensation as an employee of Orion Pharma; Dr. Cole received personal compensation as an employee of Medpace, LLC, and as an employee of Cole Imaging and Biomarker Consulting, LLC; Dr. Matthews received personal compensation as CEO of Abiant, Inc. and ADM Diagnostics, LLC; Dr. Romero received personal compensation as an employee of Critical Path Institute; Dr. Coffey received personal compensation from ZZ Biotech, LLC as a consultant and the University of Iowa as an employee; Dr. Russell received personal compensation from Teva Neuroscience and Boehringer Ingelheim as a speaker, and as an employee of Molecular NeuroImaging, LLC; Dr. Seibyl received personal compensation from Bayer Healthcare, GE Healthcare, and Navidea Biopharmaceuticals as a consultant, and as an employee Molecular NeuroImaging, LLC; Dr. Sherer received personal compensation as an employee of the Michael J. Fox Foundation; Dr. Stark received personal compensation as an employee of Teva Pharmaceuticals Ltd; Dr. Subramaniam received personal compensation as a consultant for Eli Lilly and MimVista Software, Inc. and grant support from the Michael J. Fox Foundation and Siemens Molecular Imaging, and as an employee of Johns Hopkins; Dr. Stephenson received personal compensation as an employee of Critical Path Institute.

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Key to Abbreviations

- APS-Atypical Parkinson Syndrome
- NC-Normal Control
- PD-Parkinson disease
- ET-Essential Tremor
- PS-Parkinsons Syndrome
- MSA-Multiple System Atrophy
- PSP-Progressive Supranuclear Palsy
- DLB-Diffuse Lewy Body Disease
- DIP-Drug Induced Parkinsonism
- GS-gold standard (clinical diagnosis)