Movement Disorders Phenomenology

Therapy and Management, Volume II

Steven J. Frucht
Pichet Termsarasab

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For Rachel, Emma, Clare, and Lucy (SF)

For Ploy, Boonreun, Veerachai, and Grandma Lung (PT)

Preface

Why another book on movement disorders phenomenology? Or as someone asked, "*didn't you already write that book*?" In truth, our first book on movement disorders phenomenology summarized historical elements leading to modern phenomenology and included video montages capturing clinical features of the major movement disorders. However, on completing the book we felt that something critical was missing….the experience of patients, and their evaluation and management in the clinic. This second book on phenomenology differs from the first in many crucial respects. Cases form the heart of this book—we believe that learning from patients is indispensable in the practice of movement disorders. A discussion of diagnosis, evaluation, and treatment follows each case or topic, integrated directly into the text. We have included updated references from the literature, and summary figures and tables that may be of use to the practicing movement disorders neurologist. By nature there are disorders and conditions that we have missed, as we did not encounter them in practice (e.g., DYT30, IgLON5, SCA10, DRPLA, among others). We hope that by mentioning these conditions in the appropriate context, interested readers can use the online resources of the International Movement Disorders Society to supplement their learning.

This book includes approximately 1000 patient videos, organized and edited so that they can be viewed separately, or as part of the narrative of each chapter. By basing the organization of the book on cases, we are purposely emulating William Osler's famous quote: "*To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.*" Particularly in movement disorders, the experience of patients and their examination findings are indispensable to learning. Each patient or their legal guardian signed an approved consent form, allowing presentation and publication of their videos for scientific and educational purposes. We are extraordinarily grateful to our patients and their families for allowing these de-identified videos to be shared in this manner. Just thirty years ago, assembling a book like this would have been impossible, as available technology to organize, edit, and catalogue videos did not exist. We trust that readers will honor this contribution of patients and their families by refraining from illegally copying or re-distributing these videos.

New York, NY, USA — Steven J. Frucht
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Without the selfless contribution of our patients who contributed to our education, and their generosity in allowing others to learn from their stories, this book would not exist. We dedicate this volume to them.

Contents

1 An Organized Approach to Movement Disorders: Diagnosis and Treatment

Introduction

Over the last 30 years, many textbooks devoted to movement disorders have appeared. Their format usually reviews the state of the art in the biology, anatomy, etiology and treatment of Parkinson's disease (PD), atypical parkinsonism, and the various hyperkinetic movement disorders. Most texts focus on the biology of the diagnoses and management, without much talk about how the diagnoses were made. In this book, we hope to offer a different approach—a practical guide for the neurologist in the office to diagnose and treat the major categories of movement disorders. This book picks up where our prior text, *Movement Disorders Phenomenology*, left off, focusing now on case histories and video examinations, and latest recommendations on evaluation and treatment.

Movement disorders neurology is a relatively young field, developed in the 1970s and 1980s by Stanley Fahn and C David Marsden, and then carried forward by their disciples throughout the world. There are several practical challenges facing the neurologist who decides to enter the specialty. Other subspecialities of neurology depend on ancillary testing—EEG in epilepsy; EMG and NCV in neuromuscular disease; polysomnography in sleep medicine; imaging and angiography in stroke; imaging and biomarkers in dementia. Movement disorders begins and ends with a history and examination carefully performed by an expert neurologist. Most diagnoses in the field of movement disorders do not have a gold-standard test for confirmation. For example, PD remains a clinical diagnosis; dopamine imaging may support the diagnosis, and newer biomarkers of alpha-synuclein seeding may assist, but these tests will not replace the office evaluation. Atypical parkinsonism (multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS)), focal dystonia, tics, stereotypies, essential tremor, functional movement disorders---all rely on the diagnostic acumen of the neurologist. Patients and their families may be skeptical of this approach (*"how can you be sure of that?").* The movement disorders neurologist must strive to avoid bias and cognitive traps, and to adapt the history and examination to the diagnosis on the fly.

Movement disorders occupies a unique niche in neurology. The classic approach to neurology taught to medical students and residents (*Where is the lesion? What is the lesion? What is the treatment?*) is turned on its head in movement disorders. Instead, movement disorders begins with the description and diagnosis of the type of movement (*What is the movement disorder?*), then the necessary work-up to decipher the etiology (*What work-up is needed?*), and finally, *how do I treat the patient*? Movement disorders depends on the history and the examination, in person if possible and by video if not. In this way,

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the field is like other non-neurologic fields in medicine (anatomic pathology, cytopathology, diagnostic radiology, dermatology, ophthalmology). It also has strong ties to other fields of visual expertise, such as art authenticators, bird watchers, or dog show judges. These experts spend a lifetime devoted to understanding and recognizing subtle but critical findings that separate a masterpiece from a forgery, or a prized champion mastiff from an also-ran, lovable pet. Watching a visual expert or experienced movement disorders neurologist at work, it's not uncommon for observers to wonder, "*How exactly do they know that, and why can't I see that too?*"

Movement disorders is usually divided into hypokinetic and hyperkinetic disorders. The most common hypokinetic disorder is PD, followed by forms of atypical parkinsonism (MSA, PSP, CBS) and secondary parkinsonism. Hyperkinetic disorders are often classified by the speed of the predominant movement, from fast to slow (myoclonus, chorea, tics, tremor, dystonia). Other disorders frequently seen in movement disorders clinic include ataxias, various unusual movement disorders and functional movement disorders. When confronting a new movement disorders patient in clinic, the history and examination help guide the examiner to establish the principle disorder (parkinsonism, myoclonus, chorea, tics, tremor, dystonia, or unusual disorder)—we think of this as *establishing which continent* we are on (Fig. 1.1). Then the examiner uses the history and exam to *establish the country* they are in (for example, on the continent of parkinsonism—PD, MSA, CBS, PSP, drug-induced parkinsonism, secondary parkinsonism). Once the country is established, the examination and further testing help *establish the city* (for example—tremor-predominant PD; LRRK2-related PD; GBA-related PDD). Of course, patients may have features of more than one continent (myoclonus-dystonia, tremor with myoclonus, chorea with dystonia), but we have found that this approach helps to ground the clinician and avoid the temptation of anchoring on a specific diagnosis from the start, which may in the end be incorrect (what we refer to as the "*where is Waldo*" approach).

We have included the history as well as the examination findings for case presentations to

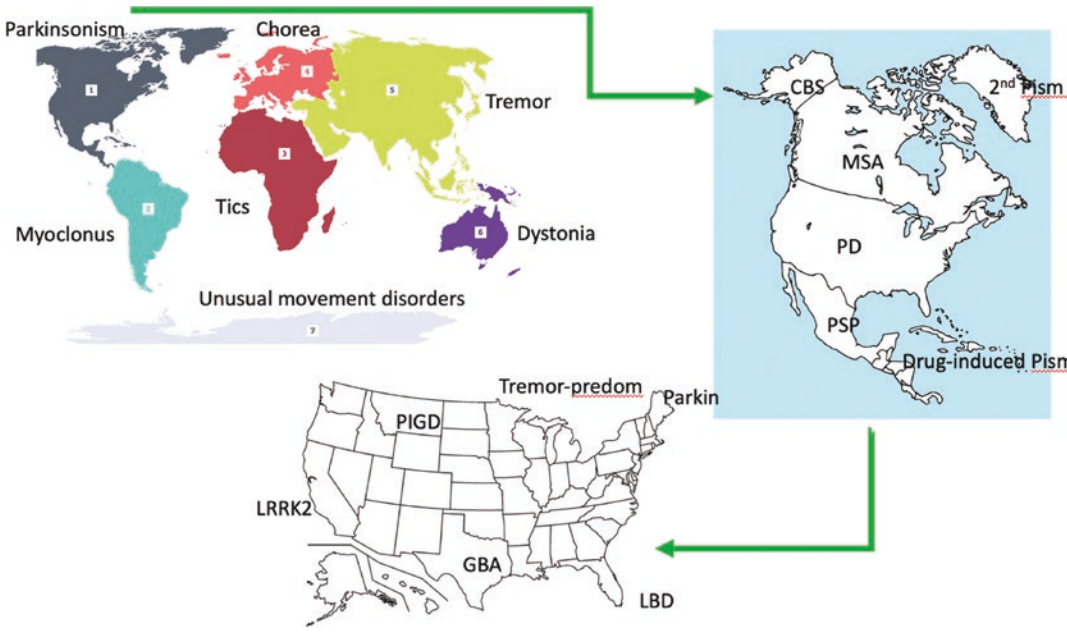

Fig. 1.1 The "continent-country-state" approach to clinical movement disorders

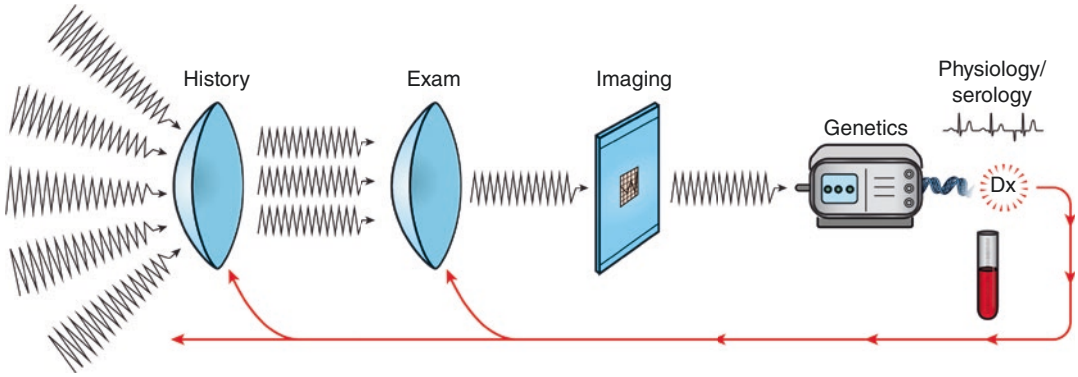

Fig. 1.2 Using the lens of history, exam, imaging, genetics, and physiology to focus the diagnosis. Information from the history is gleaned by the examiner, starting from the far left. The examiner's task is to focus the history, using the lens of their experience, to pose a limited number of questions for the exam. The examination focuses the differential on a narrow list of possibilities. As the workflow moves from left to right, imaging, genetics, physiology, and serology (when necessary) help secure the diagnosis (Dx). Throughout the process, on follow up visits over time, the neurologist re-examines the diagnosis based on the evolution of the history and exam over time (lower curved arrow from right to left), re-evaluating the diagnosis if needed

emphasize the importance of both sources of information. The experienced examiner uses the history to focus the patient's story (the first lens on the left in Fig. 1.2), usually narrowing the differential to a few possibilities. The movement disorders examination (the second lens) defines the dominant and ancillary examination findings and integrates these findings with the history to create a working diagnosis. In some cases, this diagnosis can be confirmed by imaging, genetic testing, or physiology/laboratory studies, but in many cases, the diagnosis remains clinical. Over time, the examiner must continually reassess the diagnosis, as the patient's history and examination often evolve, requiring re-evaluation and judgement whether the initial diagnosis was correct.

On each follow-up visit to the office, the patient's history and examination findings must be weighed and calibrated (Fig. 1.3), determining adjustments in treatment that help ensure the best possible outcome.

All movement disorders neurologists have been humbled by their discovery of diagnoses and features of illness that they once overlooked. Learning from each "mistake" iteratively helps the neurologist improve their diagnostic acumen and enhance patient outcomes.

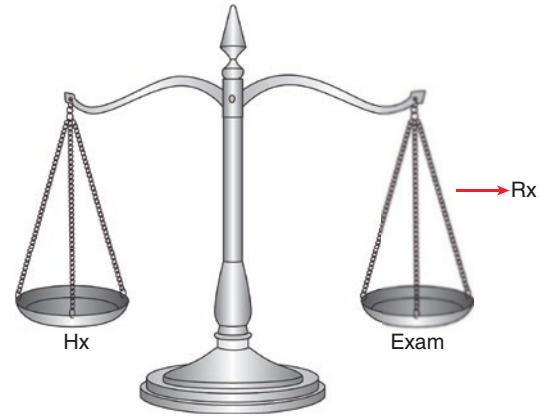

Fig. 1.3 Weighing the history and exam on follow-up visits for decision making. The neurologist weighs the interval history and examination at each follow-up visit, deciding which changes in treatment are needed to optimize care

How to Use This Book

The field of movement disorders has benefited tremendously from the rise of the internet. Prior to 2000, access to videos of patients was limited. Now, videos of almost every possible diagnosis are only a click away, and the International Movement Disorders Society and other organiza-

tions help to guide interested physicians to see and learn about the various conditions. These remarkable resources help the clinician learn about specific disorders; however we have observed that they focus less on illustrating the thought process behind evaluation and diagnosis. In this book, we have organized individual case histories and videos of patients to illustrate the diagnostic process and treatment decisions that optimize patient outcomes---to illustrate "***how to think like a movement disorders neurologist***".

Each chapter of the book follows a similar format. In the first section, clinical features, examination findings, differential diagnosis and evaluation are briefly reviewed. In the second section, video legends appear alone, allowing readers to watch the videos and understand the salient features, to focus on "***signs in the clinic***", and to use the videos as a reference guide to compare with patient experience. The third section presents each case in full, with a history and examination (illustrated by video wherever available). In-depth discussion of the specifics of each case reference recent literature, demonstrating application of updated knowledge to improve the care of patients. References appear at the conclusion of each chapter. Individual cases are noted by chapter number (capital C) and case number (lower case number), for example Chap. 8, Case 23—**C8c23** (Video 8.23). We have purposely organized the videos to illustrate the natural progression of disorders such as PD, PSP, and HD, beginning with milder forms where diagnosis is often more challenging.

The modern focus on artificial intelligence and machine learning informs the goal of this book. For those interested parties who have the stamina to read all thousand or so cases, we hope that these examples will provide an internal written and visual reference with which to learn ***applied clinical movement disorders***. In machine learning, data (for example, normal and abnormal mammography images, or cytology slides) are fed into a neural network, with signposts indicating features of concern (for example, calcifications or distortions of breast anatomy, or abnormal cytologic features of fine needle biopsy). The neural network learns iteratively, ultimately becoming better and better, until it can compete and even surpass the radiologist or cytopathologist in accuracy and speed when presented with new clinical material. ***We hope that this book will help facilitate machine learning, with the practicing neurologist as the intended "machine"***. The cases and discussion that follows hopefully can educate the "machine" (i.e. the clinical neurologist or trainee), creating an "internal memory bank" of the history and appearance of the full spectrum of clinical movement disorders. Once this internal library is established, we hope that clinicians will feel more comfortable encountering new patients, comparing them to their internal library, and allowing them to secure accurate diagnoses and treatment plans with confidence.

A table summarizing the videos for cases for each chapter appears on the following five pages. Chapters appear on the left in light blue; cases appears in the middle in red (with case numbers); diagnoses and phenomenology appear on the right in purple. In chapters where most cases relate to one diagnosis (Chaps. 2, 4, 5, 6, 7, 9, and 15), individual cases are grouped together. Using this table and the video legends that begin each chapter may allow readers to focus on the videos alone should they choose to do so.

Chapter	Case(s)	*Dx*
2 (PD)	16 cases	*PD*
3 (Other p'ism)	c1,c2	*chemoRx-induced p'ism*
	c3-c8	*drug-induced p'ism*
	c9,c10	*osmotic demyelination*
	c11	*postanoxic p'ism*
	c12	*asaccadia/p'ism*
	c13	*mitochondrial/p'ism*
	c14	*structural p'ism*
	c15	*vascular p'ism*
	c16	*dorsal midbrain p'ism*
	c17	*p'ism hyperpyrexia*
	c18,c19	*lower-body p'ism*
	c20,21	*unilateral freezing*
	c22,c23	*p'ism abulia*
	c24	*catatonia*
	c25-8	*NPH*
4 (PSP)	35 cases	*PSP*
5 (MSA)	21 cases	*MSA*
6 (CBS)	28 cases	*CBS*
7 (ET)	50 cases	*ET*
8 (Other tremors)	c1-13	*orthostatic tremor*
	c14,15	*enhanced physiolog tremor*
	c16-18	*dystonic tremor*
	c19	*PD tremor*
	c20-3	*cerebellar tremor*
	c24-6	*drug-induced tremor*
	c27	*Wilson's disease tremor*
	c28	*functional tremor*
9 (Tics)	49 cases	*tics*

Chapter	Case(s)	Dx
10 (Myoclonus)	c1	epilepsia partialis continua
	c2,3	CBS
	c4	Alzheimer's
	c5,6	poshypoxic myoclonus
	c7,8	cortical tremor/myoclonus
	c9	thalamic asterixis
	c10,11	hyperekplexia
	c12,13	reticular reflex myoclonus
	c14,15	palatal myoclonus
	c16,17	ataxia with palatal myoclonus
	c18	lower cranial myoclonus
	c19,20	brainstem myoclonus
	c21-4	spinal segmental myoclonus
	c25,6	paraneoplastic myoclonus
	c27,28	propriospinal myoclonus
	c29-32	hemifacial spasm
	c33,34	shoulder girdle myoclonus
	c35-9	peripheral myoclonus
	c40-7	myoclonus-dystonia
	c48	myoclonus in static enceph
	c49	myoclonus in alcohol withdrawal
	c50	drug-induced myoclonus
	c51	Rasmussen's
	c52-4	OMAS
	c55	Stiff person syndrome
	C56,57	SSPE
	C58,59	Whipple's
	C60,61	CJD
	c62-8	posthypoxic myoclonus
	c70,71	post-anoxic myoclonus
	c72,73	EPM1
	c74	MERRF
	c75	NUS1
	c76-8	sialidosis

Chapter	Case(s)	Dx
11 (Chorea)	c1-30	HD
	c44-6	Neuroacanthocytosis
	c47-50, 53	benign hereditary chorea
	c54,c55	anti-cardiolipin chorea
	c56	Chron's chorea
	c57	anti-thyroglobulin chorea
	c58-60	Sydenham's chorea
	c61	LGI-1 chorea
	c62,c63	NMDA-mediated enceph
	c64-9	hemiballism
	c70,c71	nonketotic hyperglycemia
	c72	post-pump chorea
	c73	biballism
	c74	choreoathetoid CP
12 (Dystonia)	c1-16	DYT-1
	c17-20	DYT-3
	c21-26	DYT-5
	c27,c28	DYT-6
	c29-33	DYT-12
	c34,c35	DYT-28
	c36-43	Blepharospasm
	c44-53	Meige/craniosegment
	c64-77	lower cranial dystonia
	c78-117	embouchure dystonia
	c118-137	abductor SD
	c138-164	adductor SD
	c165-203	cervical dystonia
	c204-230	writer's cramp
	c231-239	other arm dystonia
	c240-265	pianist's dystonia
	c266-278	violinist's dystonia
	c279-291	plectrum dystonia
	c292-304	woodwind dystonia
	c305-313	drummer's dystonia
	c314-331	lower extremity dystonia
	c332-343	truncal dystonia
	c344-7	structural injury-dystonia
	c348	glutaric aciduria type 1
	c349	L-2-OH glutaric aciduria

	c350-2	*Rasmussen's*
	c353-61	*post-stroke dystonia*
	c362	*C1-2 arthritis*
	c363	*neoplastic invasion*
	c364	*myasthenia*
	c365	*radiation injury*
	c366,c367	*congenital torticollis*
	c368	*btx injury*
	c369,c370	*AARS*
	c371	*cervical arthritis*
	c372,c373	*neck extensor myopathy*

Chapter	Case(s)	*Dx*
13 (Ataxia)	c1-7	*Friedreich's ataxia*
	c8,c9	*LOFA*
	c10	*VLOFA*
	c11-13	*Ataxia telangiectasia*
	c14-16	*AVED*
	c17-20	*CTX*
	c21	*AOA*
	c22-24	*PNPLA6*
	c25-27	*SCA-1*
	c28-30	*SCA-2*
	c31-38	*SCA-3*
	c39	*SCA-6*
	c40-42	*SCA-7*
	c43	*SCA-8*
	c44,c45	*SCA-17*
	c46	*Alexander's disease*
	c47	*CANVAS*
	c49	*post-infectious ataxia*
	c50	*OMAS*
	c51,c52	*anti-GAD ataxia*
	c53-55	*OMAS*
	c56,c57	*anti-Yo*
	c58,c59	*paraneoplastic ataxia*
	c60	*MS ataxia*
	c61,c62	*post-stroke ataxia*
	c63	*PAN*
	c64	*superficial siderosis*
	c65	*drug-induced ataxia*

Chapter	Case(s)	*Dx*
14 (Unusual mov dis)	c1-4	*athetosis*
	c5-8	*myokymia*
	c9	*oculomasticatory myorhythmia*
	c10,c11	*smile tremor*
	c12-15	*oculogyric crisis*
	c16-25	*PLMT*
	c26	*PFMH*
	c27	*PLMS*
	c28,c29	*FBDsz*
	c30	*belly-dancer's dyskinesia*
	c31,c32	*abdominal dystonia*
	c33	*benign neonatal quivering*
	c34	*benign paroxysmal torticollis*
	c35	*benign stereotypies*
	c36,c37	*benign tonic upgaze of infancy*
	c38	*juvenile PD*
	c39	*chemotherapy-induced p'ism*
	c40	*DHPR deficiency*
	c41	*PLA-2G6*
	c42	*WARS-2*
	c43	*NIHAD*
	c44	*pediatric parkinsonism*
	c45-52	*tardive akathisia*
	c53-57	*tardive OBL dyskinesia*
	c58-69	*lower cranial tardive*
	c70-79	*cervical tardive*
	c80-85	*other tardive*
	c86-93	*PKAN*
	c94	*PLA-2G6*
	c95	*BPAN*
	c96	*FAHN*
	c97-104	*Wilson's disease*
	c105-111	*Fahr's*
	c112	*myasthenia*
	c113-8	*motor neuron disease*
	c119-c120	*CJD*
	c121-3	*HSP*
Chapter 15 (Functional)	59 cases	*Functional*
Chapter 16 (Rx and btx)	3 cases	*Btx injections for HFS, bleph, tort*

Parkinson's Disease

2

Part 1: Clinical Summary

The diagnosis of Parkinson's disease (PD) remains a watershed event in the life of a patient and their family. In this chapter, we explore the natural history and practical management of PD from early to advanced stages of illness. Despite extraordinary advances in medicine, the diagnosis of PD still rests on the history and examination and is dependent on the skill and experience of the examiner. Rest tremor, bradykinesia, cogwheel rigidity and postural impairment are the four cardinal features of the illness, but after caring for PD patients one soon realizes that PD is an umbrella term, encompassing a broad range of clinical phenotypes and progression. The diagnosis of PD usually has a profound psychological impact on the patient, and often on their family. In practice, the patient with PD and their family/caregiver/support are integral parts of the care experience.

Critical Questions for the Examiner Regarding Dx and Rx of PD

Dx

1. **Critical questions:**
   (a) **Does the patient have cardinal features of parkinsonism (tremor, bradykinesia, rigidity, postural impairment)?**
   (b) **Is there a reversible etiology that might explain their parkinsonism?**
   (c) **Are the history and examination findings consistent with idiopathic PD?**
   (d) **Are there history or examination findings inconsistent with idiopathic PD?**
   (e) **Are the examination findings sufficient to make a confident diagnosis of PD?**
2. **Necessary work-up:**
   (a) **Is an MRI of the brain necessary?**
   (b) **Should the patient undergo genetic testing with a PD gene panel?**
   (c) **Should the patient undergo a dopaminergic imaging test?**
3. **Uncertainty and pitfalls:**
   (a) **Distinguishing atremulous PD from multiple system atrophy and PSP**
   (b) **Isolated rest tremor—does this patient have essential tremor or early PD?**
   (c) **A history of REM sleep behavior disorder and very mild examination findings—does this patient have PD?**

Rx

1. **Decision to begin symptomatic Rx?**
   (a) **Is the patient troubled by their symptoms?**

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-52573-5_2.

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   (b) **Does the patient have symptoms or signs that mandate symptomatic treatment?**
   (c) **Is the patient working, and is their work performance affected by their symptoms or signs?**
   (d) **Does the patient want to avoid disclosing their condition to family, friends, or coworkers?**
2. **Decision regarding symptomatic Rx?**
   (a) **Initiating treatment: levodopa vs. ancillary agents**
   (b) **Target dose and individualization of treatment**
   (c) **Treatment of PD symptoms: wearing off; dyskinesias; nausea; hypotension; constipation; depression; psychosis; freezing; sialorrhea**
3. **Priorities in ancillary support of advanced PD**
   (a) **Imbalance and fall risk**
   (b) **Dysphagia and aspiration risk**
   (c) **Advanced care planning and palliative care**
   (d) **Addressing caregiver burden**

Part 2: Video Legends

Examination **(Typical PD) C2c8** (Video 2.1) revealed a pleasant man without parkinsonian appearance, with a slight decrement in finger tapping on the left. Clear decrement in foot tap was also present. A positional tremor of the left foot, approximately 4–5 Hz, would build in amplitude and disappear with repositioning. Gait was unaffected. A young woman videotaped her hand and foot movements to illustrate her deficits **C2c27** (Video 2.2) **(parkin)**. Her local neurologist started her on Sinemet 10/100 three times daily. With her first tablet she noted a miraculous improvement in virtually all symptoms, except for her gait. Examination in the office revealed no facial masking, and normal dexterity and tone in the arms. Foot tap on the left was labored. Walking triggered dystonic curling and inversion of the left leg. She was able to run and to walk backwards without difficulty. Examination **(Typical PD) C2c31** (Video 2.3) revealed clear signs of parkinsonism, with facial masking, reduced blink rate, and voice that was softer. Mild left greater than right slowness of dexterous movements was accompanied by reduced left arm swing. Examination **(PD, off state) C2c33** (Video 2.4) in the off state revealed a 2+ tremor affecting the right arm and leg, accompanied by moderate bradykinesia, cogwheeling and reduced right arm swing. Micrographia is demonstrated, with gradual decline in letter height and width as he writes. Examination **(Advanced PD) C2c43** (Video 2.5) in the off state revealed moderate parkinsonism, with facial masking, a prominent rest tremor of the right hand, bilateral slowing of finger tapping, and cogwheeling on the right. Arm swing was reduced on the right, and recovery with pull test was preserved. Examination **(LRRK2) C2c50** (Video 2.6) revealed clear left-sided bradykinesia with breakdown in amplitude and cadence of foot tap on the left, and nearly absent left arm swing. Genetic testing revealed a G2019S mutation in the LRRK2 gene. Examination **(Pseudo-hemiparetic PD) C2c51** (Video 2.7) revealed rapid finger and hand movements on the right that were markedly slow, with moderate cogwheeling; foot tap was also slow. Her gait was characterized by extreme slowness on the right, with a **hemiparetic-like** appearance, and she tended to hold the right arm flexed in front of her. She was easily able to run down the hallway. Examination **(parkin) C2c52** (Video 2.8) showed mild facial masking, bilateral rest tremor, mild appendicular slowness, and mild inversion of the left foot with walking. Examination **(drug-induced anterocollis) C2c56** (Video 2.9) revealed moderate **anterocollis and anterior shift** of the head. Neck extensors and flexors were full strength. She was diagnosed with a rare complication of dopamine agonist therapy, agonist-induced anterocollis, and rotigotine was immediately discontinued. One month later (video) on Sinemet 25/100 1.5 tabs three times daily, anterocollis has nearly resolved. Examination **(Advanced PD) C2c68** (Video 2.10) in the office in the on state revealed moderate **dyskinesias**, affecting the head and neck, left hemi-body and trunk. Only mild slowness and cogwheeling were present, and dyskine-

sias activated when she walked. She displayed a characteristic dyskinesia on walking backwards, "retro-arm-swing". Examination **(Advanced PD) C2c69** (Video 2.11) revealed profound dyskinesias involving her head, torso, arms, and legs. She arose and walked with activation of dyskinesias throwing both of her arms behind her torso (bilateral retro-arm-swing). Examination (Advanced PD) **C2c70** (Video 2.12) in the office in the on state revealed moderately **severe dyskinesias** principally affected his arms and trunk, worsening with activation. His gait was notable for a marked tendency of his right arm to swing behind his torso (retro-arm-swing). Examination **(early-onset PD) C2c71** (Video 2.13) in the off state revealed a moderately parkinsonian woman seated in the chair with moderate facial masking, bilateral resting tremor, and marked bradykinesia with reduced arm swing and shortened stride. Over the next 4 years, multiple medication adjustments were made, including introduction of Parcopa, with ¼ or ½ tablets taken every 3 h, switch of amantadine to Gocovri, addition of entacapone, and trial of Kynmobi (pre- and post-treatment videos demonstrate the profound improvement in parkinsonism with 10 mg sublingual). Despite these efforts, the interval of her motor fluctuations shortened to 90 min and dyskinesias became increasingly problematic. She underwent successful STN DBS, allowing her to come off Sinemet and pramipexole, with elimination of motor fluctuations and dyskinesias. For the first time in 4 years, she was examined without levodopa, and an **action dystonia** of the right foot was evident with walking, triggering curling and inversion of the right foot. She was able to walk backwards and to run without difficulty. Trihexyphenidyl was begun at low dose with significant improvement in dystonia. Botulinum toxin injections produced substantial benefit, normalizing her gait (not shown). Examination **(orthostatic tremor and PD) C2c80** (Video 2.14) in the office revealed a pleasant woman with mild parkinsonism. She was asked to stand up and to remain standing without assistance. Fifteen seconds later, she developed a fine rapid tremor of the legs which could be palpated in the posterior leg muscles. When she touched the examiner's hand lightly or put a hand on the desk or on a wall, tremor was noticeably improved. Tremor disappeared with walking, only to reappear if she stopped walking and stood still. She was diagnosed with **orthostatic tremor**. Levetiracetam was started with gentle titration to 250 mg three times daily, with marked benefit. Examination **(PD camptocormia) C2c81** (Video 2.15) revealed a mildly parkinsonian man. As soon as he stood and started to walk, moderate forward truncal flexion (**camptocormia**) was triggered. Holding his hands together behind his back or pushing down on his hands in his pants pockets substantially ameliorated the camptocormia. He discovered that wearing a backpack with a heavy book or using ski poles to touch the ground also helped him to compensate.

Part 3: The Natural History of PD: A Case-Based Illustration

Clinical presentations and progression of PD are addressed in the cases below. Rather than apply an artificial staging system, cases are organized into five categories **(early, mild, moderate, advanced, and late**) to better reflect the functional challenges that patients encounter over the disease course.

Early PD

Case 1 The Parkinsonian Mask

A 47-year-old man with a 2-year history of PD was referred to clinic for a second opinion. His symptoms began at age 45, with an intermittent tremor of the left pinky when his hand was at rest. He then noticed mild progressive stiffness and slowness of the left arm and was begun on rasagiline 1 mg without benefit. A businessman and financier, he became aware of a change in his facial expression which interfered with his ability to meet with prospective clients. Examination in the office revealed mild facial masking and clear decrease in spontaneous blink rate. Little tremor was evident, but clear mild decrement in amplitude and cadence of finger taps on the left was

accompanied by mild cogwheeling and reduced arm swing. Rasagiline was discontinued and rotigotine was started with titration to 4 mg daily. On follow-up visit 3 months later, there was a clear symptomatic benefit in left-sided symptoms, with improvement in left hand dexterity and clear improvement in facial expressivity.

Discussion: This patient has cardinal features of PD including rest tremor, bradykinesia, and rigidity with clear asymmetry. Bradykinesia is the most important component in the diagnosis of PD, and treatment generally improves bradykinesia, rigidity, and tremor. Reduced facial expression (aka. hypomimia or facial masking) can interfere with ability to express emotion and interact with other people or the public [1, 2]. Some patients may be misdiagnosed with "depression". This patient demonstrates the importance of symptomatic treatment to improve facial expression. With treatment, in addition to the improvement in tremor, rigidity and bradykinesia, his facial expression was remarkably improved, aiding social interaction with his clients and the public.

This patient demonstrates good benefit from monotherapy with a dopamine agonist. Starting with its application in humans in 1960s, levodopa remains the most effective medication in the treatment of PD. In PD patients with significant motor impairment, initiation of levodopa treatment should not be delayed [3, 4]. Nevertheless, in relatively young patients with mild motor impairment, levodopa-sparing strategies using dopamine agonist monotherapy may be preferable, as in this patient.

Case 2 A Tremulous Policeman

A 46-year-old police officer presented for evaluation of a 1-year history of tremor of the right hand. Aside from mild micrographia he had no other complaints. Examination revealed an intermittent parkinsonian tremor of the right hand with only very mild right-sided impairment of dexterous movements. Due to the very mild examination findings, symptomatic treatment was deferred. A year later, trihexyphenidyl was begun for symptomatic tremor relief with good benefit and tolerability at 2 mg three times daily. However, within a year, symptoms of slowness and stiffness had become more noticeable in the right arm and leg, and rotigotine 2 mg daily was added with mild benefit. Three years after his initial evaluation he returned for a follow-up visit, describing a tense interaction at work where he was interrogated during a performance appraisal about his tremor. He was referred to the police department's physician, who removed him from active-duty status and withheld his firearm. Examination in the office revealed little change from his initial evaluation, except for a modest increase in the severity of his tremor.

Discussion: The Health Insurance Portability and Accountability Act (HIPAA) privacy rule has played an important role in protecting patients' confidential information. HIPAA is also useful in preventing discrimination such as in job or insurance applications. Patients with mild symptoms may try to use different strategies to hide their movement disorders from others. However, movement disorders including PD are visible—as we warn patients, "*movement disorders do not obey HIPAA*". This is especially true for tremor and slowness in PD. In professionals engaged in a visible job or with exposure to the public, treatment may be needed to keep the patient's illness confidential.

For the treatment of tremor in PD, anticholinergics (especially trihexyphenidyl) can be considered in relatively young tremor-predominant PD patients [5]. The initiation and titration should follow the "start low, go slow" principle. Anticholinergic side effects including dry mouth, urinary retention, constipation, blurred vision, tachycardia, and confusion may limit their use. Cognitive side effects are the main concern in the elderly. Anticholinergics should be avoided in elderly PD patients since they are more prone to these side effects. In this population, levodopa can be used to treat parkinsonian tremor, and in fact levodopa is the most effective medication for tremor treatment. Despite the effectiveness of trihexyphenidyl and dopaminergic therapies, tremor often responds less robustly to medical therapies than bradykinesia and rigidity. For medication-refractory tremor, deep brain stimu-

lation (DBS) or high-focused ultrasound may be considered [6].

Case 3 The Frozen Shoulder—A Harbinger of PD

A 52-year-old dentist presented for evaluation of a 2-year history of left shoulder pain and impaired hand dexterity. At age 50 she developed pain in the left shoulder, unfamiliar in character, not precipitated by injury or illness. She described the pain as deep, boring, extending from the shoulder down to the hand. Imaging revealed adhesive capsulitis and she was diagnosed with a frozen shoulder. Soon thereafter she noticed an intermittent tremor of the left hand. After dropping three mirrors at work one day, she decided to stop practicing as a dentist and to apply for disability. There was no family history of PD. Examination in the office revealed a classic parkinsonian rest tremor of the left hand, accompanied by moderate slowing of finger and hand movements on the left, moderate cogwheeling and absent left arm swing. A diagnosis of PD was secured and rotigotine was started. On follow-up evaluation 5 months later, there was a noticeable improvement in bradykinesia and gait with rotigotine 4 mg daily. Subsequent genetic testing revealed a pathogenic variant in the GBA gene (p.Ans409Ser).

Discussion: The "frozen shoulder" syndrome (aka. adhesive capsulitis) is characterized by pain and limitation of the range of motion of the shoulder in the absence of intrinsic intraarticular abnormalities. PD patients may present with an isolated frozen shoulder, often initially evaluated by an orthopedist with delay in diagnosis. The frozen shoulder in PD is associated with more slowness and stiffness in the ipsilateral arm [7, 8], and is likely worsened by rigidity involving the shoulder. For reasons that are unclear, symptoms of a frozen shoulder from PD often spontaneously remit, followed within the next year by more classic symptoms of hand slowness and tremor. Symptoms of frozen shoulder may improve with dopaminergic therapies. Musculoskeletal problems are common in PD, including striatal hand and foot, joint deformities, scoliosis and kyphosis [9]. Recognizing these disorders as manifestations of PD may be challenging.

Mutations in the *GBA* gene encoding glucocerebrosidase are known to cause Gaucher disease. Gaucher disease is autosomal recessive, thus mutations of two alleles (biallelic) in the *GBA* gene cause the disease. Patients with Gaucher disease can have parkinsonism, in addition to other symptoms such as hepatosplenomegaly. While Gaucher disease is due to biallelic mutations, heterozygous mutation in one allele of this gene are associated with an increased risk of PD [10, 11]. Common pathogenic variants include p.Asn370Ser (aka. N370S or p.Asn409Ser according to Human Genome Variation Society [HGVS]-recommended nomenclature) and p.Leu444Pro (aka. L444P or p.Leu483Pro according to HGVS-recommended nomenclature) [12, 13]. The p.Asn370Ser is common in the Ashkenazic Jewish population. PD patients with mutations in the *GBA* genes typically have a phenotype of an akinetic rigid syndrome, with an increased risk of dementia [14]. GBA variants can be classified by variant severity. Severe mutations are associated with younger onset and more severe motor symptoms, more rapid progression of the disease, and higher risk of cognitive decline [14–16].

Case 4 Refusing to Accept the Diagnosis of PD

A 57-year-old man developed a rest tremor of the left hand 2 years prior to evaluation, spreading over time to involve the right hand. He admitted to slowness in daily activities, but by his own admission remained in denial, refusing to accept the diagnosis of PD rendered by a local neurologist. During the COVID pandemic he was able to work in finance remotely, enabling him to hide his illness from co-workers. Examination in the office revealed an obviously parkinsonian man with moderate facial masking. Bilateral rest tremor was accompanied by moderate appendicular bradykinesia and cogwheeling, with mild slowing of stride. After an extensive discussion he agreed to begin Sinemet 25/100, increasing to three times daily. On follow-up visit 3 months

later, modest improvement in parkinsonian signs was clear.

Discussion: This patient demonstrates a common clinical scenario encountered in PD patients. Patients may cope by doctor shopping or going through extensive unnecessary investigations that create more anxiety. Some patients, as in this man, isolate or withdraw themselves from the public and limit their social interaction. In our experience, many patients view PD as a stigma. When symptoms develop, patients often turn to the internet or social media due to its accessibility. Often the information from these sources projects a clinical picture of PD with marked disability, inability to ambulate, requiring a walking aid or wheelchair. In fact, there is marked clinical heterogeneity among PD patients [17]. PD patients can be classified into several subtypes, for example, mild motor-predominant PD, intermediate PD and diffuse malignant PD [18]. Many PD patients can continue their job or perform their daily activities at a level close to their baseline with treatment. In addition to the stigma and misinformation about PD, patients may have anxiety, phobias or panic attacks [19], even early in their disease or in the prodromal phase [20]. Managing patients with denial of the diagnosis and social withdrawal can be challenging. We spend significant time explaining the diagnosis, correcting misinformation, and providing psychological support. Sometimes it may be better to advise the patient to avoid the internet. Once the patient can engage with treatment and perceive their improvement, they may adopt a more realistic approach to the disease.

Case 5 "Something Is Wrong with My Gait"

A 58-year-old woman presented with an 18-month history of decline in motor performance. She noticed that her driving had changed, as she had become much more cautious and deliberate behind the wheel. At least four family members commented that her gait had deteriorated. A recent fall resulted in a fracture of her left index finger, requiring surgical pinning and casting. She attributed slowness of movement with the left hand to her recent injury. Examination revealed a mildly anxious woman with normal expressivity. A trace 3-Hz rest tremor of the left thumb and index finger was accompanied by subtle slowing of finger tap on the left, with mild left-sided cogwheeling and reduced arm swing. After a discussion of her symptoms and signs, a definitive diagnosis of PD was deferred. On follow-up 3 months later, she acknowledged her bradykinesia, commenting on her difficulty walking downhill, and accepted the diagnosis of PD.

Discussion: Since the initial description of the disease in 1817 by James Parkinson, PD remains a clinical diagnosis. Cardinal features of PD include bradykinesia, a 4-Hz rest tremor, rigidity, and postural instability. The most important feature in the diagnosis of PD is bradykinesia. Tremor is not mandatory, as at least 30% of PD patients never manifest tremor. Postural instability is typically not an early feature. There have been at least two main criteria applied to research: UK Parkinson's disease Society Brain Bank clinical diagnostic (UKPDSBB) criteria [21] and Movement Disorder Society clinical diagnostic criteria for PD (MDS-PD criteria) [22]. These criteria require at least one or more features of rest tremor, rigidity and/or postural instability, in addition to bradykinesia. However, in clinical practice, we encounter PD patients in the early stages of their illness with bradykinesia and slight rigidity or postural instability. In addition, supportive features for the diagnosis include asymmetry, excellent and sustained response to levodopa therapy, and the presence of levodopa-induced dyskinesia. Atypical features such as cerebellar signs, severe autonomic dysfunction (excluding constipation) and significant orthostasis are never present in early stages of the disease.

Clinical history and physical examination are paramount in the diagnosis of PD. This patient has only subtle bradykinesia on left finger tapping. In addition, there is a trace 3-Hz rest tremor of the left thumb and index finger, and mild cogwheel rigidity. According to the meta-analysis by Rizzo and colleagues, the accuracy of a PD diagnosis is 73.8% (95% confidence interval 67.8–7 9.6) by non-movement disorder specialists, and 79.6% (95% confidence interval 46.0–95.1) by movement disorders experts [23]. In

patients with subtle symptoms or signs, there is no urgency to deliver the diagnosis of PD at the first visit. The diagnosis can be deferred to follow-up visits when signs become more apparent or additional features emerge. While dopamine transporter (DAT) scans can be used as supportive evidence of dopamine deficiency, (usually demonstrating reduction or loss of dopamine uptake in the posterior putamen), the diagnosis still relies mainly on clinical history and physical examination. DAT scans are abnormal in other forms of parkinsonism, and we have encountered patients with an "abnormal" DAT scan due to tilting of the head in the scanner, resulting in an appearance of asymmetrically reduced uptake.

Case 6 Fearing the Diagnosis of PD

A 59-year-old woman was referred for evaluation in the company of her husband. Two years prior to evaluation she developed pain and limitation in range of motion of the right shoulder. She admitted that she was very fearful of a diagnosis of PD and realized that she might be minimizing difficulties she was experiencing (slowness in most activities of daily living with her dominant right hand). When asked why, she revealed that a close friend's husband was diagnosed with PD, and she had followed his progressive deterioration with alarm. She also remembered that her father developed symptoms of PD in his 80's. Examination revealed a mildly parkinsonian woman seated with her right hand positioned in a dystonic posture of flexion at the MCP joint. Moderately severe slowing with breakdown in amplitude and cadence of right-sided movements was present. She walked with her right arm held flexed and immobile in front of her. After a long discussion, she accepted the diagnosis of PD. Sinemet 25/100 was begun and titrated to three times per day. On follow-up visit 6 weeks later, she commented how surprised she was to notice such a marked improvement in her shoulder pain and right-sided mobility. Examination revealed a marked improvement in facial expression, trace slowing of right finger tap, and near normal right-sided arm swing. These improvements were maintained at 1-year follow-up.

Discussion: Issues about fear and denial of a PD diagnosis are also discussed in Case 4. This patient's impressions of PD assumed a uniformity of experience based on an isolated personal observation. It is important to educate patients about the clinical heterogeneity of PD, and to correct misinformation from resources such as the internet. Patients should understand that each PD patient is different, and many PD patients have a relatively benign course. Fear of the diagnosis can be a major obstacle for receiving appropriate treatment that can significantly improve their quality of life. This patient suffered from right shoulder pain and bradykinesia, which significantly impaired her motor function and daily activities. Treatment was clearly indicated, and she experienced a robust response with marked improvement in right shoulder pain and bradykinesia. Clinicians use robustness of levodopa response as positive feedback, and patients can reasonably expect a sustained response to levodopa for years. Medication doses may need to be adjusted, and motor fluctuations and dyskinesias can develop.

Case 7 A Pilot with Tremor

A 55-year-old active commercial pilot was referred for evaluation. Eighteen months prior he developed a tremor of the right hand. Over time the tremor worsened, clearly triggered by stress (such as when he was undergoing his annual flight medical clearance). He denied any impairment in dexterity or ADLs. Rasagiline had not benefitted him, and he decided to go on short-term disability. Initial examination revealed a mild to moderate classic parkinsonian tremor of the right hand, but only trace signs of right-sided slowness. Treatment with rotigotine 4 mg daily produced a 60% reduction in tremor. Trihexyphenidyl 6 mg daily produced a further benefit in tremor. He then decided (in consultation with flight medical personnel) to see if he could attain tremor relief with Sinemet (the only PD medication allowed for active pilots). Rotigotine and trihexyphenidyl were discontinued, and Sinemet was begun. At a dose of 25/100 three times daily only very mild tremor was present. He expressed a desire to see if a higher dose

might eliminate his tremor. To the surprise of the examiner, 600 mg of daily levodopa tremor eliminated his tremor, and he was able to return to commercial aviation.

Discussion: While tremor-predominant PD is known to have a more benign course than the akinetic-rigid form [24], treatment of parkinsonian tremor can be challenging. Dopaminergic therapies in PD result in excellent and sustained response of bradykinesia and rigidity. Rest tremor can be treated with anticholinergics (also see Discussion for Case 2), dopamine agonists and levodopa. Anticholinergics (especially trihexyphenidyl) can be considered in relatively young PD patients with mild-to-moderate tremor. Anticholinergic side effects, especially confusion or hallucinations, are a concern in the elderly. Levodopa remains the most effective medication for tremor [25]. However, the response of tremor to levodopa is usually not as robust as bradykinesia and rigidity, and in some patients tremor does not improve with levodopa [26]. One study demonstrated that patients with good response of rest tremor to dopaminergic treatment have more bradykinesia and rigidity than those with poor response [26]. It is unknown whether the pathophysiology of levodopa-responsive tremor vs. levodopa-unresponsive tremor is different. A functional MRI (fMRI) study by Shen demonstrated that improvement in left upper limb postural tremor was positively correlated with changes in functional connectivity in the right upper limb region of the primary motor cortex (M1), and the left medial thalamus [27].

In cases with medication-refractory tremor, surgical treatments such as deep brain stimulation (DBS) or focused ultrasound can be considered. In general, symptoms that respond to levodopa such as bradykinesia and rigidity improve with DBS. However, tremor is the exception to this rule. The ventral intermediate nucleus (Vim) target will improve only tremor but not bradykinesia or rigidity [28], whereas the subthalamic nucleus (STN) and internal segment of globus pallidus (Gpi) targets are beneficial for not only tremor [29] but also for bradykinesia and rigidity [30].

Case 8 Leg Tremor in PD

A 47-year-old man presented for evaluation of a 4-month history of cramping of the left leg, curling of the left toes and tremor of the left leg. Curling of the toes and plantar inversion was not specifically triggered by walking. Tremor of the left leg was initially intermittent, present at rest if he sat with his leg crossed, disappearing immediately with repositioning. He denied any symptoms in the arms. Examination **C2c8** (Video 2.1) *revealed a pleasant man without parkinsonian appearance, with a slight decrement in finger tapping on the left. Clear decrement in foot tap was also present. A positional tremor of the left foot, approximately 4–5 Hz, would build in amplitude and disappear with repositioning. Gait was unaffected. A diagnosis of PD was made and pramipexole was begun, with little tremor relief even at 1.5 mg per day.*

Discussion: A 3–5-Hz unilateral leg tremor occurring in a seated position is a pathognomonic sign of PD [31]. It may be difficult to determine whether the leg tremor is a true resting tremor. Positioning the leg hanging in repose or in specific positions may trigger the tremor. Tremor in PD typically affects the hand or arm, but the leg can be affected first as an initial presentation. Nevertheless, unilateral leg tremor may occur in other conditions such as drug-induced parkinsonism, multiple system atrophy, and functional movement disorders [32]. Leg tremor in this patient is also accompanied by left-sided bradykinesia, demonstrated on finger and foot tapping.

Case 9 How To (and How Not To) Communicate the Diagnosis of PD

A 44-year-old man was referred for evaluation of a new diagnosis of PD. There was no family history of PD, and he denied non-motor symptoms such as REM sleep behavior disorder, constipation, lightheadedness, or loss of sense of smell. In retrospect, he and others had noticed that for the last 2 years he was not swinging his left arm when he walked. He also complained of pain in the left shoulder and arm. Occasional tremor of the left hand and a decline in typing proficiency prompted a referral to a movement

disorders neurologist. He described the evaluation that occurred in a backroom of his office during business hours. Twenty minutes in duration, the neurologist communicated her impression that he had PD by telehealth. Examination in our office revealed an anxious and occasionally tearful man. An intermittent classic parkinsonian rest tremor of the left hand was accompanied by very mild slowing and cogwheeling in the left arm and leg, and slight decreased arm swing. An extensive discussion reviewed the diagnosis, etiology, therapeutics, and treatment options. He expressed concern regarding his desire to have a child with his girlfriend. After discussion, PD genetic testing was performed, revealing a pathogenic heterozygous variant in the GBA gene (p.Ans409Ser). On follow-up visit 2 months later accompanied by his girlfriend, he reported much better ability to cope with the diagnosis; they planned to meet with a reproductive genetic counselor.

Discussion: Delivering the diagnosis of PD or other neurodegenerative disorders requires skill and compassion. Selection of the appropriate setting, place, and timing, as well as detecting and addressing patients' reactions are critically important. Ideally, a face-to-face visit is preferred, rather than delivering bad news over the phone or telehealth. The face-to-face visit helps clinicians better perceive patients' emotions via body language and facial expression. Two-way communication is also more efficient with a face-to-face visit: it may be easier for the patient to ask questions or tell the clinician to break if they feel overwhelmed, and easier for the clinician to react to the patient. Furthermore, during the face-to-face visit, the clinician has an opportunity to establish trust during the history taking and physical examination. Patients usually express appreciation for the thoroughness of the interview and physical examination. This is particularly important in PD where the diagnosis depends on the history and examination. During the COVID pandemic, many face-to-face visits were switched to telehealth. Nevertheless, a face-to-face visit is still preferred for an initial evaluation of a patient in whom PD is suspected. Telehealth may be more appropriate for follow-up visits or other issues that do not require delicate interaction between patients and physicians.

The issues regarding *GBA* mutations in PD are also discussed in Case 3. *GBA* mutation carriers are common, especially in specific populations such as Ashkenazic Jews in which the carrier frequency is about 1 in 15 [33]. The p.Ans409Ser is the most common *GBA* mutation in the Ashkenazic Jewish population [12]. Mutations in one allele (heterozygous mutation) increase risk of PD by approximately two to sevenfold [34]. The chance that each child will be a heterozygous carrier is 50%, if his girlfriend does not carry any mutations in this gene. However, if his girlfriend is also a carrier, the chance that each child will have a homozygous mutation in this gene (and thus Gaucher disease) is 25%, and risk of heterozygous mutations in this gene is 50%. In this case, *GBA* testing of his girlfriend can provide useful information for genetic counseling. Not all *GBA* heterozygous carriers will develop PD due to incomplete penetrance. Penetrance is age-dependent [35], approximately 10% at the age of 60 and 20% at the age of 80 years [36]. Understanding these risks is important for family planning. If parents plan to have a child, there are several methods to manage this risk, including preimplantation genetic diagnosis. These issues are ethically sensitive, and require collaboration between geneticists, genetic counselors, obstetricians, and neurologists.

Case 10 Anxiety Greater Than Slowness

A 50-year-old man was referred by his general neurologist due to concern that he had developed PD. In retrospect he noticed a poor sense of smell for many years, mild constipation, and occasional REM-sleep-behavior symptoms. Over the past 2 years, he had developed a mild tremor of the left hand at rest which had lately spread to the left leg. Examination revealed mild facial masking, a Myerson sign, a classic parkinsonian rest tremor of the left hand, mild left-sided slowness, and reduced left arm swing. A diagnosis of PD was confirmed and rotigotine 2 mg started, but it was poorly tolerated due to lethargy. He decided to remain off treatment until 5 months later, when worsening of left-sided slowness and difficulty