neuropacs™

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1 Instructions for Clinical Use

1.1 Device Description

neuropacs™ is a fully automated, generalizable software that differentiates Parkinsonian syndromes. It uses AI to analyze diffusion Magnetic Resonance Imaging (dMRI) measurements from pathologically relevant brain regions of a patient who experiences symptoms consistent with Parkinson's disease. The differentiation report generated from neuropacs™ can assist healthcare providers in accurately diagnosing if a patient has a form of atypical Parkinsonism, and, in such case, differentiate between multiple system atrophy Parkinsonian variant (MSAp) and progressive supranuclear palsy (PSP).

1.2 Indications for Use

The neuropacs™ system is a software application intended to receive and analyze diffusion MRI data from patients aged 40 years and older presenting with Parkinson's disease (PD) like symptoms. The neuropacs™ system provides a report to aid neuroradiologists and/or neurologists in identifying patients with Atypical Parkinsonism (i.e., multiple system atrophy Parkinsonian variant (MSAp), or progressive supranuclear palsy (PSP)). The results of the neuropacs™ system are intended to provide supplemental information in conjunction with a standard neurological assessment and other clinical tests. Patient management decisions should not be made solely on the basis of analysis by the neuropacs™ system.

1.3 Contraindications

- Do not use in patients with stroke, brain tumor, and seizures.
- As necessitated by the risks of Magnetic Resonance Imaging, patients who have any type of implanted electrical device (such as a cardiac pacemaker or a neurostimulator), or a certain type of metallic clip in their body (i.e., an aneurysm clip in the brain), cannot obtain the necessary dMRI scan for use in the neuropacs™ system.

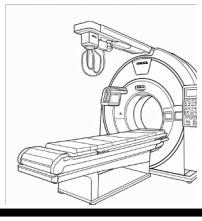
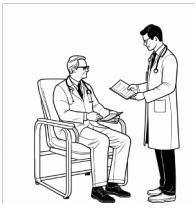
1.4 Warnings and Precautions

- The neuropacs™ system should not be used for purposes other than indicated in the Indications for Use section above.
- Caution: Federal law restricts this device to sale by or on the order of a physician.
- The neuropacs™ system has been tested with datasets from GE, Siemens, and Philips MRI scanners. It is not recommended to use scanners that have not been tested by neuropacs™.
- This software does not work with any other form of data other than dMRI acquired with the protocol specified in this user manual.
- Visually inspect the data to ensure that the MRI scan contains the full volume of the brain and is free of distortions due to patient motion or other forms of artifacts, such as tumors.
- Healthcare providers must follow the instructions from this manual on how to interpret the differentiation results.

1.5 Intended Use

The neuropacs™ system is intended to aid neuroradiologists and/or neurologists in identifying patients with Atypical Parkinsonism based on the analysis of diffusion MRI data using machine learning techniques.

1.6 Step-by-step Instructions for Health Care Providers

1		A patient experiences symptoms consistent with Parkinson's disease. The patient is 40 years of age or older. The neuropacs™ system can be used to assist with the diagnosis of atypical Parkinsonism and differentiate between MSAp, and PSP.
2		A diffusion MRI scan of the patient's brain must be acquired using the protocol parameters provided in this manual (section: Input Data Specifications). Basic image quality check is required through visual inspection to ensure that the scan contains the full volume of the brain and is free of distortions due to patient motion or other forms of artifacts, such as tumors.
3		The MRI scan can be submitted for analysis with neuropacs™ through a PACS or other software environment that provides the option to analyze data using neuropacs™.
4		The health care provider consults the result of the neuropacs™ analysis along with other clinical assessments and makes a diagnosis or other patient management decisions.

1.7 Example of results

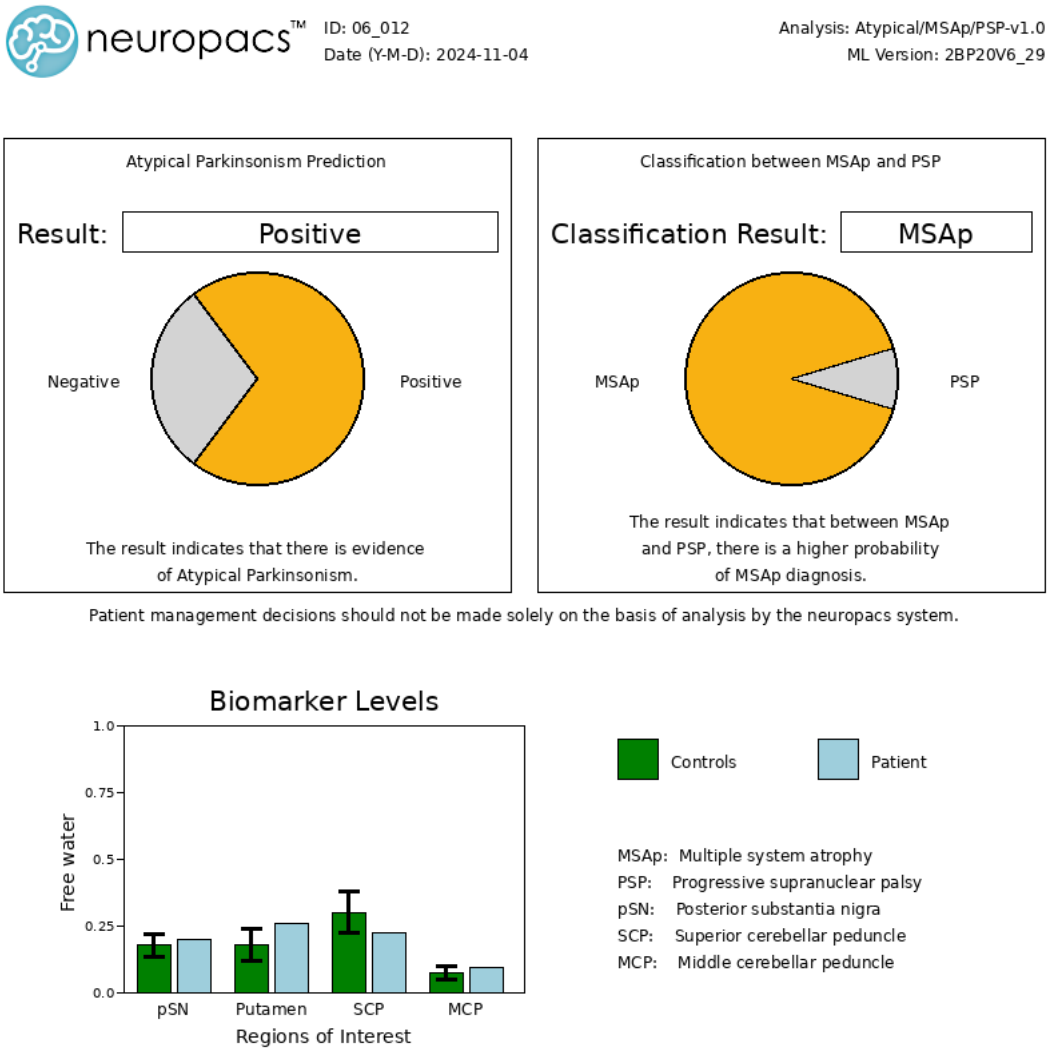
The neuropacs™ analysis report contains the results from one or two independent classifiers:

- The Atypical Parkinsonism classification result.
- If the first result indicates Atypical Parkinsonism, then the classification result between MSAp and PSP is also contained in the report.

The report also contains a unique report ID and the date of the report for future reference.

Additionally, selected free-water biomarker levels included in the classification process, which produced the above results, are compared with those of control subjects.

An example of the analysis report is shown below:



1.8 How to interpret the results

Result is generated by a machine learning algorithm intended as an adjunct for the diagnosis of Atypical Parkinsonism (MSAp and PSP) in patients with Parkinson's Disease like symptoms. The algorithm is trained and validated to identify and differentiate Atypical Parkinsonism syndromes (MSAp and PSP) by use of diffusion MRI measurements from pathologically relevant regions of the patient's brain. The device is intended to be used in conjunction with other clinical and diagnostic findings to serve as an adjunct in the diagnosis of Atypical Parkinsonism. The neuropacs™ outputs are not intended to replace clinical evaluation of the patient. All cases of suspected MSAp or PSP should be referred for evaluation by specialized neurologists. Use of neuropacs™ does not negate the standard of care and the standard clinical workflow should be followed.

You must carefully read both classification results (Atypical classification and MSAp vs. PSP if shown) before making any diagnostic decisions. Patient management decisions should not be made solely on the basis of analysis by the neuropacs™ system.

Example 1: A physician evaluates a case of a 50-year-old patient with a possible or probable diagnosis of PSP. The physician orders a neuropacs™ analysis of the patient's dMRI scan to confirm the PSP diagnosis. The following differentiation result is obtained:

The result of the Atypical classifier is: **Positive** The result of the MSAp vs. PSP classifier is: **PSP**

- The result indicates that there is evidence of Atypical Parkinsonism. This agrees with the physician's evaluation.
- The result indicates that between MSAp and PSP, there is a higher probability of the subject being diagnosed with PSP. The result agrees with the physician's evaluation.
- Both results agree with the possible or probable diagnosis of PSP and confirm the physician's evaluation. The physician considers the PSP indication among other clinical tests and assessments in order to make patient management decisions.

In this case the neuropacs™ report was used to confirm the physician's initial assessment.

Example 2: A physician evaluates a case of a 66-year-old patient with a possible or probable diagnosis of MSAp. The physician orders a neuropacs™ analysis of the patient's dMRI scan in order to confirm the MSAp diagnosis before making any patient management decisions. The following differentiation result is obtained:

The result of the Atypical classifier is: **Positive** The result of the MSA vs. PSP classifier is: **PSP**

- The result indicates that there is evidence of Atypical Parkinsonism. This agrees with the physician's evaluation.

- The results indicate that between MSAp and PSP, there is higher probability of the subject being diagnosed with PSP. This result differs from the physician's initial evaluation.
- The PSP indication questions the physician's initial assessment of MSAp. The physician decides to perform additional clinical tests and assessments in order to better differentiate between PSP and MSAp before making any patient management decisions.

In this case the neuropacs™ report questioned the physician's initial assessment.

Example 3: A physician evaluates a case of a 57-year-old patient with a possible or probable diagnosis of PD. The physician orders a neuropacs™ analysis of the patient's dMRI scan to detect an atypical Parkinsonism diagnosis. The following differentiation result is obtained:

The result of the Atypical classifier is: **Negative**
The result of the MSA vs. PSP classifier is not reported because the Atypical result was negative.

- The result indicates that there is no evidence of Atypical Parkinsonism. This agrees with the physician's evaluation.
- The physician considers the results of the neuropacs™ report among other clinical tests and assessments in order to make patient management decisions.

In this case the neuropacs™ report confirmed the physician's initial assessment.

1.9 Summary of Clinical Testing

neuropacs™ has been trained, validated, and tested in several clinical studies.

Study 1: the diagnostic classification performance of neuropacs™ was compared against clinical diagnosis of PD, PSP, and MSAp based on clinical evaluations in a multi-site study conducted on 300+ participants between 40 and 80 years old with possible or probable diagnosis of PD, MSAp, and PSP. The clinical diagnosis was performed by three separate neurologists, which is the most rigorous method to date to ascertain the clinical diagnosis of each patient. neuropacs™ was then evaluated against this clinical diagnosis when there was unanimous agreement among all three neurologists. neuropacs™ identified patients with Atypical Parkinsonism with high accuracy compared to the clinical diagnosis established by the three independent neurologists, and classified them as MSAp or PSP with high accuracy. The study also showed that the algorithm was not biased by the sex of the participants and was reliable in a test-retest study.

Study 2: while agreement among three independent neurologists is the most rigorous method to obtain a diagnosis, the only way to confirm the diagnosis is through neuropathological examination of post-mortem brain tissue. In the second study, the diagnostic performance of neuropacs™ was compared to the neuropathological diagnosis on 48 participants with PD, MSAp, or PSP from five independent imaging and pathological data repositories. The average time between *in vivo* imaging and pathological diagnosis at autopsy is 37.9 months. Clinical

diagnosis of PD, MSAp, PSP, or other neurodegenerative disease was performed by one practicing neurologist specific to each repository. neuropacs™ identified patients with Atypical Parkinsonism with high accuracy, and classified them as MSAp or PSP with high accuracy. The study also compared the diagnosis performance of neuropacs™ to the diagnostic established by neurologists when the MRI was acquired. Results showed an overall accuracy of neuropacs™ at 93.8% for pathological diagnosis prediction, while the accuracy of the diagnosis established by the neurologist at the time of imaging acquisition was 83.3%. These results demonstrate higher accuracy of neuropacs™ than clinical evaluation for predicting primary diagnosis of Atypical Parkinsonism, including MSAp and PSP.

Study 3: the effects of disease severity and scanner vendor on the diagnostic performance of neuropacs™ were evaluated on 1071 subject images from 781 PD patients, 83 MSAp patients, and 207 PSP patients.

The dataset was separated on disease severity as measured from the Unified Parkinson's Disease Rating Scale (UPDRS). The goal of the study was to determine if the level of accuracy is maintained or improved when disease severity is examined. neuropacs™ was used on each group, then receiver operator characteristics curves were generated and the area under the curve (AUC) was computed for each model and group. Results of tests on low severity cases were compared to the results of tests on high severity cases for each test (i.e., detection of Atypical Parkinsonism and MSAp vs PSP). Results obtained in low and high severity groups were comparable (less than 5% difference), indicating that the diagnostic performance of neuropacs™ is independent of the severity of symptoms.

The same dataset was used to compare the performance of neuropacs™ on data obtained with Siemens scanners against all scanners (i.e., Siemens, Phillips, and GE combined). The software was used on each group, then receiver operator characteristics curves were generated and the area under the curve (AUC) was computed for each model and group. Results obtained with Siemens only were comparable to results obtained with all scanners (less than 5% difference), indicating that the diagnostic performance of neuropacs™ is not significantly impacted by scanner vendor.

2 Technical Instructions

2.1 Product Requirements

a) Internet connection (uploading speed of at least 300 Mbps is recommended).
b) Access to a PACS or other software environment that provides the option to analyze data using neuropacs™.
c) Access to patient's dMRI data.

2.2 Input Data Specifications

Whole brain diffusion MRI obtained with a single-shot spin echo EPI sequence sensitized to diffusion effect with the following acquisition parameters:

Scan Parameter Name	Value (or Range)
Magnetic Field Strength	3 Tesla
Repetition Time (TR)	6000 msec - 13000 msec
Echo Time (TE)	58 msec - 104 msec
Flip Angle	90°
Voxel Size	2 mm Isotropic
Number of Slices	≥ 80 Interleaved
Directions	> 30
Slice Gap	Zero
b-value	0 (x5), 1000 s/mm^2

The acquired MRI scans must be provided in DICOM imaging format (Digital Imaging and Communications in Medicine Part 10). The header of the DICOM images must contain the acquisition parameters using one or more of the following tags:

DICOM tag	Use
[0008, 0070]	scanner name
[2005, 1415][a]	b-vectors
[2005, 1599][a]	b-vectors
[0019, 10bb][b]	b-vectors
[0019, 10bc][b]	b-vectors
[0019, 10bd][b]	b-vectors
[0019, 10e0][b]	b-directions
[0019, 100e][c]	b-directions
[0043, 1039][b]	b-value
[0019, 100c][c]	b-value
[0019, 1027][c]	b-matrix
[0019, 100d][c]	diffusion directionality
[0018, 1312][b]	phase encoder

[a]: usually used by Philips scanners.
[b]: usually used by GE scanners.
[c]: usually used by SIEMENS scanners.

2.3 Output specifications

The output contains the following information:

- request ID number [alphanumeric]
- the date of the processing request submission [yyyy-mm-dd]
- description of the input provided [text, example: “242 DICOM files”]
- the type of processing performed [text “Atypical/MSAp/PSP-v1.0”]
- the version of the Machine Learning model used [text “2BP20V6_29”]
- the Atypical Parkinsonism classification result [number between 0 and 1, with less than 0.5 denoting a negative result, and more than or equal to 0.5 denoting a positive result]
- description of the Atypical Parkinsonism classification result [text “The result indicates that there is no evidence of Atypical Parkinsonism.” or “The result indicates that there is evidence of Atypical Parkinsonism.”]
- If the previous result indicates Atypical Parkinsonism, then the report will also contain the following two values:
  - the differentiation result between MSAp and PSP [number between 0 and 1, with less than 0.5 denoting MSAp, and more than or equal to 0.5 denoting PSP]
  - description of the differentiation result between MSAp and PSP [text “The result indicates that between MSAp and PSP, there is higher probability of MSAp diagnosis.” or “The result indicates that between MSAp and PSP, there is higher probability of PSP diagnosis.”]
- biomarker levels of free water diffusion in the following brain regions:
  - posterior substantia nigra [number between 0 and 1]
  - putamen [number between 0 and 1]
  - superior cerebellar peduncle [number between 0 and 1]
  - middle cerebellar peduncle [number between 0 and 1]
- biomarker levels in control subjects [average and st. deviation] for each region:
  - average value in posterior substantia nigra [number between 0 and 1]
  - average value in putamen [number between 0 and 1]
  - average value in superior cerebellar peduncle [number between 0 and 1]
  - average value in middle cerebellar peduncle [number between 0 and 1]
  - standard deviation in posterior substantia nigra [number]
  - standard deviation in putamen [number]
  - standard deviation in superior cerebellar peduncle [number]
  - standard deviation in middle cerebellar peduncle [number]

2.4 Application Programming Interface

We provide an Application Programming Interface (API) for integration of neuropacs™ within your system. The API can be used in the following ways:

- Direct HTTPS requests to the API endpoints. Detailed technical specification of the endpoints is available at the following address: https://neuropacs.github.io/

- Use the API through the neuropacs™ open-source examples that show how to perform the API calls from:
  - JavaScript https://github.com/neuropacs/neuropacs-js-api
  - Python https://github.com/neuropacs/neuropacs-py-api
  - CLI (Command Line Interface) https://github.com/neuropacs/neuropacs-cli

Quick reference:

`init(apiKey,serverUrl)`
 	
Returns:
`neuropacs object`
	This function initializes the neuropacs object.
	
	Input: apiKey– String with a key provided upon registration
	serverUrl– The URL provided upon registration
	Output: A neuropacs object

`connect()`
 	
Returns:
`String`
	This function establishes a secure connection with the neuropacs server.
	
	Output: An alphanumeric connection ID or false if the connection was not established.

`newJob()`
 	
Returns:
`String`
	This function creates a new neuropacs order. An order ID is returned by the server to be used in subsequent references to this order.
	
	Output: String with the order ID.

`upload(dataset,orderId)`
 	
`dataset: array`
`orderId: String`
 	
Returns:
`Integer`
	This function uploads a DICOM dataset file to a specific analysis order.
	
	Input: dataset – An array of File objects
	orderId – String with the order ID.
	
	Output: An integer with the HTTP response code.

`runJob(productName,`
`orderId)`
 	
`productName: String`
`orderId: String`
 	
Returns:
`Integer`
	This function submits an order for processing. The type of neuropacs product to be used in this order must be specified.
	
	Input: productName – String with the product name.
	Example: “Atypical/MSAp/PSP-v1.0”
	orderId – String with the order ID.
	
	Output: An integer with the HTTP response code.

`checkStatus(orderId)`
 	
`orderId: String`
 	
`Returns:`
`String`
	This function checks the status of an order. The result is returned as a JSON-formatted string with the parameters: started (true/false), finished (true/false), failed (true/false), progress (integer), info (string).
	
	Input: orderId – String with the order ID.
	
	Output: JSON-formatted string with the status info.

`getResult(format, orderId)`
 	
`format: String`
`orderId: String`
 	
`Returns:`
`String (TXT, JSON, XML) or bytes (PNG)`
	This function retrieves the result of a completed order in a specified format such as TXT, JSON, PNG, and XML.
	
	Input: format – String with the desired file format.
	orderId – String with the order ID.
	
	Output: A string (TXT, JSON, XML) or byte array (PNG) with the result.

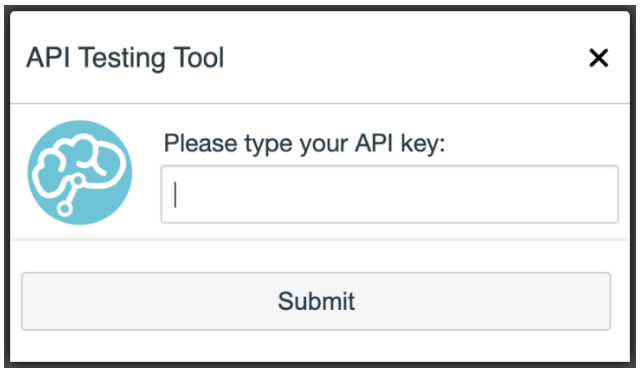
Example (in JavaScript)

```
//initialize the neuropacs object
const npcs = Neuropacs.init({serverUrl, apiKey});
//connect to the neuropacs server
await npcs.connect();
//create a new order for Parkinsonism differentiation
let orderId=await npcs.newJob();
//upload a DICOM dataset
await npcs.uploadDataset({dataset,orderId});
//submit the order for processing
await npcs.runJob({productName:"Atypical/MSAp/PSP-v1.0",orderId});
//retrieve the results
let results=await npcs.getResults({format:"JSON",orderId});
```

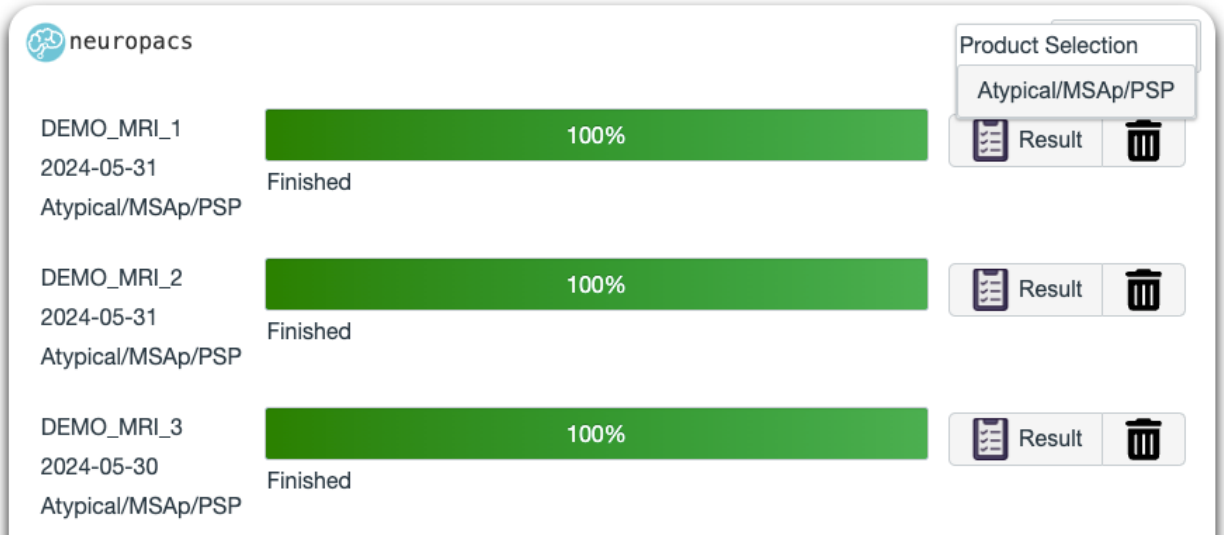
2.5 API Testing Website

We also provide a live demo of our API as a complementary product testing website. The purpose of this website is for customers to test and evaluate our products before they proceed with the integration of the products within their PACS environment.

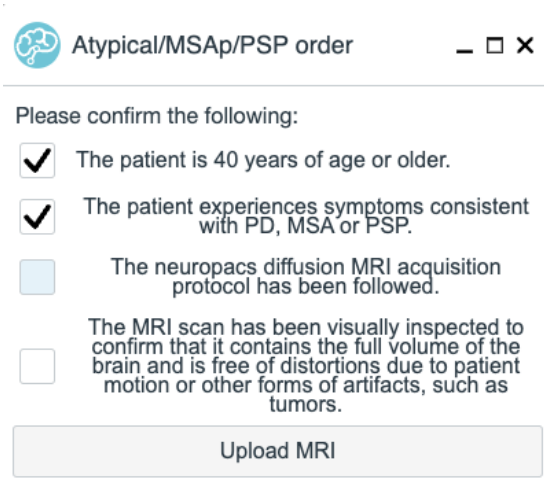
The testing site, is located at: https://neuropacs.github.io/demo/ and can be accessed using one of the following browsers: Google Chrome, Mozilla Firefox, Apple Safari, or Microsoft Edge. You must also type your testing API key as shown in the image below.



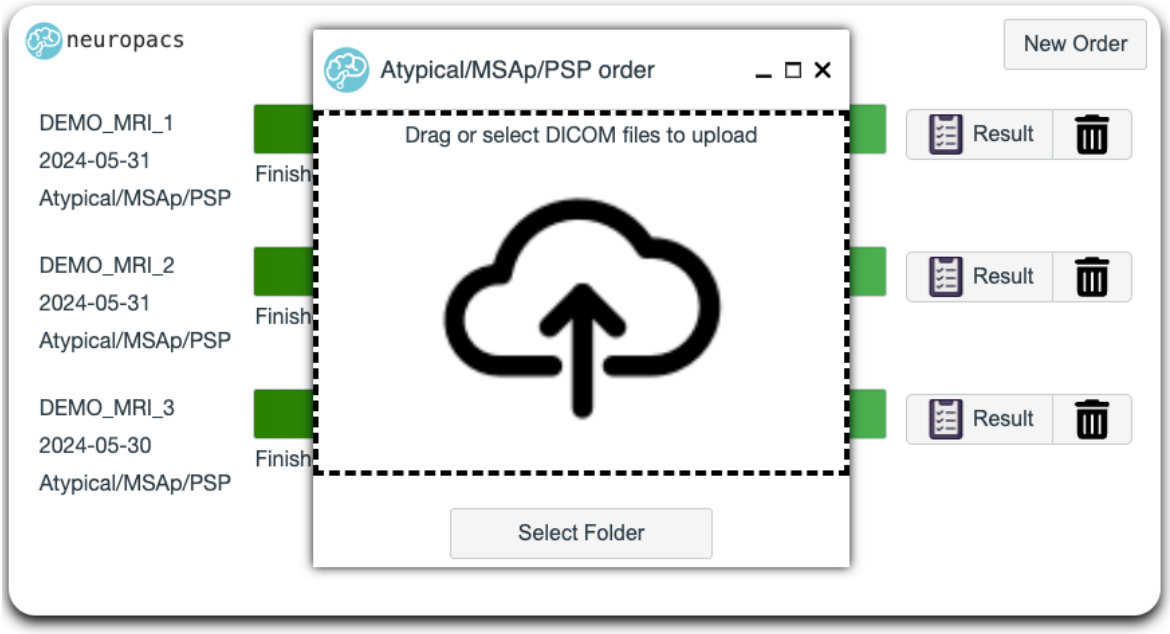
You can start a new order by clicking on the “New Order” button and select “Atypical/MSAp/PSP” from the pop-up menu on the upper right corner. If you have previously used the testing site from the same browser, you will be able to check the progress of your previous orders and view the processing results. (See image below.)



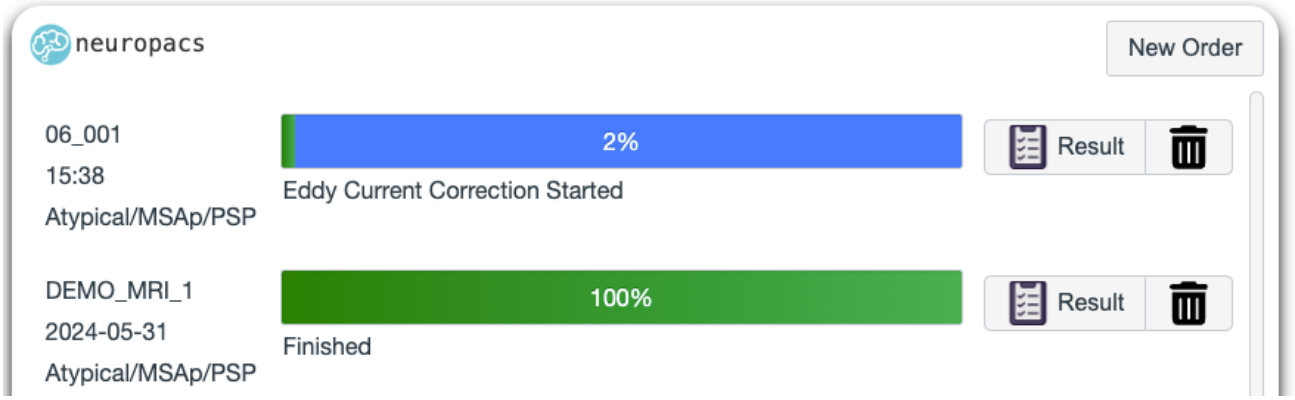
After that, a pop-up window will prompt you to confirm that the patient meets certain criteria.



After that, a pop-up window will prompt you to drag or select DICOM files to upload for processing as shown in the image below.

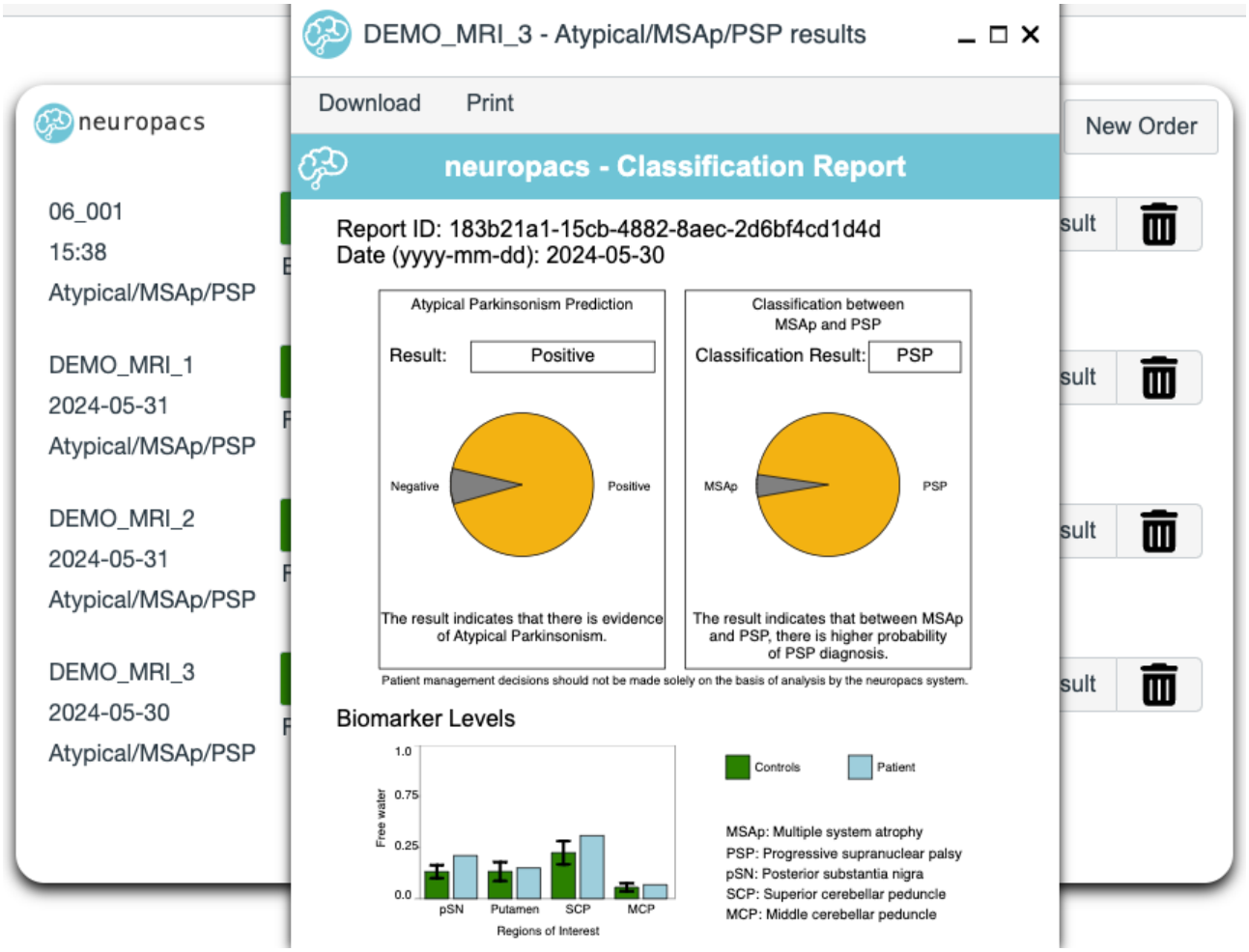


After the file selection, an order number will be assigned to your processing request and the status of the process will be indicated on the top of the list of your orders. In the image below the status of the most recent order is 2%.

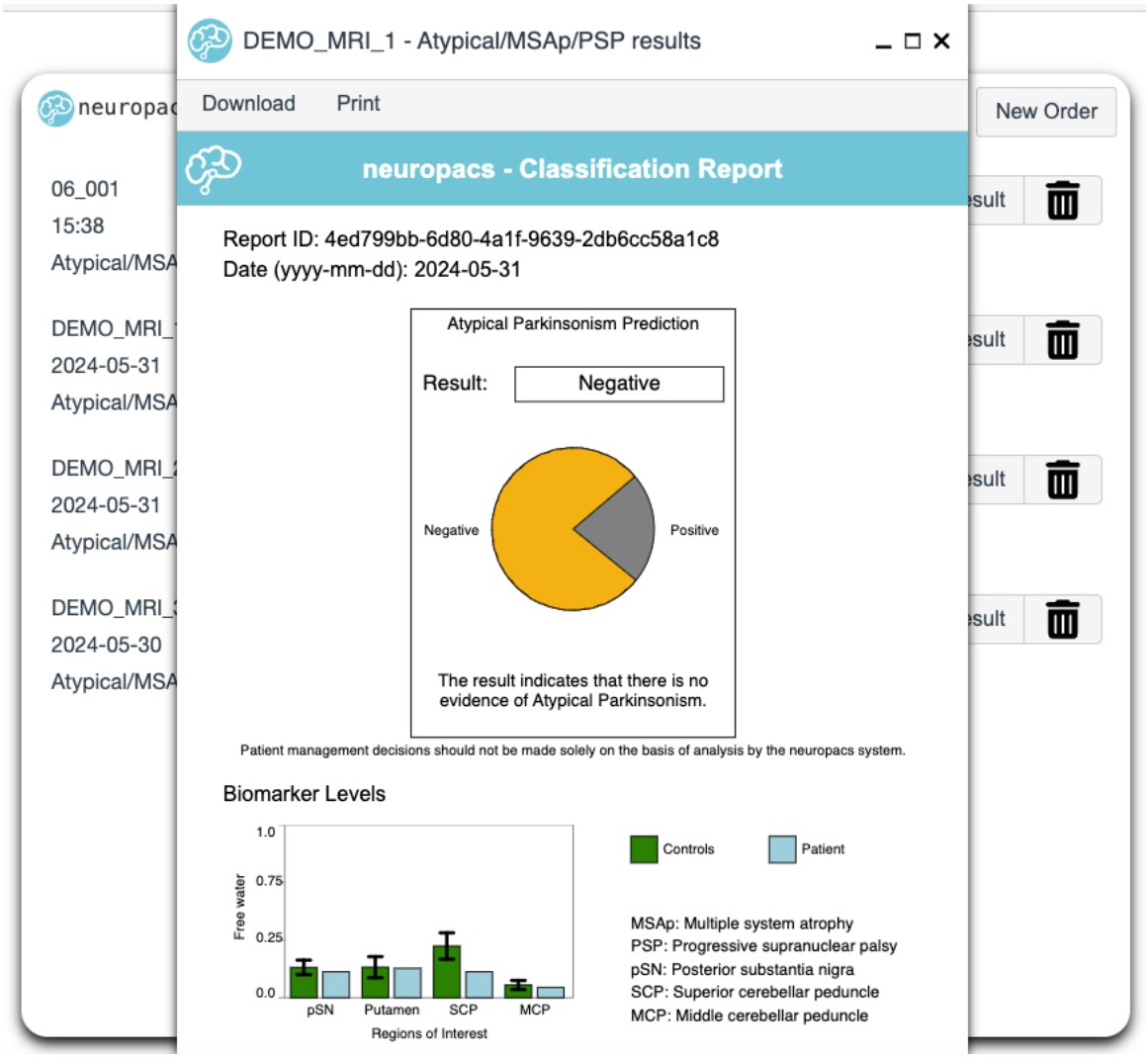


Once the processing is completed you can view the results by clicking on the “Results” button.

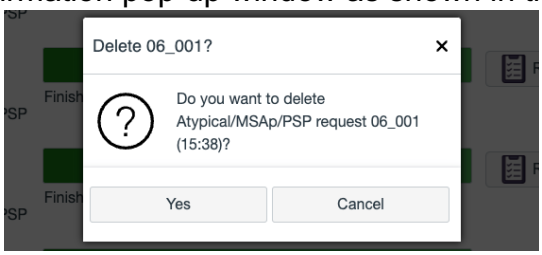
In the example below the Atypical Parkinsonism classification result is positive. The classification result between MSAp and PSP is indicating PSP. Furthermore, the result is supported by providing a chart of biomarker levels (free water) in four regions of interest (Posterior substantia nigra, Putamen, Superior cerebellar peduncle, and Middle cerebellar peduncle) and a side-by-side comparison with the corresponding biomarker levels in control subjects.



A different example is shown below. In this case the Atypical Parkinsonism classification result is negative. Therefore, there is no further classification between MSAp and PSP.



Finally, you can remove entries from your list of orders by clicking on the “trash bin” button and then “Yes” on the confirmation pop-up window as shown in the image below.



2.6 Recommended Security Controls

Cybersecurity Recommendations

It is recommended to keep your API KEY in secure digital storage such as a password vault.

Never share your API KEY with others.

Always use a new randomly generated AES key when you connect to neuropacs™.

It is recommended to follow the guidelines for AES-CTR encryption as specified in NIST SP800-38A, when sending data to neuropacs™ service for analysis.

Data de-identification Recommendations

Prior to sending data to neuropacs™ for analysis, it is recommended that all input images have been properly de-identified by removing the tags with sensitive information from the DICOM header, including but not limited to the following tags:

DICOM tag	Use
[0008, 0080]	Institution Name
[0008, 0081]	Institution Address
[0008, 0082]	Institution Code Sequence
[0008, 0090]	Referring Physician Name
[0008, 0092]	Referring Physician Address
[0008, 0094]	Referring Physician Telephone Numbers
[0008, 0096]	Referring Physician Identification Sequence
[0008, 1040]	Institutional Department Name
[0008, 1048]	Physicians of Record
[0008, 1049]	Physicians of Record Identification Sequence
[0008, 1050]	Performing Physician Name
[0008, 1052]	Performing Physician Identification Sequence
[0008, 1060]	Name of Physicians Reading Study
[0008, 1062]	Physicians Reading Study Identification Sequence
[0008, 1070]	Operators Name
[0008, 1072]	Operator Identification Sequence
[0008, 1080]	Admitting Diagnoses Description
[0008, 1084]	Admitting Diagnoses Code Sequence
[0010, xxxx]	Patient's information
[0032, xxxx]	Medical visit details
[0040, 0006]	Scheduled performing physician's name

It is recommended that other private tags are also removed.

2.7 Software Bill of Materials (SBOM)

The software components of the neuropacs™ system are listed in the following table:

Name	Source	EOL or Latest Version	Cybersecurity information
Ubuntu	Canonical Ltd.	April 23, 2025	https://ubuntu.com/security/notices
Node.js	OpenJS Foundation	April 30, 2026	https://nodejs.org/en/security
mySQL Community Server	Oracle Corporation	April 2026	https://www.oracle.com/security-alerts/
AFNI (Analysis of Functional NeuroImages)	National Institute of Mental Health, USA.	Latest version released: October 17, 2024	https://afni.nimh.nih.gov
ANTs	Penn Image Computing and Science Laboratory University of Pennsylvania	Latest version released: July 24, 2024	https://github.com/ANTsX/ANTs/wiki
dcm2niix	Chris Rorden	Latest version released: Feb. 2, 2024	https://github.com/rordenlab/dcm2niix
FSL (FMRIB Software Library)	FMRIB Centre, University of Oxford	Latest version released: October 14, 2024	https://fsl.fmrib.ox.ac.uk/fsl/fslwiki
MATLAB Compiler Runtime	MathWorks, Inc.	Latest version released: June 2024	https://www.mathworks.com/content/dam/mathworks/policies/mathworks-Information-security-practices.pdf
Miniconda3	Anaconda, Inc.	Latest version released: August 22, 2024	https://www.anaconda.com/guides/the-ultimate-guide-to-open-source-security-with-python-and-r
Python3	Python Software Foundation	October 2025	https://python-security.readthedocs.io/
R	R Core Team R Foundation for Statistical Computing	Latest version released: October 21, 2024	https://www.r-project.org/doc/R-SDLC.pdf

2.8 Software Developer's Checklist

The following checklist must be completed when integrating neuropacs™ into your software solution.

☐	Your neuropacs™ API key is securely stored in your software and is not shared with third parties.
☐	The neuropacs™ report ID must be included in the report shown to the health care provider.
☐	The neuropacs™ report date must be included in the report shown to the health care provider.
☐	An indication that the results were generated by neuropacs™ must be included in the report shown to the health care provider.
☐	The statement “Patient management decisions should not be made solely on the basis of analysis by neuropacs™.” must be included in the report shown to the health care provider.
☐	Before obtaining the report, the health care provider must be reminded that the patient must be 40 years of age or older, and must experience symptoms consistent with Parkinson's disease.
☐	A screenshot from the report generated from the provided test dataset in the intended format to be shown to the health care provider must be submitted to your neuropacs™ contact for approval. Prior to approval all diagnostic results generated by neuropacs™ will contain the text “Not for clinical use.”
☐	The data must be de-identified before submitted to neuropacs™ for analysis.

3 Software Version and Date of Manufacture

This device labeling is for neuropacs™ system (software) version 1.1. This revision of the device labeling (Rev. A) was issued on 4-Nov-2024.

4 Manufacturer Information

Automated Imaging Diagnostics, LLC
9706 SW 34th LN
Gainesville, FL 32608

Phone: 352-316-7923
Email: info@neuropacs.com
Website: https://neuropacs.com/