

EXPERT REPORT OF STUART H. ISAACSON, M.D.
DARRELL ROSE V. SYNGENTA CROP PROTECTION, LLC, ET AL.,
CASE No. 241200112

Dated: February 17, 2026



Stuart H. Isaacson, M.D.

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I. QUALIFICATIONS AND BACKGROUND

I have over three decades of experience in neurology and movement disorders, including Parkinson's disease (PD). I am recognized internationally as an expert in PD and movement disorders.

I received a Bachelor of Science in Biomedical Science from Northwestern University in 1986. I earned my M.D. from Northwestern University Medical School in 1988.

From 1988 to 1989, I completed an internship in medicine at St Luke's – Roosevelt Hospital Center and was a residency fellow in medicine at Columbia University College of Physicians and Surgeons, both located in New York. From 1989 to 1992, I completed my residency in neurology at Mount Sinai Medical Center in New York, during which time I received training in the causes and treatment of movement disorders, including PD. In my last year, I was Chief Resident in neurology with Dr. Melvin Yahr, one of the foremost authorities in PD and integral in the development of levodopa treatment for PD.

From 1992 to 1995, I completed a fellowship in neurodegenerative disease at the National Institute of Neurological Disorders and Stroke at National Institute of Health (NIH) in Bethesda, Maryland. At the NIH, I was a Lieutenant Commander in the Public Health Service, and a Clinical Associate in the NIH Clinical Center under Mark Hallett. I also led the clinical desk in the Laboratory for Central Nervous System Disorders under Nobel Laureate D. Carlton Gajdusek, and in his research laboratory developed novel laboratory methods to investigate central nervous system diseases using polymerase chain reaction in situ hybridization.

From 1995 to 1996, I completed a second fellowship in PD and movement disorders at Mount Sinai Medical Center in New York, where I received further training in the causes and management of PD and movement disorders under the mentorship of Melvin Yahr, C. Warren Olanow, and Mitchell Brin, all globally recognized experts.

I first received my license to practice medicine in the State of New York in 1989, and I have been licensed in the State of Florida since 1997. I am a diplomate of the American Board of Psychiatry and received my board certification in Neurology in 1994. I am a Fellow of the American Academy of Neurology and have also been appointed Fellow of the International Association of Parkinsonism and Related Disorders.

In 1995, I joined the Mount Sinai School of Medicine, where I was Assistant Professor in the Department of Neurology. From 1995 to 1997, I was also an attending physician at the Mount Sinai Hospital Movement Disorders Center. I previously served as Voluntary Assistant Professor of Neurology at the University of Miami School of Medicine in 2002. In 2004, I also served as Clinical Assistant Professor of Biomedical Sciences at the Florida Atlantic University Medical School, and as Clinical Associate Professor of Neurology at the Florida International University College of Medicine. Since 2018, I have also taught clinical rotations in neurology and movement disorders to medical students and neurology residents from international medical schools, and to neurology residents and medical doctors from Miami and internationally. I have also taught over 50 Continuing Medical Education (CME) courses as a Course Director, and over 100 CME courses as a Faculty member.

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In 1997, I began clinical practice in Florida. In 1999, I established the Parkinson's Disease and Movement Disorders Center of Boca Raton, in Boca Raton, Florida, a comprehensive center for the evaluation and management of patients with PD and other movement disorders. It is also an internationally recognized clinical research center that investigates emerging therapies for neurodegenerative and movement disorders.

I am a full-time clinician and clinical researcher and have served as the Director of the Parkinson's Disease and Movement Disorders Center of Boca Raton since 1999. As part of my clinical practice, I treat patients throughout the course of PD. Our center cares for over 1,500 active patients each year, including over 400 new patients with PD or movement disorders.

I have been a principal investigator or co-investigator for more than 300 clinical trials, including over 250 clinical trials on PD, and am an internationally recognized leader in the development of new therapeutics for PD. My clinical research has been focused on the development of new treatments for patients with PD, autonomic disorders, neurodegenerative disorders, hyperkinetic movement disorders, dystonia, and botulinum toxins.

I have extensively published in the field of PD and movement disorders, including peer-reviewed articles, editorials, letters, book chapters, abstracts, and presentations. Many of my publications are related to PD. I am also an external reviewer for numerous journals, including Movement Disorders, Drugs and Aging, Parkinsonism and Related Disorders, Journal of Parkinson's Disease, Journal of the Neurological Sciences, Journal of Neurology, Neurosurgery and Psychiatry, British Medical Journal Open, Adis Drug Evaluation, Therapeutic Advances in Neurological Disorders, CNS Drugs, Neurotoxicity Research, Expert Review of Cardiovascular Therapy, and Expert Opinion on Orphan Drugs, and I am on the editorial board for US Neurology and Frontiers in Neurology.

I am and have been a member of numerous academic and scientific societies and associations, including the American Academy of Neurology, Movement Disorders Society, Parkinson's Study Group, Huntington's Study Group, Melvin Yahr International Parkinson's Disease Foundation, Parkinson's Research and Education Foundation, and We Move. Since 2005, I have served as the Medical Director of the Parkinson's Research and Education Foundation. I served as Medical Director of the NPF Chapter South Palm Beach County and PRF Center of Excellence from 2007 to 2009 and 2009 to 2010, respectively.

I have served on numerous committees, including a committee for the 18th World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders, the 4th World Parkinson's Congress, XXII World Congress on Parkinson's Disease and Related Disorders, and the 5th World Parkinson's Congress. I have chaired the PD Section at the Controversies in Neurology Annual Meeting in Europe since 2018.

I have been listed in "Florida Super Doctors," "Best Doctors in America," and "America's Top Physicians" in the area of neurology.

In the past four years, I have provided expert testimony by deposition and/or at trial in the following case: *Acadia Pharmaceuticals Inc. v. Aurobindo Pharma Ltd. et al.*, C.A. No. 1:20-cv-00985-GBW (consolidated) (D. Del.).

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A copy of my curriculum vitae is attached as **Exhibit A**. My hourly rate is \$975 per hour, except for depositions and trial testimony, where my rate is \$1,750 per hour and \$14,500 per day, respectively. I am compensated \$600 per hour for travel time if over fifty miles.

II. ASSIGNMENT AND SUMMARY OF OPINIONS

A. Assignment

Counsel for Syngenta Crop Protection, LLC, Syngenta AG, and Chevron USA Inc. retained me to review the available scientific evidence and provide an opinion on whether paraquat (PQ) causes or contributes to the cause of PD, including whether the medical and scientific community has concluded that PQ causes or contributes to the cause of PD.

I was also asked to provide an opinion as to whether PQ was a cause or a substantial factor in causing PD in Plaintiff Mr. Darrell Rose. And I was asked to review and assess opinions offered by certain of the Plaintiffs' experts.

B. Methodology

In forming my opinions, I relied upon my decades of experience as a PD specialist and researcher. I conducted a review of the relevant peer-reviewed scientific literature and analyzed the results in light of my assignment. Specifically, I drew on my knowledge of the literature, keyword searches in PubMed and Google Scholar, and articles/reports that have reviewed the literature to gather potentially relevant publications (review articles, government reports, other expert reports) to identify the most relevant evidence in the following categories: human evidence (reports of poisoning survivors, clinical trials, epidemiological studies, and studies related to various alleged PD pathogenic mechanisms), animal studies, scientific review articles, and meta-analyses. I also reviewed expert reports prepared by certain other experts in this case and many of the sources that they rely upon. I also reviewed publications from US governmental agencies that have analyzed PQ and PD. I identified keyword searches in PubMed and Google Scholar using broad search terms: "paraquat" together with various terms related to PD or the causation theory being advanced by Plaintiff such as "Parkinson's," "alpha synuclein," "inflammation," "oxidative stress," "microglia," "Lewy bodies," "blood brain barrier," "neurodegeneration," and "genetic."

This report explains my analysis of the evidence and presents the conclusions I reached based on the totality of the evidence as well as my education, training, and experience in the field as a researcher and clinician specializing in PD. My opinions are provided to a reasonable degree of medical and scientific certainty.

C. Summary of Opinions

1. The weight of the scientific evidence does not prove, and in fact contradicts, the hypothesis that PQ causes or contributes to the cause of PD.
2. Parkinson's disease is a common progressive, widespread neurodegenerative disorder. Historically, PD was thought to be restricted to a loss of striatal dopamine caused by degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNc). But current research shows PD involves progressive degeneration

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of systems far beyond DA neurons in the SNc, and degeneration outside the SNc—and even outside the brain—often precedes degeneration in the SNc. A variety of normal cellular mechanisms have been hypothesized to become dysregulated leading to PD neurodegeneration, including oxidative stress, neuroinflammation, microglial activation, calcium dysregulation, protein aggregation, and others. But the various hypotheses regarding where, when, how, and why degeneration begins and progresses in PD remain unproven.

3. If there were a causal relationship, I would expect to see a strong, consistent association with significant dose response in epidemiological studies, and evidence of PD among high-dose poisoning cases, but the evidence shows the opposite. The epidemiology literature shows weak, inconsistent associations with no consistent or significant dose response. And exposure to high, lethal, or near-lethal doses of PQ in humans (such as accidental ingestions or suicide attempts) has not been reported to cause any of the clinical or pathological features of PD.
4. Animal experiments involving PQ exposure have many limitations and cannot be reliably extrapolated to humans for multiple reasons, including the use of doses that are thousands of times higher than those reported in worker exposure studies, and routes of PQ exposure that often differ from human PQ exposure. And with respect to PD in particular, animals do not get PD. In any event, the results of animal studies of PQ toxicity are inconsistent, none demonstrates the widespread, progressive degeneration seen in PD, and even the positive high-dose studies report effects and mechanisms which have only been hypothesized to be linked with PD. Reliance on animal studies as evidence of causation thus would require unwarranted speculation (that effects reported in rodents at high doses would occur at far lower doses) upon speculation (that effects reported in rodents at high doses would occur in humans at high doses, let alone far lower doses) upon speculation (that the effects reported in mice actually cause—as opposed to result from—widespread PD pathogenesis).
5. Consistent with my opinion, I have not found any peer-reviewed scientific publications that have systematically reviewed the available evidence and concluded that PQ causes PD.
6. Based on my review of Mr. Rose’s medical history, records, and relevant deposition transcripts, in my medical opinion, Mr. Rose has various findings that are indicative of an atypical parkinsonism; he does not meet the MDS Clinical Diagnostic Criteria for PD.
7. Dr. Nabila Dahodwala stated that she conducted a differential diagnosis to rule in and rule out potential causes of Mr. Rose’s alleged PD. But this differential diagnosis is not a recognized, accepted, or scientifically valid method to determine the cause of an individual’s PD, as the cause of PD is unknown outside of genetic mutations present in 15–20% of PD cases.

III. PARKINSON'S DISEASE BACKGROUND

A. Overview of PD

Parkinson's disease is a common progressive, widespread neurodegenerative disorder. Estimates of worldwide prevalence range from 6 to 9.4 million individuals. PD is estimated to affect approximately one million adults in the United States. (Marras 2018; Maserejian 2020) Estimates of age-adjusted incidence ranges from 44 to 77 per 100,000 people age 45 or older, and 108 to 212 per 100,000 for ages 65 and older. (Willis 2022) PD is estimated to affect 1–2% of persons age 60 and over. (Olanow 2009) The incidence of PD increases with age, and rates are higher in men, particularly those aged 60 years and older. (Hirsch 2016) Age is the most consistent risk factor for PD. (Willis 2022) PD is among the most prevalent age-related neurodegenerative diseases, second only to Alzheimer's disease.

PD is characterized by progressive, typically decades-long, degeneration of a wide range of body systems, including progressive degeneration of certain neurochemical producing nerve cells in the peripheral and central nervous system. Lewy bodies are the pathologic hallmark of PD. The cause of this progressive widespread degeneration is unknown. Degeneration begins decades before clinical symptoms are recognized. In PD patients, progressive degeneration occurs in multiple areas of the neuroaxis, including: peripheral, autonomic, and enteric nervous systems; brain stem nuclei; subcortical and cortical brain regions. This degeneration leads to progressive reduction in the levels of many neurotransmitters, including acetylcholine, serotonin, norepinephrine, dopamine, glutamate, and others. (Jellinger 2017; Jellinger 1991; Tolosa 2009) A variety of normal cellular mechanisms have been hypothesized to become dysregulated leading to PD neurodegeneration, including oxidative stress, neuroinflammation, microglial activation, calcium dysregulation, protein aggregation, and others. To date, they remain hypothesized mechanisms; none has been demonstrated to cause PD.

This widespread degeneration results in a variety of motor and non-motor symptoms. Degeneration of the substantia nigra can lead to cardinal motor symptoms that include: bradykinesia (slowness of movement and decreased movement amplitude), resting tremor, rigidity (stiffness), and impaired gait with postural instability. Many motor symptoms are responsive to dopaminergic therapies, and also to some non-dopaminergic therapies. (Hauser 2021; Isaacson 2025; Pahwa 2017)

Myriad non-motor symptoms reflect widespread degeneration beyond the nigrostriatal pathway and are common in PD patients. (Olanow 2009; Olanow 2011) Sensory symptoms of PD include hyposmia, visual disturbances, pain, and paresthesia. Neuropsychiatric symptoms of PD include anxiety, depression, apathy, cognitive impairment, and psychosis. Circadian/sleep disorders of PD include REM sleep behavior disorder, primary and secondary insomnia, sleep fragmentation, excessive daytime somnolence, fatigue, and circadian dysregulation. Autonomic dysfunction issues include blood pressure dysregulation (neurogenic orthostatic hypotension and supine hypertension), bladder dysfunction, temperature dysregulation, sexual/erectile dysfunction, and seborrheic dermatitis. Gastrointestinal dysfunction issues include esophageal, gastric, intestinal, and colonic dysmotility. (Olanow 2011; Schapira 2017) Some non-motor symptoms are responsive to non-dopaminergic therapies targeting their neurochemical pathophysiology. (Cummings 2014; Hauser 2015; Emre 2004; Isaacson 2020)

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James Parkinson, in his 1817 “Essay on the Shaking Palsy” described the disorder that would become known as PD. Parkinson’s account described both motor and non-motor features, including rest tremor, slowness or absence of voluntary movements, stooped posture and festinating gait, and non-motor features like disturbed sleep and constipation. But there are descriptions of people with PD-like symptoms dating back to ancient times. (Goetz 2011)

B. Diagnosis of PD

Currently, there is no standard diagnostic test for PD, so clinicians rely on evaluation of clinical symptoms and examination to diagnose PD. Multiple other neurological conditions can display parkinsonian motor features and can often be difficult to differentiate in initial diagnosis.

While PD is the most common degenerative parkinsonism, other neurodegenerative diseases can have parkinsonism, including Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Cortico-Basal Degeneration (CBD), Lewy Body Dementia (LBD), and genetic disorders. Patients with these other causes of degenerative parkinsonism may have atypical features, including early dementia, hallucinations, early falling, eye movement abnormalities, and prominent dysautonomia. (McFarland 2016) These are distinct diseases with differing etiologies, pathologies, and progression.

Historically, PD was diagnosed based on a patient having cardinal motor features, but this led to a high rate of misdiagnosis. (Hughes 1992a) In an effort to improve diagnostic accuracy, various diagnostic criteria for PD have been proposed over the years. (Adler 2014)

The UK Brain Bank Criteria (Hughes 1992a) intended to improve diagnostic accuracy. In that method, step 1 is diagnosis of Parkinsonian Syndrome, meaning the patient must demonstrate bradykinesia, and at least one of the following: (1) muscular rigidity; (2) 4-6 Hz rest tremor; or (3) postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction. In step 2, the physician considers any exclusion criteria that apply. These include: (1) history of repeated strokes with stepwise progression of parkinsonian features; (2) history of repeated head injury; (3) history of definite encephalitis; (4) oculogyric crises; (5) neuroleptic treatment at onset of symptoms; (6) more than one affected relative; (7) sustained remission; (8) strictly unilateral features after 3 years; (9) supranuclear gaze palsy; (10) cerebellar signs; (11) early severe autonomic involvement; (12) early severe dementia with disturbances of memory, language, and praxis; (13) Babinski sign; (14) presence of cerebral tumor or communication hydrocephalus on imaging study; (15) negative response to large doses of levodopa in absence of malabsorption; and (16) MPTP exposure. Step 3 requires a review of the supportive prospective positive criteria for PD, three or more of which are required for a definite PD diagnosis: (1) unilateral onset; (2) rest tremor present; (3) progressive disorder; (4) persistent asymmetry affecting side of onset most; (5) excellent response (70-100%) to levodopa; (6) severe levodopa-induced chorea; (7) levodopa response for 5 years or more; or (8) clinical course of ten years or more.

Gelb (1999) also proposed diagnostic criteria for PD, requiring at least two cardinal features among rest tremor, bradykinesia, rigidity, or unilateral onset, and at least one among tremor and bradykinesia. Atypical features must be excluded, and sustained levodopa or dopamine agonist response is required. Gelb distinguishes three diagnostic certainty levels: (1) Possible PD:

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2 cardinal features (1 being tremor or bradykinesia), symptom duration of less than 3 years, and no need for a levodopa response; (2) Probable PD: 3 cardinal features, absence of atypical features for at least 3 years, and a proven levodopa response; and (3) Definite PD: confirmed only by neuropathological examination. (Gelb 1999)

The Movement Disorder Society has developed additional criteria to attempt to improve the diagnostic accuracy for PD. (Postuma 2015) According to the MDS criteria, diagnosis of *clinically established* PD requires: (1) absence of absolute exclusion criteria; (2) at least two supportive criteria; and (3) no red flags. (Postuma 2015, Table 1) Diagnosis of *clinically probable* PD can be made in the absence of absolute exclusion criteria, and where the presence of red flags is counterbalanced by supportive criteria. If more than two red flags exist, clinically probable PD cannot be diagnosed. (Postuma 2015, Table 1) Supportive criteria for a diagnosis of PD include: (1) clear and beneficial response to dopaminergic therapy; (2) presence of levodopa-induced dyskinesia; (3) rest tremor of a limb, documented on clinical examination; and (4) presence of either olfactory loss or cardiac sympathetic denervation. Absolute exclusion criteria, the presence of which rules out PD, are: (1) unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities; (2) downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades; (3) diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 years of disease; (4) parkinsonian features restricted to the lower limbs for more than 3 years; (5) treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism; (6) absence of observable response to high-dose levodopa despite at least moderate severity of disease; (7) unequivocal cortical sensory loss; (8) normal functional neuroimaging of the presynaptic dopaminergic system; and (9) documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD.

But even using these more detailed diagnostic criteria, diagnostic error rates for PD are still relatively high. (Beach & Adler 2018) While post-mortem pathology can confirm diagnosis of PD, “[f]ull diagnostic certainty is impossible during life; between 75% and 95% of patients diagnosed with PD by experts have their diagnosis confirmed on autopsy.” (Postuma 2015) A recent retrospective UK Brain Bank case-control study found that the diagnostic accuracy through in-vivo clinical examination applying diagnostic criteria of current clinical practice was 90.96% with a sensitivity of 99% and a specificity of 86%. The authors concluded that the “findings of this study underscore the persistent challenges in achieving an accurate in-vivo diagnosis of PD using clinical criteria alone.” (di Biase 2025)

Although there is no definitive test to diagnose PD, some diagnostic testing can be clinically useful. DaTscan imaging can determine if nigrostriatal dopaminergic degeneration is present or not. (Isaacson 2017) Alpha synuclein can be detected using antibodies applied to skin biopsies, and alpha-synuclein seed amplification assays have shown promise as a test for biochemical diagnosis of synucleinopathies. (Gibbons 2024; Concha-Marambio 2023) Enhanced diagnostic accuracy may be possible using: DaTscan imaging (Isaacson 2017), synuclein skin biopsy (Isaacson 2024), and gene testing. Gene testing can detect potential genetic causes in 15% and up to 25% for those with a family history of PD. (Westenberger 2024; Cook 2024)

C. PD Etiology

Despite decades of intensive research, the cause of PD remains largely unknown. Genetics are the only known cause of PD. The two most common genetic mutations associated with PD are variants of the glucocerebrosidase gene (GBA) and LRRK2. In the recently reported ROPAD study, the percentage of PD patients with a known monogenic gene disorder was 15%, 20% in individuals with young onset PD (<50 years), and 27% in those with young onset PD and a positive family history. (Westenberger 2024) Family history is important in diagnosing PD caused by a genetic mutation, and is a recognized risk factor for PD. (Rajan 2020)

Researchers have identified mutations in many genes that can lead to clinical parkinsonism or PD, sometimes clinically indistinguishable from idiopathic PD. (Blauwendraat 2020) Genome-wide association studies on European populations “identified 90 independent genome-wide significant risk signals across 78 genomic regions, including 38 novel independent risk signals in 37 loci. These 90 variants explained 16–36% of the heritable risk of Parkinson’s disease depending on prevalence.” (Nalls 2019)

Researchers continue to work to identify additional genetic causes of PD. For this reason, failure to identify a specific genetic mutation that is known to cause PD does not rule out genetic factors as contributing to the cause of a patient’s PD because we have not yet discovered all the ways in which genetics drive this disease. (Nalls 2019) Further, because the cause of PD is unknown in approximately 85% of cases, in practice, aside from conducting genetic testing to determine whether a patient’s PD is caused by a genetic mutation, neurologists are not able to determine what caused an individual’s PD.

IV. HYPOTHESIZED MECHANISMS OF PD DEGENERATION AND PROGRESSION

Not only is the cause of PD largely unknown, but the mechanisms of neurodegeneration are also unknown. Historically, PD was thought to be restricted to a loss of striatal dopamine caused by degeneration of dopamine (DA) neurons in the SNc. But research in the past two decades has shown that PD involves progressive degeneration of systems far beyond DA neurons in the SNc, and degeneration outside the SNc and even outside the brain often precedes degeneration in the SNc. Over the years, various hypotheses have emerged regarding where, when, how, and why degeneration begins and progresses in PD, including oxidative stress, neuroinflammation, microglial activation, calcium dysregulation, protein aggregation, and others, but so far we are not able to answer this question and all hypothesized mechanisms remain unproven. (*e.g.*, Braak 2003; Hawkes 2007; Hawkes 2009; Hirsch 2012; Przedborski 2017; Burré 2024)

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Oxidative stress has been a particular focus of various hypotheses. Production of reactive oxygen species (ROS) and other free radicals is a normal part of human life. Our bodies daily produce countless trillions of ROS through a host of natural processes including metabolizing oxygen, metabolizing dopamine, immune responses, and many others, (Zhang 2016), and production of ROS can also occur due to regular activities like exercise, exposure to sunlight, and many other factors. (Gomes 2012) Free radicals also have important signaling functions in our bodies and play a role in our immune system's ability to combat infection. Our bodies have the robust ability to maintain homeostasis by increasing the production of antioxidants (*e.g.*, glutathione, superoxide dismutase, and ascorbate) in response to increasing free radicals. (Pizzino 2017; Dong-Chen 2023)

Oxidative stress and oxidative damage can occur if free radical levels exceed our bodies' ability to produce neutralizing antioxidants, and a state of oxidative stress can last until our bodies' antioxidant production catches up with free radical levels. Thus, whether oxidative stress occurs in a particular cell or tissue, how long it lasts and whether it causes damage are functions of free radical levels, antioxidant capacity, and how long it takes for antioxidant capacity to bring free radical levels back within homeostatic range. (Dokalis 2019)¹ It is not possible to directly measure whether oxidative stress is occurring or to what degree, we can only look for molecular markers that oxidative stress has occurred in the past. But these markers do not provide information about the cause of the oxidative stress (*i.e.*, whether free radicals increased or antioxidants decreased). (Jiang 2018)

It is hypothesized that in some diseases, this homeostatic system can become imbalanced. Specifically, it has been hypothesized that oxidative stress may be a mechanism that causes degeneration in PD. Evidence of oxidative stress has been found in the SNc of PD patients post-mortem, which has raised the possibility that oxidative stress might contribute to the degeneration of nigral neurons and/or alpha synuclein pathology. (Jenner 1996; Burré 2024) But we still do not know where in the CNS or PNS PD begins (Burré 2024), or whether oxidative stress is found in the SNc of all PD patients. (Sofic 1992) Despite extensive experimental research, the role, if any, of oxidative stress (and other proposed mechanisms) in the etiopathogenesis of PD is not yet known. (Olanow 2007; Przedborski 2017)

Researchers have tested the oxidative stress hypothesis repeatedly by developing various potential antioxidant therapies in hopes of slowing or stopping PD's progressive neurodegeneration. Such therapies have shown promise in animal models but have repeatedly failed when tested in humans.² Collectively, these results indicate: (1) human clinical trials do not

¹ Dr. Richardson, one of Plaintiff's experts, agrees that no one can categorically say whether an increase in ROS or free radicals in a cell or group of cells will or will not induce oxidative stress and damage without knowing the concentration, the time that it exists, and how it relates to the available antioxidant capacity. (10/24/2024 J. Richardson Dep. Tr. 303:20–304:3)

² For example, researchers conducted a 600-participant, double-blind, randomized, placebo-controlled study of the effect of coenzyme Q10 (an antioxidant that supports mitochondrial function) on PD patients. Researchers concluded that, while "coenzyme Q10 was safe and well tolerated in this population, [it] showed no evidence of clinical benefit." (PSG 2014) In contrast, in laboratory studies, antioxidants such as coenzyme Q10 had been shown to protect against PQ toxicity. (Attia 2018) Vitamin C and E likewise exhibited promise in laboratory studies but have not been shown to provide a clinical benefit to humans. (Park 2020; Fahim 2013; PSG 1993) Clinical studies do not show a reduction in PD risk for the development of PD where individuals have previously

support the hypothesis that oxidative stress causes PD or PD neurodegeneration, and (2) animal experiments frequently fail to predict the neuropathology of PD in humans.

Significant interest and research have also focused on the role of alpha synuclein in PD pathology. Alpha synuclein is one of the most common proteins in all brains, not only PD brains, demonstrating that alpha synuclein is not generally pathogenic. After a mutation in a gene coding for synuclein was identified in a family with PD, alpha synuclein was found to be both a normal protein in the nervous system and also a component of Lewy bodies. (Spillantini 1997) But how and why Lewy bodies form, and whether they have an effect on PD disease progression remains unknown, and some have argued that Lewy pathology may in fact be protective. (Olanow 2004; Burré 2024) Alpha synuclein pathology is not limited to PD—it has also been observed other neurodegenerative disorders, like Alzheimer’s disease, MSA, and pure autonomic failure. (Shim 2022; Reddy 2022)

Some researchers have hypothesized that alpha synuclein may play a role in progressive degeneration, perhaps through deficiency of alpha-synuclein, aggregation, propagation, or toxic forms, while others have hypothesized that only certain forms of alpha synuclein are pathogenic and potentially cause PD degeneration. But despite some evidence that alpha synuclein may play a role in PD, the nature of that role, if any, remains unknown, hotly debated, and the subject of many competing hypotheses within the PD research field. (Fernandez 2025; Espay 2019; Espay 2024; Burré 2024) As one recent review paper explained: it remains unknown “whether α Syn aggregation in the form of Lewy pathology (LP) constitutes a toxic insult leading to degeneration, represents an epiphenomenon that is not directly toxic but co-occurs with an alternative pathogenic process, or rather has protective functions for cells in a state of altered proteostasis.” (Burré 2024)

V. ANALYSIS OF THE HYPOTHESIZED CONNECTION BETWEEN PQ AND PD

A. Origin of the Hypothesis

In the late 1970s and early 1980s, scientists discovered that methyl phenyl tetrahydropyridine (MPTP)—a byproduct formed during illicit synthetic heroin production—causes levodopa-responsive motor parkinsonism in humans. The first such patient was discovered in 1976 and by the mid-1980s a total of eight such patients were identified. (Langston 1983; Davis 1979) From these cases, doctors learned that humans who injected MPTP quickly developed severe parkinsonism, including motor features (tremor, stiffness, generalized slowing and difficulty moving) and certain non-motor features (such as facial seborrhea and mild deficits in higher cognitive functioning) that mimic certain aspects of PD.

MPTP is lipophilic, which allows it to readily cross the BBB. (Imai 1988) On entering the brain, MPTP is oxidized in astrocytes to form MPP⁺. MPP⁺ is taken up by the dopamine transporter into DA neurons in the SNc where it kills DA neurons by inhibiting complex 1 of neurons’ mitochondrial respiratory chain. This significant loss of DA neurons leads to a loss of dopamine that causes the dopamine-related motor and non-motor features noted above. (Langston

taken antioxidants. Hughes 2016 conducted a prospective cohort study of over 1,000 PD cases. The authors concluded that their results did not support the hypothesis that intake of antioxidant vitamins reduces the risk of PD. (Hughes 2016)

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1983; Langston 2017; Lambert & Bondy 1989; Richardson 2005; Miller 2007) These symptoms were alleviated by levodopa treatment and, in at least some of the MPTP cases, the symptoms were transient such that ongoing levodopa treatment was not required. Thus, although the significant loss of DA neurons caused by MPTP can cause certain parkinsonism features (though not PD), it does not cause permanent (let alone progressive) degeneration or loss of dopamine in the SNc, nor does it replicate the other non-dopamine features and pathological pattern of PD. For example, in MPTP patients, the locus coeruleus and dorsal motor vagus nucleus were also normal, unlike PD patients. (Langston 1983)

MPTP is not considered a cause of PD, but has been used as a tool to investigate toxicity in nigral DA neurons in animal experiments. Based on the structural similarity between PQ and MPP+, PQ was one of many chemicals researchers began to investigate. On further investigation, researchers discovered that the structural similarity between MPTP and PQ was a red herring.

Researchers ultimately discovered that PQ differs immensely from MPTP both in its chemical properties and its effects in the human body. Unlike MPTP, PQ is not lipophilic and is a charged molecule. So unlike MPTP, PQ does not readily cross the blood brain barrier (BBB). (Imai 1988) Unlike MPTP, PQ is not preferentially transported to DA neurons in the SNc by the dopamine transporter. Unlike MPTP, PQ is not a complex 1 mitochondrial inhibitor. Most importantly (as discussed below), and likely because of these chemical differences, unlike MPTP, even high doses of PQ in humans do not cause any PD-like clinical or pathological features, let alone the profound levodopa-responsive motor parkinsonism MPTP causes.

B. Blood Brain Barrier

The blood brain barrier is made up of tightly connected cells that help to protect the brain from endogenous and exogenous substances, including medications. Many medications are designed not to cross the BBB to avoid side effects; other medications, like PD medications, are designed to cross the BBB. As noted above, PQ is a charged molecule that does not readily pass through the BBB. There is no clear evidence that sub-lethal doses of PQ can cross the BBB in humans.

In rodents, it appears PQ can cross the BBB, but the literature is mixed and there is no consensus as to *how* PQ crosses the BBB. While certain studies with rodents given high-dose PQ injections showed that small amounts of PQ reached portions of the brain protected by the BBB (Shimizu 2001; McCormack & Di Monte 2003), others show minimal entry into the brain (*e.g.*, Smeyne 2016). Some researchers suggest that PQ crosses the BBB via neutral amino acid transporters. (McCormack & Di Monte 2003; Shimizu 2001) Another suggests that PQ might cross the BBB via the choline-uptake system. (Vilas-Boas 2013) And yet another identifies unspecified organic cation transporters (“OCT”) as potential options. (Smeyne 2016)

Pharmacokinetic animal studies indicate that even when given large doses, only small amounts of PQ enter the brain and affect areas not protected by the BBB (the SNc and basal ganglia are protected by the BBB). For example, in a study of neonatal (10 day old), adult (3 month old) and elderly (18 month old) Wistar rats exposed to lethal doses of PQ, the authors found that “concentrations of paraquat remained very low in brains of neonatal, adult, and elderly rats, (0.25%, 0.07% and 0.08% of administered dose in brain measured 30 min following paraquat

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administration, respectively).” (Widdowson 1996a) Despite slightly higher PQ entry into the neonatal rat brain, the authors could find no evidence for PQ-induced neuronal cell damage following a detailed histopathological examination of perfused-fixed brains. Another study in rodents used radio-labeled PQ to track distribution throughout the brain and reported that “[m]ost of the [¹⁴C]paraquat was associated with five structures, two of which, the pineal gland and linings of the cerebral ventricles lie outside the blood/brain barrier whilst the remaining three brain areas, the anterior portion of the olfactory bulb, hypothalamus and area postrema do not have a blood/brain barrier.” (Naylor 1995)

Importantly, as shown through the example of MPTP, the BBBs in different animal species differ from one another, and differ from the human BBB. For example, originally, researchers thought that that only primates experienced the effects of MPTP. Later, rats were found to have very high levels of MAO in the BBB, and were effectively converting MPTP to MPP⁺, which is not lipophilic and does not readily permeate the brain. Mice have moderate levels of MAO in their BBB, so moderate levels of MPTP can cross their BBB. And human BBB poorly converts MPTP to MPP⁺, allowing ready movement of MPTP across the BBB. (Langston 2017)

In non-human primates, researchers at the University of Wisconsin studied adult, male rhesus macaques dosed with radio-labeled PQ (0.1–0.4 µg/kg, intravenously), and used PET imaging on the animals (while anesthetized with 1–2% isoflurane) to trace PQ movement through the animals’ bodies. The study showed minimal PQ uptake and retention in the whole primate brain. The authors concluded that “paraquat is excluded from the brain by the blood:brain:barrier and thus does not readily support the causative role of paraquat exposure in idiopathic Parkinson’s Disease.” (Bartlett 2009) In a follow-up study of female rhesus monkeys and their fetuses *in utero*, Bartlett again found “minimal uptake of paraquat” in both the maternal and fetal brains. Further, “the highest regional cerebral uptake in the maternal brain (0.0009% injected dose) was seen in the pineal gland, a structure known to lack a blood brain barrier.” (Bartlett 2011) The study concluded that the findings “extend the contention that acute paraquat exposure either *in utero* or postnatally is unlikely to play a role in PD.”

Despite this evidence suggesting PQ does not cross the BBB in primates, Stevens (2021) used data from rodents, dogs, and monkeys to develop a mathematical model (PBPK) of PQ distribution in those animals, as well as humans. Based on the Bartlett (2009) data, Stevens estimated that 0.0095% of an administered dose of PQ would reach the human brain, but acknowledges that Bartlett did not find any PQ in areas of the brain inside the BBB, and did not estimate what (if any) fraction of PQ would be found inside the BBB. (Stevens 2021)

C. Evidence In Highly Exposed Humans

Several studies have examined the effect on humans poisoned as a result of the accidental or suicidal ingestion of lethal or near-lethal doses of PQ. Consistent with data showing little to no PQ crosses the primate BBB, although PQ is highly toxic and often fatal if ingested (*e.g.*, Campbell 1968), PQ poisoning does not cause any of the clinical or pathological features of PD.

Following a study of reports concerning 83 patients who suffered PQ poisoning and survived a least 30 days (primary analysis) or 15 to 30 days (secondary analysis), Brent and Schaeffer concluded that their review of the literature was “unable to find any documented cases

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of humans exposed to doses of paraquat sufficient to cause major toxicity that manifested signs of parkinsonism. Because of its chemical similarity to the parkinsonism-inducing drug MPTP, if paraquat did cause this condition, it would almost certainly do it in a similar manner and time frame. ... The fact that high-dose paraquat exposure does not appear to cause this syndrome indicates that it does not appear to be a substantia nigra toxin and thus is unlikely to be a cause of PD.” (Brent & Schaeffer 2011)

Other reports of humans exposed to lethal or near-lethal doses of PQ similarly do not reveal any cases with the neuropathologic features of PD. Specifically, reports show no SNc neuron degeneration, no reduced striatal dopamine, nor lewy pathology. Instead, the relatively limited set of neuropathology reviews following acute PQ toxicity report diffuse cerebral edema, hemorrhage, purpura, and cerebral inflammation. (Grčević 1977, Mukada 1978, Hughes 1988; Wong 1998) These are not classic neuropathologic features of PD and are consistent with damage seen after hypoxia and anoxia.

Chen (2021) conducted a retrospective cohort study at a poison center of a tertiary care hospital in Taiwan. The study included 299 cases of acute pesticide poisoning, and examined in-hospital mortality and neurological sequelae, among other things. Notably, none of the patients exposed to PQ were reported to have neuropathy, tremor, or other neurological sequela. (Chen 2021)

An MRI of the brain of one patient after PQ poisoning showed abnormalities in the frontal lobe cortex/subcortical areas, parietal lobe, and basal ganglia, with a fuzzy boundary. Two weeks later, most of the abnormalities disappeared. MRI results for another patient showed abnormalities in the parietooccipital junction. (Wu 2012) While these changes are consistent with the pathological reports from acute systemic toxicity from PQ exposure, they are not consistent with changes seen in the MRIs of PD patients.

Pathology reports of acute PQ poisoning after ingestion of lethal amounts typically show damage to lungs, liver, kidneys, skin, and other peripheral organs, and some show central nervous system toxicity secondary to other organ failure and end-of-life failures. (Spector 1978, Rebello 1978, Mukada 1978, Hughes 1988, Pazos 1989, Soontornniyomkij 1992, Han 2014) Again, peripheral organ damage is not a pathological feature of PD.

Clinical and pathological features of PD are different than those seen in PQ toxicity and have not been replicated by acute PQ exposure. In general, if PQ caused neuronal damage that leads to PD, then like MPTP, high dose exposure should result in acute onset of parkinsonian features, but it doesn't. I have conducted searches to identify additional cases or reviews of human PQ poisoning. High dose human exposure studies do not demonstrate pathologies of the systems that would be expected if PQ caused PD.

D. Worker Exposure Studies

As Dr. Plavicki notes in detail in her report, multiple studies have been conducted on humans applying PQ in occupational settings to determine routes of exposure and amount of the doses of PQ in human workers. The research subjects in these studies used varying amounts of PPE (or none at all), and used various methods of applying PQ. The results of these studies

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demonstrate that there was little to no systemic absorption in human workers. Two of those studies calculate the absorbed dose to workers based on urine biomonitoring, and thus provide the best point of comparison with doses used in experimental animal studies.

In the Meier (1995) study, researchers assessed PQ absorption in 17 mixer loader-applicators using tractor-mounted sprayers to apply PQ. Varying levels of PPE were used across subjects. (Meier 1995) No PQ was detected in the urine of 11 out of 17 subjects, and where PQ was detected, the absorbed dose ranged from 0.00007 – 0.00044 mg/kg/day body weight. Further, no PQ was detected in any subject on days 2 and 3 post-application.

In the Findlay (1998) study, researchers again measured PQ absorption during mixing, loading, and application of PQ, this time in 20 operators using knapsack sprayers. Subjects wore long-sleeve cotton shirts, long cotton pants, cotton underwear, cotton socks, and rubber boots during the application, and they wore gloves and a face shield during mixing and loading. Researchers using a more sensitive testing method than Meier found that 18 of 20 workers had an estimated mean absorbed dose of 0.000149 mg/kg/day (with the highest dose for any subject of 0.0004089 mg/kg/day), and the remaining 2 subjects had undetectable PQ levels. (Findlay 1998)

Thus, the highest daily dose reported among PQ workers in the U.S. or similar application conditions was 0.00044 mg/kg (Meier 1995) and the highest mean daily dose among the two studies was 0.000149 mg/kg (Findlay 1998). These doses are thousands of times lower than i.p. doses used in the animal studies on which Plaintiff's experts rely and are > 20,000 times lower than the 10 mg/kg doses used in most animal studies.

E. Epidemiology Literature

Over the course of my approximately 30-year career, I have reviewed and kept abreast of peer-reviewed scientific literature across disciplines with respect to the known and hypothesized causes of PD, and I consider that research when I clinically evaluate and treat my patients with PD. That literature includes epidemiological studies that have evaluated whether various factors are associated with PD. In addition, I have undertaken for this case a focused review and evaluation of the epidemiological literature addressing any association between PQ and PD.

In assessing epidemiological literature, I first consider if and how a given publication fits into the existing medical and scientific understanding of PD. I also focus on consistency of findings, robustness of effect, and reproducibility of results (and what those results are) within and across populations. In addition, I look for patterns of dose-response, that is, whether any observed association increases with increased exposure. Needless to say, any exposure to a studied factor needs to occur before disease onset and the studies must address the specific exposure and disease at issue.³ To the extent these factors are lacking, causal conclusions cannot follow. These are the steps I take into consideration in assessing the epidemiologic literature and how it fits into and informs our knowledge of neurologic diseases including PD.

³ While I do not put a title on my methodology in assessing the epidemiological literature, I am aware that my methodology and the factors I look at when assessing that literature as a whole mirror the Bradford Hill guidelines.

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In reviewing the relevant epidemiologic literature, I found that epidemiological studies on the relationship between PQ and PD report inconsistent results: some report statistically significant positive associations (Liou 1997 (ever/never; >20 years); Firestone 2005; Kamel 2007 (prevalence); Tanner 2011; Lee 2012; Goldman 2012; Furlong 2015; Sanders 2017; Pouchieu 2018 (model 1); Paul 2024) but many others do not (Hertzman 1994; Kuopio 1999; Liou 1997 (1-19 years); Kamel 2007 (incidence); Dhillon 2008; Costello 2009; Gatto 2009; Tanner 2009 (parkinsonism); Elbaz 2009; Firestone 2010; Rugbjerg 2011; van der Mark 2014; Pouchieu 2018 (model 2); Caballero 2018; Shrestha 2020; Tomenson 2011; Tomenson 2021).

Likewise, the studies are inconsistent with respect to dose-response, with a number of the more recent, larger epidemiologic studies reporting inverse dose-response (van der Mark 2014; Shrestha 2020) and others reporting some dose-response. (Liou 1997, Tanner 2011)

I paid particular attention to the NIH/NIEHS funded Agricultural Health Study (AHS) given it is an intramural program directed by two institutes (NIEHS and NCI) at the NIH in collaboration with the EPA, as well as due to its size, its investigators, and its focus on U.S. agricultural workers.⁴ The only prospective study of PQ-PD to be reported in the literature is the most recent report from the AHS reported no association between PQ and PD. (Shrestha 2020)⁵

The interim nested case control study within the AHS population discussed in Tanner (2011) reported a statistically significant increased risk.

I note that Shrestha (2020) and Tanner (2011) had different study designs (prospective vs. nested case-control study) and used different diagnostic assessments (self-report of PD diagnosis by a physician with multiple confirmation steps vs. medical examination), and exposure assessments (AHS vs. FAME data). Regardless, neither study can nor should be ignored. Both must be considered—and add to the inconsistency seen among the PQ-PD epidemiology literature. I have not found any published peer-reviewed studies or literature reviews that have concluded a causal association between PQ-PD.

F. High-Dose Animal Studies Generally

Multiple toxic agents have been reported to cause dopamine cell loss in animal experiments, but have not been established to cause PD, including MPTP, 6-OHDA, rotenone, LPS, iron, proteasome inhibitors, maneb, dieldrine, and amphetamines. (Olanow & Kordower

⁴ The most recent publication assessing the AHS cohort analyzed “Self-Reported Motor and Nonmotor Symptoms, Prodromal Parkinson’s Disease Probability, and Incident Parkinson’s Disease in US Farmers.” (Song 2025)

⁵ In addition to Table 2 of the publication, Shrestha 2020 provides supplemental tables which provide additional data supporting their findings: Supp. Table 2 (Ever-use of pesticides reported at enrollment and Parkinson’s disease (PD) risk in male pesticide applicators and female spouses); Supp. Table 3 (Ever-use of pesticides reported at enrollment and incident PD in all participants, stratified by follow-up period (≤ 10 years versus > 10 years)); Supp. Table 4 (Ever-use of pesticides reported at enrollment and PD in all participants including prevalent cases); Supp. Table 5 (Intensity-weighted lifetime days of pesticide use reported at enrollment and PD in male applicators (including prevalent cases); Supp. Table 7 (Ever-use of pesticide reported through Phase 2 and PD risk in applicators).

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2009, Simola 2007, McNaught 2002, Greenamyre 2003, Deng 2020, Bentea 2017, Kanthasamy 2005, Liu 2011, Sengstock 1993, Krasnova 2001)

A number of studies in experimental animals (mostly rodents) have explored whether high doses of PQ can cause the type and pattern of progressive degeneration similar to that observed in PD patients. None have done so.

Animal experiments which seek to understand PD have many limitations. They cannot be reliably extrapolated to humans without replicated confirmatory evidence in humans, and have a poor record of translating therapies from animal experiments to humans with PD. In the context of PQ animal studies, such limitations include:

- *No animal is known to develop PD.* Studies using animals can only attempt to artificially mimic certain physical features or isolated pathological markers of human disease. No experimental animal replicates the complexity of human PD.
- *Animals are not humans.* The anatomical structure, physiology, cellular metabolism, immune modulation, and defense mechanisms differ from rodents to non-human primates to humans.
- *Artificial routes of exposure.* Animal studies of PQ use routes of administration that differ significantly from PQ exposure in humans. Animal studies generally inject PQ into animals either subcutaneously or intraperitoneally, which bypasses bodily defenses and does not replicate human use scenarios.
- *High doses.* Animal studies of PQ typically use high doses that are thousands of times higher than reported in biomonitoring studies of workers under typical use scenarios. For example, the most common dosing program in rodent studies is 10 mg of PQ for every kg of body weight, with multiple 10 mg/kg injections over a few weeks. And 10 mg/kg is 22,727 times higher than the highest daily dose reported in the Meier (1995) and Findlay (1997) biomonitoring studies, which was 0.00044 mg/kg. I have not located (and Plaintiff's experts do not cite) any study that has reported PQ exposure at realistic levels (akin to those reported in the Meier and Findlay biomonitoring studies) caused any kind of toxicity or harmful levels of oxidative stress.

Primate Studies

No studies in the peer-reviewed, published literature report any neuropathological effects following PQ dosing in primates. Though not a high dose study, Bartlett (2009) studied adult, male rhesus macaques dosed with 0.1–0.4 µg/kg, intravenously. Bartlett (2009) found minimal PQ uptake and retention by the primate brain. In the Bartlett (2011) study of female rhesus monkeys and their fetuses *in utero*, Bartlett again found minimal uptake of PQ in the brain.⁶

⁶ Plaintiff's experts have cited notes and other unpublished materials containing limited information about experiments Dino DiMonte performed on squirrel monkeys in the early 2000s using 6 doses of 2.5 and 5 mg/kg injected. (SYNG-PQ-01691168; SYNG-PQ-00044965; SYNG-PQ-3961577; SYNG-PQ-29623366; SYNG-

Rodent Studies

No studies in peer-reviewed, published literature report that PQ can cause anything like the pattern of widespread progressive degeneration in PD. In addition, animal studies use unrealistically high doses ranging from 1 mg/kg to 10 mg/kg and have many other limitations discussed below.

Certain studies in rodents have reported a reduced number of DA neurons in the SNc following high-dose injections of PQ. (*e.g.*, Brooks 1999, McCormack 2002, McCormack 2006, Peng 2004, Fei 2008, Kang 2009, Rappold 2011, Jiao 2012) Other studies do not report a loss of DA neurons. (*e.g.*, Widdowson 1996, Breckenridge 2013, Watson 2013, Minnema 2014, Smeyne 2016) Studies in which animals are fed high doses of PQ are similarly conflicting. Some studies report no loss of DA neurons (Widdowson 1996; Minnema 2014), and other studies report some loss. (*e.g.*, Anselmi 2018 (no effect from PQ alone; some effect with addition of high-dose lectin); Ren 2009) Studies examining the effects of intranasal or inhalation administration of high doses of PQ also report conflicting results. (*e.g.*, Rojo 2007 (no effect); Anderson 2020 (some effects))

Some studies also report conflicting results concerning loss of DA in the striatum. Some rodent studies report a reduction in striatal dopamine from PQ (*e.g.*, Prasad 2009, Zhou 2011, Chen 2008, Cristovao 2020), but many other studies show no significant reduction in striatal dopamine (*e.g.*, Smeyne 2016, Minnema 2014, Breckenridge 2013, Perry 1986, Woolley 1989, McCormack 2002, Shepherd 2006, Rojo 2007, Littlejohn 2011).

Some studies report some evidence of changes in synuclein (*e.g.*, Cristovao 2020, Manning-Bog 2002, Manning-Bog 2003, Wills 2012, Naudet 2017, Bove 2019, Musgrove 2019), but others do not report significant changes (*e.g.*, Gollamundi 2012, Anselmi 2018). As discussed above, the role of alpha synuclein in the pathogenesis of PD is unclear.

Some high-dose experiments have reported evidence of microglial/inflammatory effects (*e.g.*, Dwyer 2021, Yang 2020, Peng 2009, Cristovao 2009, Mangano 2009, Purisai 2007, Cristovao 2020), or markers of oxidative stress (*e.g.*, McCormack 2006, Chen 2008, Kang 2009, Rappold 2011), but others have not (*e.g.*, Rojo 2007, Breckenridge 2013, Minnema 2014, Smeyne 2016).

The inconsistencies noted above suggest the need for skepticism about the interpretation of the reported results. In addition, the dose administration (mostly i.p. injection) is not comparable to humans and the doses are far higher than doses measured in human workers. Indeed, virtually all the animal studies in this area use high doses that are at or near levels known to cause systemic toxicity or death.⁷ Animals at or near a state of acute systemic toxicity do not predict effects (even

PQT-ATR-15302324; data from DiMonte.xls) It is not possible to draw any reliable conclusions from the limited information available about these experiments.

⁷ For example, Dwyer (2021) reported that repeated dosing at 10 mg/kg caused animals to lose overall body weight, increase lung weight, and increase heart weight. Li (2005) reported that repeated 10 mg/kg dosing caused an animal to die. Prasad (2009) reported that repeated 10 mg/kg dosing caused mice to start losing weight and many died within 7 doses. Rojo (2007) reported that animals given 20 mg/kg intranasally daily developed agitated breathing, weight loss, and lung damage.

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in the same species and strain, to say nothing of different species) of lower doses that do not cause systemic toxicity. And given that Plaintiff's hypothesized mechanism of PQ neurotoxicity is oxidative stress, which is by definition a naturally occurring, dose-dependent phenomenon, high-dose studies cannot be taken as evidence of any toxic effect at far lower, human-relevant doses.⁸

The vast majority of animal studies focus narrowly on the dopamine system, and thus (even ignoring conflicting results) those studies do not provide evidence that even high doses of PQ can induce in lab animals the pattern of widespread degeneration that characterizes PD in humans. And even as to the dopamine system, the evidence does not show progressive degeneration like that in PD. For example, the Dwyer study, which had the longest post-dosing follow-up period, reported a loss of DA neurons shortly after dosing then no change or progression over six months post-dosing (and in fact indicated a slight *increase* in DA neurons at six months versus earlier time points). (Dwyer 2021, fig.3) The authors concluded that "unlike PD, the paraquat-induced loss of TH+ neurons was not a progressive phenomenon and might be more useful in modeling the overall impact of elevated oxidative stress and inflammation upon an organism rather than strictly modeling disease per se." (Dwyer 2021 at 20)

Similarly, as discussed above, while alpha synuclein is a potential marker of PD pathology, alpha synuclein pathology is not limited to PD, and PD can occur without alpha synuclein in some genetic forms of PD. The role of alpha synuclein in the pathogenesis of PD is unclear. Scientists do not know and continue to debate what (if any) role alpha synuclein may play in PD etiology, and thus scientists can only speculate about whether any of the above experiments involving alpha synuclein are relevant to PD causation. (Espay 2019, Burré 2024, Espay 2024, Fernandez 2025)

Finally, it is worth noting that while certain antioxidants, minocycline, and nicotine have been reported to protect against nigral damage induced by PQ in animal models (Muthukumara 2014, Attia 2018, Khwaja 2007, Ortega-Arellano 2017, Peng 2005), they have not been effective in preventing or slowing progression of PD in double-blind human clinical trials. (e.g., PSG 1993, PSG 2014, NINDS NET-PD Investigators 2008, Park 2020, Fahim 2013) These are further examples of animal models' failure to replicate or predict the pathogenesis of human PD.

Overall, the animal experimental evidence in the literature does not support the conclusion that PQ can cause PD in humans.

VI. CONCLUSION

It is my opinion to a reasonable degree of medical and scientific certainty, based on my review of the totality of the evidence and my decades of experience, that the scientific evidence has not established that exposure to PQ causes or contributes to the cause of PD, and that the weight of the evidence does not permit a conclusion that PQ is a cause or contributes to the cause of PD.

⁸ As discussed above, researchers continue to hypothesize and debate about what (if any) role oxidative stress or microglial activation might play in the pathogenesis of PD.

VII. SPECIFIC CAUSATION

I reviewed the available medical records for Plaintiff Darrell Rose and the deposition transcript of his treating Movement Disorder Specialist, Dr. Dimitrios Nacopoulos. I have also reviewed the deposition transcripts of Mr. Rose's wife, Dianna Rose, sister, Darlene Wisniewski, and brother, Duane Rose. I also reviewed the expert reports of Dr. Nabila Dahodwala and Dr. Richard Krolewski. I base my opinion as to Mr. Rose's diagnosis on review of these materials and my own knowledge and experience.⁹ In forming my medical opinions, I often rely on information provided by other clinicians and scientists with the requisite skills, qualifications, and judgment. The materials available to me in this case were sufficient for me to hold my conclusions regarding Mr. Rose to a reasonable degree of medical certainty. I reserve the right to supplement the opinions in this report upon receipt of additional information.

A. Medical Records Overview

Darrell Rose developed a neurological disorder with gait imbalance and falls in his late 70's that has progressed over five years to his using a walker and/or wheelchair; he also has documented cognitive impairment, dysphagia, and urinary incontinence. He was diagnosed with parkinsonism, with varying differential diagnoses of Parkinson's disease, Multiple System Atrophy, and Lewy Body Parkinsonism over time. Although treated with low dose carbidopa/levodopa, Mr. Rose did not have robust or sustained benefit, and the dosage was never increased. Despite this diagnostic uncertainty and suboptimal response to carbidopa/levodopa, DaTscan imaging was never performed. Mr. Rose's family reports an extensive family history of neurological disease: his father had tremor, his paternal grandfather was disabled and died in his 50's with a neurological condition affecting mobility, two paternal uncles had a neurological disorder with tremor and parkinsonism, another relative had a neurological disorder, other relatives required wheelchair use, and a maternal grandmother required institutionalization for a psychiatric disorder. Mr. Rose has never had genetic counseling or genetic testing. Apart from an MRI of the brain, other diagnostic evaluations were not performed, including evaluation of skin biopsy for alpha synuclein.

B. Medical Records Review

Darrell Rose was born on July 12, 1941. Past medical history is noted for type 2 diabetes, chronic kidney disease, hypercholesterolemia, and essential hypertension. Family history is significant for tremor in his father, reported "Parkinson's" in two paternal uncles that progressed to wheelchair use, and mobility issues progressing to wheelchair use in one paternal aunt and other paternal relatives. Also, a maternal grandmother had a psychiatric disorder requiring institutionalization.

At the age of 79, Mr. Rose was referred to a Movement Disorder Specialist, Dr. Dimitrios Nacopoulos by his primary care practitioner Dr. Patrick Murphy, for evaluation of "neuropath[ic], movement changes."

⁹ I requested a physical examination of Mr. Rose to determine whether he meets diagnostic criteria for PD and have been informed that, to date, counsel for Mr. Rose has not consented to scheduling such an examination.

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On initial evaluation by Dr. Nacopoulos on August 25, 2020, Mr. Rose, by his report, was noted to have difficulty with walking and balance, with multiple falls. Dr. Nacopoulos also noted that Mr. Rose reported tremor when drinking, difficulty with writing and dressing, weight loss, change in voice and facial expression, short term memory troubles, and possible visual hallucination. Mr. Rose reported a lot of “day naps,” urinary frequency, urgency, and “urinary accidents,” swallowing problems, and neuropathic symptoms. Medications included aspirin, statin, insulin, metformin, pantoprazole, and vitamins D, E, and B-complex. Social history noted that Mr. Rose was married, retired, and did not use alcohol or tobacco. Family history was obtained for only Mr. Rose’s parents, both of whom were reported to have had “cancer.” Examination noted right arm weakness, soft voice, reduced facial expression, no resting tremor, polyminimyoclonus, increased rigidity, slower speed of movement, clumsy left leg tapping, inability to rise from a chair without using arms, and narrow, slowed gait. Dr. Nacopoulos’s impression and plan was, “evaluate for stroke with MRI brain study. He may have Parkinson’s features if study is negative, we discussed consider trial of carbidopa/levodopa to see if he has benefit.”

On November 25, 2020, Mr. Rose returned to see Dr. Nacopoulos. MRI brain did not reveal a stroke. Since his last visit, Dr. Nacopoulos reports that Mr. Rose “thinks ‘everything has improved’ with vitamins that he started,” but Mr. Rose’s wife reported that his “equilibrium is way off” and that he “looks like he will fall on [h]is face, he has fallen a few times since the visit, he may deny these.” Mr. Rose reported seeing an occasional “shadow figure,” memory loss, and described some trouble writing and dressing. Dr. Nacopoulos’s impression was “likely has Parkinsonism, unclear type at this point, may represent idiopathic PD versus possible atypical Parkinson’s including Lewy body Parkinson’s or MSA-P.” Dr. Nacopoulos prescribed trial of carbidopa/levodopa 25/100 one tablet three times a day.

Mr. Rose returned on March 25, 2021. Mr. Rose reported “benefit with Sinemet, improving his gait” but noted cramping in the legs, seeing a shadow, urinary accidents, more drooling, and swallowing worse. His wife “thinks he is still slow with movement but still functional.” Dr. Nacopoulos noted still with some features of parkinsonism on exam and “some question of atypical type,” and that Mr. Rose “has a diagnosis of Parkinsonism, suspected Multiple System Atrophy-Parkinsonism versus Lewy body Parkinsonism.” Carbidopa/Levodopa 25/100 one tablet three times a day was continued without change.

On October 25, 2021, Mr. Rose sustained a fall and was hospitalized. During evaluation, he reported that he had been taking carbidopa/levodopa for about 6 months and that it initially helped, “but [] feels like this medication is no longer effective for him.”

On December 8, 2021 Mr. Rose was reevaluated by Dr. Nacopoulos while still recovering in a nursing facility from the October 2021 fall. Mr. Rose reported insomnia, memory loss (slight), and “a little confusion” when anxious. Dr. Nacopoulos’s impression was, “Parkinsonism. He has noticed benefit with Sinemet, improving his gait without side effect. Still with some features noted on exam of Parkinsonism, and some question of atypical type, either MSA-P, we will monitor over time.” Mr. Rose “has a diagnosis of Parkinsonism, suspected Multiple System Atrophy-Parkinsonism versus Lewy Body Parkinsonism.” Mr. Rose was continued on carbidopa/levodopa without change in dose.

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On May 24, 2022, Mr. Rose returned to see Dr. Nacopoulos. He was noted to be “walking pretty good.” Movement disorders examination identified “Voice: slight stuttered, not too tachypneic; Facial expression: slight reduced; Tremor: tremor is minimal today; Rigidity: tone is slight-mild increased in the right side; Speed of Movements: global slight slowed; spontaneous movement of the left hand is easier than the right hand.” He was able to “rise from a chair without using arms.” Gait was “narrow based and mild slowed.” Dr. Nacopoulos’s impression included “some features noted on exam of Parkinsonism, and some question of atypical type, either MSA-P.” He felt Mr. Rose was stable and continued the current dose of carbidopa/levodopa unchanged.

Mr. Rose reported feeling “a little worse until only recently” on a November 28, 2022 visit. He again noted short term memory issues, trouble with dexterity, walking difficulty, and impaired balance. Dr. Nacopoulos’s impression was, “Parkinsonism, and some question of atypical type, either MSA-P.” Carbidopa/levodopa continued unchanged.

On December 27, 2023, Mr. Rose returned for follow-up. He continued to report slow walking, imbalance, falls, impaired memory, and now reported having to “wear protective pads” due to urinary issues. Dr. Nacopoulos’s impression was “Parkinsonism, and some question of atypical type, either MSA-P.” Carbidopa/levodopa continued unchanged.

On September 10, 2024, Mr. Rose returned for a follow-up visit for his “diagnosis of Parkinsonism, Lewy Body Parkinsonism.” Mr. Rose reported continuing difficulty with walking, balance, memory, and urinary issues. Carbidopa/levodopa remained unchanged, and “some days may miss dose if wife is not home.”

Mr. Rose presented similarly on March 10, 2025. He reported a “good response of medication throughout the day” although he misses some doses. He reported “more trouble with memory,” “incontinent of urine,” and on exam, had “0/3 recall 2/3 with clues.” Dr. Nacopoulos’s impression included “diagnosis of Parkinsonism,” with some feature of “Lewy Body Parkinsonism with cognitive changes.” He suggested physical therapy exercises, consideration for donepezil, and continued carbidopa/levodopa unchanged.

When reevaluated on January 7, 2026, he reported a hospitalization in November 2025 followed by rehabilitation and was now back home. Since hospitalization, he reported more difficulty with memory, word finding, cognition, walking, falls, urinary incontinence, and daily activities. Dr. Nacopoulos’s impression was to evaluate for stroke with MRI brain study, and he ordered labs for B12 and thyroid, PT exercises, but carbidopa/levodopa was not changed.

C. Conclusion

At the age of 79, Mr. Rose was referred to Dr. Nacopoulos with walking and balance difficulty. Dr. Nacopoulos evaluated Mr. Rose for possible stroke and subsequently began carbidopa/levodopa for parkinsonism. Although some improvement in gait was noted after beginning carbidopa/levodopa, there was no robust response; Mr. Rose did not return to near-normal level of function. Dr. Nacopoulos followed Mr. Rose for over 5 years, considered various atypical parkinsonism syndromes reflecting the lack of reported robust response and the reported atypical symptoms at diagnosis (including falls, cognitive impairment, bladder dysfunction, and

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other symptoms), and never increased carbidopa/levodopa dose. The low dose of this medication initially prescribed did not lead to a robust or sustained improvement.

Since his diagnosis over 5 years ago, Mr. Rose has developed cognitive impairment, dysphagia, and urinary incontinence, but without a clear change in parkinsonism on movement disorders examination. He now also uses a walker and wheelchair. He has not had his dose of levodopa increased, nor does he have motor fluctuations.

Despite the extensive family history of progressive mobility, gait, and balance impairment leading to wheelchair use, other hereditary neurogenetic disorders have not been diagnosed or even considered, and genetic testing was not recommended or performed. Additional diagnostic testing with DaTscan to determine if Mr. Rose has degeneration in the nigrostriatal dopaminergic system was also not recommended or performed, despite his lack of a robust and sustained response to levodopa and the lack of progression on his motor parkinsonism examination. Despite diagnostic uncertainty by his treating Movement Disorder Specialist, there has been no evaluation for alpha synuclein that can be detected in skin biopsy.

Dr. Nacopoulos noted in his medical records that Mr. Rose had mild bradykinesia and rigidity indicative of parkinsonism. While Mr. Rose's reported initial benefit after starting carbidopa/levodopa treatment may be consistent with early Parkinson's disease, the lack of robust and sustained improvement to levodopa, striking family history of a progressive neurological disorder, lack of motor parkinsonism progression, no emergence of motor fluctuations or dyskinesia, and early falls with cognitive impairment, dysphagia, urinary incontinence, and other atypical symptoms strongly indicate a hereditary genetic neurological disorder, an atypical neurodegenerative parkinsonism syndrome, or a non-neurodegenerative cause.

In considering the MDS Diagnostic Criteria for Parkinson's Disease, Mr. Rose does not meet the criteria for either Clinically Established PD or Clinically Probable PD, because he does not meet the supportive criteria. Additionally, Dr. Nacopoulos recorded and reported an inability to identify a clear diagnosis of Mr. Rose's parkinsonism for over 5 years in the medical records, but he conducted no additional diagnostic testing to obtain information that may have assisted in diagnosing Mr. Rose's neurological condition (*e.g.*, genetic testing, DaTscan imaging, skin biopsy for alpha synuclein).

Dr. Dahodwala in her expert report briefly describes a "consultation" with Mr. Rose and his wife on January 29, 2026. Dr. Dahodwala concludes "to a reasonable degree of medical certainty that he meets Movement Disorders Society criteria for clinically established Parkinson's disease," based on "the medical records" and her "meeting with Mr. Rose." (2/3/2026 Dahodwala Rpt. at 6). This conclusion cannot be reconciled with the Movement Disorders Society criteria, which are specifically detailed in the Postuma 2015 publication that describes these criteria.¹⁰ Mr.

¹⁰ Dr. Dahodwala diagnosed Mr. Rose with Parkinson's disease based on her claims that he has a "[c]lear and dramatic beneficial response to dopaminergic therapy" and "[t]he presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy." (2/3/2026 Dahodwala Rpt. at 7). But Mr. Rose does not evidence either of these supportive criteria based on the clear definitions laid out in the MDS diagnostic criteria. According to the MDS Clinical Diagnostic Criteria for PD, to meet the criteria of a "[c]lear and dramatic beneficial response to dopaminergic therapy . . . during initial treatment, patients should have returned to normal or near-normal level of function." (Postuma 2015 at 1596). As the explanatory notes describe, "[t]o meet this criterion, it

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Rose does not meet the supportive criteria. Mr. Rose has remained on 300 mg of levodopa daily for over 5 years, since diagnosis. Mr. Rose has not developed motor fluctuations or dyskinesia. Mr. Rose also has repeatedly described early and continued falls, urinary incontinence, cognitive impairment, and possible hallucinations. Additionally, despite these features that are not typical for a diagnosis of Parkinson's disease, Mr. Rose has never undergone reevaluation of his parkinsonism diagnosis (the American Academy of Neurology recommends to reevaluate a diagnosis of Parkinson's disease annually in the first five years due to the high error rate of clinical diagnosis) nor has he had any clinically established diagnostic testing (*e.g.*, DaTscan imaging, alpha synuclein skin biopsy, genetic testing) that can be informative when disease course is clinically atypical for Parkinson's disease to confirm diagnosis or to identify an alternative diagnosis.

Aside from genetic mutations, the cause of PD is not known, and cannot be stated to any degree of medical certainty. Mr. Rose has an extensive family history of neurological disease but has not had genetic testing to identify whether he has a known gene that caused his current medical condition, whether or not it is PD. As such, a genetic cause cannot be excluded as the cause of Mr. Rose's alleged diagnosis of PD. Known genetic mutations that cause PD can be seen in approximately 15% of patients, even without a family history. New genetic mutations that cause PD continue to be identified. (Noyce 2012). In addition to genetic mutations not being evaluated, Mr. Rose also has factors in his history that have been considered possible risk factors for PD, including a family history of tremor and disability, and also of potential PD in two paternal uncles.

Dr. Dahodwala stated that she conducted a "differential diagnosis/etiology" to rule in and rule out other potential causes of Mr. Rose's alleged PD. (2/3/2026 Dahodwala Rpt. at 2). However, a differential etiology is not possible in this context, where, outside of genetic mutations, the cause of PD is unknown. Dr. Dahodwala fails to rule out "unknown causes." And in this case, Dr. Dahodwala certainly can't rule out genetic causes given that genetic testing was not done. Further, and specifically with respect to PQ, PQ has not been established to cause PD and thus cannot be "ruled in" as a cause. It is my opinion that Mr. Rose's alleged PD is not caused by PQ.

is not sufficient to document some beneficial response to dopaminergic therapy; the response must be unequivocal and of large amplitude. If treatment response is of modest amplitude, the patient does not meet this criterion." As detailed above, Mr. Rose never returned to near-normal function on carbidopa/levodopa; rather, he continued to have significant balance and gait issues and cognitive problems. Likewise, in the absence of documentation of initial response, the criteria can be fulfilled by showing "[m]arked improvement with dose increases or marked worsening with dose decreases" or "[u]nequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off." Here, Mr. Rose has never necessitated an increase in medication, nor has he had any documented on/off fluctuations or end-of-dose wearing off, despite 5+ years of dopaminergic therapy. As the MDS criteria notes explain, "[t]he requirement of predictable end-of-dose wearing off is to ensure that these are true dopaminergic fluctuations," and Mr. Rose has no such fluctuations.

Likewise, to fulfill the supportive criteria of olfactory loss, the MDS criteria describe that a patient must have "[p]ositive results from at least one ancillary diagnostic test" (*e.g.*, University of Pennsylvania Smell Identification Test (UPSIT)) "having a specificity greater than 80% for differential diagnosis of PD from other parkinsonian conditions." (Postuma 2015 at 1596). Though Mr. Rose has subjectively reported some hyposmia, he has never undergone ancillary diagnostic testing for olfactory loss according to the medical records. As such, Dr. Dahodwala does not have a basis to conclude that Mr. Rose meets either of these supportive criteria under the clear guidelines of the MDS Clinical Diagnostic Criteria for PD.

VIII. RESPONSE TO PLAINTIFF’S EXPERTS

A. Dr. Richard Krolewski

Dr. Krolewski provides the opinion that PQ exposure in humans is a cause of PD. Dr. Krolewski’s analysis and conclusion that PQ exposure can cause PD in humans is unfounded (for all the reasons explained above in my analysis of the evidence). In addition, I have the following specific comments on Dr. Krolewski’s report and opinions:

- Dr. Krolewski argues that PQ is a “plausible” cause of PD because animal experiments have reported that high doses of PQ can initiate various mechanisms (loss of dopaminergic neurons in the midbrain and substantia nigra, alpha synuclein aggregation in DA neurons, and oxidative stress) hypothesized to have a potential role in PD pathogenesis. This is speculative because (1) we do not know what causes PD, where it begins in the body, or by what mechanisms it begins and progresses; and (2) Krolewski cites no evidence that low doses of PQ can initiate any of the hypothesized mechanisms.
- Contrary to Dr. Krolewski’s report, PQ exposure does not cause PD, and the evidence is not coherent. As noted above, high dose exposure to PQ in humans (*e.g.*, when someone ingests lethal or near-lethal amounts), causes a host of non-specific toxic effects in lungs, liver, kidneys, skin, and other organs, but has not been reported to cause PD or PD-related symptoms. Even in high-dose animal experiments, PQ is not “specific” to PD and does not support “coherence” because it has not been reported to cause the pattern of widespread progressive neurodegeneration seen in PD.
- Dr. Krolewski wrongly argues that PQ is analogous to certain highly penetrant genetic mutations that are known to cause PD several decades after birth, and claims that “the lag time seen with this type of genetic ‘exposure’” suggests that environmental factors may also take decades to cause the disease. (09/30/24 Krolewski Rpt. at 4) This analogy is wrong. We do not know how genes cause PD or when degeneration begins. Also, an environmental agent reported to cause dopamine-responsive parkinsonism in humans (MPTP) does so rapidly (within days of exposure), even in young adults. If PQ could cause effects similar to MPTP, we would see such effects among poisoning patients on a similar timeline, but no such toxic effects have been reported.¹¹ Thus analogy and temporality oppose causation.
- Dr. Krolewski also wrongly claims the epidemiology evidence shows a consistent and strong association between PQ and PD. As noted above, the results of epidemiologic studies with respect to a possible relationship between PQ and PD are inconsistent and most positive associations are weak.

¹¹ Dr. Krolewski attempts to avoid the clear implications of the MPTP analogy and temporality by noting that MPTP does not produce “the more prolonged progression of disease seen in genetic models or other toxicant models,” (09/30/24 Krolewski Rpt. at 4), but this too cuts against his PQ hypothesis because PQ also fails (even in high dose animal experiments) to demonstrate the prolonged, progressive, widespread degeneration seen in actual PD.

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- Dr. Krolewski wrongly claims the epidemiology evidence demonstrates a dose response or “biological gradient.” As noted above, among the epidemiology studies that report odds ratios across different exposure categories, the results are highly inconsistent, and none of the few studies Dr. Krolewski cites for this criteria (Liou 1997, Tanner 2011, Paul 2024) report a statistically significant dose response.
- Dr. Krolewski has not published his analysis and opinion that PQ use can cause PD in a peer-reviewed journal, nor does he cite any peer-reviewed publication that has reviewed the relevant evidence and concluded that PQ causes PD. This is in contrast to the many peer-reviewed publications that have systematically reviewed the literature and did not conclude PQ causes PD. (*e.g.*, Weed 2021; Weed 2024)

B. Dr. Nabila Dahodwala

Dr. Dahodwala provides the opinion that “paraquat is a cause of Parkinson’s disease.” (2/3/2026 Dahodwala Rpt. at 4). She also asserts that “Mr. Rose’s exposure to paraquat is the etiologic driver and a substantial cause of his Parkinson’s disease.” (2/3/2026 Dahodwala Rpt. at 8, 11). Dr. Dahodwala’s conclusion that PQ exposure can cause PD is unfounded for all the reasons explained above in my analysis of the evidence. In addition, I have the following specific comments on Dr. Dahodwala’s report and opinions:

- Dr. Dahodwala argues that PQ is a cause of PD because there is a “known biological mechanism of neurotoxicity of paraquat.” (2/3/2026 Dahodwala Rpt. at 4). As detailed above, not only is the cause of PD largely unknown, but the mechanisms of neurodegeneration are also unknown. All hypothesized mechanisms regarding where, how, when, and why neurodegeneration begins and progress in PD remain unproven.
- Dr. Dahodwala wrongly asserts that there are “consistent findings” of the relationship between PQ and PD “across study samples and different study designs.” (2/3/2026 Dahodwala Rpt. at 4). As noted above, the results of epidemiologic studies with respect to a possible relationship between PQ and PD are inconsistent and most positive associations are weak.
- Dr. Dahodwala has not published her analysis and opinion that PQ use can cause PD in a peer-reviewed journal, nor does she cite any peer-reviewed publication that has reviewed the relevant evidence and concluded that PQ causes PD. This is in contrast to the many peer-reviewed publications that have systematically reviewed the literature and did not conclude PQ causes PD (*e.g.*, Weed 2021; Weed 2024).

With respect to Dr. Dahodwala’s specific causation opinion, she purports to apply a “differential diagnosis/etiology” which involves “‘ruling in’ and considering all identifiable known causes of and risk factors for the disease in question and ‘ruling out’ those for which there is inadequate evidence.” (2/3/2026 Dahodwala Rpt. at 2). Applying this methodology, Dr. Dahodwala concludes that that Mr. Rose’s exposure to PQ “is the etiologic driver and a cause of his Parkinson’s disease.” (2/3/2026 Dahodwala Rpt. at 2). Dr. Dahodwala’s methodology, reasoning, and conclusion are wrong for several reasons:

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- The evidence does not show that PQ can cause PD generally, so there is no basis to consider PQ a potential cause of an individual's PD.
- I am not aware of any peer-reviewed papers, medical textbook, or guidance from a movement disorder professional organization that endorses differential etiology as a way to identify the etiology of a patient's PD, nor have I ever seen this approach used in my clinical experience.
- Differential etiology is not possible in the context of PD. Outside of specifically identified genetic mutations, we do not know the cause of PD. It is, by definition, impossible to rule out unknown causes, which account for approximately 85% of PD cases. Dr. Dahodwala's assessment that "the only elevated risk factor Mr. Rose had for developing his Parkinson's disease, other than his age or gender, was his prolonged and repeated exposure to paraquat" and subsequent conclusion that PQ is the "etiologic driver and a substantial cause" of his alleged PD fails to account for unknown causes and that PQ is not a demonstrated cause of PD. (2/3/2026 Dahodwala Rpt. at 5, 11).
- Dr. Dahodwala fails to rule out family history and known genetic mutations, even after acknowledging that Mr. Rose potentially had "two paternal uncles" with PD. Despite this significant family history, she dismisses a potential genetic cause because "there is no medical evidence to verify this." (2/3/2026 Dahodwala Rpt. at 8-9). But a failure to locate those paternal uncles' medical records does not make Mr. Rose's potential significant family history of PD less relevant to his own illness or allow that and the other extensive neurological family history to be properly "ruled out." Dr. Dahodwala then states that genetic testing "was not clinically indicated" for Mr. Rose, overlooking the most obvious vehicle to examine a potential genetic link in the face of a family history of PD. (2/3/2026 Dahodwala Rpt. at 9). Dr. Dahodwala summarily rules out a genetic cause for Mr. Rose "given his older age of PD onset," despite the fact that Mr. Rose has extensive family history of neurological disease but did not undergo any genetic testing. (2/3/2026 Dahodwala Rpt. at 9). Older age of onset is not a basis to dismiss a genetic cause, particularly when a patient possesses a potential family history of PD and/or another neurological disease.

C. Dr. Beate Ritz

Dr. Ritz applied the Bradford-Hill criteria and concluded that "[t]he epidemiological studies as a whole support an increased risk of PD with exposure to paraquat." (Ritz Rpt. at 45) In support of this conclusion, Dr. Ritz pointed to a "general[]" finding of dose response across epidemiological studies, which she believes "can be considered a strong endorsement of causal relation." (Ritz Rpt. at 42, 45) Dr. Ritz also relied on "animal and mechanistic data" to conclude that PQ causes PD (Ritz Rpt. at 45), and states that there is "clear coherence" between the epidemiological studies and "laboratory findings in paraquat treated animals and cells." (Ritz Rpt. at 44)

My opinions above detail why Dr. Ritz's opinions are not supported by the scientific literatures and include, among others, the following:

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- The epidemiological studies are inconsistent—some find an association, while many do not. This inconsistency demonstrates a lack of causal association, especially when the Agricultural Health Study—the most recent analysis of data on those U.S. agricultural workers (which includes up to twenty years of follow up)—shows no association.
- As to dose-response, the epidemiological studies not only show inconsistent dose response, but also some of the largest and most recent studies report inverse dose response.
- While Dr. Ritz claims that the results from meta-analyses are “consistent and unequivocal” (Ritz Rpt. at 45), she fails to note that no published meta-analysis or other systematic review of the literature has ever concluded that PQ causes PD.
- With respect to Dr. Ritz’s opinions on the “animal and mechanistic data”—as I detail above, while animal studies have explored whether PQ can cause the type and pattern of progressive degeneration similar to what is seen in PD patients, none have done so.
- Finally, Dr. Ritz’s statements that PQ “induces the two pathologic hallmarks of PD: selective loss of dopaminergic neurons in the substantia nigra pars compacta and an up-regulation of alpha-synuclein” because it causes oxidative stress (Ritz Rpt. at 44), and her reference to oxidative stress as a “PD related biologic mechanism[.]” (Ritz Rpt. at 27), are theories inconsistent with the current state of knowledge. First, PD is characterized by widespread multi-system degeneration, not merely DA neuron loss or the presence of synuclein. Second, as I detail above, the nature of the role of alpha synuclein in PD remains unknown. Third, oxidative stress is part of normal body processes and the role of oxidative stress in the etiopathogenesis of PD is not yet known. In other words, it is unknown whether oxidative stress in the PD brain is a cause, effect, or artifact.

D. Dr. John Meeker

Dr. Meeker concludes that evidence from the epidemiological literature “consistently” supports a causal relationship where “people with high frequency, duration, and/or magnitude of exposure to paraquat are at significantly increased risk” of PD. (Meeker Rpt. at 55) Dr. Meeker’s conclusions are unfounded for all the reasons explained above, including in the following ways:

- Dr. Meeker incorrectly claims that evidence shows a consistent and strong association between PQ and PD. As stated above, the results of epidemiologic studies with respect to a possible relationship between PQ and PD are inconsistent.
- Dr. Meeker wrongly concludes that “[m]ost epidemiological studies ... have reasonably established” a temporal relationship between PQ and PD (*i.e.*, that an association is observed when exposure to PQ precedes PD onset). (Meeker Rpt. at 50) The large, prospective studies designed to capture this temporal relationship (Kamel 2007 and Shrestha 2020) reported no association. Dr. Meeker ignores these studies and instead relies on case-control studies (Liou 1997 and Tanner 2011), which, due to their

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design, do not allow any conclusions regarding whether exposure occurred prior to PD onset among the study populations. Dr. Meeker also contends that the temporality requirement is met because “a potential explanation in support of reverse causality (i.e., the disease caused the exposure) ... is not readily apparent.” (Meeker Rpt. at 51) But this contention assumes that there is an association between PQ and PD, which, as explained above, is not supported by the epidemiological literature.

- Dr. Meeker wrongly concludes that the epidemiological literature “largely” shows a dose-response relationship between PQ and PD. (Meeker Rpt. at 52). However, none of the studies he relies upon for this finding (Tanner 2011, Liou 1997, Elbaz 2009, Brouwer 2017, and Paul 2024), report a statistically significant dose-response, while other studies that Dr. Meeker discounts (van der Mark 2014, Shrestha 2020), actually report an inverse dose-response.
- Dr. Meeker contends that “[p]araquat causes oxidative stress,” which he claims plays “a role in the loss of dopaminergic neurons in PD.” (Meeker Rpt. at 52) However, as discussed above, the role of oxidative stress in the etiopathogenesis of PD is not yet known, and degeneration occurs in dopaminergic and non-dopaminergic neurons in PD patients. Dr. Meeker also points to several unproven hypotheses connecting PQ to “cellular mechanisms relevant to the pathophysiology of PD” (Meeker Rpt. at 52), none of which have been accepted as true by the scientific community.
- Dr. Meeker contends that PQ can penetrate the BBB. (Meeker Rpt. at 13) To support this contention, Dr. Meeker references several high-dose animal studies that, for reasons described above, are largely inapplicable to humans. Dr. Meeker further ignores non-human primate studies (Bartlett 2009 and 2011), which found that PQ was excluded from portions of the brain protected by the BBB. Dr. Meeker also cites early autopsies from human poisoning cases that reported PQ in the brain to support his contention. (Cravey 1979, Russell 1981) However, these autopsies do not indicate whether PQ was found in regions of the brain protected by the BBB, and even if it were, the acute doses involved in poisoning cases are not an accurate model for exposure in occupational settings.
- Dr. Meeker claims that surfactants “may impact exposure, uptake, distribution, absorption, and toxicity” of PQ. (Meeker Rpt. at 14) However, these statements are purely speculative and Dr. Meeker does not provide any citations to support his theories.

E. Dr. Jason Richardson

Dr. Richardson’s causation analysis and opinions are wrong because PQ does not cause PD, as explained above. In addition, Dr. Richardson’s analysis suffers from several other specific flaws:

- Dr. Richardson focuses on high-dose animal studies but does not cite a single low-dose animal study that shows any effect from PQ. Dr. Richardson testified that the lowest i.p. dose used in the published literature on which he relies, 1 mg/kg, is thousands of

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times the highest absorbed dose of 0.00044 mg/kg/day in Meier. (10/24/2024 Richardson Dep. Tr. at 118)

- Dr. Richardson states that Anderson (2021) demonstrates that PQ can reach in the brain via inhalation (Richardson Rpt. at 7), but admits that air concentration of PQ in the inhalation chambers was several hundred times higher than the concentrations reported during occupational exposure reported in Chester (1981) (10/24/2024 Richardson Dep. Tr. at 141-142), and ignores the fact that inhalation chamber produced PQ particles that were many times smaller than PQ particles during occupational exposure.
- Dr. Richardson further argues that primates “appear to retain brain levels of paraquat far longer than rodents.” (Richardson Rpt. at 8) But he bases this on incomplete and unpublished information on a primate experiment. (Richardson Rpt. at 8; SYNG-PQ-00044965) Notably, the information in the document he cites shows no loss of DA neurons after dosing with 2.5 mg/kg of PQ via subcutaneous injection once per week for six weeks. (SYNG-PQ-01691168) Dr. Richardson admits that he is not aware of any studies in non-human primates that report loss of DA neurons following PQ dosing. (10/24/2024 J. Richardson Dep. Tr. at 128)
- Dr. Richardson claims Bartlett (2009) is flawed because the primates were anesthetized with ketamine during the experiment, which he says would interfere with transport molecules that allegedly allow PQ to cross the BBB. But Bartlett used ketamine to permit transport of the animals, not during the PET scan; the animals were anesthetized using isoflurane during the scan. And in any event, Dr. Richardson admittedly failed to cite any evidence that ketamine would inhibit PQ’s entry into the brain. (10/24/2024 J. Richardson Dep. Tr. at 106-107) Bartlett (2011) reported similar results but does not indicate use of ketamine.
- Dr. Richardson acknowledges that “many neurotransmitter systems are now known to be disrupted in PD” which cause many of the non-motor symptoms of PD but could not identify any animal studies reporting that PQ can affect non-dopamine neurotransmitters. (Richardson Rpt. at 5; 10/24/2024 Richardson Dep. at 48, 50-51)

F. Dr. Briana De Miranda

Dr. De Miranda’s causation analysis and opinions are wrong because PQ does not cause PD, as explained above. In addition, Dr. De Miranda’s analysis suffers from several other specific flaws:

- Dr. De Miranda asserts that epidemiological data has confirmed a “strong link” between PQ and PD, but selects and bases her opinion on only a few studies reporting an apparent association while largely ignoring the contrary studies that find no association. Dr. De Miranda attempts to discredit the latest data from the Agricultural Health Study (Shrestha 2020) by wrongly claiming it is a “retrospective” study, when in fact one of its strengths is its prospective design and long-term follow-up. (De Miranda Rpt. at 5)

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- Dr. De Miranda attempts to discredit Shrestha (2020) by claiming that the investigators only “relied on self-reported PD diagnoses,” which she claims are “less rigorous than using medical coding or neurologist review.” (De Miranda Rpt. at 5) First, it is important to note that the “self-report” in Shrestha (2020) is individuals reporting being diagnosed with PD by a physician. Dr. Tanner noted that her examination of PD cases for Tanner (2011) confirmed PD in 84% of the cases that reported that they had been diagnosed with PD by a physician. Second, Shrestha (2020) did not rely solely on self-report—which in itself was over 80% accurate. Shrestha used a detailed screening questionnaire and other confirmatory steps. Notably, Drs. Tanner and Kamel were involved in PD case validation. As I noted above, even among experienced Movement Disorder Specialists, diagnosis may be inaccurate in up to 25% of cases.
- Dr. De Miranda does not cite any evidence supporting her assertion that Shrestha’s diagnostic accuracy was significantly different from Tanner’s. The only supposed evidence Dr. De Miranda cites is Darweesh 2024, but that is not a diagnostic accuracy study; it’s a “commentary” (or opinion piece) advocating a policy position. (Darweesh 2024) Darweesh also claims Shrestha’s methodology is “prone to error,” but cites only Bloem 2021, which says “up to 15% of people with the disease are diagnosed incorrectly; this misclassification rate is even higher among non-experts.” (Bloem 2021) Bloem does not compare error rates for one-time clinical exam versus self-report confirmed by movement disorder specialist based on record review (as in Shrestha), but notably, the 15% diagnostic error rate Bloem notes among movement disorder specialists is virtually identical to the 16% error rate for self-report found by Tanner 2011. (Bloem 2021; Tanner 2011)
- Dr. De Miranda claims that meta-analyses confirm elevated odds ratio for PQ and PD, but fails to note that no meta-analysis or other systematic review of the literature has ever concluded that PQ causes PD. (Weed 2021; Weed 2024)
- Dr. De Miranda contends that “much of PD etiology is predicated on evidence that dopaminergic neurons in the SN are a selectively vulnerable population of cells” (De Miranda Rpt. at 6), and most of her analysis is focused on dopaminergic neurons, but as explained above, PD is a disease of widespread progressive degeneration that affects many different areas of the central and peripheral nervous system. Dr. De Miranda fails to cite evidence that PQ (at any dose, by any route of administration, in any animal) can cause the widespread, progressive degeneration seen in PD.
- Dr. De Miranda claims that oxidative stress “plays a key role in PD pathogenesis” (De Miranda Rpt. at 8), but critically does not say exactly what that role is because, as noted above, we still do not know role that oxidative stress plays in PD. Dr. De Miranda concedes that the presence of ROS in our cells does not result in oxidative stress or oxidative damage unless ROS levels rise to a level that overwhelms the cellular antioxidant systems. But Dr. De Miranda incorrectly assumes without evidence that PQ causes oxidative stress and damage at doses workers are likely to encounter while working with PQ. More broadly, Dr. De Miranda cites no evidence reporting any toxic effect in experiments using human-relevant doses and fails to acknowledge that most

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of the experimental evidence she cites uses doses thousands of times higher than doses measured in worker biomonitoring studies.

- Dr. De Miranda acknowledges that animal studies have conflicting results and concedes “there is no clear reason for the variability between studies.” (De Miranda Rpt. at 12) She claims certain studies that “better recapitulate exposure conditions in human populations show more robust dopaminergic pathology” (De Miranda Rpt. at 12), but those studies involve in vitro cell studies, high dose injection, intravenous infusion by minipump or forced inhalation of high-concentration nebulized mist that do not remotely recapitulate worker exposure. (Cicchetti 2005 (8 i.p. injections of PQ 10 mg/kg each), Che 2018 (12 i.p. injections of PQ 10 mg/kg each), Roede 2011 (in vitro), Cristavao 2020 (daily 2.5 mg/kg by s.c. minipump x 28 days), Anderson 2021 (4hr/day x 20 days in inhalation chamber filled with highly concentrated nebulized PQ mist))
- Dr. De Miranda claims that Qi (2022) and Anderson (2021) show inhalation “provides a more direct route to the brain than ingestion or dermal exposures.” (De Miranda Rpt. at 10) But those studies used extremely small particles (10-50 nm in Qi; 160-180 nm in Anderson). For reference, a nanometer is 1,000 times smaller 1 micron, and PQ droplets produced during application are estimated as hundreds of microns in size (Plavicki Rpt. at 17; Hogarty 1975), meaning that the Qi and Anderson studies are not relevant to PQ exposure because they used particles that are hundreds or thousands of times smaller than PQ particles in the field. The Qi study also did not involve PQ.
- Dr. De Miranda fails to acknowledge that Anderson (2021) did not perfuse the brain tissues analyzed (notably, Anderson did perfuse lung tissue before analysis). Failure to perfuse brain tissue before analysis means that some or all of the supposed detections of PQ in the brain were actually measuring PQ from blood.
- Dr. De Miranda cites some evidence that PQ may cross the BBB in rodents at high doses, but she fails to discuss the results of Bartlett 2009 or 2011, which reported that PQ does not cross the blood brain barrier in non-human primates.
- Dr. De Miranda acknowledges that the death of neurons, appearance of Lewy bodies, and inflammation may be pathological hallmarks of PD but we do not know what, if any, role they play in PD disease process. She also acknowledges that oligomers and fibrils are only “suspected” (not proven) to be factors that “drive synucleinopathy.” (De Miranda Rpt. at 17) So when Dr. De Miranda hypothesizes that “there are many examples of how PQ could induce cellular dysfunction within the brain” (emphasis added), she is speculating on speculation: speculating about PQ’s hypothesized role in mechanisms that are only speculated to have some as yet unknown role in PD pathogenesis. (De Miranda Rpt. at 17)

Appendix

Exhibit A

Curriculum Vitae

Stuart H. Isaacson, M.D.

(rev. 06/2025)

Birth: July 15, 1964; Brooklyn, NY

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Family: Married, five children

Education: B.S., Northwestern University, Evanston, IL (1986)
M.D., Northwestern University Medical School, Chicago, IL (1988)

Professional history:

1988-89	Internship (Medicine), St. Luke's - Roosevelt Hospital Center, New York, NY; Residency fellow (Medicine), Columbia University College of Physicians and Surgeons, New York, NY
1989-92	Residency (Neurology), Mount Sinai Medical Center, New York, NY: Drs. Melvin D. Yahr (1989-91) and Howard Lipton (1992-92), Chairmen
1991-92	Chief Resident (Neurology), Mount Sinai Medical Center, New York, NY
1992-95	Clinical Associate, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD Research Fellow (Neurodegenerative Disease), Laboratory of Central Nervous System Studies, NINDS, NIH, Bethesda, MD: Dr. D. Carleton Gajdusek (Nobel Laureate) LCDR, United States Public Health Service
1995-96	Fellowship (Movement Disorders), Mount Sinai Medical Center, New York, NY: Drs. C. Warren Olanow, and Mitchell F. Brin and Melvin Yahr
1995-97	Assistant Professor, Department of Neurology, Mount Sinai School of Medicine, New York, NY: C. Warren Olanow, Chairman Attending Physician (The Mount Sinai Hospital / Faculty Practice Associates), Movement Disorders Center, Mount Sinai Medical Center, New York, NY
1997-	Director, Parkinson's Disease and Movement Disorders Center of Boca Raton
2002-2005	Voluntary Assistant Professor of Neurology, University of Miami School of Medicine, Miami, FL
2004-2009	Clinical Assistant Professor (Biomedical Sciences), Florida Atlantic University Medical School, Boca Raton, FL
2009-2016	Clinical Associate Professor (Neurology), Florida International University College of Medicine, Miami, FL

Case ID: 220300429

2024-	Executive Director, Parkinson's Research Centers of America (CA, FL, NY, TX)
Certification:	Diplomate, American Board of Psychiatry and Neurology (Board Certified, 1994) Florida Medical License (1997) New York Medical License (1989) National Board of Medical Examiners (1989) Certifications in GCP, NIH-HSP
Organizations:	American Academy of Neurology, Fellow (1990-) Movement Disorders Society (1995-) Parkinson's Study Group (2005-), Credentials Committee (2007-9) Huntington's Study Group (2012-), HDCRS Program Committee (2015) AAN - Movement Disorders Section (2000-), Strategic Plan Committee (2008-9) International Association for Parkinson and Related Disorders, Fellow (2017-) Melvin Yahr International PD Foundation, Scientific Advisory Board (2005) Parkinson's Research and Education Foundation, Director (2005-) We Move, Education Committee (2006-2012) Florida Super Doctors (2008-) Best Doctors in America (2005-) America's Top Physicians (2006-) NPF Chapter South Palm Beach County (Medical Director, 2007-2009) PRF Center of Excellence (Medical Director, 2009-2010)
Scientific Meetings:	Local Organizing Committee, 18th World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders, Miami, December 2009 Industry Relations Committee, 4th World Parkinson's Congress, Portland OR, 2016 Scientific Program Committee, XXII World Congress on Parkinson's Disease and Related Disorders, HoChiMinh City, Vietnam, 2017 Controversies in Neurology Annual Meeting, PD Section Co-Chair, Warsaw, 2018 Co-Chair, Industry Relations Committee, 5th World Parkinson's Congress, Kyoto, 2019 Scientific Program Committee, XXII World Congress on Parkinson's Disease and Related Disorders, Montreal, 2019 Controversies in Neurology Annual Meeting, PD Section Co-Chair, Madrid, 2019 Controversies in Neurology Annual Meeting, PD Section Co-Chair, virtual, 2020-22 Controversies in Neurology Annual Meeting, PD Section Co-Chair, Dubrovnik, 2023 Industry Relations Committee, World Congress on Parkinson's Disease and Related Disorders, Chicago, 2023 Controversies in Neurology Annual Meeting, PD Section Co-Chair, London, 2024 Scientific Program Committee, World Congress on Parkinson's Disease and Related Disorders, Lisbon, 2024 Controversies in Neurology Annual Meeting, PD Section Co-Chair, Prague, 2025 Industry Relations Committee, World Congress on Parkinson's Disease and Related Disorders, Brooklyn, 2025 Co-Chair, Industry Relations Committee, 7th World Parkinson's Congress, Phoenix, 2026 Controversies in Neurology Annual Meeting, PD Section Co-Chair, Krakow, 2026
External Reviewer:	Movement disorders US Neurology (editorial board) Drugs and Aging Parkinsonism and Related Disorders Journal of Parkinson's Disease Journal of the Neurological Sciences Journal of Neurology, Neurosurgery and Psychiatry British Medical Journal Open Adis Drug Evaluation

Therapeutic Advances in Neurological Disorders
Drugs & Aging
CNS Drugs
Neurotoxicity Research
Expert Review of Cardiovascular Therapy
Expert Opinion on Orphan Drugs

Subspecialty interests: Parkinson's Disease
Hyperkinetic Movement Disorders
Dystonia and Botulinum toxins
Autonomic Disorders
Neurodegenerative Disorders

Teaching: South Florida residency programs (2023-)
Movement Disorders residency rotation

Caribbean/Global Medical Schools (2018-)
Year 3-4 Neurology / Movement Disorders Clinical Rotation

Florida Atlantic University School of Medicine (2011-17)
Year 4 Neurology / Movement Disorders Clinical Rotation

Miller School of Medicine/Florida Atlantic University (2004-2010)
Year 2 Basal Ganglia
Year 2 PD Clinical Cases (Content Leader, 2007)
Voluntary Faculty Award (2007)
Student Interest Group in Neurology (2009)

Mount Sinai School of Medicine (1995-1997)
Year 1-2 Clinical Correlations
Year 3 Student Clerkship
Resident Rounds Ward Attending

Additional Teaching
Botox Injection Training Center (Allergan-sponsored, 2012-22)
AAN Botulinum Toxin Course (2008)
RITE cadaver courses (2012-2017)
Apomorphine Masterclass
Cicely Saunders Institute, King's College Hospital, London (2014)
Rome, Italy (2016)

Clinical Trials: Principal Investigator in >400 phase 1-4 clinical trials
Steering Investigator in >100 phase 2-4 clinical trials

Invited / Academic Lectures (partial):

in situ PCR detection of nucleic acids in archival brain tissue: Second International
Workshop on Analytical Morphology, Orlando, 1994.

Cellular localization of poliovirus in the spinal cord: NY Acad Sci, The Postpolio
Syndrome: Advances in pathogenesis and treatment, Bethesda, 1994.

Symposium on in situ Amplification and Hybridization: Techniques and Applications,
Bethesda, 1994.

University of Alabama at Birmingham Symposium on in situ PCR, UAB Comprehensive
Cancer Center Virology Program and Center for AIDS Research, Birmingham, 1994.

Second International Workshop on Analytical Morphology, Orlando, 1994.

Advances in Molecular Biology, Catholic University, Washington, 1995.

Third International Workshop on Analytical Morphology, Atlantic City, 1995

End-of-Dose “Wearing-Off” in Patients with Parkinson’s Disease: New Management Strategies for the Long-Term Care Setting, AMDA Annual Meeting, 2006.

Mount Sinai Medical Center, NY (Grand Rounds, 1996)

WPB VAMC (Grand Rounds, 2005)

Creighton University Medical Center (Grand Rounds, 2006)

LA VAMC (Grand Rounds, 2006)

University of Illinois-Chicago Medical Center (Grand Rounds, 2007)

Beth Israel Medical Center, NY (Grand Rounds, 2007)

Hackensack Medical Center (Grand Rounds, 2008)

LSU Medical Center (Grand Rounds, 2011)

Neurology Practicum, Montreal, 2012

Symposium, Vienna, Austria, September 2013.

Symposium, 20th World Congress on Parkinson’s Disease and Related Disorders. Geneva Switzerland, December 2013.

8th World Congress on Controversies in Neurology (CONY), Berlin Germany, May 2014.

Boston University, Movement Disorders Conference, 2014

Lecture Presentations at Scientific Meetings, 2015-

Peer reviewed Publications:

- Pahwa, R., Molho, E., Lew, M., Dashtipour, K., Gil, R. A., Revilla, F. J., Clinch, T., Qin, P., Isaacson, S. H. (2025). Long-Term Safety and Efficacy of Repeated Cycles of RimabotulinumtoxinB in the Treatment of Chronic Sialorrhea: Results of the OPTIMYST Trial. *Neurol Ther.* <https://doi.org/10.1007/s40120-025-00777-z>
- Isaacson, S. H., Nasrallah, H., Pahwa, R., Alva, G., Kremens, D., & Stahl, S. M. (2025). Management of Parkinson's disease psychosis: first-line antipsychotic selection and rationale for continuing, combining, or switching. *Expert Opin Pharmacother*, 26(6), 707-717. <https://doi.org/10.1080/14656566.2025.2481205>
- Isaacson, S. H., & Jenner, P. (2025). Moving to a non-dopaminergic approach for the treatment of OFF fluctuations in Parkinson's disease. *Clin Park Relat Disord*, 12, 100303. <https://doi.org/10.1016/j.prdoa.2025.100303>
- Isaacson, S. H., Espay, A. J., Pahwa, R., Agarwal, P., Shill, H. A., Hui, J., Dashtipour, K., Lew, M., Qin, P., Formella, A. E., Ceresoli-Borroni, G., LeWitt, P. A., & Infus, O. N. S. G. (2025). Continuous, subcutaneous apomorphine infusion for

- Parkinson disease motor fluctuations: Results from the phase 3, long-term, open-label United States InfusON study. *J Parkinsons Dis*, 15(2), 361-373. <https://doi.org/10.1177/1877718X241310727>
- Hattori, N., Elmer, L., Isaacson, S. H., Pahwa, R., Rascol, O., Sethi, K., Stocchi, F., Nakajima, Y., Cummings, H., & Kostiuk, L. (2025). Safety and efficacy of istradefylline in Parkinson's disease patients with and without pre-existing dyskinesia: Pooled analysis of 8 randomized controlled trials. *J Mov Disord*. <https://doi.org/10.14802/jmd.25047>
- Chaudhuri, K. R., Bouchard, M., Freire-Alvarez, E., Pahwa, R., Bergmann, L., Gupta, R., Kukreja, P., Shah, M. B., & Isaacson, S. H. (2025). Post hoc exploratory analysis of the effect of foslevodopa/foscarbidopa continuous subcutaneous infusion on nocturia in patients with Parkinson's disease. *Clin Park Relat Disord*, 12, 100330. <https://doi.org/10.1016/j.prdoa.2025.100330>
- Westenberger, A., Skrahina, V., Usnich, T., Beetz, C., Vollstedt, E. J., Laabs, B. H., Paul, J. J., Curado, F., Skobalj, S., Gaber, H., Olmedillas, M., Bogdanovic, X., Ameziane, N., Schell, N., Aasly, J. O., Afshari, M., Agarwal, P., Aldred, J., Alonso-Frech, F.,...Bauer, P. (2024). Relevance of genetic testing in the gene-targeted trial era: the Rostock Parkinson's disease study. *Brain*, 147(8), 2652-2667. <https://doi.org/10.1093/brain/awae188>
- Kassubek, J., Factor, S. A., Balaguer, E., Schwarz, J., Chaudhuri, K. R., Isaacson, S. H., Wu, S., Denecke Muhr, C., & Kulisevsky, J. (2024). Long-term safety, tolerability and efficacy of apomorphine sublingual film in patients with Parkinson's disease complicated by OFF episodes: a phase 3, open-label study. *J Neurol*, 271(6), 3554-3570. <https://doi.org/10.1007/s00415-024-12323-2>
- Isaacson, S. H., Pahwa, R., Pagan, F., Abler, V., & Truong, D. (2024). Retrospective analyses evaluating the mortality risk associated with pimavanserin or other atypical antipsychotics in patients with Parkinson disease psychosis. *Clin Park Relat Disord*, 10, 100256. <https://doi.org/10.1016/j.prdoa.2024.100256>
- Isaacson, S. H., Dewey, R., Hauser, R. A., Kremens, D., Kumar, R., Lew, M., Ondo, W., Pagan, F., Lyons, K. E., & Pahwa, R. (2024). Apomorphine titration with and without anti-emetic pretreatment in patients with Parkinson's disease experiencing OFF episodes: A modified Delphi panel. *Clin Park Relat Disord*, 11, 100264. <https://doi.org/10.1016/j.prdoa.2024.100264>
- Gibbons, C. H., Levine, T., Adler, C., Bellaire, B., Wang, N., Stohl, J., Agarwal, P., Aldridge, G. M., Barboi, A., Evidente, V. G. H., Galasko, D., Geschwind, M. D., Gonzalez-Duarte, A., Gil, R., Gudesblatt, M., Isaacson, S. H., Kaufmann, H., Khemani, P., Kumar, R.,...Freeman, R. (2024). Skin Biopsy Detection of Phosphorylated alpha-Synuclein in Patients With Synucleinopathies. *JAMA*, 331(15), 1298-1306. <https://doi.org/10.1001/jama.2024.0792>
- Espay, A. J., Stocchi, F., Pahwa, R., Albanese, A., Ellenbogen, A., Ferreira, J. J., Giladi, N., Gurevich, T., Hassin-Baer, S., Hernandez-Vara, J., Isaacson, S. H., Kieburtz, K., LeWitt, P. A., Lopez-Manzanares, L., Olanow, C. W., Poewe, W., Sarva, H., Yardeni, T., Adar, L.,...Bou, N. S. G. (2024). Safety and efficacy of continuous subcutaneous levodopa-carbidopa infusion (ND0612) for Parkinson's disease with motor fluctuations (BouNDless): a phase 3, randomised, double-blind, double-dummy, multicentre trial. *Lancet Neurol*, 23(5), 465-476. [https://doi.org/10.1016/S1474-4422\(24\)00052-8](https://doi.org/10.1016/S1474-4422(24)00052-8)
- Bergmans, B., Clark, V., Isaacson, S. H., & Baumer, T. (2024). Corrigendum to "Recommendations for a paradigm shift in approach to increase the recognition and treatment of sialorrhea in Parkinson's disease" [Clin. Parkinsonism Related Dis. 9 (2023) 100223]. *Clin Park Relat Disord*, 10, 100250. <https://doi.org/10.1016/j.prdoa.2024.100250>
- Usnich, T., Olmedillas, M., Schell, N., Paul, J. J., Curado, F., Skobalj, S., Csoti, I., Ertan, S., Gruber, D., Zittel, S., Sammler, E., Isaacson, S. H., Kuhn, A. A., Pedrosa, D. J., Reetz, K., Kasten, M., Rolfs, A., Bauer, P., Skrahina, V.,...Group, L. S. (2023). Frequency of non-motor symptoms in Parkinson's disease patients carrying the E326K and T369M GBA risk variants. *Parkinsonism Relat Disord*, 107, 105248. <https://doi.org/10.1016/j.parkreldis.2022.105248>
- Sabbagh, M., Small, G. W., Isaacson, S. H., Torres-Yaghi, Y., Pagan, F., & Pahwa, R. (2023). Unmet needs in the diagnosis and treatment of Parkinson's disease psychosis and dementia-related psychosis. *Int J Psychiatry Clin Pract*, 27(1), 69-81. <https://doi.org/10.1080/13651501.2022.2058406>

- Pahwa, R., Isaacson, S. H., Small, G. W., Torres-Yaghi, Y., Pagan, F., & Sabbagh, M. (2023). Correction to: Screening, Diagnosis, and Management of Parkinson's Disease Psychosis: Recommendations From an Expert Panel. *Neurol Ther*, 12(5), 1803. <https://doi.org/10.1007/s40120-023-00507-3>
- Pahwa, R., Aldred, J., Merola, A., Gupta, N., Terasawa, E., Garcia-Horton, V., Steffen, D. R., Kandukuri, P. L., Bao, Y., Ladhani, O., Yan, C. H., Chaudhari, V., & Isaacson, S. H. (2023). Long-term results of carbidopa/levodopa enteral suspension across the day in advanced Parkinson's disease: Post-hoc analyses from a large 54-week trial. *Clin Park Relat Disord*, 8, 100181. <https://doi.org/10.1016/j.prdoa.2022.100181>
- Isaacson, S. H., Pahwa, R., Brillman, S., Lu, C., & Kent, A. R. (2023). Clinical benefit of transcutaneous afferent patterned stimulation (TAPS) in essential tremor patients with high unmet need: a secondary analysis of TAPS studies. *Expert Rev Med Devices*, 20(12), 1211-1218. <https://doi.org/10.1080/17434440.2023.2274604>
- Isaacson, S. H., Kremens, D., Torres-Yaghi, Y., Stocchi, F., & Antonini, A. (2023). Importance of time to ON versus wearing OFF in total daily OFF time experienced by patients with Parkinson's disease. *Parkinsonism Relat Disord*, 114, 105495. <https://doi.org/10.1016/j.parkreldis.2023.105495>
- Isaacson, S. H., Hauser, R. A., Pahwa, R., Gray, D., & Duvvuri, S. (2023). Dopamine agonists in Parkinson's disease: Impact of D1-like or D2-like dopamine receptor subtype selectivity and avenues for future treatment. *Clin Park Relat Disord*, 9, 100212. <https://doi.org/10.1016/j.prdoa.2023.100212>
- Isaacson, S. H., Goldstein, M., Pahwa, R., Singer, C., Klos, K., Pucci, M., Zhang, Y., Crandall, D., Koblan, K. S., Navia, B., & Parkinson's Psychosis, T. S. G. (2023). Ulotaront, a Trace Amine-Associated Receptor 1/Serotonin 5-HT(1A) Agonist, in Patients With Parkinson Disease Psychosis: A Pilot Study. *Neurol Clin Pract*, 13(4), e200175. <https://doi.org/10.1212/CPJ.0000000000200175>
- Isaacson, S. H., Dewey, R. B., Jr., Pahwa, R., & Kremens, D. E. (2023). How to manage the initiation of apomorphine therapy without antiemetic pretreatment: A review of the literature. *Clin Park Relat Disord*, 8, 100174. <https://doi.org/10.1016/j.prdoa.2022.100174>
- Isaacson, S. H., Bowling, A., Zhang, I., Pappert, E., Stocchi, F., Cth, & Investigators, C. T. H. S. (2023). Motor response with apomorphine sublingual film and levodopa in patients with OFF episodes. *Neurodegener Dis Manag*, 13(2), 75-84. <https://doi.org/10.2217/nmt-2022-0038>
- Isaacson, S. H., Achari, M., Bhidayasiri, R., Comella, C., Farmer, J. G., Gupta, F., Jones, S., Kreitzman, D., Kremens, D., Lewis, S. J. G., Poewe, W., Tolosa, E., Campos, C., Gibbs, S. N., & Broder, M. S. (2023). Expert Consensus on the Use of On-Demand Treatments for OFF Episodes in Parkinson's Disease: A Modified Delphi Panel. *Mov Disord Clin Pract*, 10(4), 652-657. <https://doi.org/10.1002/mdc3.13690>
- Hauser, R. A., Ondo, W. G., Zhang, Y., Bowling, A., Navia, B., Pappert, E., Isaacson, S. H., & Investigators, C. T. H. S. (2023). Dose Optimization of Apomorphine Sublingual Film for OFF Episodes in Parkinson's Disease: Is the Prophylactic Use of an Antiemetic Necessary? *J Parkinsons Dis*, 13(3), 403-414. <https://doi.org/10.3233/JPD-223537>
- Hauser, R. A., Espay, A. J., Ellenbogen, A. L., Fernandez, H. H., Isaacson, S. H., LeWitt, P. A., Ondo, W. G., Pahwa, R., Schwarz, J., Stocchi, F., Zeitlin, L., Banisadr, G., Fisher, S., Visser, H., & D'Souza, R. (2023). IPX203 vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease: The RISE-PD Randomized Clinical Trial. *JAMA Neurol*, 80(10), 1062-1069. <https://doi.org/10.1001/jamaneurol.2023.2679>
- Brillman, S., Khemani, P., Isaacson, S. H., Pahwa, R., Deshpande, R., Zraick, V., Rajagopal, A., Khosla, D., & Rosenbluth, K. H. (2023). Non-Invasive Transcutaneous Afferent Patterned Stimulation Therapy Offers Action Tremor Relief in Parkinson's Disease. *Tremor Other Hyperkinet Mov (N Y)*, 13, 25. <https://doi.org/10.5334/tohm.762>
- Bergmans, B., Clark, V., Isaacson, S. H., & Baumer, T. (2023). Recommendations for a paradigm shift in approach to increase the recognition and treatment of sialorrhea in Parkinson's disease. *Clin Park Relat Disord*, 9, 100223. <https://doi.org/10.1016/j.prdoa.2023.100223>

- Peterschmitt, M. J., Saiki, H., Hatano, T., Gasser, T., Isaacson, S. H., Gaemers, S. J. M., Minini, P., Saubadu, S., Sharma, J., Walbillic, S., Alcalay, R. N., Cutter, G., Hattori, N., Hoglinger, G. U., Marek, K., Schapira, A. H. V., Scherzer, C. R., Simuni, T., Giladi, N.,...Investigators, M.-P. (2022). Safety, Pharmacokinetics, and Pharmacodynamics of Oral Venglustat in Patients with Parkinson's Disease and a GBA Mutation: Results from Part 1 of the Randomized, Double-Blinded, Placebo-Controlled MOVES-PD Trial. *J Parkinsons Dis*, 12(2), 557-570. <https://doi.org/10.3233/JPD-212714>
- Pahwa, R., Isaacson, S. H., Small, G. W., Torres-Yaghi, Y., Pagan, F., & Sabbagh, M. (2022). Screening, Diagnosis, and Management of Parkinson's Disease Psychosis: Recommendations From an Expert Panel. *Neurol Ther*, 11(4), 1571-1582. <https://doi.org/10.1007/s40120-022-00388-y>
- Pahwa, R., Fox, S., Hauser, R. A., Isaacson, S., Lytle, J., Johnson, R., Llorens, L., Formella, A. E., & Tanner, C. M. (2022). Clinically important change on the Unified Dyskinesia Rating Scale among patients with Parkinson's disease experiencing dyskinesia. *Front Neurol*, 13, 846126. <https://doi.org/10.3389/fneur.2022.846126>
- Pahwa, R., Aldred, J., Gupta, N., Terasawa, E., Garcia-Horton, V., Steffen, D. R., Kandukuri, P. L., Chaudhari, V. S., Jalundhwala, Y. J., Bao, Y., Kukreja, P., & Isaacson, S. H. (2022). Patterns of Daily Motor-Symptom Control with Carbidopa/Levodopa Enteral Suspension Versus Oral Carbidopa/Levodopa Therapy in Advanced Parkinson's Disease: Clinical Trial Post Hoc Analyses. *Neurol Ther*, 11(2), 711-723. <https://doi.org/10.1007/s40120-022-00332-0>
- Jackson, R., Brams, M. N., Carlozzi, N. E., Citrome, L., Fritz, N. E., Hoberg, A. R., Isaacson, S. H., Kane, J. M., & Kumar, R. (2022). Impact-Tardive Dyskinesia (Impact-TD) Scale: A Clinical Tool to Assess the Impact of Tardive Dyskinesia. *J Clin Psychiatry*, 84(1). <https://doi.org/10.4088/JCP.22cs14563>
- Isaacson, S. H., Pahwa, R., Pappert, E. J., & Torres-Russotto, D. (2022). Evaluation of morning bradykinesia in Parkinson's disease in a United States cohort using continuous objective monitoring. *Clin Park Relat Disord*, 6, 100145. <https://doi.org/10.1016/j.prdoa.2022.100145>
- Isaacson, S. H., Pagan, F. L., Lew, M. F., & Pahwa, R. (2022). Should "on-demand" treatments for Parkinson's disease OFF episodes be used earlier? *Clin Park Relat Disord*, 7, 100161. <https://doi.org/10.1016/j.prdoa.2022.100161>
- Isaacson, S. H., & Citrome, L. (2022). Hallucinations and delusions associated with Parkinson's disease psychosis: safety of current treatments and future directions. *Expert Opin Drug Saf*, 21(7), 873-879. <https://doi.org/10.1080/14740338.2022.2069240>
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Expert Reports

Amended Expert Report of Dominik D. Alexander, PhD, MSPH, dated February 17, 2026
Expert Report of Briana R. De Miranda, PhD., dated October 4, 2024
Expert Report of Richard Krolewski, M.D., PhD., Paraquat and Parkinson's Disease, dated September 30, 2024
Expert Report of Nabila Dahodwala, M.D., M.S., dated February 3, 2026
Expert Report of Dr. John Meeker, ScD, CIH, dated June 6, 2025
Expert Report of J.S. Plavicki, dated February 17, 2026
Expert Report of Jason Richardson, MS, PhD., DABT, dated October 4, 2024
Expert Report of Beate Ritz, M.D., PhD., dated October 3, 2024

Deposition and Other Transcripts

Deposition Transcript of Darlene Wisniewski 2/6/2026
Deposition Transcript of Dianna Rose 1/22/2026
Deposition Transcript of Duane Rose 1/28/2026
Deposition Transcript of Dimitrios Nacopoulos, M.D., 1/23/2026
Deposition Transcripts of Richard Krolewski, M.D., PhD., 5/22/2023, 1/15/2026
Deposition Transcripts of Jason Richardson, PhD., 4/17/2023, 10/24/2024
Deposition Transcripts of Beate Ritz, PhD., 8/11/2020, 2/5/2021, 5/12/2023
Deposition Transcript of Dr. John Meeker, ScD, CIH, 1/12/2026

Medical Records & Other

Darrell Rose MRI/ CT Images from September 16, 2020
RoseD-BayfrontOpenMRICT-00001-00013
RoseD-GadeDrJames-00001-00012

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DRose-Nightengale-000001-000009
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Darrell Rose Day in the Life Video Clips