A Personalized Medicine Approach to the Management of Parkinson’s Disease

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Can We Predict Parkinson’s Disease?

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Parkinson’s Disease Background

- First described as “shaking palsy” by James Parkinson in 1817
- Approximately 1 million patients in the United States
- Annual incidence: 60,000
- Increase with age
- Mean age at onset: 55 to 60 years old


Clinical Features of PD

Parkinson’s disease is traditionally characterized by motor symptoms

- The four cardinal clinical features of PD are:
  - Tremor (3-6 Hz rest tremor);
  - Bradykinesia;
  - Rigidity (cogwheeling);
  - Postural instability.

- The supportive features are:
  - Symptoms begin asymmetrically
  - Hypomimia and hypophonia
  - Micrographia
  - Stoooped-flexed posture
  - Shuffling gait and festination
While James Parkinson’s monograph is best remembered for its descriptions of motor signs, Parkinson also described multiple non-motor signs:

“The sleep becomes much disturbed. Tremulous motions of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm...[t]he bowels which all along have been torpid, now in most cases, demand stimulating medicines...the expulsion of the faeces from the rectum sometimes requiring mechanical aid...”

## Non-motor Symptoms in PD

<table>
<thead>
<tr>
<th>Neuropsychiatric</th>
<th>Sleep Disorders</th>
<th>Autonomic</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Insomnia and sleep fragmentation</td>
<td>Excessive sweating</td>
<td>Pain</td>
</tr>
<tr>
<td>Anxiety</td>
<td>RBD</td>
<td>Orthostatic hypotension</td>
<td>Anosmia/Hyposmia</td>
</tr>
<tr>
<td>Apathy</td>
<td>RLS</td>
<td>Sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>EDS</td>
<td>Urinary dysfunction</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment/ Dementia</td>
<td></td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Pathology of PD

- Loss of the pigmented dopaminergic cell in the substantia nigra pars compacta and the formation of Lewy bodies in the brainstem.
- Lewy bodies are cytoplasmic inclusion bodies that contain alpha-synuclein.

Braak Hypothesis

- Traditional view is that PD begins in SNpc
- Braak has challenged the traditional view with a six-stage pathological process that, in part, explains the development of pre-motor and non-motor symptoms.
The Impact of Treatment

- The treatment of PD has focused on pharmacological management of dopaminergic symptoms.
- The pathology of PD however is much more widespread and manifests in non-dopaminergic symptoms before dopaminergic symptoms.
- By the time of clinical PD, 50-70% of neurons are degenerated and striatal dopamine content is reduced by 80% suggesting the remaining neurons are sick.
- Disease modification is therefore limited by the extent of neuronal damage by the time of diagnosis.
- Impacting the disease will require diagnosis of patients at risk of disease or very early on when there is little damage.
Some Non-Motor Symptoms May Precede Motor Disease

- Recent clinical, pathological and neuroimaging studies suggest that some non-motor signs may precede classic motor features by years.
- The most compelling evidence of premotor PD relates to:
  - Rapid eye movement (REM) sleep behavior disorder (RBD)
  - Constipation
  - Olfactory dysfunction (hyposmia)
REM Behavior Disorder (RBD)

- RBD is characterized by loss of normal muscle atonia during REM sleep resulting in violent limb and body movements and vocalizations allowing people to act out dreams
- Occurs in at least 30% of PD patients
- Associated with hyposmia and poor color discrimination
RBD

- Ability to identify prodromal PD has been demonstrated in three cohort studies done at sleep centers

- 28% to 45% of RBD patients converted to a neurodegenerative syndrome (PD or Lewy Body Dementia) at 5 years and 40% to 65% at 10 years

- The mean latency between RBD symptom onset and defined PD ranged from 12-14 years


Constipation

- Constipation is reported in 60-80% of patients with PD and may predate motor symptoms by years.
- Lewy body pathology in the myenteric plexus resulting in colonic denervation
- Honolulu Heart Program, a large population based epidemiologic study, looked at the bowel habits of 6790 men for 24 years.
  - Patients who had fewer than 1 BM daily had odds ratio (OR) of 2.3 of developing PD compared to patients having one BM and an OR of 4.8 compared to 2 or more BM daily.
  - Another record linkage prospective study demonstrated a 2.5 fold increased risk of PD in patients with constipation


Olfactory Dysfunction

- Olfactory dysfunction ultimately affects up to 90% of PD patients
- It may help differentiate PD from other forms of parkinsonism. Vascular parkinsonism, PSP, CBD have intact olfaction
- Olfactory testing may discriminate IPD from healthy controls with a sensitivity of 88% and a specificity of 83%
- Olfactory loss occurs bilaterally despite the fact that motor signs are generally asymmetric or unilateral.
Olfactory Dysfunction

- In Honolulu Heart Program, olfaction was assessed in 2,267 subjects without PD or dementia
  - After 8 years, 35 subjects developed PD
  - Subjects with a higher risk of developing PD scored in the lowest quartile in smell testing
  - Appeared to predate PD diagnosis by 4 years

Olfactory Dysfunction

- Hyposmia in asymptomatic 1\textsuperscript{st} degree relatives of PD patients is associated with an increased risk to develop PD
  - Olfaction was tested in 361 1\textsuperscript{st} degree relatives
  - 40 were hyposmic
  - Within 2 years, 10% of hyposmic relatives developed PD and another 12% had abnormal DAT SPECT scans compared to none of the normosmic relatives

The Parkinson’s At Risk Syndrome (PARS) Pyramid

Clinical PD
Features of PD
Non-motor symptoms
Neuroimaging
Genetic Predisposition

Treatment of Early Parkinson’s Disease

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Director, Parkinson’s Disease and Movement Disorders Center
University of South Florida
Tampa, FL
Levodopa Therapy in Parkinson’s Disease

• Most efficacious symptomatic drug
• Improves patients’ QOL
• Improves survival
• Long-term use is associated with motor complications


Levodopa/Carbidopa

- T½ of levodopa alone is 60 minutes

- T½ of levodopa/carbidopa is 90 minutes
Synthesis of Dopamine from Levodopa in Presynaptic Neuron
Change in Clinical Response Over Time

**EARLY PARKINSONS DISEASE**

Clinical response

Serum levodopa

**MODERATE PARKINSONS DISEASE**

Clinical response

Serum levodopa

**ADVANCED PARKINSONS DISEASE**

Clinical response

Serum levodopa

DYSKINESIA
Effect of Disease Progression on Levodopa Therapeutic Window

Levodopa (mg/mL)

Time (minutes)

0 100 200 300

0 100 200 300

0 100 200 300

Incidence of L-dopa–Associated Motor Complications: Fluctuations

Based on 49 publications appearing between 1978 and 2000.
Incidence of L-dopa–Associated Motor Complications: Dyskinesias

Based on 50 publications appearing between 1978 and 2000.
Dopamine Agonists

• Pramipexole
• Ropinirole
• Rotigotine Patch
Pharmacokinetics of Dopamine Agonists

- Oral agents – half lives >6 hours
- Rotigotine patch – relatively constant delivery over 24 hours
Dopamine agonist
Dopamine Agonists

- Comparable symptomatic benefit to levodopa early in disease
- Less symptomatic benefit than levodopa as disease progresses
- Potential Dopamine Replacement Strategies in early PD:
  - Levodopa
  - Dopamine agonist to which levodopa can be added
Dyskinesia in MPTP Primates Treated with Levodopa or Ropinirole

Pearce RK, et al. Mov Disord 1998. 13(2) 234-41
Occurrence of Dyskinesia: Initial DA Agonist Therapy

- **L-Dopa**
- **Pergolide**
- **Ropinirole**
- **Bromocriptine**

Proportion of Patients Remaining Free of Dyskinesia

Survival Distribution Function

% Free of Motor Complications from the Onset of Treatment

*P = .0003*
## CALM-PD: Pramipexole vs Levodopa

### Adverse Events by Treatment Group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pramipexole (%)</th>
<th>L-Dopa (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>32.4</td>
<td>17.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>9.3</td>
<td>3.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>17.9</td>
<td>8.0</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>14.6</td>
<td>4.0</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>6.0</td>
<td>10.0</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>36.4</td>
<td>36.7</td>
<td>ns</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25.5</td>
<td>24.0</td>
<td>ns</td>
</tr>
</tbody>
</table>
### Safety: Ropinirole vs. Levodopa

Percentage emergent adverse experiences (those occurring >10%)

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Ropinirole (N = 179)</th>
<th>L-dopa (N = 89)</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>48.6</td>
<td>49.4</td>
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<tr>
<td><strong>Somnolence</strong></td>
<td><strong>27.4</strong></td>
<td><strong>19.1</strong></td>
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<tr>
<td>Insomnia</td>
<td>25.1</td>
<td>23.6</td>
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<tr>
<td>Parkinsonism Aggravated</td>
<td>22.3</td>
<td>20.2</td>
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<tr>
<td>Dyspepsia</td>
<td>20.7</td>
<td>16.9</td>
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<tr>
<td>Dizziness</td>
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<td>19.1</td>
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<tr>
<td>Injury</td>
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<td>19.1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>17.9</td>
<td>16.9</td>
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<tr>
<td><strong>Hallucination</strong></td>
<td><strong>17.3</strong></td>
<td><strong>5.6</strong></td>
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<tr>
<td>Tremor</td>
<td>16.2</td>
<td>12.4</td>
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<td>Vomiting</td>
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<td>11.2</td>
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<td>Abdominal Pain</td>
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<td>Arthralgia</td>
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<tr>
<td>Depression</td>
<td>14.5</td>
<td>22.5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Ropinirole (N = 179)</th>
<th>L-dopa (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>14.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Edema Legs</td>
<td>14.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Pain</td>
<td>11.7</td>
<td>15.7</td>
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<tr>
<td>Anxiety</td>
<td>11.7</td>
<td>9.0</td>
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<tr>
<td>Hypotension Postural</td>
<td>11.2</td>
<td>12.4</td>
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<tr>
<td>Urinary Tract Infection</td>
<td>10.6</td>
<td>12.4</td>
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<tr>
<td>Constipation</td>
<td>9.5</td>
<td>12.4</td>
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<tr>
<td>Dyskinesia</td>
<td>8.9</td>
<td>25.8</td>
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<tr>
<td>Infection Viral</td>
<td>8.4</td>
<td>13.5</td>
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<tr>
<td>Dyspnea</td>
<td>7.3</td>
<td>10.1</td>
</tr>
<tr>
<td>Dystonia</td>
<td>6.7</td>
<td>12.4</td>
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<tr>
<td>Sweating Increased</td>
<td>6.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4.5</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Study 056, Data on File
Recent Issues with Dopamine Agonists

• All Agonists
  - Sudden onset sleep
  - Impulse Control Disorders
Conclusions

- Initial treatment with a dopamine agonist (ropinirole or pramipexole) delayed the onset of motor fluctuations and dyskinesias compared to levodopa alone.
- Less hallucinations and somnolence in the levodopa groups.
Diagnosis

Functional Disability

Stable Response

Motor Fluctuations

YOUNG

DA

OLD

LD

LD
MAO-B Inhibitors

- Oral Selegiline
  - Approved as adjunct therapy
- Zydis selegiline (orally disintegrating tablets)
  - Approved as adjunct therapy
- Rasagiline
  - Approved as monotherapy and adjunct therapy
MAO-B Inhibitors

- Irreversibly bind to brain MAO-B
- Loss of effect is dependent on MAO-B turnover in the brain – half-time ~30 days
Neuroprotective Anti-apoptotic Actions of Rasagiline

- Caspase activation
- Rasagiline
  - Bcl-2, Bcl-Lx, PKCa & ε SOD
    - Cytochrome C release
    - Opening of mitochondrial permeability transition pore
- Neurotoxin
  - ROS
  - Nuclear translocation of GAPDH
- Nucleus
- Apoptosis
  - Caspase activation
- Mitochondrion
Delayed-Start Design: Symptomatic vs Disease-Modifying Effect

Symptomatic

Symptom improvement

Symptomatic & Disease-modifying

Symptom improvement

Early-start vs Delayed-start

Placebo

Delayed-start catches up

Delayed-start does not catch up...

...and the difference persists
A Controlled Randomized Delayed-Start Study of Rasagiline in Early Parkinson’s Disease

TEMPO
Rasagiline Mesylate (TVP-1012) in Early Monotherapy in PD Outpatients

Parkinson Study Group

TEMPO: Delayed-Start Design

Randomization

N=404

N=138

Placebo

Rasagiline 1 mg/day

N=134

Rasagiline 2 mg/day

N=132

N=124

N=134

N=132

At 6 months in Delayed Start:

Placebo group receives 2mg

Double-Blind Placebo-Controlled Phase

6 Months

Double-Blind Active Treatment Phase

6 Months

TEMPO: Primary Efficacy Measure - Treatment Effect on Total UPDRS at 6 months

(Please note: Adjusted Mean ± SE)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from baseline in Total UPDRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.13</td>
</tr>
<tr>
<td>Rasagiline 1 mg</td>
<td>0.51</td>
</tr>
<tr>
<td>Rasagiline 2 mg</td>
<td>4.07</td>
</tr>
</tbody>
</table>

P < 0.0001

TEMPO: 12-Month Results
Mean Change in Total UPDRS

TEMPO: 12-Month Results
Mean Change in Total UPDRS

Week 0 - 52

UPDRS Change from baseline

Rasagiline 2 mg
Placebo
Delayed-rasagiline 2 mg

† P = .01

Delayed-Start

TEMPO: Mean Percent Change in Total UPDRS: Early vs. Delayed Rasagiline Treatment

Overall difference between Early and delayed start groups is 16% (p=0.006)

(Data cutoff June 4, 2004)
A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson’s Disease

C. Warren Olanow, M.D., Olivier Rascol, M.D., Ph.D., Robert Hauser, M.D.,
Paul D. Feigin, Ph.D., Joseph Jankovic, M.D., Anthony Lang, M.D.,
William Langston, M.D., Eldad Melamed, M.D., Werner Poewe, M.D.,
Fabrizio Stocchi, M.D., and Eduardo Tolosa, M.D.,
for the ADAGIO Study Investigators*

ABSTRACT

BACKGROUND
A therapy that slows disease progression is the major unmet need in Parkinson’s disease.

METHODS
In this double-blind trial, we examined the possibility that rasagiline has disease-modifying effects in Parkinson’s disease. A total of 1176 subjects with untreated Parkinson’s disease were randomly assigned to receive rasagiline (at a dose of either 1 mg or 2 mg per day) for 72 weeks (the early-start group) or placebo for 36 weeks followed by rasagiline (at a dose of either 1 mg or 2 mg per day) for 36 weeks (the delayed-start group). To determine a positive result with either dose, the early-start treatment group had to meet each of three hierarchical end points of the primary analysis based on the Unified Parkinson’s Disease Rating Scale (UPDRS, a 176-point scale, with higher numbers indicating more severe disease): superiority to placebo in the rate of change in the UPDRS score between weeks 12 and 36, superiority to delayed-start treatment in the change in the score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72.

RESULTS
Early-start treatment with rasagiline at a dose of 1 mg per day met all end points in the primary analysis: a smaller mean (±SE) increase (rate of worsening) in the UPDRS score between weeks 12 and 36 (0.09±0.02 points per week in the early-start group vs. 0.14±0.01 points per week in the placebo group, P=0.01), less worsening in the score between baseline and week 72 (2.82±0.53 points in the early-start group vs. 4.52±0.56 points in the delayed-start group, P=0.02), and noninferiority between the two groups with respect to the rate of change in the UPDRS score between weeks 48 and 72 (0.085±0.02 points per week in the early-start group vs. 0.085±0.02 points per week in the delayed-start group, P<0.001). All three end points were not met with rasagiline at a dose of 2 mg per day, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47±0.50 points in the early-start group and 3.11±0.50 points in the delayed-start group, P=0.60).

CONCLUSIONS
Early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not. Because the two doses were associated with different outcomes, the study results must be interpreted with caution. (ClinicalTrials.gov number, NCT00256204.)
✓ Endpoint 1 (divergence of slopes from wk 12-36)
✓ Endpoint 2 (change from baseline to endpoint)
✓ Endpoint 3 (non-convergence of slopes wk 48-72)

Endpoint 2 = -1.68±0.75
(95% CI −3.15 to −0.21, p=0.02)
✓ Endpoint 1 (divergence of slopes from wk 12-36)
X Endpoint 2 (change from baseline to endpoint)
   Endpoint 3 (non-convergence of slopes wk 48-72)

Endpoint 2 = 0.36±0.68
(95% CI −0.99 to 1.70, p=0.60)
Norwegian-Danish Study – randomized double-blind trial of 163 patients treated with levodopa/benserazide plus selegeline or placebo for 5 years

At 5 years, in the selegiline group, levodopa dose 16% lower (p<0.05) and total UPDRS score 26% better (~9.5 units, p<0.01)

**FIGURE 1.** Mean (SD) total UPDRS score for patients with Parkinson’s disease treated with selegiline or placebo in addition to levodopa during 60 months of follow-up and during the one month wash-out period. Difference over time until 5 years of observation was statistically significant (P = 0.010)

**FIGURE 2.** Mean (SD) motor UPDRS score for patients with Parkinson’s disease treated with levodopa alone or in combination with selegiline for 5 years and during the one-month wash-out period. Difference over time until 5 years of observation was statistically significant (P = 0.019)
MAO-B Inhibitors

- Increasing benefit with increasing duration of treatment
- Mechanism not proven
  - Disease Modification
    - Neuroprotection?
    - Avoidance of bad compensatory mechanisms?
    - Maintenance of good compensatory mechanisms?
- Very slowly increasing dopaminergic effect?
- Future
  - Long term follow up
  - Non-dopaminergic symptoms
  - Other diseases
Diagnosis

Functional Disability

Stable Response

Motor Fluctuations

MAO-B Inhibitor

DA (young)

LD

DA = dopamine agonist
LD = levodopa
ENT = entacapone
Improving Patient Outcomes

Ray Dorsey, MD
Associate Professor of Neurology
Director, The Johns Hopkins Parkinson's Disease and Movement Disorders Center
The Johns Hopkins University Medical School
Baltimore, MD
At age 65, Gary faces many of the same challenges other patients with PD do:

- He has had PD for 10 years.
- His mobility has markedly decreased.
- His neurologist for the past 10 years has just retired and he is having trouble finding a new one.
- He has started to have difficulty driving.
- His wife also has a chronic condition.

Source: http://thefamouslastword.blogspot.com/2012/01/google-thinks-im-old-man.html

Gary is part of a growing number of patients around the world who have PD.

Distribution of individuals with Parkinson disease by country from 2005 to 2030*

2005
- 100% = 4.1 million individuals
  - China, 48%
  - Europe, 20%
  - Brazil, 4%
  - U.S. 8%
  - India, 8%
  - Others, 12%

2030
- 100% = 8.7 million individuals
  - China, 57%
  - Europe, 14%
  - Brazil, 4%
  - U.S. 7%
  - India, 8%
  - Others, 10%

*Among individuals over 50 in the world’s ten most and Western Europe’s five most populous nations

Neurology 2007;68:384-6
Many patients with PD have limited access to care for their condition.
Thankfully, Gary can access a PD specialist in his home using technology he may already own. Telemedicine can be used to reach people anywhere.

**Equipment**
- Laptop or portable device
- Internet connectivity
- Web cam, microphone
- Encrypted software

**Personalized care**
- In-home care
- Remote patient monitoring
- Remote study participation

**Global reach**

Using telemedicine, we have extended our reach into homes in 5 states and 13 countries.

Movement disorders care provided globally via telemedicine.

Our program has saved patients over 150,000 miles of travel.
Telemedicine visits are similar to in-person visits in content.
Telemedicine visits save patients like Gary three hours of time and 100s of miles of travel.

Patient time spent on in-person versus telemedicine visits

- **Door-to-door**: 100% = 255 minutes
  - Time spent traveling and waiting: 78%
  - Time spent with physician: 22%

- **On-to-off**: 100% = 53 minutes
  - Time spent connecting: 28%
  - Time spent with physician: 72%
Telemedicine allows different care providers to be involved with a Gary’s care

<table>
<thead>
<tr>
<th>Idea</th>
<th>Description</th>
</tr>
</thead>
</table>
| Parkinson disease specialist        | • Conduct visit with patient remotely via web-based videoconferencing and provide recommendations and referrals  
• Send clinic note to both patient and local physician or neurologist  
• Expand reach into underserved areas                                                                                                                                                                                                                                           |
| Local primary care physician/neurologist | • Integrate recommendations provided by PD specialist into patient’s overall neurological and general care  
• Receive training remotely via webinar, online courses or educational material to better understand movement disorder care  
• Provide occasional follow-up care remotely in order to improve understanding of condition, answer important questions, and maximize quality of life between visits  
• Attend clinic visit with PD specialist and nurses remotely via three-way calling in order to better participate in their loved one’s care                                                                                                                                 |
| Parkinson disease Nurses            |                                                                                                                                                                                                                                                                                                                                             |
| Remote caregiver                    | • Allows patient to improve health and quality of life, receive the highest quality care available, and decrease time and travel                                                                                                                                                                                                                  |
| Patient                             |                                                                                                                                                                                                                                                                                                                                             |
We are just scratching the surface of what is possible for patients like Gary

Growth horizons

- **Phase 1**
  - Provide care to individuals with Parkinson disease directly in their homes ("virtual house calls")

- **Phase 2**
  - Increase scale and reach of model nationally and globally

- **Phase 3**
  - Expand scope to other conditions (e.g., Huntington disease, ataxia)

**Time**

Our vision is to provide patient-centered care to individuals with Parkinson disease anywhere they live.
More importantly, Gary will value and appreciate the care he receives

- “From my perspective, the consultation was no different than in-person. He requested acts that he could view over the teleconferencing just as a doctor in the office would view.”
- “I think it is great that I can connect with leaders in the field at great distances from my home.”
- “It’s made such a difference. I truly feel, personally, that I got the type of attention I needed but [that] was not accessible to me because of the area that I lived and because of my Parkinson condition.”

Actual patient comments