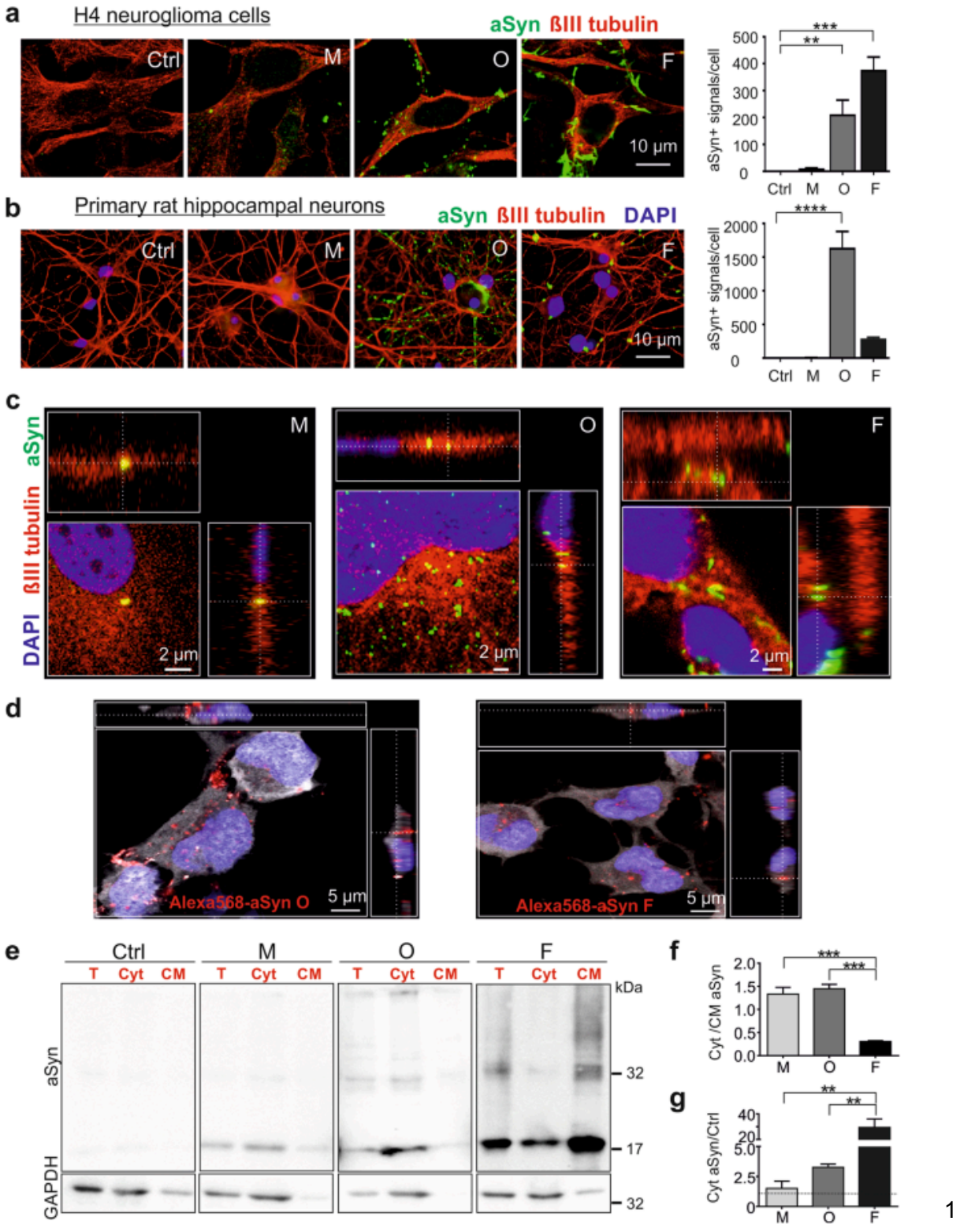
A Novel Biomarker Panel Using Multi-Omic Approaches for Early Parkinson's Disease Diagnosis: PD-INSI

Name: *Sage Guan - Westmount Charter School Mid-High - Junior Category Grade:8*



Scientific Challenge:

Problem:

- Parkinson's disease disorder
- Late and inaccurate diagnosis
- PD is currently mainly being diagnosed via clinical symptoms, which only appear after roughly 70-80% of dopaminergic neurons in the brain have already been destroyed or damaged.
- The misdiagnosis rate sits around 10-50%, usually higher in the earlier stages of PD

Who (Who does this impact?):

- Current PD patients
- Advances clinical trials and PD diagnostic success/accuracy
- Accelerates research on current biomarker panels for Parkinson's

What (What am I doing?):

- Building a ML discovery pipeline through python to run simulations to measure performance of biomarker panel
- Utilizing benchling to test out and analyze data from each biomarker within the panel and performance stats

Why (Why am I doing this?):

- Aim to create a multi-omic high accuracy biomarker panel capable of accelerating earlier Parkinson's disease diagnosis

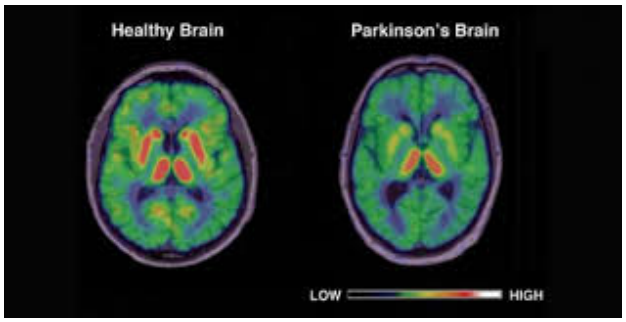
Basis Research & Fundamentals:

Parkinson's Disease (PD) Intro.

What is it - Parkinson's disease is a progressive movement disorder impacting the nervous system. It causes neurons (nerve cells) in certain parts of the brain to weaken and become damaged; eventually dying. This leads to symptoms that include issues with movement, tremor, stiffness, and difficulties balancing. As symptoms progress, people with PD may develop difficulties walking, talking, or even completing simple tasks in everyday life.

Parkinson's & the Neurosystem/Brain - Many areas of the brain are affected by Parkinson's, however the most common symptoms result from the loss of neurons in the substantia nigra (an area near the base of the brain). The neurons in this area produce dopamine; which is the chemical in the brain that signals the body to produce smooth and purposeful movements. Studies have shown that the majority of people with PD have lost 60-80% or more of their dopamine-producing cells in the substantia nigra; consistent with the time the symptoms appear. PD causes people to also lose the nerve endings that produce norepinephrine (a neurotransmitter for automatic functions) which controls many automatic functions in the human body including, pulse, and blood pressure. The loss of norepinephrine (NE) is believed to explain several symptoms of Parkinson's that are not necessarily related to movement, such as fatigue, and blood pressure changes/fluctuations.
The affected brain cells contain Lewy bodies; which are deposits of the protein aSyn which becomes toxic). While the exact reason for Lewy bodies to form or their exact role is unclear, some research suggests that the cell's protein disposal system could fail in people with PD, causing the protein build up to reach harmful levels, hence triggering cell death. Additional studies have found evidence that clumps of protein that develop inside the brain cells of people with PD may contribute to the overall death of neurons.

Figure 1. Comparison of a Healthy brain (Control) vs. a Parkinson's brain. Credit: *Neuro Challenge Foundation for Parkinson's. What is Parkinson's Disease? (Dr. Dean P. Sutherland)*



<u>Symptoms of Parkinson's Disease (PD)</u> - PD affects different people in different ways, and the rate of progression and particular symptoms differ among individuals. That being said, Parkinson's symptoms tend to originate on one side of the body. However, it progresses and eventually affects both sides, although symptoms are often less severe on one side than the other. The four primary symptoms of PD include:

1. **<u>Tremor</u>** usually begins in a person's hand, although being first affected in the foot or jaw is not uncommon either. The specific tremor associated with PD exhibits a rhythmic back and forth motion; the tremor will cause the person to put their thumb and forefinger together. This may appear as "pill rolling". This symptom is most prominent when the hand is at rest or when the individual is under stress. This tremor tends to disappear during sleep and may actually improve when the person makes a purposeful, intended movement.
2. **<u>Rigidity</u>** (muscle stiffness), or resistance to movement affects the majority of people with PD. The muscles stay tense and tight, causing the person to experience an aching or stiff sensation. If another person attempts to move the individual's arm, it will only move in short, jerky movements; known as "cogwheel" rigidity.
3. **<u>Bradykinesia</u>** is a slowing down of spontaneous and some automatic movement. This can make simple tasks become more difficult, and can extend the amount of time needed for a simple task such as washing or dressing much longer. The person's face could also be less expressive (masked face).
4. **<u>Postural instability</u>**, examples include, balance problems and changes in posture. This may also increase the risk of falls.

In addition to the four symptoms listed, people with PD often develop a "Parkinson's gait." This is characterized by a tendency to lean forward, taking small, quick steps (festination), and

reduced swimming in one or even both arms. They may experience trouble initiating movement, as well as stop suddenly while walking -freezing in place.
Other unlisted characteristic symptoms of people with PD, include:

- **Mental and emotional health issues** - Depression or Anxiety could occur during the earlier stages of PD, or even before the onset of movement issues.
- **Difficulty with swallowing/chewing** - This is seen more commonly in the later stages of Parkinson's; food and saliva might collect in the mouth or back of the throat, causing choking or drooling. It can make it difficult for people in the later stages of PD to get sufficient nutrients.
- **Speech Challenges** - Most people with PD have speech difficulties, which may lead to quieter speech, or for them to talk in a monotone. Some individuals may also hesitate before speaking, slurred speech or super quick speech may occur as well.
- **Urinary problems or constipation** - In PD, the automatic nervous system is not able to function correctly.
- **Skin issues** - People with Parkinson's may see an increase in facial oils, especially on the forehead, and sides of the nose. Oily scalp, resulting in dandruff is common too. In other cases, the skin can become very dry, and the person may experience excessive sweating.
- **Sleep difficulties** - Common sleep problems seen in PD include, difficulty staying asleep at night, restless sleep, nightmares, emotional dreams, and drowsiness, as well as suddenly falling asleep in the day. Another problem is REM sleep behavior disorder. This causes people to act out their dreams, leading to possible injury to themselves or their partner. Certain medications used to treat PD could contribute to some sleep issues.
- **Dementia/other cognitive problems** - Some people with Parkinson's develop memory problems and slowed thinking. Cognitive issues are most severe in the late stages of PD, and some may be also diagnosed with Parkinson's disease dementia. Memory, visuospatial skills, attention, language, and cognitive reasoning can also be affected.
- **Orthostatic hypotension** - This is a sudden drop in blood pressure when a person stands up from sitting or lying down, leading to dizziness and lightheadedness, and in extreme cases fainting.
- **Muscle cramping & dystonia** - The rigidity and lack of movement often causes muscle cramps, primarily in the legs and toes. PD can also be associated with dystonia (sustained muscle contractions that cause forced or twisted positions).

- **Pain** - It is common for people with Parkinson's to experience aches and pains in their muscles and joints due to stiffness and abnormal postures.
- **Fatigue or loss of energy** - The majority of people with PD typically have fatigue, mainly late in the day. Fatigue could also be associated with depression or the sleep disorders, but can also stem from motor control issues such as trouble initiating or carrying out movement, tremors, or stiffness.
- **Sexual dysfunction** - It occurs, because Parkinson's disease affects nerve signals from the brain, which can cause sexual dysfunction. Related depression or medications may cause decreased sex drive.

Primary Age Group at Risk.

Age - The average age of onset is usually a person in their early to mid 60s, and the risk rate rises significantly with older age. However, a small percentage of people with PD have "early-onset" Parkinson's, which begins before the age of 50.
Biological sex - PD affects more men than women
Heredity - Individuals with one or more close relatives who have or have had PD have a statistically increased risk of developing the disease themselves.
Environmental Exposure - Studies have shown an increased risk of PD for people who live in rural areas where pesticide exploration is common. Exposure to specific toxins has caused parkinsonian symptoms in rare circumstances such as MPTP, illicit drugs, or exposure to the metal manganese in welders.

While the actual cause of PD is unknown, some cases are entirely hereditary and can be traced to certain genetic mutations, however the majority of cases tend to be sporadic. Researchers currently believe PD likely results from a combination of genetics and explore to one or more environmental factors that trigger PD.

Parkinson's Disease Biomarkers.

Biomarker Def. - Biological markers, commonly referred to as biomarkers are substances within the body that can give researchers and doctors information about an individual's health. For example, high cholesterol is a primary biomarker of heart disease. Biomarkers are located in body tissues or fluids such as blood or urine.

The Significance of Biomarkers in PD.

While there is no singular test that can alone diagnose an individual with Parkinson's, doctors are able to draw conclusions from your past and present symptoms, your medical history and in-office exams. In some cases, blood testing and other diagnostic tools such as MRIs or DaT scans can support diagnosis'.
Parkinson's researchers believe that biomarkers hold great potential for earlier PD diagnosis, with greater precision, as well as a possible way to track the progression of the disease severity. Biomarkers could also be used to improve the way we currently design and administer clinical trials.
There are different types of biomarkers: Genetic (genes), clinical (motor symptoms, non-motor symptoms), imaging (DAT), biochemical (aSyn, other protein biomarkers).

Existing Genetic Biomarkers for PD (Parkinson's Disease).

Alpha-synuclein (aSyn) - *This is the first widely applied biomarker in early clinical research on PD. aSyn is central to Parkinson's, since it is a brain protein directly tied to cell loss within the brain. Healthy human brains are rich in aSyn; but can also be found in lesser amounts throughout the body.*
In PD, researchers have been led to believe that damaged aSyn folds into an irregular shape. From there on out, the aSyn may behave somewhat like a seed; causing regular aSyn to form toxic clumps (Lewy bodies).
Recent research has shown that researchers are now able to spot misfolded aSyn in the cerebrospinal fluid of people with PD. The method used for this abnormal protein is called aSyn seed amplification assay (SAA).

SNCA - This gene in specific, makes the protein aSyn which was the first gene identified to be with Parkinson's disease. Lewy bodies were seen in all cases of PD, this discovery revealed the link between hereditary and sporadic forms of PD.

LRRK2 - Code for a complex protein called dardarin that plays a role in many cellular functions. Research has proven that LRRK2 mutations affect how cells metabolize aSyn. These changes might lead to the formation of Lewy bodies. The activity of this protein is commonly increased in sporadic PD.

DJ-1 - This gene defends cells from oxidative stress and mutations in this gene can cause rare early onset forms of Parkinson's.

PRKN (Parkin) - The Parkin gene creates a protein that assists cells breaking down and recycling proteins. Mutations within this gene can cause early-onset PD.

PINK1 - Codes for a protein active in mitochondria. Mutations within this gene appear to increase susceptibility to cellular stress. PINK1 has been linked to early-onset Parkinson's disease.

GBA (glucocerebrosidase-beta) - Mutations in GBA are known to cause Gaucher disease, a type of lipid storage disorder. Different abnormalities in this gene are commonly associated with an increased risk for Parkinson's disease and faster progression of symptom development.

Clinical Biomarkers.

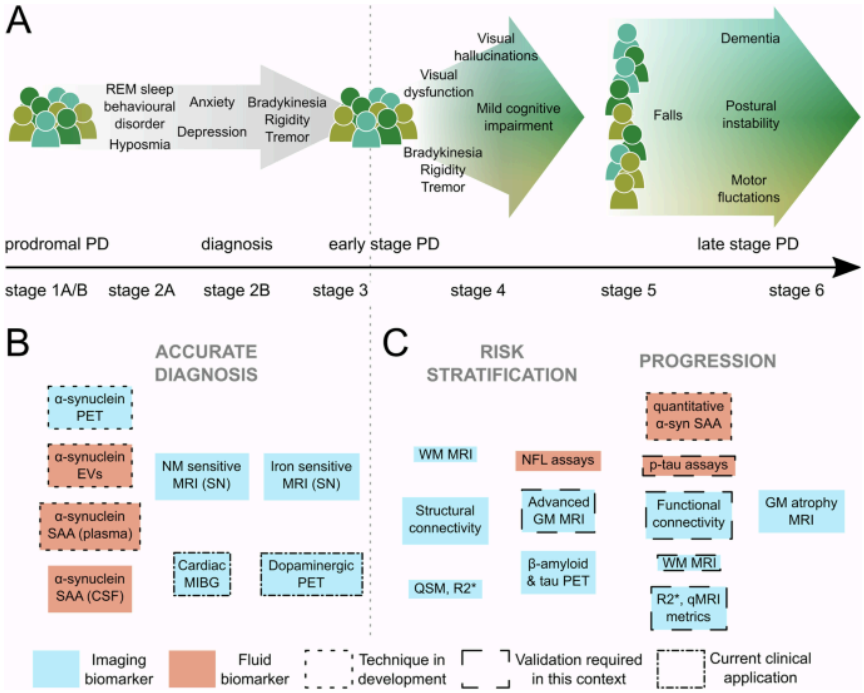
Anything which falls under the category of non-motor symptoms, such as loss of smell, constipation, REM sleep behavior disorder, as well as motor symptoms including tremor, rigidity, and bradykinesia.

Stages of Parkinson's Disease & Types.

Stages of PD:

1. Stage 1 - *Early Stage* - This stage is the first stage of PD, and is characterized by mild symptoms, and typically found on one singular side of the body. These symptoms may include tremor, rigidity, or changes in posture or walking. Symptoms in this stage generally do not interfere with everyday activities.
2. Stage 2 - *Mid-stage (early)* - The mid-stage of Parkinson's (on the earlier side), is where symptoms begin to progress and worsen. Now, the disease can affect both sides of the body, and movement symptoms begin getting more prominent. Usually these are present around the midline (around the neck or trunk).
3. Stage 3 - *Mid-stage (turning point)* - After PD enters the stage 3 threshold, doctors typically consider it the "turning point", since it can now severely impact your balance. Loss of balance and frequent falls are common. The movement of the person becomes collectively slower, and here is where PD can really start affecting their daily life.
4. Stage 4 - *Advanced Stage* -
5. Stage 5 - *Advanced Stage (Late)* -

Figure 1. The Stages of PD. Credit: *Nature communications. Neuroimaging and fluid biomarkers in Parkinson's disease in an era of targeted interventions.*



Current PD Diagnosis Methods.

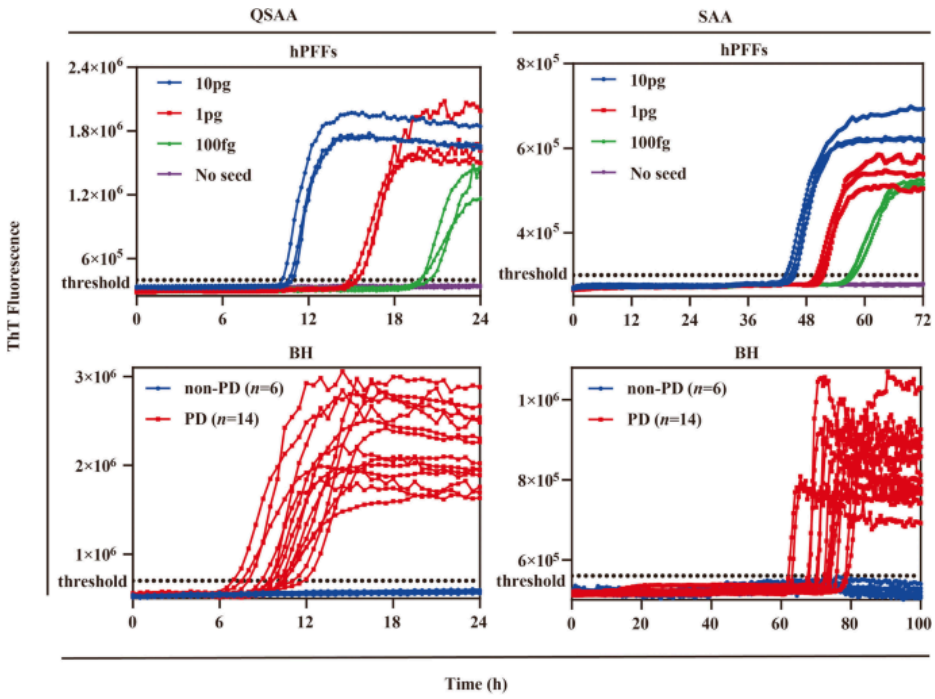
Alpha-synuclein Seed Amplification Assay (SAA).

Intro. Although commercially available, this testing method has not yet been widely standardized and not all scientists have achieved the same results which confirms minor inaccuracies and deficiencies in this methodology.

While the SAA biomarker test detects misfolded aSyn, it cannot predict whether someone who has misfolded aSyn will eventually develop PD later on. The test currently does not differentiate between the various types of synucleinopathy and it might not identify all cases of Parkinson's accurately nor consistently. One primary example of this is the fact that there are people with the LRRK2 genetic variant of PD, which has an increased risk of being missed by SAA.

Additionally, another limitation is that the test cannot track Pd progression throughout the body. Testing in some centers requires a lumbar puncture (spinal tap) which basically removes a small portion of cerebrospinal fluid.

Figure 2. SAA sample results (example). Credit: *Translational Neurodegeneration. Ultrasensitive detection of aggregated aSyn using quiescent seed amplification assay for the diagnosis of Parkinson's disease.*



The Syn-One (Skin Biopsy) Test.

Intro. This method uses a skin sample to confirm the presence of aSyn in the nerves. The test functions by identifying whether aSyn has undergone phosphorylation (when phosphate is added to a molecule such as sugar or protein). Results from the test can potentially assist PD doctors in confirming a Parkinson's diagnosis.

CND Life Sciences is the organization which manufactures this test, and processes the tests.

The hallmark protein associated with Parkinson's is aSyn. Phosphorylation is a crucial biological process that helps cells regulate storage and energy. In PD, phosphorylated aSyn could be present in nerves throughout the body and can deposit in the nerve fibers of the skin. The Syn-One Test detects the presence of these abnormalities in the body.

The only function of this test is to confirm an abnormality is present. It cannot distinguish between Parkinson's disease, dementia with Lew bodies, and multiple system atrophy or REM

sleep behavior disorder. Doctors use the test results alongside other tests to confirm PD diagnosis.

Sample Case Study Summary. Research Team: Led by Dr. Christopher Gibbons of Beth Isreal Deaconess Medical Centre.
Scientific Challenge: Identify accessible biomarkers that could potentially aid in the diagnosis of synucleinopathies (groups of neurodegenerative diseases which originate from an abnormal accumulation of aSyn)
What: They designed a study to test whether the presence of P-SYN in simple skin biopsies could successfully identify people with synucleinopathies.
Environment: The study was conducted as 30 sites, with >400 participants who were enrolled in the study between February 2021 and March 2023. This included 277 people who had been diagnosed prior to the study with 1 in 4 synucleinopathies based on clinical criteria. With another 151 people with no history whatsoever of neurodegenerative disease served as controls. The ratio of male to female was ~1:1.
Methodology/Procedure: All participants underwent an expert panel to confirm their diagnoses. They each had small skin biopsies measuring 3mm taken from three locations: the neck, knee, and ankle. These samples were tested for P-SYN.
Results: The results showed that skin biopsies could detect a high proportion of participants with synucleinopathies. P-SYN was found in 9% of those with clinically diagnosed Parkinson's disease (89/96 people). The biopsies were proven even more successful for other conditions, accurately identifying 98% of those with multiple system atrophy (54/55), and 96% of those with dementia with Lewy bodies (48/50). In addition to the other results, the biopsies recognized all of the 22 participants clinically diagnosed with pure autonomic failure. P-SYN was detected in only 3% of the control participants.

Brain Imaging, SPECT (Single-photon emission computed tomography).

Intro. A SPECT scan is a type of imaging test which uses radioactive substances and a specialized camera to create 3D pictures. This can be able to show how well the organs are functioning. For instance, a SPECT scan can single handedly show how well blood is flowing to the heart; what areas of the brain are more or less active; or what specific parts of the bone are affected by cancer.

The most common uses of SPECT include diagnoses or monitoring the progression of the following: brain disorders, heart problems, and bone disorders.
Brain Disorders (Relevance to PD).
The SPECT test curates an intricate and detailed, 3D map of the blood flow activity within the brain, which helps researchers see which parts of the brain are being affected by Parkinson's disease. Although in rarer cases, healthcare professionals may suggest a more specific type of SPECT called a dopamine transporter scan more commonly known as a DaTscan; in order to confirm PD diagnosis.

SPECT radiotracers are radioactive chemical substances or radiopharmaceuticals, used in SPECT imaging to visualize and measure physiological processes within the body. Examples. Technetium-99m: Most frequently used radioisotope in SPECT. Iodine-12, Thallium-201, & Fluorine-18: Other common radioisotopes.

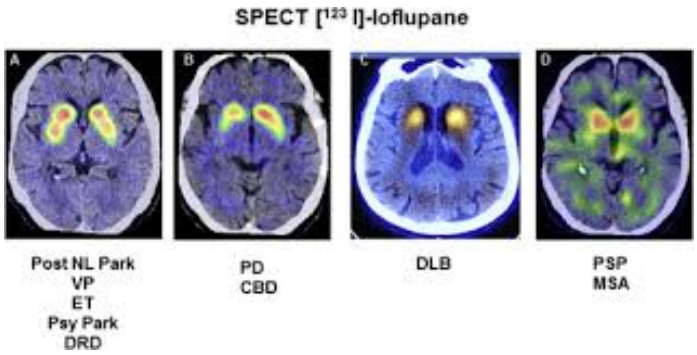
Table 3. Radiotracers in SPECT for PD diagnosis. Credit: *National Library of Medicine. SPECT Molecular Imaging in Parkinson's Disease*
The tracer used for SPECT in Parkinson's disease.

Biological variable	**Radiotracer**
Dopamine reuptake (dopamine transport)	^{123}I-β-CIT, ^{123}I-FP-β-CIT, ^{123}I-IPT (presynaptic dopamine transporter), ^{123}I-Altropane, ^{123}I-β-PE2I ^{99}Tc^{m}-TRODAT-1
D2 dopamine receptor	^{123}I-Iodospiperone, ^{123}I-Iodobenzamide (123I-IBZM), (postsynaptic dopamine D2 receptor) ^{123}I-Iodolisuride, 123I-IBF, ^{123}I-Epidepride (extrastriatal DA receptors)

Current Limitations of SPECT/MRI (Hybrid) - While SPECT/MRI offers imaging that combines high spatial resolution, the implementation of an integrated SPECT/MRI scanner has not yet

happened in clinical practice due to the incompatibility of SPECT components with magnetics fields the absolute foundation of MRIs. However, ongoing research for the development of SPECT/MRI is underway, semiconductor detectors have been used in preclinical settings that show no reaction to magnetic fields up to a limit of 7T, and could exhibit high application potential in the near future.

Figure 4. SPECT Scan Sample of Parkinson's disease. Credits:



CSF Analysis (Cerebrospinal Fluid Analysis)

This method is widely used to diagnose a variety of neurological diseases. CSF is an ultrafiltrate of the serum which encompassess the central nervous system (CNS) parenchyma. What CSF does is detect pathophysiologic changes in the CNS. It is able to do this due the fact it is in direct contact with the CNS extracellular space. 20% of CSF proteins originate from the brain, with that CSF offers a deep look into the pathology of the brain, and is used to identify people at risk of developing various neurological diseases. CSF is also known to be a powerful tool in distinguishing different infectious, autoimmune and degenerative diseases.
In PD, the blood brain barrier becomes disrupted, so CSF analysis is able to identify biomarkers associated with PD. The majority of patients who show clinical symptoms of Parkinson's are of a late presentation of the disease, and therefore less responsive to treatment. Early diagnosis of P via biomarkers is necessary for better monitoring of the PD progression and responses to treatments.

Figure 3. CSF studies in Parkinson's disease. ResearchGate. Elizabeta B Mukaetova-Ladinska. (Sample of CSF Study)

Study	Type(s) of Biomarker	Sample(s) taken	Type(s) dementia
Almonti et al. [73]	Metals	CSF	PD
Asai et al. [74]	Orexin	CSF	PD
Bibl et al. [75]	Amyloid-Beta/ Tau	CSF/Plasma	VaD
Compta et al. [76]	Amyloid-Beta/ Tau	CSF	PD/PDD
Lunardi et al. [77]	DA and metabolites*	CSF	PD
Salehi and Mashayekhi et al. [78]	BDNF	CSF	PD

BDNF: Brain-Derived Neurotrophic Factor; DA: Dopamine; CSF: Cerebrospinal fluid; VaD: Vascular Dementia; PD: Parkinson's Disease; *Homovanillic acid (HVA), Dihydroxyphenylacetic acid (DOPAC).

Parkinson's Disease (PD) Medications & Treatments.

At the moment there is no cure for Parkinson's, however, medications and surgery can improve many movement symptoms of PD.

PD Treatment Medications.

Typical medications for Parkinson's Disease fall into three primary categories:

1. Drugs focused on increasing the level of dopamine within the brain. The most common drugs for PD are dopamine precursors, like levodopa that cross the blood-brain barrier and are then changed into dopamine. Other drugs can closely mimic dopamine or slow down or even prevent its breakdown.
2. Drugs which affect other neurotransmitters in the body to ease some of the symptoms of Parkinson's. For instance, anticholinergic drugs tend to interfere with production or uptake of the neurotransmitter acetylcholine. This is especially effective in reducing tremors.
3. Medications that assist in controlling the non-motor symptoms of PD, or the symptoms that do not affect movement.

After-affects/Symptoms - Motor symptoms may drastically improve in the initial stages of the medication, but can reappear over time as PD progresses, rendering the medications less effective. When professionals recommend a certain course of treatment, they will assess how much the symptoms disrupt the person's daily life, and then tailor the therapy to the person. Since no two people will react in the exact same way when given a certain drug, it usually takes time and patience to get the correct dose and combination of medication.

PD Therapy: Carbidopa-Levodopa (L-dopa).

L-dopa is the cornerstone of Parkinson's disease therapy. This medication aims to reduce the movement-related symptoms of PD, but cannot replace lost nerve cells, nor stop its progression. Nerve cells can utilize L-dopa to produce dopamine and replenish the brain's reduced supply of it. The reason why this is a much better option than simply taking dopamine pills is because, dopamine is not able to easily cross the blood-brain barrier, which is a protective lining of cells inside blood vessels; in charge of regulating the transport of oxygen, glucose, medications, and other such substances in the brain. People with PD are given levodopa in addition to another substance called carbidopa. When combined it can prevent the conversion of levodopa into dopamine except for within the brain. This stops or gets rid of the side effects of excess dopamine inside of the bloodstream, which includes nausea. L-dopa is often highly successful at reducing or even eliminating the tremors and other motor symptoms of PD during the early stages. People might have to increase their initial dosage of L-dopa gradually to maximize the benefits.

Additional side effects - nausea, low blood pressure, restlessness, and drowsiness. Longer term uses of L-dopa can cause someone to experience dyskinesia (involuntary movements such as twisting and writhing), hallucinations, or even psychosis.

Dopamine Agonists.

This drug mimics the role of dopamine within the brain and can be administered alone or with L-dopa. They are most commonly used in the early stage of PD or in combination with levodopa for later stages. Many of the possible side effects are similar to those associated with the use of levodopa. Drugs which fall under the Dopamine agonist drugs include apomorphine, pramipexole, ropinirole, and rotigotine.

MAO-B Inhibitors.

These drugs block or reduce the activity of the enzyme monoamine oxidase B or MAO-B, which breaks down dopamine inside of the brain. MAO-B inhibitors cause the dopamine to accumulate

in surviving nerve cells and reduce the symptoms of PD. This medication includes selegiline and rasagiline. When selegiline is administered with levodopa, it enhances and prolongs the response to L-dopa. Selegiline is usually well tolerated, however side effects might include nausea, orthostatic hypotension, as well as insomnia.

COMT Inhibitors.

COMT stands for catechol-O-methyltransferase, and is another enzyme that breaks down dopamine. COMT inhibitor drugs entacapone, opicapone, and tolcapone prolong the effects of levodopa by preventing the breakdown of dopamine. This drug can decrease the duration of "off periods" of someone's dose of levodopa. Side effects include diarrhea, nausea, sleep disturbances, dizziness, urine discolouration, abdominal pain, low blood pressure, or hallucination. In rare cases, tolcapone has led to severe liver disease.

Anticholinergics.

Drugs under this umbrella include, trihexyphenidyl, benztropine, and ethopropazine. The main effects of Anticholinergics is to decrease the activity of the neurotransmitter acetylcholine and can be especially helpful for PD tremor. Side effects of this medication include dry mouth, constipation, urinary retention, hallucination, memory loss, blurred vision, as well as confusion.

Amantadine.

This is an antiviral drug which can help reduce symptoms of Parkinson's and L-dopa-induced dyskinesia. It can be prescribed alone in the early stages of PD, and can be paired with an anticholinergic drug or levodopa. After several months, amantadine's effectiveness declines drastically in up to half of the people taking it. Amatadine's side effects may include insomnia, mottled skin, edema, agitation, or hallucinations. Researchers are not exactly certain as to how amantadine works in PD, but it could possibly increase the effects of dopamine.

Medications to Treat Motor Symptoms of PD.

Carbidopa levodopa - Drugs that increase levels of dopamine in the brain
Apomorphine, Pramipexole, Ropinirole, Rotigotine - Drugs that mimic dopamine (agonists)
Rasagiline, Selegiline (deprenyl) - Drugs that inhibit dopamine breakdown (MAO-B inhibitors)
Entacapone, Tolcapone - Drugs that inhibit dopamine breakdown (COMT inhibitors)
Benztropine, Ethopropazine, Trihexyphenidyl - Drugs that decrease the action of acetylcholine (anticholinergics)
Amantadine - Drugs with unknown mechanisms of action for PD

The Use of Surgery in Parkinson's Disease Treatments.

Surgery may be a consideration for people with PD when drug therapy is no longer a sufficient method to manage symptoms. Studies in the past few decades have paved the path to the discovery of great improvements in surgical techniques.

One type of surgery commonly used for Parkinson's is called lesion surgery, which involves selectively destroying specific parts of the brain contributing to PD symptoms. The most popular lesion surgery is called pallidotomy. This procedure involves a neurosurgeon operating precisely on the globus pallidus. Pallidotomy can improve tremor, rigidity, and bradykinesia symptoms, however, there is a possibility of interrupting the connections between the globus pallidus and the striatum or thalamus. Certain studies have proven pallidotomy highly effective in improving gait and balance and reducing the amount of levodopa people require, hence reducing drug-induced dyskinesias.

Another different surgical procedure used to treat PD is called thalamotomy. This involved surgically destroying part of the thalamus. The primary aim of this procedure is to reduce tremor. Since these variants of procedures cause permanent destruction of small portions of brain tissues, they have largely been replaced by deep brain stimulation to further treat PD. In addition to that, a method that utilizes focused ultrasound from outside the head can now curate brain lesions with zero surgery.

Deep Brain Stimulation.

Deep brain stimulation, commonly known in its abbreviated form, DBS, uses an electrode which is surgically implanted into the brain, usually in the subthalamic nucleus or the globus pallidus. This is something of which can be compared to a cardiac pacemaker, a pulse generator which is implanted into the chest area under the collarbone and sends minor controlled electrical signals to the electrode(s) by wire placed underneath the skin. When powered on, the pulse generator and electrodes are able to painlessly stimulate the brain in a way that blocks out signals that are causes of many motor symptoms in Parkinson's. DBS has been approved by the U.S. Food and Drug Administration (FDA) and is a widely used treatment for PD.

DBS however, does not stop Parkinson's from progressing; some issues could gradually return. The motor function benefits of DBS can be significant, but does not usually help with speech problems, posture ("freezing"), balance, anxiety, depression, or dementia.

DBS is more targeted, and generally appropriate for people who respond well to L-dopa and who have developed dyskinesias, as well as other symptoms despite drug therapy.

Deep Dive into the Creation of Biomarkers:

How are Biomarkers Created/Discovered?

Biomarker discovery Intro.

In order to successfully discover a new biomarker, the target population (specific to the intended use) must be tested and defined clearly early in the development process. The use of a biomarker in relation to the progression and course of a disease as well as specific clinical contexts, and the nature of the disease itself should also be pre-specificed beforehand.
The patients and specimens should both directly reflect the target population and intended use.

Primary Considerations for Biomark Discovery.

Bias is one of the greatest causes of ultimate failure in biomarker validation studies. Bias usually enters a study during patient selection, specimen collection, specimen analysis, and patient evaluation. Randomization and blinding are two of the most important and widely used tools to avoid bias.
Randomization for biomarker discovery should be carried out to control for non-biological experimental effects caused by changes in reagents, technicians, machine drift, and things alike. The specimens specific to the control group and cases should be assigned to individual arrays, testing plates or batches by random assignment. What this does is it ensures the distribution of cases, controls, and overall age of specimens that are equally distributed.
Blinding may be carried out by keeping the people who produce the biomarker data from knowing the clinical outcomes. The purpose of this is to prevent the bias which is induced by unequal assessment of biomarker results.
Randomization and blinding should be applied in the process of biomarker data generation and should also be incorporated at each stage of the study when able to.

Identification of Prognostic & Predictive Biomarkers.

Prognostic Biomarker - A biological or clinical characteristic that predicts a patient's most likely health outcome or disease course/progression.
Predictive Biomarker - A measurable indicator that identifies individuals who are more likely to benefit from a certain medical treatment or be harmed by it (predicting the most probable outcome of a treatment).
Prognostic biomarkers can be identified in successfully conducted retrospective studies that do not completely rely on convenience samples, but instead use biospecimens prospectively collected from a cohort, representing the target screening population, case-control studies and single-arm trials. This specific type of biomarker is identified through a main effect test of the relationship between the biomarker and the outcome within a statistical model. An example of a prognostic biomarker is the STK11 (serine/threonine kinase 11) mutation; associated with poorer outcome in non-squamous NSCLC (most common type of non-small cell lung cancer). Various samples of tissue were collected from a consecutive series of people with non-squamous NSCLC who underwent curative-intent surgical resection in 2001 to 2006 at two separate hospitals. A priori power calculation was performed as well, to ensure a sufficient quantity of overall survival (OS) events to provide adequate statistical power to assess five candidate biomarkers found. Although convenience samples were used, the prognostic effect was validated through 2 external datasets which further strengthened the validity of the discovery.
A predictive biomarker must be identified through secondary analyses utilizing data from a randomized clinical trial, through an interaction test between the treatment, as well as a biomarker within a statistical model (regression models, survival analysis, ANOVA, chi-squared). Secondary analyses typically refer to subsequent correlative studies which may or may not be pre-defined as a protocol objective.
An example of predictive biomarker identification is the IPASS study. In the IPASS study they enrolled people with advanced pulmonary adenocarcinoma (most common type of lung-cancer), who were nonsmokers or former light smokers, and they randomly assigned patients to receive gefitinib or carboplatin plus paclitaxel (CP). The patients' EGFR mutation was unknown at the time of enrollment and was later determined retrospectively. The interaction between EGFR mutations was extremely statistically important being, $P<.001$, and indicated that among the patients with the EGFR mutated tumors, PFS (progression free survival) was much longer. Showing a hazard ratio (HR) of 0.48:95% confidence interval (CI).

Derived & Composite Biomarkers for Parkinson's

Derived biomarker - A measured value that is mathematically or statistically created from one or more primary measurements, such as a ratio, a normalized score, a principal component, or things alike.
Composite biomarker (multi-component/multi-parameter biomarker) - A single indicator created by combining multiple biomarkers including molecular, imaging, clinical, or digital; often made via algorithm into a singular score.
Intro. Derived biomarkers are commonly formed from raw measurements by transforming it through mathematics or statistics. For instance, log-transform of protein concentration, ratio of two proteins, z-score normalization against age or sex, the slope over time, or a PCA component score summarizing analytes are all examples.
In current practices the definition of derived features covers a much larger umbrella since things such as features engineered by machine learning from time series or embeddings from deeper networks fall underneath it.
A composite biomarker intentionally combines two or more measurements that could include homogeneous ones (two lab tests) or heterogenous (CSF aSyn, DAT imaging, gait metrics, and age). The FDA and professional groups explicitly discuss muti-component biomarkers as a class, which includes algorithmic combinations and demographic/clinical covariates.
Derived biomarkers represent a class of signals which do not exactly exist directly in raw biological data, but are created after manipulation (statistical and mathematical). In PD the pathological progression, destruction of dopamine, Lewy-bodies and aSyn, mitochondrial stress, and neuroinflammation all produce biological traces that usually appear subtle or inconsistent in examinations. A derived biomarker becomes a constructed variable, which is typically collected or discovered by integrating raw signals in the form of ratios, normalized indices, dimensionality reduction methods or computational inferences. This particular approach operates under the assumption that the actual and true biological signature of early PD is rarely successfully captured single handedly by one measurement in its raw form. However, derived biomarkers understand disease processes leave behind distributed traces that should be mathematically filtered through.
One of the most classic examples of this is the striatal binding ratio (SBR) which is derived from radiotracer SPECT. The SBR is not the radiotracer uptake itself, but instead, a new value that subtracts background uptake and normalizes striatal activity in relevance to a reference region.

Biomarker Panels for Parkinson's Disease.

Biomarker panel - By definition, biomarker panels are tests which analyze the combination of multiple biomarkers, including genes, proteins, and other molecules. The main purpose of these is to provide a more comprehensive understanding of someone's health, disease, or response to current treatments/medication. In short, biomarker panels bring together numerous data points, sometimes using multi-omic approaches and basically combine multiple biomarkers.

Main Components in PD Biomarker Panels.

- (alpha-synuclein) aSyn - Misfolded aSyn aggregates are considered a hallmark of PD. Tests commonly used to detect these aggregates include SAA, which can detect these through blood or CSF.
- (neurofilament light chain) NfL - Specific levels of NfL within CSF and blood can be studied as a marker for neurodegeneration and disease progression.
- (Tau and Amyloid-beta) Aβ - Biomarker panels for PD often include total tau, phosphorylated tau, and a variety of Aβ, especially in CSF too.

Other biochemical and genetic markers.

- *DJ-1: Found to be particularly useful in cases with the LRRK2 gene mutation.*
- *GFAP: Glial fibrillary acidic protein can be utilized to predict disease progression.*
- *Circulation circRNAs:*

Case Studies: (goal: 10 [by school fair], 30-40 [by cysf])

(case studies theme [4 parts])

1. Dopaminergic Dysfunctioning + imaging based biomarkers for PD
2. aSyn pathology + lew body biology
3. Cellular stress, mitochondrial dysfunct, proteostasis failure
4. Neuroinflammation + multi-domain integration

Section 1: Dopaminergic Dysfunction & Imaging Based Biomarkers in PD

1. **Review of "Case Report: Dopamine Dysregulation Syndrome, mania, and compulsive buying in a patient with Parkinson's disease". National Library of Medicine**

Abstract:

Dopamine Dysregulation Syndrome is a rather uncommon complication seen in the treatment of PD, usually characterized by "an addictive use of dopamine" with levels far surpassing than the actual dosage required for treatment of motor impairment. This leads to severe dyskinesia, euphoria, aggressivity or psychosis.

Introduction:

DDS (Dopamine Dysregulation Syndrome) is an addictive pattern of dopamine replacement therapy use. DDs is found in Parkinson's patients with a prevalence of around 8.8%. Reports of mania and hypomania are also associated with dopamine replacement therapy in PD with similar functions associated commonly with DDS and ICDs (Impulsive Compulsive Behaviors).

Case Report Summary:

A 55 year old male with PD was referred to this institution for a psychiatric evaluation to undergo (DBS) Deep Brain Simulation surgery because of his debilitating dyskinesias and unpredictable periods of "off" like states.

- He was diagnosed with PD 5 years prior (50 years old).
- The first symptoms were reported at 43.
- This male also had a history of Depression since he was 41.
- No known history in the family of neurologic or psychiatric diseases reported.

At admissions, he was presented dressed in colourful clothes and gold necklaces.

- Had an "elated" mood
- Disinhibition and logorrhea
- Increased speed of speech
- Increased self-esteem
- Lower necessity of sleep
- Paranoia and delusions centered around the paranoid

The patient also displayed ICD behaviors. He bought over 5,000 pocket watches, 42 old and unusable cars, plus he stored old radio devices.

Current medication: 2,150 g levodopa total. Ropinirole 8 mg/daily. LEDD 2,310 mg total.

Discussion & Conclusions:
It has been concluded that knowledge as to why DDS occur in patients with PD is still limited, and overall reports with DDS comorbid with other ICDs and Mania are also scarce in data as a whole. DDS was first described by Giovannoni et al, with an estimated prevalence of 3.4-4%. Pathophysiology is not clear but is thought to occur from the loss of domanergic neurons in SNc (substantia nigra pars compacta), as well as the VTA (ventral tegmental area).
In this study they found that dopaminergic simulation of NAc is "essential" to complement the effects of medication. However over-simulation in the mesolimbic system can impact the development of these dopamine rewarding behaviors.

Causes of DDS:
Addictive properties of dopaminergic medication is explained by the dysregulation of dopamine in ventral striatum. Compulsive use and chronic stimulation by dopaminergic medication can lead to the seen hypersensitivity of D3 receptors.

Findings:
PD patients treated with dopamine agonists have more ICD, in contrast to people who weren't treated with them. The use of pramipexole and ropinirole showed higher risk levels for ICD because of their selectiveness for D2 like receptors such as D3 and D4. This is localised in the mescorcolimbic system explaining the risk of ICD development.

2. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature

Abstract:
This review attempts to explain the different possible mechanisms behind depletion of dopamine in people with PD such as aSyn, abnormalities, mitochondrial dysfunction and 3,4-DOPAL (dihydroxyphenylacetaldehyde) toxicity.

Introduction:

Parkinson's disease was first described in 1817 by British physician James Parkinson in his essay "An Essay on Shaking Palsy". Following that, over decades "Parkinson's disease" became widely used to describe the illness.

Apart from environmental factors, genetic factors play a role in the eventual development of PD. These genes are implicated in its pathogenesis, including:

- Various mutations
    - SNCA
    - LRRK2
    - GBA genes

They all have proven to significantly increase the risk of PD. Studying rare familial cases of PD, genetically have led to the discovery of monogenic forms, the first PD gene being SNCA also known as alph-synclein or aSyn. Since then numerous other genes have been found as either a causing or risk causing for PD. These include:

- LRRK
- Parkin
- PINK1
- DJ-1
- VPS35

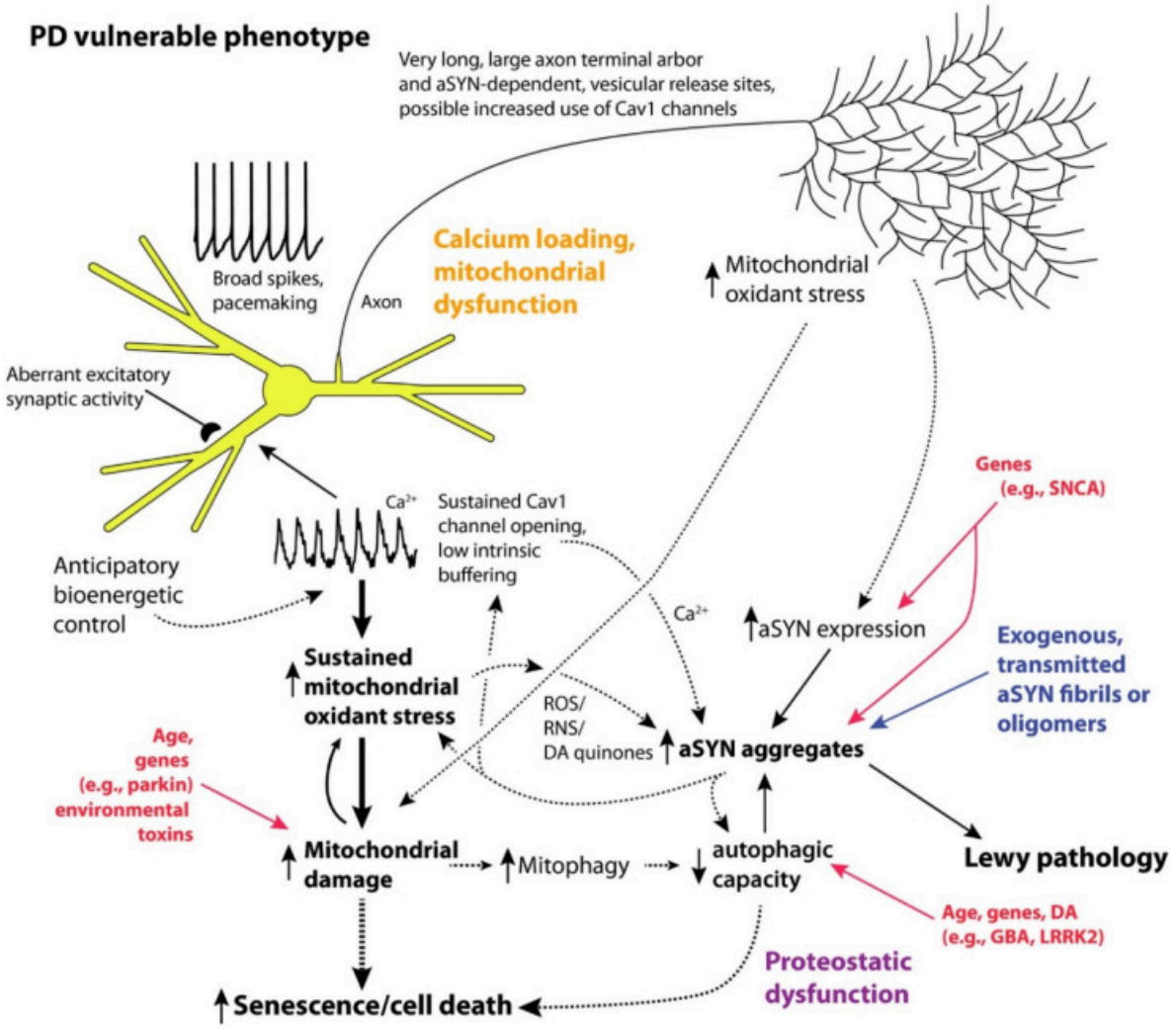
The ones listed above are only 5 of many others.

Dopamine and Parkinson's disease:

The reason as to why dopaminergic neurons of SNpc are at a higher risk of PD is still unknown and still to this day remains a paramount topic in the research field. The loss of SNpc DA neurons causes bradykinesia as well as stiffness, which are the 2 main motor symptoms of PD.

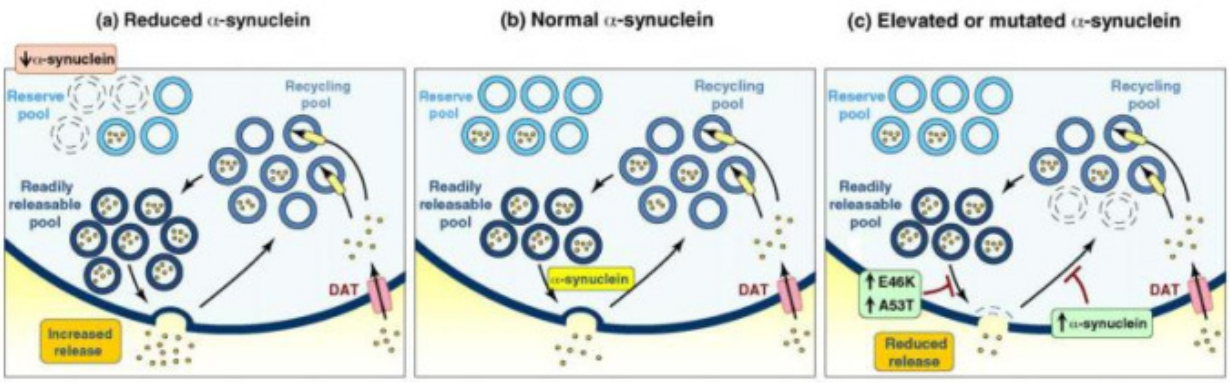
Why dopaminergic neurons in the SNpc are destroyed in Parkinson's:

1. The SNpc of people with PD tends to have Lew pathology. This basically includes protein aggregates which are rich in fibrillary forms of aSyn.
   Figure 1. Credits: National Library of Medicine. Representation of the main traits of vulnerable neurons in Parkinson's disease. Neurons susceptible to PD have seen key traits. The disease itself is predominantly driven by a malfunction in mitochondria.



<u>Figure 2.</u> Credits: National Library of Medicine. Showing proposed functions of aSyn in controlling the cycling of presynaptic vesicles under different levels of aSyn.

a) *Decreased aSyn levels, reserve pool of vesicles is reduced. There is a higher quantity of readily available vesicles for release. (could lead to an augmentation in dopamine release)*
b) *Normal conditions. ASyn is believed to have physiological roles in regulating vesicle availability among different pools.*
c) *Increased aSyn amounts or mutations like E46K or A53T aSyn led to a decrease in dopamine release.*



Conclusion:

Diagnosis of Parkinson's in early stages is challenging with high error rates, sitting at approximately 24%. These statistics include specialized medical centres. While using clinical criteria like the UK Parkinson's Disease Society Brain Bank can improve accuracy, it still only reaches barely above 80% during the first visit.

One promising area of research includes the use of SAA in either the blood or cerebrospinal fluid. This aims to detect these abnormal protein aggregates even before motor symptoms appear.

3. Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study

Abstract:

LOD (late onset depression) might follow with the diagnosis of PD or dementia with Lewy bodies (DLB). This study aimed to determine the rate of clinical and imaging features associated with prodromal PD and DLB in patients with LOB.

Methods:

Within a cross-sectional design, they had a total of 36 patients with first onset of a depressive disorder diagnosed after the age of 55. The LOD group and 30 healthy controls (HC) underwent a comprehensive clinical assessment.

- 28/36 LOD patients and 20/30 HC got a head MRI SPECT imaging.
- Image analysis of both was done by a rater blind.

Results:

Patients with LOD (n=36) had worse scores than HC (n=30) by huge margins on the PD screening questionnaire. The mean (SD) was 1.8 (1.9) vs 0.8 (1.2); p=0.01).

Movement Disorder Society Unified Parkinson;s Disease Rating Scale: (mean (SD) 19.2 (12.7) vs 6.1 (5.7); p<0.001)

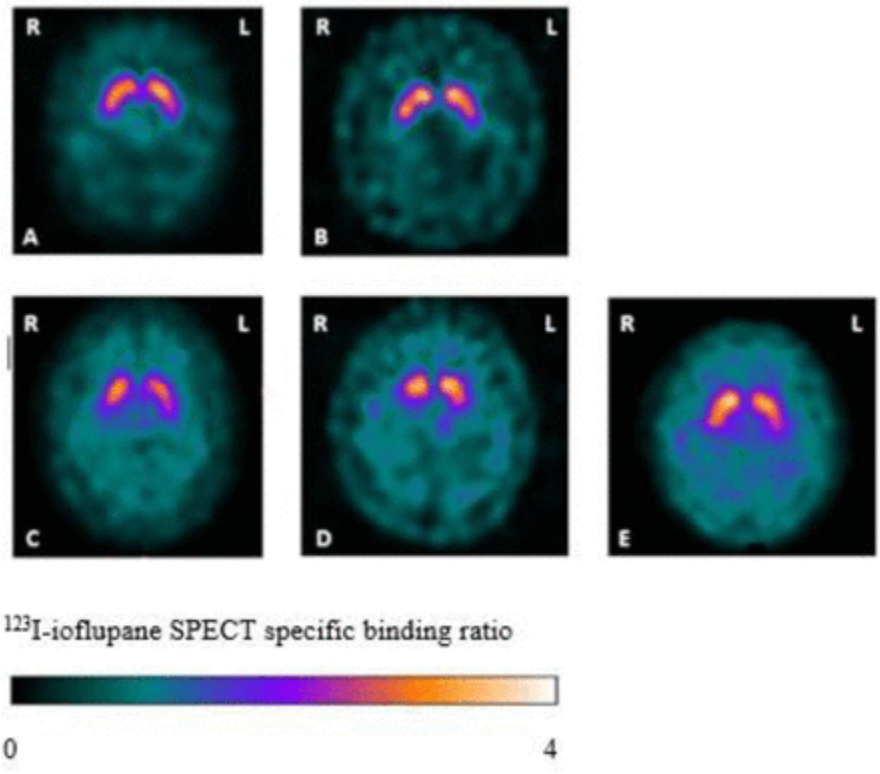
REM-sleep behaviour disorder screening questionnaire: (mean (SD) 4.3 (3.2) vs 2.1 (2.1); p=0.001)

Lille Apathy Rating Scale: (mean (SD) - 23.3 (9.6) vs -27.0 (4.7); p=0.04)

Scales for Outcomes in PD-Autonomic: (mea (SD) 14.9 (8.7) vs 7.7 (4.9); p<0.001)

24% of patients with LOD vs 4% HC had an abnormal I-ioflupane SPECT scan (p=0.04)

Figure 1. Examples of I-ioflupane SPECTs from this study. A = normal, B = equivocal, C = abnormal type 1, D = abnormal type 2, E = balanced striatal loss L (leftside) R (rightside).



Conclusion:

LOD is associated with higher rates of motor and non motor features of PD/DLB and of abnormal I-ioflupane SPECTs. Results suggest that patients with LOD should be considered at a higher risk of PD or DLB development.

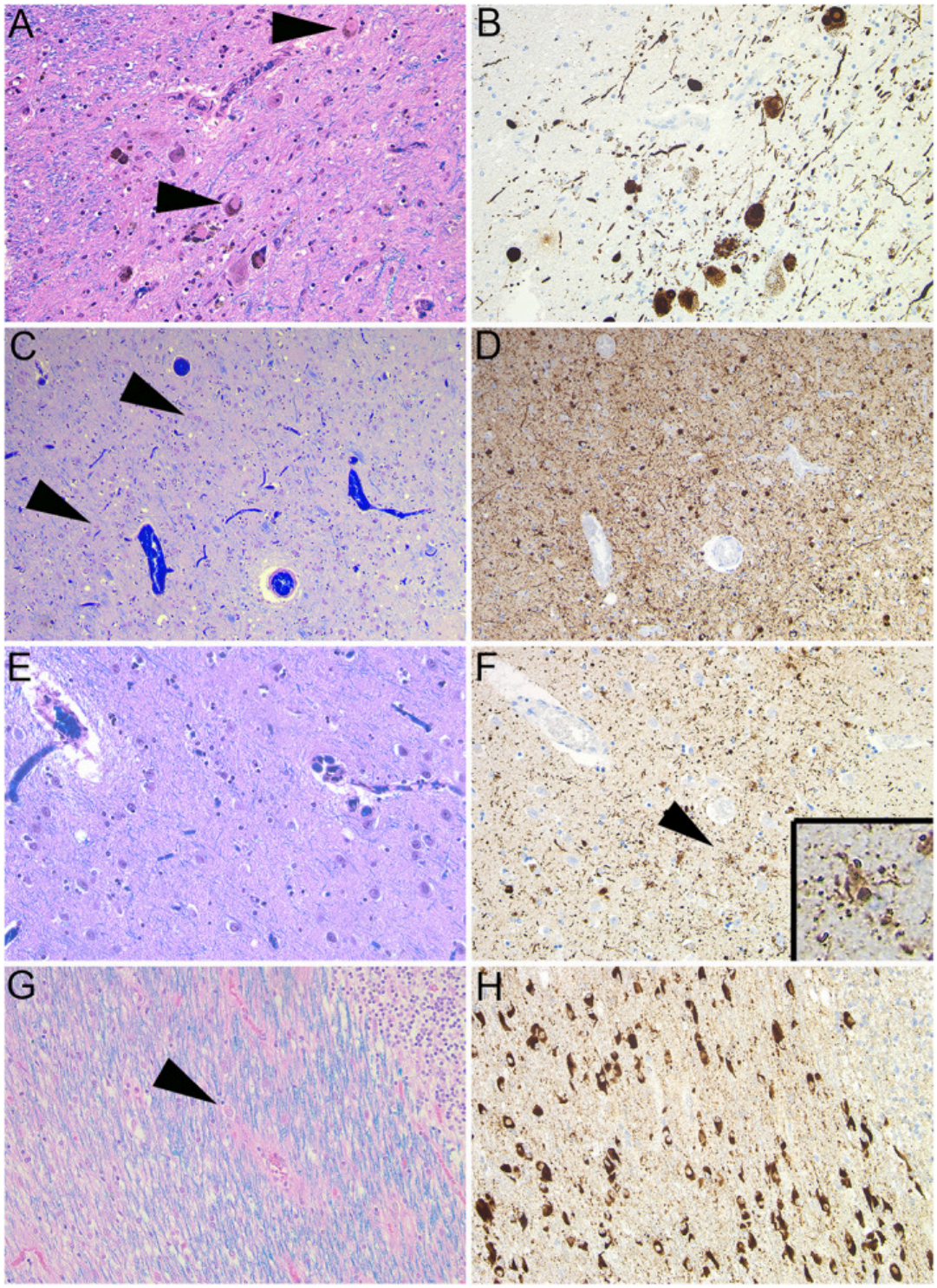
4. The Discovery of a-Synuclein in Lewy Pathology of Parkinson's Disease: The Inspiration of a Revolution

Background:
In 1912, Friedrich Lewy described the inclusion bodies we now currently refer to as Lewy bodies and recognize as a pathological hallmark of Parkinson's, and 85 years later identified a causative single base mutation in SNCA.

Proteinopathies:
We now know that Lewy Bodies (LBs) have myriad components and proteome of over 300 proteins. There is a defined target in aSyn, which brings proteins to the forefront of PD pathology which places PD under the the vast umbrella of neurodegenerative conformational proteinopathies. The synucleinopathies were soon expanded to include MSA (multiple system atrophy), which was a disease previously thought to be completely unrelated to Parkinson's.

Staging:
Topographical distribution of aSyn is evaluated in 168 post mortem brains. These are furthermore characterized by the 6 different progressive stages of PD.

Figure 1. Comparison of classical histopathology for diseases associated with aSyn.



aSyn as a Biomarker:
aSyn is a great candidate for biomarker developments because it represents the main pathology, is also found within peripheral tissues and biofluids, and abnormalities tend to appear early on in the disease. Additionally, an imagining agent was actually able to fully visualize aSyn aggregation inside of patients, this is something that we can compare to amyloid imaging in AD, they both would have a significant impact, but currently remains elusive and has produced relatively inconsistent results.
SSAs were initially created for prion disease, but now are being applied to different types of tissues and fluids in syncleinopathies. Recent reports have distinguished PD and MSA in CSF ith a >95% sensitivity.

Conclusion:
The discovery of aSyn in LBs has undoubtedly revolutionized our overall understanding of PD pathogenesis. This study referred to aSyn has the "holy grail" for disease modification and detections especially early on.

5. Lewy Body-Associated Proteins A-Synuclein (a-syn) as a Plasma-Based Biomarker for Parkinson's Disease

Abstract:
Exploring the combined diagnostic statistics and value of plasma LB-associated proteins including, p-Asyn at ser129, total a-syn, and oligomeric a-syn) for the diagnosis of PD in comparison to controls (HCs) and other syndromes of PD (PDs).

Methodology:

- The study included 145 participants. 79 of which with PD, 24 with PDs, and 42 in the HCs group.
- Panel of plasma levels was measured by ELISA (enzyme-linked immunosorbent assay)
    - p-Asyn
    - Total a-syn
    - Oligomeric a-syn
- Main outcome was a discriminative accuracy of the combined 3 plasma biomarkers for PD

Results:

Figure 1. Showcases the basic demographics and clinical characteristics of the cohort participants.

Characteristics	Control	PD	PDS	*p-value*[a]
Number	42	79	24	NA
Sex (Male: Female)	16:26	42:37	17:7	0.036[b]
Age [years], Mean (SD)	65.43 (7.467)	64.49 (8.224)	69.25 (7.952)	0.057
Duration [years], Mean (SD)	–	4.58 (3.849)	3.17 (3.315)	<0.0001
Education [years], Mean (SD)	3.76 (4.178)	4.12 (3.759)	3.79 (3.856)	0.682
H&Y stages, Mean (SD)	–	2.14 (0.974)	2.85 (1.048)	<0.0001
UPDRS, Mean (SD)	2.67 (3.986)	40.77 (17.746)	55.42 (27.204)	<0.0001
UPDRS-I, Mean (SD)	0.31 (0.517)	2.51 (2.124)	4.33 (4.429)	<0.0001
UPDRS-II, Mean (SD)	0.29 (0.742)	11.67 (6.091)	15.50 (7.846)	<0.0001
UPDRS-III, Mean (SD)	1.64 (3.655)	23.59 (11.709)	32.79 (16.922)	<0.0001
UPDRS-IV, Mean (SD)	0.44 (0.770)	2.85 (2.865)	2.79 (2.284)	<0.0001
MMSE, Mean (SD)	23.33 (4.65)	22.85 (5.897)	17.63 (7.216)	0.002

HAMD, Mean (SD)	3.31 (3.751)	7.09 (5.221)	7.83 (4.280)	<0.0001
HAMA, Mean (SD)	5.36 (4.95)	11.13 (7.436)	10.71 (6.003)	<0.0001
RBDQ-HK, Mean (SD)	6.83 (7.705)	24.13 (20.096)	23.46 (21.821)	<0.0001
ADL, Mean (SD)	20.29 (0.970)	26.70 (7.771)	38.88 (15.037)	<0.0001
BMI [kg/m^2], Mean (SD)	24.26 (2.66)	24.88 (5.087)	24.60 (4.180)	0.925
p-Asyn ser129 (ng/ml), Mean (SD)	15.34 (2.042)	17.13 (3.055)	16.91 (2.264)	0.006
Total α-syn (ng/ml), Mean (SD)	27.55 (5.762)	34.95 (8.002)	33.70 (7.012)	<0.0001
Oligomeric α-syn (ng/ml), Mean (SD)	2.41 (0.512)	2.80 (0.540)	2.84 (0.411)	<0.0001

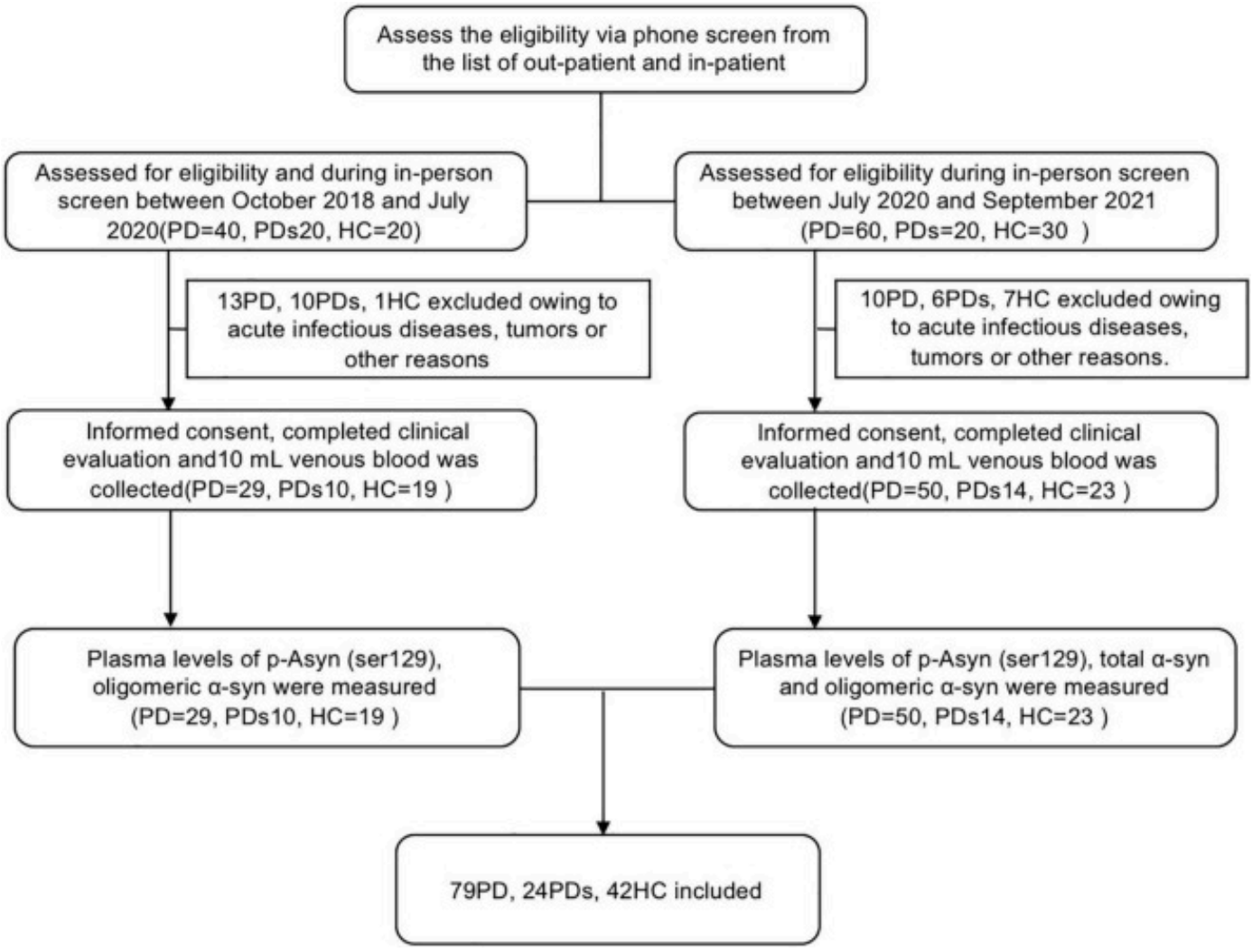
- Mean age:
    - Control group = 65.43 (SD, 7.467)
    - PD patients group = 64.49 (SD, 8.224)
    - PDs group = 69.25 (SD, 7.952)
- Plasma LB-associated protein levels were a lot higher in PD than in HCs within the same age/age group.
    - No difference between PD group and the PDs group
- Plasma p-Asyn, total a-syn, and oligomeric a-syn was a better biomarker differentiating PD and HCs.
    - AUC = 0.8552 ($p < 0.0001$, 95%CI, 0.7635-0.9409)
        - Much higher than plasma p-Asyn (△AUC = 0.1797)
        - Total a-syn = △AUC= 0.0891
        - Oligomeric a-syn = △AUC= 0.1592

- (above are all individual scorings)

Conclusion:

Results suggested plasma LB-associated proteins could potentially become a non-invasive biomarker to diagnose Parkinson's and separate them from HCs.

Figure 2. The flow chart includes the entire process of this study.



Tools/Applications Used & Descriptions.

Benchling.

Benchling is commonly described as a cloud platform for life sciences R&D. The primary intent of this tool is to use their software to provide pharmaceutical and biotech companies with a platform for all of their scientific data. Benchling is a software company founded in 2012 at MIT, where the founders' motivation was driven by their understanding of the demand for technology and tools alike capable of enabling their scientific research.
With benchling at their disposal, scientists and researchers no longer have to resort to grueling data sheets and lost data.

Visual Studio Code (VSC).

Open source AI code editor and integrated development platform developed by Microsoft, which was made for Windows, Linux, and MacOS, as well as web browsers.

What I used it for:

- Coding my pipeline
- Generating my synthetic data

SECTION: How is PD-INSI different in Comparison to Current Panels?

Introduction -

Early and accurate PD diagnosis is a modern medical need which is still unmet despite continuous efforts. This is mainly from the fact that current methods rely heavily on neurological examinations, and symptoms which often only appear after 70-80% of dopamine producing brain cells have been deformed or completely destroyed. While DTI and CSF have both shown high potential in clinicals these individual biomarkers generally have a limited adoption into clinics. Recent PD research has put a particular emphasis on integrating biomarker panels with combinations of neuroimaging, fluid, inflammatory, and molecular signaling to achieve higher diagnostic precision, further surpassing single variable approaches.

Summary Review of Current Biomarker Implementation into Diagnosis & Approaches -

Individual Biomarker Approaches -

Wide varieties of individual biomarkers have been comprehensively studied within PD over generations, however dopamine imaging such as DAT-SPECT still remains a paramount biomarker revealing nigrostriatal degeneration, however, its sensitivity and availability hold backs limit standalone usability. ASyn specific in CSF such as phosphorylated and oligomeric variants have been thoroughly researched and showed major differences in results with PD patients and the control group. CSF NfL (neurofilament light chain), and tau proteins, as well as other analytics have shown differential expression in PD in comparison to atypical PD syndrome, which demonstrates a potential differential diagnosis. Despite this, biomarkers individually usually exhibit a moderate level of sensitivity and specificity, usually overlapping with other neurodegenerative diseases, and not PD alone. This has led me to test panels and attempt more novel approaches to add more constraints onto diagnosis hopefully towards a more accurate and precise biomarker panel tailored for PD.

Biomarker Panels -

Combining multiple biomarkers into a uniform panel has shown promising results in the context of improving diagnosis accuracy and overall performance of methods. A primal example of this would be the numerous studies in which they summarize the combination of aSyn, tau, and NfL have shown an improved discrimination of people with PD in comparison to normal people which was the control group. Also, the biomarker panels using SAA showed a high level of sensitivity and precision when observed in cohorts.

Multi-omic literal reviews have emphasized the biomarker panel's ability to integrate oxidative stress, neuroprotection, inflammation, and neuroimaging indicators directed to the complex nature of PD.

Conclusion: Current biomarker panels vary drastically in make up and not a singular one has become universally adopted within clinics. A large majority tends to also rely on CSF biomarkers which require invasive sampling.

The PD-INSI Biomarker Panel: The Logic & Rationale Behind it -

`I conducted research and literature reviews surrounding the behavior and mechanisms of disease. My proposed panel incorporates neurodegenerative imaging, molecular aggregation, measurements of inflammatory activity, cellular stress levels, and proteostasis dysfunction. My novel approach has been meticulously curated to align with the multi-etiological nature of

Parkinson's. This involves dopaminergic neuro loss, aSyn pathology, proteasomal dysfunction, chronic neuroinflammation, and mitochondrial impairment.

Biomarker Name:	**Developmental Process & Reasoning:**
Dopamine Ethic Score (Using DAT)	Widely known as the "hall mark" of nigrostriatal degeneration in PD, and acts as the foundational framework in comparison to other current imaging technologies.
aSyn Aggregation Strain	Extends deep research, revealing accelerated oligomeric and phosphorylated aSyn variants in PD CSF in contrast to controls.
Mitochondrial Stress Index	In PD, mitochondrial dysfunction is a pathogenic mechanism and is backed up through imaging and biofluid research.
Proteostasis Failure Salient	PD tends to implicate proteasome and autophagy pathway disruptions in protein aggregation and cell decay/death.
Neuroinflammatory Activity Index	Brains with PD exhibit chronic neuroinflammation, and have a connection with the progression of the disease, as well as, cytokine dysregulation.
Cross-Domain Correlation Scoring	Here to capture the statistical difference as well as similarities of the various biomarkers. (Main Innovation part of PD-INSI panel)

Comparison of PD-INSI in Contrast to Current Biomarker Panels for PD -

Current panels mainly consist of CSF proteins such as aSyn, tau, and NfL being the most popular. These methods are effective but have been proven invasive and specific to certain variables not always found. My panel really puts an emphasis on the diversity of biological pathways and accommodates components that are able to be simulated or derived from less invasive sources, but still just as, if not more effective.

Modern biomarker panels with multi-omic signatures, like miRNAs and hybrid protein biomarkers, have proven sensitive in small groups, and overall fall short with integration in structure and cellular stress measurements.

My panel represents a novel combination across various biological domains, with the aim to achieve excellence in revealing the complexity of PD comprehensively.

Limitations of PD-INSI & the Future of it -

PD-INSI is a proposed biomarker panel which is completely computation and based on simulated data sources at the moment. While it is not clinically validated at the moment, that would definitely be a next step and future goal. A next step that is realistically achievable for upcoming advancements within the next few months would be comparing my panel's performance with other possible combinations open sources, and of course publicly available.

Conclusion: My proposed biomarker panel summarizes real evidence from neuroimaging, molecular integration, cellular stress, proteostasis, and inflammation research into a concise ML framework, hopefully laying the groundwork for further advancements and acceleration of a more precise, accurate, and early parkinson's diagnostic technique with widespread adoption clinically speaking.

Actual Panel Notes:

Possible Names:

- ☑ ~~PD-MOBI 7~~
- ☐ PD-INSI
- ☑ ~~PD-BIO 7~~
- ☑ ~~PD-STRESS INDEX~~

Panel Name: PD-INSI [FINALIZED]

- Fill for representative of DAT related signals (dopamine losses)
- Fill for Lewy Body Burden/aSyn levels/amounts?
- Fill for representative of oxidative stress and energy failures
- Fill for impaired protein clearance? (yes or no, because not commonly done or shown within existing panels for PD seen in medicine)
- Fill for inflammatory activation within the neurosystem??
- Fill for Cross Domain overall scores

(Note: fill spots for biomarker panel components, now I must find the best and most practical fill in to represent each appropriately and efficiently)

- Copy Down List -

    - Fill for representative of DAT related signals (dopamine losses)
        - Dopamine Ethic Score (using DAT)
    - Fill for Lewy Body Burden/aSyn levels/amounts?
        - aSyn Aggregation Strain
    - Fill for representative of oxidative stress and energy failures
        - Mitochondrial Stress Index
    - Fill for impaired protein clearance? (yes or no, because not commonly done or shown within existing panels for PD seen in medicine)
        - Proteostasis Failure Salient
    - Fill for inflammatory activation within the neurosystem??
        - Neuroinflammatory Activity Index
    - Fill for Cross Domain overall scores
        - Cross-Domain Correlation Scoring

(Note: time for consultation and re-look)

- Copy Down Previous List)

    - Fill for representative of DAT related signals (dopamine losses)
        - Dopamine Ethic Score (using DAT)
    - Fill for Lewy Body Burden/aSyn levels/amounts?
        - aSyn Aggregation Strain
    - Fill for representative of oxidative stress and energy failures
        - Mitochondrial Stress Index
    - Fill for impaired protein clearance? (yes or no, because not commonly done or shown within existing panels for PD seen in medicine)
        - Proteostasis Failure Salient
    - Fill for inflammatory activation within the neurosystem??
        - Neuroinflammatory Activity Index
    - Fill for Cross Domain overall scores
        - Cross-Domain Correlation Scoring

CSF -

- Low CSF concentrations of 3,4-dihydroxyphenylactic acid (DOPAC) and DOPA identified in pre-clinical PD in “at-risk” individuals (Parkinson’s Disease: Biomarkers, Treatment, and Risk Factors. Fatemeh N. Emamzah, Andrei Surguchov. From the University of Lancaster, UK & the Kansas University Medical Centre, USA.)

Project Methology:

1. **The End Objective:** My goal for this project was to create a discovery pipeline to evaluate a proposed biomarker panel with an aim to achieve clinically standard scores and results (0.9+), within a controlled experimental computed environment via Visual Studio Code on Python.
   Since I do not have access to a clinic and test groups, I used a machine learning framework to mathematically model values.

2. **Case Study Analysis:** Various case studies, mainly from the National Health Institute, were rigorously reviewed to deepen my understanding of the complexity of Parkinson's disease and its pathology as a whole. This later contributed to my thought process as seen above to create my biomarker panel.

3. **Creating the Biomarker Panel**

4. **Generating the synthetic data via simulation on VSC with Python:** Peer-reviewed literature was analyzed to extract statistical distributions to later be used to create parameters.

5. **Statistical analysis and comparison**

Performance Report:

Overview: What I did and How?

PD-INSI is officially evaluated via a machine learning based classification model. Within this model I simulated 300 patient records with a ratio of 72 : 28 in percentage of Parkinson's patients to the control group which were defined as "healthy" people. Additionally, these were split into cohorts to guarantee unbiased testing in the ML model.

My ML model was trained solely on biomarker based aspects. The primary purpose behind this was to properly measure the biomark panel's performance alone.

Raw Output Scores:

Training samples: 215
Testing samples: 85
Confusion Matrix: [[4 16] [0 65]]
Accuracy: 0.812
AUC: 0.999

Translated Performance Statistics: PD-INSI achieved a total accuracy score of 81.2% (roughly ⅘ saw a correct diagnosis).

Error Analysis in the Confusion Matrix: Revealed 0 false negatives, although there were a few false positives. However, this is mainly from the fact that when clinics attempt to detect early PD, parameters are often stricter and emphasize sensitivity.

ROC AUC (receiver operating characteristic area under the curve):
Achieved scores of 0.999 (near perfect)
(Index: 1.0 perfect score, 9+ clinically acceptable, 0.5 random, just guessing)

Scores from Current Biomarkers:

AUC Ranges -

DAT & SPECT = 0.8 - 0.88
CSF aSyn = 0.65 - 0.78
MRI structure based biomarkers = 0.7 - 0.85
Inflammation = 0.6 - 0.75

PD-INSI:
My high AUC score represents my panel's ability to successfully capture the discriminative disease produced signals across various biological domains in my environment. My accuracy score is a representation of real world trade-offs. This proves that cross domain panels significantly out do single variable biomarker approaches, by adding parameters leading to higher precision.
Individual markers achieved average to good AUC scores in isolation. My study proves that cross domain integration for biomarker panels and this framework significantly increase accuracy. However, this panel has only been tested in a controlled experimental environment.

Conclusions & Results: In conclusion, my proposed biomarker panel revealed strong potential with an accuracy score of 81.2% and a total AUC of 0.999. From these statistics I can conclude that the combination of multiple biological domains into a singular diagnostic framework offers far more advantageous results and opportunities than in comparison to traditional singular variable approaches. Through this research my discovery pipeline and proposed framework is evidence that it can accelerate Parkinson's research and our understanding of what it truly takes to diagnose PD efficiently, accurately, and precisely.

RESEARCH RESOURCES: (alphabetically ordered)

1. *BMC Medical Research Methodology. (September 29, 2021). Statistical model building: Background "knowledge" based on inappropriate preselection causes misspecification. Lorena Hafermann, Heiko Becher, Carolin Herrmann, Nadja Klein, Georg Heinze & Geraldine Rauch.*
2. *Cureus. 02/20/2025. Cerebrospinal Fluid. Biomarkers for Diagnosis of Parkinson's disease: A Systematic Review. Meghana Dasari, Rooth V Medapati.*
3. *Chinese Medical Journal. Biomarkers and neuroimaging markers in Parkinson's disease. October 05, 2025. Su Dongning, Zheng Yuachu, Feng Tao, (editor Gao Ting).*
4. *Dementech Neurosciences. (November 10, 2022). What are the 5 stages of Parkinson's Disease?. Dementech*
5. *Healthline. (Last edited June 6, 2025). The 5 Stages of Parkinson's. Kristeen Cherney.*
6. *Mayo Clinic. (January. 05. 2024) - Mayo Clinic Staff - Tests & Procedures SPECT scan*
7. *MDS Abstracts. (Meeting: 2025 International Congress). Biomarker Panels for Parkinson's Disease Using Multi-Omics Approach: Recent Developments and Future Directions. PRA Shara, RK. Dhamija (Delhi, India)*
8. *National Library of Medicine. (October, 13 2021). Human disease biomarker panels through system biology. Bradley J Smith, Licia C Silva-Costa, Daniel Martins-de-Souza.*
9. *National Institute of Neurological Disorders and Stroke. Parkinson's Disease (Accessed Nov.17/2025)*
10. *National Library of Medicine. National Center for Biotechnology Information. SPECT Molecular Imaging in Parkinson's Disease. Ling Wang, Qi Zhang, Huanbin Li, Hong Zhang. (2012 Mar 24)*
11. *National Institute of Biomedical Imaging and Bioengineering. Nuclear Medicine. (September 2025)*
12. *National Institutes of Health. (April 2, 2024). Skin test detects evidence of Parkinson's and related disorders. Vicki Contie. Gibbons CH, Levine T, Adler C, Bellaire B, Wang N, Stohl J, Agarwal P, Aldridge GM, Barboi A, Evidente VGH, Galasko D, Geschwind MD, Gonzalez-Duarte A, Gil R, Gudesblatt M, Isaacson SH, Kaufmann H, Khemani P, Kumar R, Lamotte G, Liu AJ, McFarland NR, Miglis M, Reynolds A, Sahagian GA, Saint-Hillaire MH, Schwartzbard JB, Singer W, Soileau MJ, Vernino S, Yerstein O, Freeman R. JAMA.*
13. *National Library of Medicine. (July 20, 2020). Cerebrospinal Fluid Biomarkers in Parkinson's Disease: A Critical Overview of the Literature and Meta-Analyses. Takayuki Katayama, Jun Sawada, Kae Takahashi, Osamu Yahara.*
14. *National Library of Medicine. (October 11, 2018). Recent Advances in Biomarkers for Parkinson's Disease. Runcheng He, Xinxiang Yan, Jifeng Guo, Qian Xu, Beisha Tang, Qiying Sun.*
15. *National Library of Medicine. (November 18, 2024). Parkinson's Disease: Biomarkers for Diagnosis and Disease Progression. Rakesh Arya, A K M Ariful Haque, Hemlata,*

Shakya, Md Masum Billah, Anzana Parvin, Md-Mafizur Rahman, Khan Mohammed Sakib, Hossain Md Faruquee, Vijay Kumar, Jong-Joo Kim.

16. *National Institutes of Health (NIH). Prognostic and Predictive Biomarkers: Tools in Personalized Oncology. (January 3, 2014)*
17. *National Library of Medicine. (December 22, 2016). Understanding Prognostic versus Predictive Biomarkers.*
18. *National Library of Medicine. (December 22, 2016). Predictive Biomarker*
19. *National Library of Medicine. (June 13, 2011). Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). Masahiro Fukuoka, Yi-Long Wu, Sumitra Thongprasert, Patrapim Sunpaweravong, Swan-Swan Leong, Virote Sriuranpong, Tsu-Yi Chao, Kazuhiko Nakagawa, Da-Tong Chu, Nagahiro Saijo, Emma L Duffield, Yuri Rukazenkov, Georgina Speake, Haiyi Hiang, Alison A Armour, Ka-Fai To, James Chih-Hsin Yang, Tony S K Mok.*
20. *Parkinson's Foundation (Accessed Nov.17/2025) - Parkinson's Biomarkers*
    a. *Okuumi, A., Hatano, T., Matsumoto, G., Nojiri, S., Ueno, S., Imamichi-Tatano, Y., Kimura, H., Kakuta, S., Kondo, A., Fukuhara, T., Li, Y., Funayama, M., Saiki, S., Taniguchi, D., Tsunemi, T., McIntyre, D., Gérardy, J.-J., Mittelbronn, M., Kruger, R., ... Hattori, N. (2023). Propagative α-synuclein seeds as serum biomarkers for synucleinopathies. Nature Medicine, 29(6), 1448–1455.*
    b. *Yamashita, K. Y., Bhoopatiraju, S., Silverglate, B. D., & Grossberg, G. T. (2023). Biomarkers in parkinson's disease: A state of the art review. Biomarkers in Neuropsychiatry, 9, 100074.*
21. *Parkinson's Foundation. (Accessed November 19, 2025). Stages of Parkinson's.*
22. *PubMed. Parkinson's Disease: Biomarkers for Diagnosis and Disease Progression. 2024 Nov 18. Rakesh Arya, A K M Ariful Haque, Hemlata Shakya, Md Masum Billah, Anzana Parvin, Md-Mafizur Rahman, Khan Mohammed Sakib, Hossian Md Faruquee, Vijay Kumar, Jong-Joo Kim.*
23. *PubMed. A meta-analysis of the diagnostic utility of biomarkers in cerebrospinal fluid in Parkinson's disease. Nov 29, 2022. Chunchen Xiang, Shengri Cong, Xiaoping Tan, Shuang Ma, Yang Liu, Hailong Wang, Shuyan Cong.*
24. *ScienceDirect. Single-Photon Emission Computed Tomography. Chapter - Diagnostic Procedures. (2017). Arm Schneider, Hubertus Feussner*
25. *ScienceDirect. (January 2012). Recent advances in CSF biomarkers for Parkinson's disease. Peter LeWitt.`*
26. *ScienceDirect. (May 11, 2025). AI-driven predictive biomarker discovery with contrastive learning to improve clinical trial outcomes. Gustavo Arango-Argoty, Damian E. Bikiel, Gerald J.Sun, Elly Kipkogei, Kaitlin M. Smith, Sebastian Carrasco Pro, Elizabeth Y. Choe, Etai Jacob.*

27. *ScienceDirect. (June 14, 2025). Statistical analysis and significance tests for clinical trial data. Gregory L Ginn, Clare Campbell-Cooper.*
28. *ScienceDirect. (April, 2021). Biomarker Discovery and Validation: Statistical Considerations. Fang-Shu Ou PhD, Stefan Michields PhD, Yu Shyr PhD, Alex.A Adjei MD PhD, Ann L. PhD, Oberg PhD.*

CASE STUDIES:

1. *National Library of Medicine. Case Report: Dopamine Dysregulation Syndrome, mania, and compulsive buying in a patient with Parkinson's. (November 20, 2023) . Carlos Silvia, Marta Rebelo, Ines Chendo.*
2. *National Library of Medicine. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. (August 14, 2023). Sairam Ramesh MD, Arosh S Perera molligoda Arachige MD.*
3. *Journal of Neurology, Neurosurgery, & Psychiatry. Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study. (Accessed January 9, 2025). Hiba Kazmi, Zuzana Walker, Jan Booij, Faraan Khan, Sachit Shah, Carole H Sudre, Joshua E.J. Buckman, Anette-Elanore Schrag.*
4. *National Library of Medicine. Discovery of a-Synuclein in Lewy Pathology of Parkinson's Disease: The Inspiration of a Revolution. (August 23, 2021). Naomi Visanji, Gabor G Kovacs, Anthony E Lang.*
5. *Lewy Body-Associated Proteins A-Synuclein (a-syn) as a Plasma-Based Biomarker for Parkinson's Disease. (May 12, 2022). Xuemiao Zhao, Haijun He, Xi Xiong, Qianqian Ye, Feifei Feng, Shuoting Zhou, Weian Chen, Kai Xia, Shuangjie Qian, Yunjun Yang, Chenglong Xie.*

MEDIA CREDITS:

1. *ResearchGate. CSF studies in Pakrinson's disease. Table 4. Elizabeta B Mukaetova-Ladinska*
2. *Nature communications. Neuroimaging and fluid biomarkers in Parkinson's disease in an era of targeted interventions. (July, 05, 2024). Angeliki Zarkali, George E.C. Thomas, Henrik Zetterberg & Rimona S. Weil*
3. *Translational Neurodegeneration. Ultrasensitive detection of aggregated a-synuclein using quiescent seed amplification assay for the diagnosis of Parkinson's disease. (July 24, 2024). Hengxu Mao, Yaoyun Kuang, Du Feng, Xiang Chen, Lin Lu, Wencheng Xia, Tingting Gan, Weimeng Huang, Wenyuan Guo, Hancun Yi, Yirong Yang, Zhuohua Wu, Wei Dai, Hui Sun, Jieyuan Wu, Rui Zhang, Shenqing Zhang, Xiuli Lin, Yuxuan Yong, Xinling Yang, Hongyan Li, Wenjun Wu, Xiaoyun Huang, Zhaoxiang Bian, Hoi Leong Xavier Wong, Xin-Lu Wang, Michael Poppell, Yi Ren, Cong Liu, Wen-Quan Zou, Shengdi Chen & Ping-Yi Xu*

4. *Parkinsonism & Related Disorders. (February 2019). What a neurologist should know about PET and SPECT functional imaging for parkinsonism: A practical perspective. Stephane Thobois, Stephane PRange, Christian Scheiber, Emmanuel Broussolle.*
5. *Medium Benchling Engineering. (May 21, 2021). What is benchling? Neena Parikh*

BIOMARKER PIPELINE AND DISCOVERY RESOURCES & TOOLS:

1. *Benchling (Molecular Biology Model) - Application: Discovery of biomarker, and validation of performance potential. (Side by Side comparison of existing biomarkers to draw results)*
2. *Visual Studio Code (VSC) - Application: To build the actual panel through machine learning, utilizing raw data to teach models/training set*
3. *Oxford Dictionary - Application: Glossary and learning key terms/ definitions*

ACKNOWLEDGEMENTS:

1. *Western University - Professor Jessica Grahn, Director of Undergraduate Program in Neuroscience, Director of the Western Centre for Brain and Mind*
2. *Stack Overflow AI Assist - Used purely for Minimal debugging assistance and code skeleton planning (not to be confused. All the code was written by myself.)*
3. *Garry Guan - Senior Software Engineer - For input and feedback on ML pipeline and code*
4. *Westmount Charter School - Mrs. Lai- For input and feedback on my research and organizing science club (school coordinator)*

Western

PD-MOBI-7 Biomarker for Parkinson's Disease

<u>Brainstorming: Rough Initial Outline of Project for the biomarker discovery portion</u>

<u>Discovery Procedure:</u>

1. Intense research of Biomarkers, Parkinson's, Treatments & Medications, and Symptoms
2. Collect and analyze descriptive data on detection methods (SPECT/SAA/MRI, etc.)
3. Decide on seven final biomarkers after cross evaluation to incorporate within the new biomarker (derivative is aSyn)
4. Extract data and research characteristics of each biomarker and its compatibility
5. Deep dive into the creation and discovery of new biomarkers (the process of combining existing ones)
6. Plan-out out ML discovery pipeline
7. Gather input data directly for Machine Learning (raw data)
8. Write up the code in coding language C++ or Python & train basic ML model and simulate Parkinson's alongside other biomarkers (to decide in step 1.)
9. Validate PD-MOBI-7 and assess characteristics and stats (efficiency rate + accuracy)
10. Sum up and organize into a report.

Brainstorming - What is Benchling and Requirements for Originality and Novel Research?

Benchling:

- Simulate biomarker curves (MUST be based on published ranges, average means/standard deviations, known progression curves from PPMI/NIH papers)
    - Purpose: Discoveries from each and trajectories, density patterns, risk score distributions, degradation, transport decline in percentage SBR and aSyn levels. (Analytical purposes)
- Synthetic Biomarkers?
- Creating derived biomarker/composite biomarker

Brainstorming: Next topics to research ideas and next step, plus goals

Next Steps in Research - What else do I need to know or understand?

- *Begin on timeline of project*
- *Wrapped up background research (finished today)*
- *How to utilize benchling? (tutorial)*
- *Research various and relevant genes*
- *Later write a document/handbook for elementary students to achieve gold at CYSF*
- *Goal for tomorrow: finish the biomarker research*
    - *Put a section in the logbook of sample tests/data?*
    - *Explore and make mini projects on bench long then figure out the actual procedure for the molecular biology model of benchlinking.*

Brainstorming: New Timeline -

1. Complete the entirety of the research portion by December 15, 2025
2. Learn Benchling and Programming basics December 17- December 20, 2025
3. Build the discovery pipeline and utilize benchline December 20th-January 20th 2026
4. Write up reports and wrap up (plus design trifold) January 25th- January 31st.
5. February 1st to 6th - Trifold construction

Brainstorming: Adjusted Timeline -

Abbreviations:
FC = Functional code
BD = Before Debugging
BDR = Before Debugging & Review

- Majority (85-90%) of research in logbook - November 31st, 2025
- Code Skeleton Outline + Install all Libraries needed - December 2, 2025

- Programming guidance and learning extra (build off fundamentals) - December 3rd - 7th, 2025
- Do Synthetic Data Portion of Code (BEFORE DEBUGGING/REVIEW) - December 7th - 10th, 2025 (~50-60 lines FC)
- Pre-processing data part of code (BDR) - December 11th - 13th, 2025 (~45 lines FC)
- Research Backed Data Organization done - December 16th, 2025
- Configuration - December 17th
- Data loader - December 18th
- Simulation - December 19th-20th
- Feature Engineering - December 21
- Model - December 22nd
- Evaluation - December 23rd
- Main - December 24th-25th
- Review code so far (BD) - December 14th, 2025
- ALL CODE DONE - December 20, 2025
- FINAL DEBUGGING DONE - December 26 - January 1, 2026
- January 1-7, 2026 - benchling extras
- January 7-14, 2026 - Final Report Due
- January 14, 2026 - January 25 Presentation and Trifold Creation

Glossary & Key Terms:

A:
Alpha-Synuclein (aSyn, a-syn) - a fundamental protein in the brain involved with synaptic communication

Assay - determine the content or quality of something through testing

AUC-ROC (receiver operating characteristic Area under the curve) - a main metric in machine learning for evaluating binary classification models, and representing the model's ability to distinguish between positive and negative classes

Autoimmune - disease caused by antibodies or lymphocytes produced against substances naturally present in the body

B:
Bias - prejudice in favor of or against one thing, person, or group (generally in a way considered to be unfair)

Biofluid - any liquid found in a living organism

Biomarker - a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure

Biomarker Panel - a group of multiple biological indicators measured together in a single test

Biopsy - an examination of tissue removed from a living body to discover the presence, cause, or extent of a disease

Bradykinesia - slowed movement, with slowness in executing voluntary actions

C:
Chronic - persisting for a long time or constantly recurring

Composite Biomarker - a combination of two or more individual biomarkers

Control Group - a baseline group that does not receive the treatment or intervention being tested

D:
Degenerative Disease - the progressive, and gradual deterioration of the structure or function of body tissues and organs, leading to worsening impairment and disability over time

G:
Genetics - the study of heredity and the variation of inherited characteristics

Gene - a distinct sequence of nucleotides forming part of a chromosome

H:
Hybrid - of mixed character; composed of different elements

I:
Impairment - the state or fact of being weakened or damaged

Invasive - tending to spread prolifically and undesirably or harmfully

L:
Lewy-Body - abnormal clumps of aSyn that builds up inside brain nerve cells

M:

Machine Learning (ML) - A type of artificial intelligence that teaches computers to learn from data and automatically improve

Mesolymbic System - Dopamine rich neuro circuit, which connects the ventral tegmental area (VTA) to limbic structures

N:
Neurodegeneration - progressive death or dysfunction of neurons in the brain and nervous system

Neuroinflammation - central nervous system's (CNS) response to injury, toxins, or neurodegenerative processes

O:
Onset - Beginning of something

P:
Pathology - the science of the causes and effects of diseases

Parkinson's Disease (PD) - a progressive brain disorder affecting movement, causing tremors, rigidity, bradykinesia, and balance issues

Plasma - pale yellow liquid part of your blood that carries cells, water, and proteins

Progressive - happening or developing gradually in stages; proceeding step by step

Protein(s) - any of a class of nitrogenous organic compounds that have large molecules composed of one or more long chains of amino acids and are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, etc., and as enzymes and antibodies

R:
Radiotracer - a substance with a radioactive atom attached used to track biological processes

S:
Simulation - imitation of a situation or process

SNpc (Substantia Nigra pars compacta) - a critical midbrain nucleus and a primary component of the basal ganglia circuitry

Symptoms - a physical or mental feature which is regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient

Synthetic - made by chemical synthesis, especially to imitate a natural product

T:
Tremor - an involuntary quivering movement

V:
Variable(s) - able to be changed and adapted