College of Health & Human Performance
Department of Applied Physiology & Kinesiology

200 FLG
PO Box 118200
Gainesville, FL 32611-8200
352-392-0578
352-392-3186 Fax

January 30, 2021

Dear Biomarker Qualification Program Representative:

This is a letter of intent for Stage 1 submission for the Biomarker Qualification Program at the FDA. I have included a description of the biomarker consistent with the guidelines provided at the website address https://www.fda.gov/media/120058/download.

Thank you for considering this letter of intent.

Sincerely,

David E. Vaillancourt

David E. Vaillancourt, Ph.D.

Professor and Chair
Department of Applied Physiology and Kinesiology
University of Florida
Appointments in Neurology and Biomedical Engineering
Director – Laboratory for Rehabilitation Neuroscience (www.lrnlab.org)

Title
Web-based Automated Imaging Differentiation of Parkinsonism

Requesting Organization
David Vaillancourt, PhD
Professor and Chair
University of Florida
1864 Stadium Road
Gainesville, FL 32611
352-294-1770
vcourt@ufl.edu

Co-Investigators
Angelos Barmpoutis, PhD
University of Florida
angelos@digitalworlds.ufl.edu

Michael Okun, MD
University of Florida
okun@neurology.ufl.edu

Primary Point of Contact
David Vaillancourt, PhD
vcourt@ufl.edu

Alternate Point of Contact
Marissa Schauder (Clinical Coordinator)
University of Florida
schauderm16@ufl.edu

Drug Development Need Statement
Across the globe, there has been a considerable growth in the number of people diagnosed with Parkinsonism. Estimates indicate that from 1990 to 2015 the number of Parkinsonism diagnoses doubled, with more than 6 million people currently carrying the diagnosis[1]. Dorsey and Bloem suggest that 12 and 14.2 million people will be diagnosed by 2040[2]. Parkinson's disease (PD), multiple system atrophy Parkinsonian variant (MSAp), and progressive supranuclear palsy (PSP) are neurodegenerative forms of Parkinsonism, which can be difficult to diagnose as they share similar motor and non-motor features, and each have an increased risk for dementia[3-5]. Diagnostic accuracy in early PD (<5 years duration) is approximately 58%, and 54% of misdiagnosed patients have either MSA or PSP[6-8]. While the FDA has approved dopamine transporter imaging (DaTscan) to help distinguish PD from essential tremor, it unfortunately cannot distinguish between forms of Parkinsonism that also share dopaminergic deficiency[9] and also result in an abnormal DaTscan. As such, there remains no clinically approved diagnostic marker available to adequately distinguish between forms of Parkinsonism. The treatment, prognosis (often more rapid in atypical Parkinsonism), and pathology of these diseases differs, and critically effects both clinical trials testing new medications and patient care. Thus, there is an urgent need for both clinic and clinical-trial ready markers to improve diagnosis of PD, MSAp, and PSP.

Biomarker Information and Interpretation

Biomarker Name: Free-water and fractional anisotropy of human brain

Anatomical Structures: Key regions in the basal ganglia, cerebellum, midbrain, thalamus, corpus callosum, and cortex are used in a machine learning algorithm.

Background: Diffusion MRI (dMRI) is an excellent candidate biomarker because it facilitates non-invasive, tracer-free, *in vivo* quantification of brain microstructure and has a strong link associated with histology[5] and neurobiology of Parkinsonism[10-12]. In a neurodegenerative disease such as PD, MSAp, and PSP, atrophy and reduced cellular density occur, affecting the microstructural environment around cells and axons. In the context of Parkinsonism, dopaminergic neurons in the substantia nigra produce dopamine for the nigrostriatal pathway that facilitates motor function[13]. It is known that in Parkinsonism, there is a loss of >50% of the dopaminergic neurons in the substantia nigra[13]. After administering MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in a mouse model of PD[14], diffusion MRI measures were abnormal compared to saline controls. The authors suggested that diffusion MRI provides an indirect measure of dopamine cell loss within the SN. In a study investigating diffusion imaging in macaques, the authors found that diffusion measures in the nigrostriatal tract correlate with nigral dopamine neurons and striatal fiber density[10]. In the context of MSAp, neurodegeneration in the putamen is a key finding, and this structure has consistently shown altered diffusion MRI signals[11, 15]. In the context of PSP, the superior cerebellar peduncle is a region that shows neurodegeneration, and this is a structure that consistently shows altered diffusion MRI signals[11, 16]. Diffusion MRI as a technique can use several types of analysis procedures, and the two-compartment free-water model[17] is used in the automated imaging biomarker used in this letter of intent[11, 12, 18-21].

Analytical Methods and Measurement Units: The dMRI analysis technique uses a two-compartment model to facilitate the estimation of the fractional volume of free-water within a voxel, as an index of tissue microstructure, and has been associated with neurodegeneration[10, 12, 17, 22]. The data collection takes 6-12 minutes and is compatible on current 3 Tesla MRI systems worldwide. There is no injected contrast and the technique is safe using already FDA approved pulse sequences. The free-water and fractional anisotropy measurements are consistent with prior work[20, 21] and assess a unitless normalized value between 0-1 for free-water and 0-1 for fractional anisotropy. The free-water and fractional anisotropy values are used in a machine learning procedure that uses 60 regions and brain tracts to quantify free-water and fractional anisotropy. The machine learning algorithm uses quantitative values to provide a predicted biomarker score to predict the diagnosis of the patient. Two stages of the biomarker are used. The first stage is to use the biomarker score from the machine learning model for PD vs (Atypical Parkinsonism). This first stage will tell the physician if the patient falls into PD or MSA/PSP. The second stage is to use the biomarker score from the machine learning model for MSA vs. PSP, and tell the physician if the patient falls into MSA or PSP. The biomarker score is between 0-1 but the information to the physician will be categorial.

Biomarker Interpretation and Utility: The biomarker would be used in the differential diagnosis of Parkinsonism, to identify PD, MSAp, and PSP. The dMRI data are acquired using a 3 Tesla MRI machine including Siemens, Philips, or General Electric machines. The pulse sequences used are vendor specific, and FDA approved. The analysis procedure leverages the algorithm and dataset from prior work to predict diagnosis of PD, MSAp, and PSP with the probable clinical diagnosis as the standard. Our software is Code of Federal Regulations compliant. To allow for this technology to be disseminated and have the broadest impact it will be integrated into a web-based portal accessible across the United States. This client interface will establish a secure connection with a server system that will run an automated diffusion analysis pipeline powered by machine learning algorithms[18]. The system will allow users to submit dMRI data for processing, as well as other options for organizing, browsing, and previewing the data, and inspecting or exporting the results to their local computer. The

client interface will be Chrome, Firefox, Edge, and Safari compliant, and the server side will leverage hardware and software based at the University of Florida.

Context of Use

Differential diagnosis of PD, MSAp, and PSP which are forms of Parkinsonism. The use can be in clinical drug trials to diagnose patients for entry into study and/or enrich the cohort in the clinical drug trial.

Analytical Considerations

The biomarker used in the machine learning algorithm is free-water and fractional anisotropy from 60 defined regions and tracts of interest[18]. Further details are provided below.

Pre-processing and regions of interest: Custom UNIX shell scripts are used to preprocess the data[23]. Each scan is corrected for signal distortions due to eddy currents and head motion. Next, gradient directions are rotated in response to the eddy current corrections, and non-brain tissue is removed. Free-water and fractional anisotropy images are calculated using custom MATLAB scripts (MATLAB R2013a, The Mathworks, Natick, MA). The free-water model calculates the signal attenuation as the sum of attenuations arising from two compartments: one that models free-water and another that models the tissue compartment. The free-water corrected tensor images are also used to calculate corrected fractional anisotropy maps.

Data preprocessing using custom MATLAB scripts is conducted for all datasets to obtain free-water and fractional anisotropy images for each individual[17, 18]. Quality control is performed by visually inspecting each individual free-water and fractional anisotropy map. Subjects in which the field of view do not encompass the whole brain and/or there are distortions are not included. This is an issue on data collection and not due to the analysis described herein. We use custom software to normalize data to standard imaging space. We next quantify free-water and fractional anisotropy in regions and tracts of interest. We include 17 regions in the basal ganglia (anterior substantia nigra, posterior substantia nigra, subthalamic nucleus, globus pallidus, putamen, caudate nucleus), midbrain/thalamus/cortex (premotor corpus callosum, prefrontal corpus callosum, pedunculopontine nucleus, red nucleus, thalamus), and cerebellum (middle cerebellar peduncle, superior cerebellar peduncle, inferior vermis, dentate nucleus, cerebellar lobule V, cerebellar lobule VI). We include subthalamo-pallidal, nigrostriatal, and corticostriatal tracts. We also incorporate several existing tractography templates, which include the sensorimotor area tract template (S-MATT), a transcallosal tractography template (TCATT), and a cerebellar white matter atlas. The S-MATT includes 6 different sensorimotor tracts, including the tracts descending from the primary motor cortex, dorsal premotor cortex, ventral premotor cortex, supplemental motor area, pre-supplemental motor area, and somatosensory cortex. The TCATT includes 5 parietal, 6 occipital, 6 frontal, and 12 prefrontal commissural tract. We also use the superior and middle cerebellar tracts from the cerebellar probabilistic white matter atlas.

Machine Learning: Each combination of variables has been evaluated using training and validation of a support vector machine (SVM) learning algorithm using a linear kernel in the scikit-learn package in Python. We chose the widely accepted SVM method because it is a robust machine learning model for classification. The rationale for using a linear kernel is due to the fact that data in this study could be separated linearly, and interpretability for feature importance could be easily obtained. Disease-specific comparisons are made to predict diagnosis (PD vs. Atypical and MSA vs. PSP). A recent study setup the current machine learning SVM model. In that study, training/validation sets for each disease-specific comparison consisted of 80% of the total relevant data while the remaining 20% was reserved

for a test dataset. Subjects were randomly assigned to the training/validation set or the test dataset using stratified sampling to ensure that the training/validation and test dataset group proportions were equal to the total dataset group proportions. In the training/validation cohort, the data were randomly split into 5 subgroups for 5 fold cross-validation. The purpose of the 5 fold cross-validation was to optimize the F1 score (i.e., the harmonic mean of the precision and recall) by optimizing the penalty parameter (C, a measure which directly represents the tolerance for error) across the 5 distinct folds. This penalty parameter was used to train the machine learning model using the training/validation dataset and the performance of this optimized model was evaluated on the test dataset. To evaluate the performance of the machine learning models in the training/validation cohort and the test cohort, we conducted receiver operating characteristic (ROC) analyses using the trained models. The area under the curve (AUC) was calculated for each model for each comparison (PD vs. Atypical Parkinsonism and MSA vs. PSP). The models were statistically evaluated using Delong's test to compare AUCs. We also calculated several measures from the confusion matrix, including accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. Further, we evaluated the pathophysiological relevance of the models by relating feature importance to the absolute value of the coefficients of the hyperplane that defines the optimized SVM model. The ComBat batch-effect correction tool was used to harmonize the data multisite dMRI data.

In recent work, models were developed on a training/validation cohort and evaluated in a test cohort. In the test cohort for both disease-specific comparisons, the wAID-P area under the curve for PD vs. Atypical Parkinsonism was 0.955 and for MSA vs. PSP was 0.926. We also calculate several measures from the confusion matrix, including accuracy, sensitivity, specificity, positive predictive value, and negative predictive value and all are reported in our manuscript[18].

Clinical Considerations

The biomarker would be used to aid in the diagnosis of different forms of Parkinsonism (PD, MSAp, PSP). The inclusion criteria for clinical trials of PD, MSAp, and PSP require a clinical diagnosis. This diagnosis can be incorrect because of the lack of training for the referring physician. The current biomarker (wAID-P) will provide a diagnostic score that will provide an evaluation if the patients falls into PD, MSAp, or PSP. This can be integrated into clinical practice or in clinical trials testing new medications. The risks are consistent with other associated risks for MRI. There is no injected contrast.

Supporting Information

We are currently proposing a new U01 grant to prospectively test the biomarker over the next five years. We will be including the results from this new prospective study in our full biomarker qualification package. The new study is a 21-site study with 315 total patients, 105 PD, 105 MSAp, and 105 PSP. The grant application has been submitted to the NIH. The outcome of this newly proposed study will be the basis for cut-off points. The name of the software to be used is wAID-P version 1.0.

Future Business Model

The future business model for this application is to provide this as a service that is accessible through a software license fee. Users can access the site from anywhere in the United States. The user would upload an imaging dataset, and the algorithms would produce a diagnostic assessment and provide the user with a probability for diagnosis of PD, MSAp, or PSP.

Attachments

Below, we list three key publications that support the development of the biomarker.

Summary: This is retrospective study exploring the use of the biomarker in over 1000 diffusion MRI datasets and 17 MRI sites at 3 Tesla. The study provided > 90% accuracy for diagnosing Parkinsonism. The study also included Siemens and Phillips MRIs. This study provides the basis for the biomarker qualification plan and allowed us to propose the new study with NIH to validate this procedure.

Archer, D.B., Bricker, J.T., Chu, W.T., Burciu R., McCracken J.L., Lai, S., Coombes, S.A., Fang, R., Corcos, D.M., Kurani, A.S., Mitchell, T., Black, M.L., Herschel, El., Simuni, T., Parrish, T.B., Comella, C., Xie, T., Seppi, K., Bohnen, N.I., Muller, M.L.T.M., Albin, R.L., Krismer, F., Du, G., Lewis, M.M., Huang, X., Li, H., Pasternak, O., McFarland, N.R., Okun, M.S., Vaillancourt, D.E. (2019). Development and Validation of the Automated Imaging Differentiation in Parkinsonism: A Machine Learning Study. The Lancet Digital Health 1(5):PE222-E231.

Summary: This study compared free-water and fractional anisotropy biomarker to neurite density orientation dispersion biomarker. The direct comparison of the two biomarker approaches indicated that free-water and fractional anisotropy had better performance and required less MRI time for differential diagnosis of Parkinsonism. This study included two MRI sites using Siemens.
Mitchell, T., Archer, D.B., Chu, W.T., Coombes, S.A., Lai, S., Wilkes, B., McFarland, N.R., Okun, M.S., Black, M.L., Herschel, E., Simuni, T., Comella, C., Xie, T., Parrish, T.B., Kurani, A.S., Corcos, D.M., Vaillancourt, D.E. (2019). Neurite orientation dispersion and density imaging (NODDI) and free-water imaging in Parkinsonism. Human Brain Mapping 40(17):5094:5107. PMID: 31403737.

Summary: This is the key study from a single site that showed that the free-water and fractional anisotropy biomarker could detect patterns for differential diagnosis in different forms of Parkinsonism. This study provided the foundation for the two studies above.

Planetta, P.J., Ofori, E., Pasternak, O., Burciu, R., Shukla, P., DeSimone, J.C., Okun, M.S., McFarland, N., Vaillancourt D.E. (2016). Free water imaging in Parkinson's disease and atypical Parkinsonism. Brain. 139(Pt2): 495-508. PMID: 26705348.

References

1. Group GBDNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877-897.
2. Dorsey ER, Bloem BR. The Parkinson Pandemic-A Call to Action. JAMA Neurol 2018;75:9-10.
3. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47:1-9.
4. Litvan I, Goetz CG, Jankovic J, et al. What is the accuracy of the clinical diagnosis of multiple system atrophy? A clinicopathologic study. Arch Neurol 1997;54:937-944.
5. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861-870.
6. Adler CH, Beach TG, Hentz JG, et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. Neurology 2014;83:406-412.
7. Beach TG, Adler CH. Importance of low diagnostic Accuracy for early Parkinson's disease. Mov Disord 2018;33:1551-1554.
8. Jankovic J, Rajput AH, McDermott MP, Perl DP. The evolution of diagnosis in early Parkinson disease. Parkinson Study Group. Arch Neurol 2000;57:369-372.

9. Perlmutter JS, Eidelberg D. To scan or not to scan: DaT is the question. Neurology 2012;78:688-689.
10. Shimony JS, Rutlin J, Karimi M, et al. Validation of diffusion tensor imaging measures of nigrostriatal neurons in macaques. PLoS One 2018;13:e0202201.
11. Planetta PJ, Ofori E, Pasternak O, et al. Free-water imaging in Parkinson's disease and atypical parkinsonism. Brain 2016;139:495-508.
12. Burciu RG, Ofori E, Archer DB, et al. Progression marker of Parkinson's disease: a 4-year multi-site imaging study. Brain 2017;140:2183-2192.
13. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron 2003;39:889-909.
14. Boska MD, Hasan KM, Kibuule D, et al. Quantitative diffusion tensor imaging detects dopaminergic neuronal degeneration in a murine model of Parkinson's disease. Neurobiol Dis 2007;26:590-596.
15. Seppi K, Schocke MF, Esterhammer R, et al. Diffusion-weighted imaging discriminates progressive supranuclear palsy from PD, but not from the parkinson variant of multiple system atrophy. Neurology 2003;60:922-927.
16. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med 2012;2.
17. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. Magn Reson Med 2009;62:717-730.
18. Archer DB, Bricker JT, Chu WT, et al. Development and validation of the automated imaging differentiation in parkinsonism (AID-P): a multicentre machine learning study. Lancet Digital Health 2019;1:222-231.
19. Ofori E, Krismer F, Burciu RG, et al. Free water improves detection of changes in the substantia nigra in parkinsonism: A multisite study. Mov Disord 2017;32:1457-1464.
20. Ofori E, Pasternak O, Planetta PJ, et al. Increased free water in the substantia nigra of Parkinson's disease: a single-site and multi-site study. Neurobiol Aging 2015;36:1097-1104.
21. Ofori E, Pasternak O, Planetta PJ, et al. Longitudinal changes in free-water within the substantia nigra of Parkinson's disease. Brain 2015;138:2322-2331.
22. Metzler-Baddeley C, O'Sullivan MJ, Bells S, Pasternak O, Jones DK. How and how not to correct for CSF-contamination in diffusion MRI. Neuroimage 2012;59:1394-1403.
23. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. Neuroimage 2012;62:782-790.