Minimizing the Devastating Impact of Synucleinopathies: The Utility of Biomarker Testing

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Introduction

Neurodegenerative diseases are progressive conditions that lead to the deterioration and death of cells in the nervous system over time, resulting in the loss of normal physiological signaling and functions. Synucleinopathies are a collection of neurodegenerative disorders that involve the accumulation of a protein called alpha-synuclein in cells of the central nervous system. Such accumulation can disrupt normal cellular functions and result in diseases including Parkinson's disease, dementia with Lewy bodies and multiple system atrophy. As these diseases progress, patients develop problems with movements as well as other symptoms that can have devastating impacts on the patients themselves as well as their caregivers. Unfortunately, there are currently no available medications that can prevent, reverse or slow the progression of these diseases. Synucleinopathies are also difficult to recognize because many of their symptoms are similar to those of other diseases, resulting in delayed treatment and prolonged patient suffering. However, new biomarker tests are emerging that may enable early diagnosis and appropriate treatment of symptoms. They may also promote the development of new treatments. Therefore, such tests have the potential to greatly improve the quality of life of patients and their families.

Alpha-synuclein (αSyn)

αSyn is a small protein encoded by the *SNCA* gene that is expressed in cells of the central (brain and spinal cord) and peripheral (body) nervous systems. In synucleinopathies, αSyn proteins are misfolded or modified in ways that cause them to stick to each other or other proteins, forming clumps. These clumps disrupt normal cell functions and signaling between neurons. They can also cause cell death.[1]

Synucleinopathies

Synucleinopathies, specifically Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, are alike in that they are all associated with the abnormal collection of alpha-synuclein (αSyn) protein in cells (neurons or glia) in the central nervous system. As αSyn accumulates, it can form clumps that damage cells and disrupt normal neuronal signaling. It is these signaling disruptions in various cell types and areas of the brain that contribute to disease symptoms.

While there is some overlap in the symptoms of Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, there are also distinct differences. These symptom variations are caused by differences in the primary cell types involved in the onset and progression of each disease.

> "Parkinson's disease, dementia with Lewy bodies and multiple system atrophy are all distinct disorders, even though they share a common abnormal protein. Multiple system atrophy is a glial synuclein disease. It has young onset and patients have a bunch of weird collective symptoms that, outside of a movement disorder clinic, are really hard to diagnose. Dementia with Lewy bodies is a dementing illness that begins late in life, and Parkinson's disease is a movement disorder for 5, 7 maybe 10 years before cognitive symptoms develop."
>
> **–James E. Galvin, MD, MPH**

Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder, behind Alzheimer's disease, affecting around 1 million people in the United States.[2–4] Advanced age is the single

greatest risk factor for Parkinson's disease,[5] with 60 being the average age at diagnosis. However, about 4% of patients are diagnosed with the disease before the age of 50 (young-onset Parkinson's).[3,6] Parkinson's disease affects people of all races, ethnic groups, nationalities and income levels.[4] However, a study of U.S. Medicare beneficiary data (from patients age 65 and older) found that Parkinson's disease was more prevalent in White populations (50% higher) than Black and Asian populations.[7] It also affects males 1.5 to 2 times more often than females.[7–10]

Parkinson's disease is caused by αSyn deposits called Lewy bodies in neurons that release dopamine (dopaminergic neurons) in an area of the brain called the substantia nigra. This area is responsible for controlling body movements.[5] Over time, as the number of Lewy bodies increases and more and more neurons die, the motor (movement) symptoms of the disease gradually worsen. These symptoms include bradykinesia (slowed movements), rigidity, resting tremor and postural instability.[11]

In addition to motor symptoms, Parkinson's disease patients also experience non-motor symptoms. Many of these non-motor symptoms can start years before the motor symptoms begin and tend to get worse with age.[12,13] Examples of non-motor symptoms include hyposmia (decreased sense of smell), sleep disorders (particularly REM sleep behavior disorder), depression, anxiety, constipation, cognitive impairment/dementia, pain, sexual dysfunction and visual hallucinations.[14,15]

> "The symptoms are individualized. No one is going to necessarily have all of the symptoms; they will have a mix of them."
>
> **–Erin Zinn, MSN, APRN-CNP, ANP-BC**

Overall, the progression of Parkinson's disease symptoms is usually relatively slow, with most patients surviving 15–20+ years after their diagnosis, resulting in largely normal lifespans.

> "You don't really die of Parkinson's. You die with it, which is not the case with dementia with Lewy bodies or multiple system atrophy."
>
> **–David Houghton, MD, MPH**

Dementia with Lewy bodies

Dementia with Lewy bodies is the second most common cause of dementia in the United States. It accounts for up to 30.5% of all dementia cases and affects approximately 1.4 million people in the country.[18] On average, dementia with Lewy bodies onset occurs at the age of 75, and the incidence of the disease increases with age.[19] It also affects more males than females.[20]

> "Dementia with Lewy bodies is the most common disease that no one's ever heard of and no one can diagnose."
>
> **–James E. Galvin, MD, MPH**

Dementia with Lewy bodies is notable for the accumulation of Lewy bodies in cortical neurons;[21] however, the loss of dopaminergic neurons in the substantia nigra has also been observed.[22] Due to the disruption of normal functions in these cells as well as cell death, dementia with Lewy bodies patients experience problems with thinking and cognition in addition to many of the motor and non-motor symptoms that are experienced by patients with Parkinson's disease. Some of the main

features of dementia with Lewy bodies include progressive declines in thinking ability, memory and problem solving as well as recurrent visual hallucinations, sleeping problems and depression. These symptoms occur along with the motor symptoms that are characteristic of Parkinson's disease.[16,23]

In contrast to Parkinson's disease, dementia and cognitive problems occur early on in dementia with Lewy bodies, and symptoms progress much more rapidly. Studies have shown that the average survival time of patients following diagnosis is only around 4 years.[24,25]

Multiple system atrophy

Multiple system atrophy is a relatively rare and aggressive synucleinopathy. Roughly 15,000–50,000 Americans suffer from this disease, and it usually occurs in people who are in their 50s.[26] It also affects people of all racial groups, and, in contrast to Parkinson's disease and dementia with Lewy bodies, it affects males and females equally.[26,27]

Dementia with Lewy bodies vs. Lewy body dementia

Dementia with Lewy bodies and Lewy body dementia are not the same. Dementia with Lewy bodies is the name of a single disease. Lewy body dementia is a term that is used to refer to two related diseases: dementia with Lewy bodies and Parkinson's disease dementia.[16,17]

> "Since symptoms occur in younger persons, diagnosis of multiple system atrophy is often delayed and confused with Parkinson's disease after they don't have an expected good response to dopaminergic replacement therapies."
>
> **–Pinky Agarwal, MD, FAAN**

There are two types of multiple system atrophy: multiple system atrophy with predominant parkinsonism (MSA-P) and multiple system atrophy with predominant cerebellar ataxia (MSA-C). More than two-thirds of the people in Western countries have the MSA-P subtype.[27] Both forms have glial cytoplasmic inclusions (GCIs), which are areas of αSyn accumulation in oligodendrocytes, a type of glial cell in the brain that surrounds neurons (myelination) and supports their signaling functions.[1,27]

Individuals with MSA-P experience the motor symptoms that are associated with Parkinson's disease, including bradykinesia, rigidity, postural instability and tremor.[16] Individuals with MSA-C have problems with gait and limb ataxia (poor muscle control leading to clumsy movements), dysarthria (slurred speech) and eye movement disturbances.[16] In addition to these motor symptoms, people with either type of multiple system atrophy experience autonomic dysfunction, which can include urinary incontinence, orthostatic hypotension (blood pressure drop when standing up) and sexual dysfunction.[16,23]

Overall, the symptoms of multiple system atrophy progress fairly rapidly. From symptom onset, autonomic dysfunction starts after 2.5 years, wheelchair confinement occurs at 3.5–5 years, patients are bedridden at 5–8 years, and death occurs after 6–10 years.[16]

Synucleinopathy snapshot

	Parkinson's Disease	Dementia with Lewy Bodies	Multiple System Atrophy
Number of people living with the disease in the US	~1,000,000[3]	1,400,000[18]	15,000–50,000[26]
Usual age of onset	60 years old[6]	75 years old[19]	50–60 years of age[28]
Sex dimorphism	More males affected than females[7–9]	More males affected than females[20]	Affects males and females equally[27]
Life expectancy	Largely normal[29]	~4 years after diagnosis[24,25]	6–10 years after diagnosis[16]
Time to reach a diagnosis	3–10 years[30]	1–2 years[31,32]	3–4 years[28]
Primary neurons affected	Dopaminergic neurons in the substantia nigra	Cortical neurons	Glial cells (oligodendrocytes)
Motor symptoms	• Bradykinesia • Postural instability • Resting tremor • Rigidity	• Bradykinesia • Postural instability • Resting tremor (rare) • Rigidity	• MSA-C: ataxia, problems swallowing, speech abnormalities, abnormal eye movements • MSA-P: bradykinesia, rigidity, tremor, problems with balance
Non-motor symptoms	• Anxiety • Cognitive impairment/ dementia • Constipation • Depression • Hyposmia • Pain • Sexual dysfunction • Sleep disorders • Visual hallucinations	• Anxiety • Cognitive impairment/ dementia • Constipation • Depression • Hyposmia • Orthostatic hypotension • Sensitivity to antipsychotics • Sexual dysfunction • Sleep disorders • Visual hallucinations	• Anxiety • Cardiovascular problems • Depression • Gastrointestinal problems • Orthostatic hypotension • Sleep disorders • Sweating • Sexual dysfunction • Urinary problems

Burdens of disease

Patients

There are many burdens associated with synucleinopathies. For patients, the symptoms of disease, particularly the non-motor symptoms, are significant burdens that continually get worse over time and can greatly reduce well-being and quality of life. In fact, it is often the non-motor symptoms that determine when an individual can no longer be independent and needs to be placed in a residential care facility.[33,34] Many patients may also experience side effects related to the medicines that are prescribed to treat their symptoms that can lower their quality of life.[16,35]

> “Sometimes the non-motor symptoms more negatively affect patient quality of life than the tremor or some of the other motor symptoms that you see.”
>
> **–Erin Zinn, MSN, APRN-CNP, ANP-BC**

> “Things that lead to hospitalization, such as incontinence, psychosis, falls and aspiration, are big causes of institutionalization.”
>
> **–Pinky Agarwal, MD, FAAN**

As symptoms progress, patients may also have trouble with social interactions and/or relationships. This can be due to problems communicating (impaired speech) and expressing emotions, difficulty recognizing the emotions of others, and/or struggles with intimacy (sexual dysfunction, such as erectile dysfunction or difficulty achieving orgasm).[36–38] These issues often leave the patient feeling frustrated, worried or embarrassed, which further leads to self-isolation to minimize the discomfort of these social interactions.[37,39] There can also be stigma associated with their visible symptoms that causes them to isolate themselves even further.[40] Such isolation can lead to loneliness and depression, which have additional negative impacts on their quality of life.

> “One thing my patients always want to bring up—because it can be a real lifestyle hindrance—is the regular autonomic dysfunction that results in erectile dysfunction, anorgasmia (inability to achieve orgasm), and diminished libido. It can have a really negative impact on their relationships.”
>
> **–David Houghton, MD, MPH**

Patients may also experience a great deal of stress and/or anxiety related to their diagnosis. Indeed, waiting years for a diagnosis can have a negative impact on their emotional well-being. In addition, while having a diagnosis can offer some relief, there is still a great deal of fear and uncertainty related to not knowing how their disease will progress.[41]

> "It's really hard on patients to not have a diagnosis. So, while no one wants to have Parkinson's, there is often a sigh of relief when they are finally diagnosed correctly. There is an emotional advantage to diagnostic certainty."
>
> **–David Houghton, MD, MPH**

> "There's a lot of anxiety living with the unknown. One of the most asked questions I get is, 'How do you think my Parkinson's will progress?' and, unfortunately, we don't have any way to predict that."
>
> **–Cherry Yu, MD**

Families/caregivers

As their disease progresses, patients with synucleinopathies need more help, and family members are often the ones who provide this additional care.[42] This places a significant burden on caregivers that can also negatively affect additional members of the caregiver's family (e.g., spouse, children). The level of burden experienced by caregivers depends on various factors, including the age of the patient, speed of disease progression, amount of time spent providing care and the severity of non-motor symptoms. In addition, as the burden of care increases, the quality of life of the carer decreases.[14,34,43–45] Many caregivers also report experiencing stress, loneliness, isolation, depression and fear of the future; however, these feelings can be diminished with more social support (i.e., support groups, social interactions).[37,43,46,47]

> "These diseases have impacts on more than just the patients themselves. They can affect the whole world of their caregivers—their family, their friends—and as the disease progresses, it becomes more and more of a burden."
>
> **–Cherry Yu, MD**

> "Another burden is the caregiver hours. It's hours of lost wages and time spent with children or spouses. If it's a relatively young onset, then the caregiver burden in hours is a pretty devastating number."
>
> **–Daniel Press, MD**

> "Urine and bladder problems are a big deal. They are a significant burden on caregivers because they have to wake up in the middle of the night to take the patient to the restroom. Caregivers then have to report to work or do household chores after being sleep deprived. Nighttime awakenings are also when falls happen."
>
> **–Pinky Agarwal, MD, FAAN**

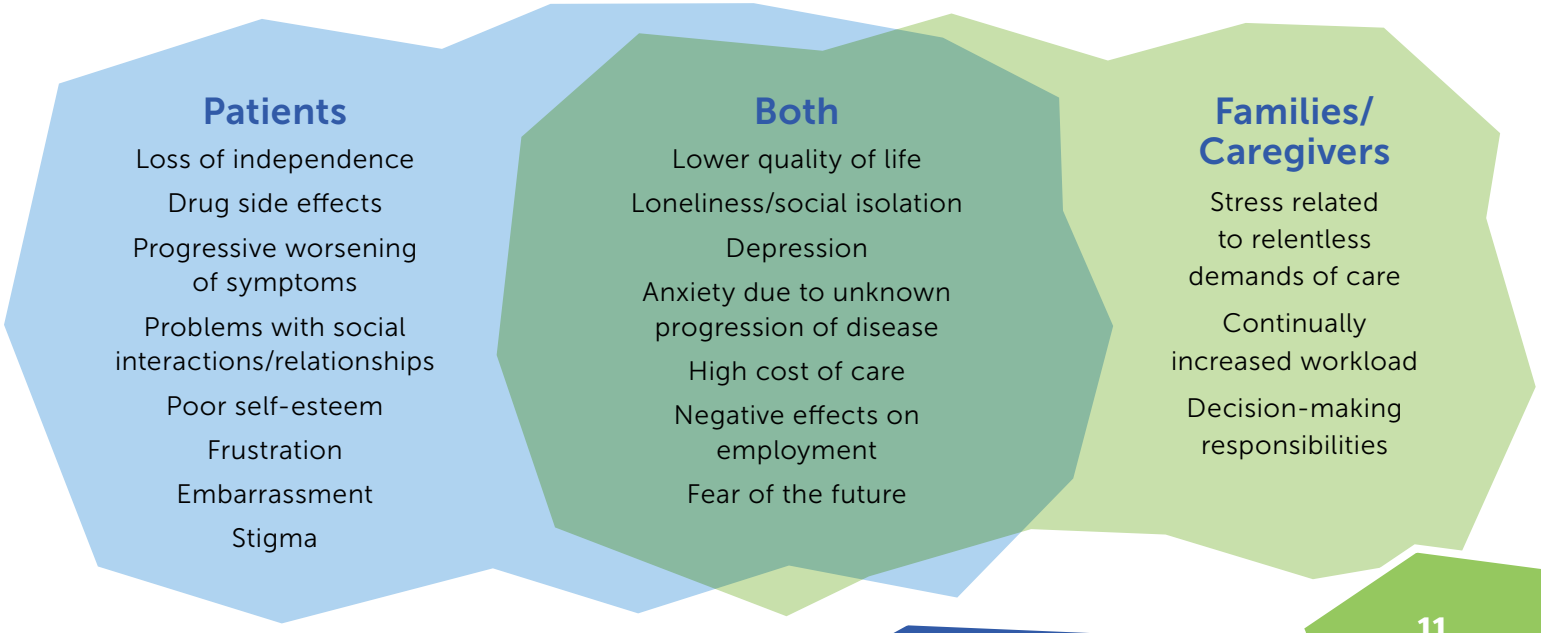
Economic impacts

While the specific cost of care varies for each condition due to differences in the length of time affected by the disease and the severity of symptoms, the economic impact of each disease on patients, their families and the national health system is still significant.[2,34,48] For both patients and their caregivers, income can be greatly reduced due to lost wages from being absent from work or having to quit/reduce work hours/retire/go on disability in order to manage the disease. This loss of income can also lead to greater burdens on the US government due to the reduced collection of taxes and the increased expense of providing disability assistance. In addition, because these diseases primarily affect older people and get worse with age, Medicare often bears a large share of the direct medical costs of treatment, such as those for prescriptions, doctor visits, hospitalizations, therapy sessions and nursing home care.[2,42,49]

> "The financial burden with these diseases varies. For Parkinson's disease patients, they don't become disabled until they are 10, 15, 20 years into their disease, but they still have to live with their symptoms for a long period of time. Patients with dementia with Lewy bodies and multiple system atrophy have a shorter course of disease, so the financial burden is less than Parkinson's disease overall, but within a year span, the economic and healthcare system burden is higher because they have a higher risk of complications."
>
> **–Cherry Yu, MD**

> "The financial aspect of these diseases is big. Once patients have dementia or incontinence and need to be placed in assisted living or an adult family home, they suddenly have to come up with $10,000 a month and may need to sell their homes in order to afford it."
>
> **–Pinky Agarwal, MD, FAAN**

> "Early retirement is also a significant cost for those patients who are younger and have really tough cases where they just cannot work anymore."
>
> **–Erin Zinn, MSN, APRN-CNP, ANP-BC**



Challenges of diagnosis

Access to care

There are several challenges that individuals with a synucleinopathy face on their journey to a diagnosis. One of these challenges is timely access to a neurologist. In a recently published study, researchers found that only 60% of Medicare beneficiaries with Parkinson's disease saw a neurologist in 2019.[50] This low level of specialist use can at least partially be explained by the shortage of neurologists to supply the appropriate care. According to the American Association of Medical Colleges, there were 14,146 neurologists in the United States in 2019, which means that there was one neurologist for every 23,429 people in the country.[51] In addition, while the prevalence of synucleinopathies does not vary significantly geographically, the number of neurologists can vary substantially from region to region.[52,53] One study reported that 94.33% of neurologists were practicing in metropolitan areas, while 5.211% were practicing in nonmetropolitan areas, and only 0.458% were practicing in rural areas.[53] For patients, the lack of a sufficient number of neurologists to meet demand as well as the uneven distribution of these specialists across the country often results in long wait times for appointments, increased financial burden (e.g., lost wages, travel expenses) and treatment delays, particularly for those living in rural areas.

> "Patients often have to see multiple doctors to get a diagnosis and the wait time for a specialist is a barrier to care. This is a problem because by the time they are finally diagnosed correctly, they may be a lot more advanced in their disease course and have missed out on early treatment opportunities."
>
> **–Cherry Yu, MD**

> "If you have dementia with Lewy bodies, where you only have 4 to 6 years to live with the disease, and you have to wait 6 to 8 months to see a neurologist, you end up not being diagnosed for the first quarter of the disease course."
>
> **–James E. Galvin, MD, MPH**

> “For Parkinson’s disease and the dementia syndromes that overlap with movement disorders, there’s only a handful of neurologists in the country who are comfortable with handling both the movement and the cognitive issues, so often these patients end up seeing either no neurologists at all—if they live in an area where there aren’t enough neurologists—or they try to see 2 or 3 neurologists to take care of all of their symptoms.”
>
> **–Daniel Press, MD**

> “Patients from rural areas have to travel long distances and sometimes stay in a hotel the night before to be able to access care, which is often localized in urban areas.”
>
> **–Pinky Agarwal, MD, FAAN**

Difficulty identifying disease

Another challenge that patients face is difficulty achieving a final diagnosis. Parkinson’s disease, dementia with Lewy bodies, and multiple system atrophy are all clinically diagnosed.[54–57] This means that doctors rely on medical history, pertinent symptoms, and their examinations to diagnose these diseases. Reaching a diagnosis is challenging because many of the symptoms of these diseases overlap with each other and with other conditions that are not synucleinopathies. For example, the motor symptoms that are characteristic of Parkinson’s disease can also be caused by specific brain lesions, head trauma, medications, metabolic conditions, and exposure to toxins.[23,58] Therefore, it is often necessary for doctors to monitor the progression of symptoms over time and perform tests to try to rule out some of these conditions before making a definitive diagnosis. This helps explain why the diagnostic processes for these diseases can last for years.[28,30–32]

> “There are a number of other conditions that can mimic Parkinson’s disease that are not synucleinopathies.”
>
> **–Daniel Press, MD**

Another hurdle to overcome when diagnosing synucleinopathy patients is misdiagnosis. Because of the significant overlap of symptoms in Parkinson’s disease, dementia with Lewy bodies, multiple system atrophy and other disorders, misdiagnosis is common, particularly early on in the disease course. Indeed, reported misdiagnosis rates range from 6–47%, depending on who is performing the diagnosis (primary care physician, neurologist or movement disorder specialist).[55,58–68] For example, based on a collective analysis of three separate studies, only 58% of the patients that had an initial, early diagnosis of Parkinson’s disease were confirmed to have Parkinson’s disease at autopsy.[62] Consistent with the strong similarity of synucleinopathies, multiple system atrophy was one of the conditions that was most commonly assigned after autopsy in those who were initially clinically misdiagnosed with Parkinson’s disease.[62] In another study of 134 patients clinically diagnosed with multiple system atrophy, only 62% were found to have been correctly diagnosed based on autopsy results, with Parkinson’s disease and dementia with Lewy bodies often being mistaken for multiple system atrophy.[66]

> Dementia with Lewy bodies and multiple system atrophy patients are often misdiagnosed with Parkinson's first."

–Cherry Yu, MD

> The clinical overlap between dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease dementia is pretty broad and can complicate making a correct diagnosis."

–James E. Galvin, MD

Such high rates of misdiagnosis can cause a variety of problems for synucleinopathy patients. In addition to misdiagnosis delaying appropriate treatment, some of the medications used to treat these diseases can have harmful side effects, so having a correct diagnosis from the start is essential for picking the right therapies and avoiding unnecessary patient discomfort.

> We did a large study by surveying nearly a thousand families living with Lewy body dementia and found that the average person sees 2 to 3 doctors over 12 to 18 months, and 75% get misdiagnosed the first time around. Some of the misdiagnoses are not harmful, like getting diagnosed with AD first. The harmful one is getting diagnosed with geriatric schizophrenia or bipolar disease first. These patients bounce around from doctor to doctor, resulting in a huge delay and a great burden on the family just to get a diagnosis."

–James E. Galvin, MD

> There's a lot of benefit to being on the right medications and, just as importantly, not being on the wrong medications."

–Daniel Press, MD

Biomarkers as diagnostic tools

Since no cures are available for synucleinopathies,[11,26,54,69–71] a primary focus of current research is the development of diagnostic tools for early disease recognition. Because the symptoms get worse over time, early diagnosis would allow for prompt treatment that would help patients maintain a higher quality of life and lower their long-term treatment costs. It would also allow patients and families more time to prepare for their future living with the disease. Furthermore, early diagnosis would help advance research and clinical trials studying new and more effective treatments for these diseases.[35,58,72,73]

> "In terms of future planning and making sure that patients have the best quality of life going forward, getting an accurate diagnosis early on is very important."
>
> **–Cherry Yu, MD**

> "For the cognitive disorders, you want an early diagnosis so that the patient can participate in advanced care planning."
>
> **–James E. Galvin, MD**

> "Having a diagnosis helps patients better plan for their future—career, life, and finances."
>
> **–Pinky Agarwal, MD, FAAN**

The identification of biomarkers holds much promise for enabling early disease diagnosis and preventing misdiagnosis.[58] Biomarkers are biological traits that are measured to provide information about a patient's health status.[74] Some biomarkers are physical features, such as blood pressure, that can be measured in the clinic, and some are molecules, such as blood cholesterol, that can be measured using laboratory tests. There are also imaging biomarkers that are measured using technologies such as computed tomography (CT) or magnetic resonance imaging (MRI). Ideally, biomarkers for synucleinopathies would enable early,

Features of ideal diagnostic biomarkers

- **Specific**
  - Patients without the disease will not test positive (no false positives)
- **Sensitive**
  - Patients who have the disease will not test negative (no false negatives)
- **Easy to measure**
  - Found in biological samples that are easy to access (e.g., blood, urine, cerebrospinal fluid, skin)
  - Can be assayed quickly in a laboratory or clinical setting
- **Recognize the disease early (before most symptoms start)**
- **Tests are inexpensive**
- **Tests are accessible**
  - Do not require highly specialized health professionals or equipment
- **Tests are reproducible**
  - Provide the same results on repeat measurements
- **Can also indicate/monitor disease severity/progression**

specific identification of each disease. Such biomarkers would also be found in biological samples that are easily collected (e.g., blood, urine, cerebrospinal fluid, skin). Furthermore, biomarker testing would be quick and inexpensive and would not require the use of highly specialized resources (staff and/or equipment). It would also be best if the biomarker could indicate disease severity/progression to help monitor the course of disease.

> "An important thing about biomarkers is that not only do they help you detect the condition when it is present, they can tell you if it isn't present."
>
> **–Daniel Press, MD**

> "Biomarkers need to be both sensitive and specific so that they can be used for both a rule in and a rule out in the right scenarios."
>
> **–David Houghton, MD**

> "One of the biggest values of biomarkers is that they can be used to determine whether a disease is an actual synucleinopathy or whether the parkinsonism is caused by something else, like dopamine blocking drugs."
>
> **–Pinky Agarwal, MD, FAAN**

> "The currently available biomarkers don't correlate with disease severity, so we can't say where patients are in their disease path."
>
> **–Cherry Yu, MD**

Current biomarkers for synucleinopathies

> "There are really only three assays that I know of that work: the skin biopsy, the seed assay, and the DaTscan."
>
> **–Daniel Press, MD**

αSyn skin biopsy

Unsurprisingly, one of the major biomarkers being explored to identify synucleinopathies is αSyn. Researchers have found that detecting a modified (phosphorylated) form of αSyn in nerves in skin biopsies is an effective way to determine whether someone has a synucleinopathy.[75,76] This method involves taking small skin biopsy samples from three different areas on the body (one on the back of the neck and two on the leg) and testing them in a laboratory for the presence of phosphorylated αSyn. One study found that such testing exhibited greater than 92% sensitivity for a number of synucleinopathies, including Parkinson's disease (92.7%), dementia with Lewy bodies (96%), and multiple system atrophy (98.2%). This same study also determined that the test was more than 96% specific for synucleinopathies.[76] These results, and those from additional studies,[76–88] suggest that phosphorylated skin αSyn is an extremely effective biomarker for distinguishing those patients with a synucleinopathy from those patients without a synucleinopathy. Consistent with these findings, this test was also recently shown to have a significant impact on clinical care. In a study of 97 patients with a suspected synucleinopathy, 78% had a change in their clinical care, 66% had a change in their diagnosis, and 55% had a change

in their treatment after receiving the results of this biomarker test.[89] Taken together, these results indicate that phosphorylated skin αSyn is a useful and reliable biomarker for synucleinopathies, and that testing for this marker can significantly affect patient treatment and outcomes.

> "The current biomarkers cannot differentiate between Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, but they can differentiate between synucleinopathies and non-synucleinopathies."
>
> **–James E. Galvin, MD**

Interestingly, there is additional evidence that differences in the cell types affected or the locations of the αSyn deposits in skin may be used to help identify specific synucleinopathies.[77,80,82,84,86,90] Furthermore, studies in patients with idiopathic REM behavior disorder, a condition that is highly associated with future development of a neurodegenerative synucleinopathy (over 70% will develop parkinsonism or dementia within 12 years of their REM behavior disorder diagnosis[91]), suggest that phosphorylated skin αSyn may be an early synucleinopathy marker.[92–96] More work is necessary to validate these findings and determine their clinical value; however, such results indicate that this biomarker may prove to have even more diagnostic benefits than those that are currently recognized.

αSyn seed amplification assay

Another test for αSyn is called the αSyn seed amplification assay (αSyn SAA). This assay is primarily used on cerebrospinal fluid samples to detect the presence of misfolded αSyn that has the ability to form aggregates.[59,92,97,98] In a number of research studies, the αSyn SAA was able to identify patients with Parkinson's disease and dementia with Lewy bodies with high sensitivity (86–96%) and specificity (82.3–100%).[98–106] The αSyn SAA has also been shown to effectively detect defective αSyn protein present in the cerebrospinal fluid of patients with idiopathic REM behavior disorder,[92,99,100,105] ultimately providing the opportunity to recognize Parkinson's disease and related diseases before any motor symptoms emerge. Based on these findings, the U.S. Food and Drug Administration (FDA) recently issued a letter of support for the use of the αSyn SAA to identify patients for clinical trials for Parkinson's disease and related diseases.[107] This step should significantly advance research into treatments to slow or prevent disease onset.

> "For all of these disorders, alpha-synuclein proteins misfold and build up for years before symptoms develop. That's sort of terrifying, but it is also an incredible opportunity because it means that a therapy could be started after the protein has started building up but before someone has symptoms."
>
> **–Daniel Press, MD**

While the αSyn SAA has been shown to be tremendously effective for detecting the presence of Lewy body-related diseases (Parkinson's disease and dementia with Lewy bodies), results reported for the detection of multiple system atrophy are more variable.[59,98,101,108,109] Such variation is thought to be due to differences in αSyn variants that could be present in these diseases.[98,101,109] In support of this notion, one study has shown that the aggregates generated from the cerebrospinal fluid of Parkinson's disease patients in the αSyn SAA have different properties than the aggregates

generated from the cerebrospinal fluid of multiple system atrophy patients,[109] thus demonstrating the potential for this assay to be adapted to recognize specific synucleinopathies, which could expand its clinical utility.

DaTscan imaging

DaTscan imaging is an FDA-approved biomarker that can be used to help confirm suspected cases of Parkinson's disease/related neurodegenerative disorders.[110–112] For this test, patients are injected with a special drug that labels dopaminergic neurons in the brain so that they can be visualized by single-photon emission computed tomography (SPECT) imaging. This test has been shown to be up to 90% sensitive and up to 92% specific when differentiating between Parkinson's disease and non-degenerative conditions with similar motor symptoms (vascular or drug-induced parkinsonism).[113,114] Moreover, in a meta-analysis of dementia with Lewy bodies studies, researchers determined that the pooled sensitivity and specificity of DaTscan imaging in distinguishing between patients with and without dementia with Lewy bodies was 86.5% and 93.6%, respectively.[115] However, it is important to note that while DaTscan imaging can aid in the diagnosis of conditions with parkinsonism, it cannot specifically differentiate between similar neurodegenerative movement disorders, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy.[116]

> "Biomarkers found in skin and CSF may be more accurate than the DaTscan. They're similar in specificity, but they tend to be higher in sensitivity. Combinations of such high sensitivity and specificity together changes their predictive value in the real world."
>
> **–David Houghton, MD, MPH**

Conclusion

Collectively, millions of people in the United States are affected by Parkinson's disease, dementia with Lewy bodies and multiple system atrophy. As progressive neurodegenerative diseases, these synucleinopathies place enormous physical, emotional, and financial burdens on patients and their families. While there are currently no cures for these diseases, new hope has emerged with the identification of clinically reliable biomarkers. Such biomarkers are facilitating correct and early diagnoses, which are essential for prompt and appropriate treatment that can drastically improve the quality of life of patients and their families. They are also significantly contributing to the advancement of continuing research into effective treatments for these diseases, which is crucial for minimizing and, hopefully, eliminating patient suffering.

CNSA's Clinical Proceedings

The Clinical Neurological Society of America has 50 years of experience bringing together leading experts and clinical neurologists for educational programming. CNSA's Clinical Proceedings—a white paper series—are informational resources intended to raise awareness and address unmet needs in neurology. CNSA recognizes the expert panel members who contributed to the development of this white paper.

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