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Inpatient Video-EEG Epilepsy Monitoring: Key Diagnostic Tool for Intractable Recurrent Seizures and Unconfirmed Seizure Diagnosis



Gregory D. Cascino, MD

For the majority of patients with epilepsy, routine electroencephalography (EEG) is sufficient to classify seizure type and initiate treatment. However, for those with intractable recurrent seizures and those with an unconfirmed seizure diagnosis, inpatient video-EEG monitoring is the best diagnostic tool available. Continuous behavioral and EEG monitoring over time in a controlled environment helps localize seizure focus, determine seizure type, and quantify the number of seizures. Equally important, video-EEG monitoring can differentiate seizures from psychologically based seizurelike episodes and from physiologic events that may be confused with epilepsy (see sidebar on page 2).

When appropriate, inpatient video-EEG monitoring offers several advantages. First, patients can safely be taken off medications that might otherwise mask seizure activity during routine EEG. Second, the studies are long enough to overcome sampling effects of shorter-duration EEG studies and the nonspecific findings and artifacts that may incorrectly suggest or refute a diagnosis of epilepsy.

Video-EEG monitoring is available at all 3 Mayo Clinic sites. Patient rooms are hard-wired with ceiling cameras for 24-hour behavioral observation and continuous EEG monitoring via external or intracranial EEG leads (eg, subdural grid or implanted depth electrodes). Other functions such as heart rate and blood pressure may be monitored as well. Monitoring may take anywhere from 24

hours to several days, depending on the number of seizures recorded in a given period of time. Patients are typically monitored long enough to capture at least 3 seizures. Digital recording allows analysis of the EEG record in a number of formats.

Upgrading Epilepsy Monitoring

Over the past few years, each Mayo Clinic campus has upgraded monitoring capacity to meet demand and improve patient experience. Mayo Clinic Arizona has expanded monitoring to 6 beds, admitting approximately 250 patients a year. Mayo Clinic Jacksonville will expand its monitoring capacity from 3 to 5 beds when the new hospital opens in April 2008. Currently, St. Luke's Hospital at Mayo Clinic Jacksonville admits approximately 120 patients per year. With 8 adult and 3 pediatric beds and the capacity to monitor in the neurology intensive care unit (ICU), Mayo Clinic Rochester can now monitor 12 patients at any one time

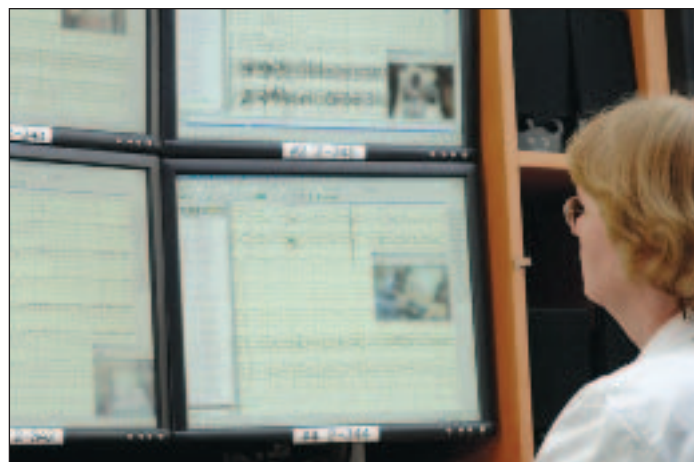


Figure. Inpatient video-EEG monitoring unit at Mayo Clinic in Rochester. Continuous behavioral and EEG monitoring helps localize seizure focus, determine seizure type, and quantify the number of seizures.

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(Figure). Adult epilepsy and pediatric epilepsy experts staff the respective monitoring units. In 2006, the Rochester units admitted 755 patients, including 236 children and 404 adults, and monitored an additional 115 patients in the ICU.

The real measure of success is not how well a patient is monitored, says Gregory D. Cascino, MD, chair of Mayo Clinic's Division of Epilepsy, Department of Neurology, "but whether we can help patients become seizure-free or characterize clinical spells that are not epileptogenic." He likes the term "epilepsy monitoring" because at Mayo Clinic, the EEG is only one of several diagnostic tools used in the monitoring units. For example, psychiatry and dedicated neuropsychology colleagues may be on site to evaluate cognitive function and mental health of patients admitted to the monitoring unit at all Mayo Clinic campuses. Other studies, particularly for patients being considered for surgical intervention, may include a speech-language evaluation and cerebral arteriography with an intracarotid sodium amobarbital test.

Cognitive status and orientation are also monitored by nurses during and immediately after seizures. The degree of patient orientation helps establish the depth and extent of the seizure.

Imaging studies using SISCOM are another aspect of inpatient epilepsy monitoring at Mayo Clinic. SISCOM stands for subtraction ictal single-photon emission computed tomography (SPECT) coregistered to MRI. Developed at Mayo Clinic, SISCOM fuses the MRI image with the SPECT image. This recent innovation is particularly useful for localizing seizure focus in patients with intractable partial epilepsy whose MRI studies are normal. The radioactive tracer is injected by nurses immediately after a seizure. The first imaging study is performed as soon as possible and the second study within 24 hours.

Improving Diagnosis and Seizure Control

Epilepsy occurs in approximately 1% of the US population, and the elderly have one of the highest incidences of seizures and epilepsy. Joseph I. Sirven, MD, head of the epilepsy program at Mayo Clinic Arizona, notes, "Seizures are sometimes confused with dementia, cardiac-related problems, transient ischemic attack, or other conditions of the elderly, so these patients may be under- or misdiagnosed. Seizures are considered a disease of the

young, but a large portion, about one-quarter of the patients we see, are elderly."

Up to 20% of patients who are referred to comprehensive epilepsy programs with a diagnosis of intractable seizures do not have epilepsy. Jerry J. Shih, MD, head of Mayo Clinic



Jerry J. Shih, MD

Jacksonville's epilepsy program, notes that particularly in the elderly, cardiac arrhythmia and vasovagal syncope may be confused with epilepsy. He explains, "Sometimes on passing out, patients with these conditions may jerk a bit or have some urinary incontinence and be somewhat disoriented when they regain consciousness. They may be given a diagnosis of seizure disorder and started on medications. Once a patient has that diagnosis, considering other diagnostic possibilities may be difficult." Video-EEG monitoring helps not only to rule out epilepsy, but also to establish the accurate diagnosis.

Inpatient video-EEG monitoring has been shown to detect previously undiagnosed seizures in up to 20% of monitored patients. As a precision tool for classifying and characterizing seizure type, it helps determine the best type of medication for the patient. In candidates for surgery, it can aid in establishing seizure locus, especially when combined with SISCOM imaging. Finally, video-EEG monitoring has been shown to improve seizure control in as many as 60% to 70% of patients.

Conditions With Symptoms That May Be Confused With Epilepsy

- Anxiety disorders
- Behavioral spells
- Autonomic disorders
- Cardiac arrhythmias
- Cerebrovascular disease
- Drug toxicity
- Migraine
- Mood disorders
- Orthostatic hypotension
- Panic attacks
- Transient ischemic attack
- Tremor
- Valvular heart disease
- Vasovagal syncope
- Vestibular disorders

Stereotactic Radiosurgery: A Noninvasive Option

Mayo Clinic has performed radiosurgery in Rochester since 1990. With nearly 4,000 patients treated to date, it has one of the busiest radiosurgery practices in the world. All 3 Mayo campuses offer stereotactic radiosurgery, and the treatment teams include neurosurgeons, radiation oncologists, and medical physicists with specialized training in radiosurgical case management. Patients range in age from toddlers to the elderly.

Stereotactic radiosurgery is the single-session, focused delivery of radiation to an image-defined intracranial target. Used as an alternative to or in conjunction with traditional neurosurgery, radiosurgery is an excellent noninvasive option for a number of conditions (see sidebar on page 4).

Distinguishing Radiosurgery From Radiotherapy

Radiosurgery is sometimes confused with radiotherapy. Both deliver radiation but use different mechanisms and dosing regimens to minimize the chance of radiation damage to healthy tissue. Radiotherapy delivers low doses of radiation over time in multiple treatment sessions. Radiosurgery delivers radiation in highly conformal dose plans with steep fall-off. This allows safe delivery of higher doses of radiation so that the entire dose is administered in a single session. For some patients, such as those with large arteriovenous malformations or large skull base tumors, radiosurgery may be performed in multiple sessions over several months. In such cases, the target is divided into



Michael J. Link, MD, and Bruce E. Pollock, MD

several smaller targets, each of which is addressed with the same total high-radiation dose, but in separate sessions until the radiation coverage is complete.

Expanding Radiosurgery Practice

At the Mayo Clinic campuses in Arizona and Florida, radiosurgery is conducted using a linear accelerator with an image-guided targeting system that allows the delivery of focal radiation as either a single, 1-time dose or a hypofractionated regimen (1 time per day for 5 days). The radiation source moves around the patient.

At Mayo Clinic Rochester, the Gamma Knife (Elekta Instrument AB, Stockholm, Sweden) is used. Beams of radiation are delivered through holes in a collimator unit or helmet. The beams are arranged in a circular array and converge on a central target. The radiation source remains stationary, and the patient is positioned to accommodate radiation delivery. The Rochester campus has expanded its practice in stereotactic radiosurgery with the acquisition of new equipment that will open radiosurgery to new applications.

The next generation of Gamma Knife, called the Leksell Gamma Knife Perfexion, was installed at the Rochester campus in September 2007 (Figure). It expands Mayo Clinic's radiosurgery practice to include treatment of head and neck cancers as well as ocular disorders (neoplasms and macular degeneration), peripheral skull base carcinomas, and tumors of the upper cervical spine. The new instrument increases accuracy and precision in radiation delivery, improves patient comfort, and reduces treatment time up to 60%.

Discussing the new Gamma Knife, Bruce E. Pollock, MD, a Mayo neurosurgeon says, "Unlike all linear accelerator-based radiosurgery in which the radiation source moves around the patient, with Gamma Knife radiosurgery, the patient moves relative to the radiation source. This design feature remains the same in the Perfexion, but the

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Figure. The next-generation Gamma Knife was installed at the Rochester campus in September 2007.

new model automates patient position adjustments, saving time and reducing the chance of human error. In addition, because the unit itself is larger, we are able to treat a wider range of head and neck disorders.”

His neurosurgical colleague, Michael J. Link, MD, adds, “Gamma Knife has been a great tool for neurosurgery and neuroscience at Mayo Clinic. The new model will expand our practice to include paragangliomas (glomus tumors), more meningiomas and schwannomas, and tumors of the skull base and spine. It will allow us to increase the number of patients treated for brain metastases.” The new model uses a robotic system to improve the reach of the radiation beams without repositioning the headframe, changing helmets, and performing additional imaging studies. “It gives us more freedom to treat lesions on the periphery of the brain or skull base and to treat multiple tumors without the need to reapply the headframe and reimage the patient,” explains Dr Link.

Radiosurgery is the fastest growing neurosurgical subspecialty at Mayo Clinic, with the majority of cases presenting with brain metastases. For benign tumors such as vestibular schwannomas (acoustic neuromas), meningiomas, and pituitary adenomas, tumor control is achieved in more than 95% of treated patients. Since the inception of the program in 1990, Mayo Clinic has maintained a continuous database of all the patients having radiosurgery, including patient characteristics, radiosurgical dosimetry, and outcomes. As Dr Pollock notes, “We are proud to have contributed to the science and practice of radiosurgery over the past 2 decades. The database has been an important addition to the practice of not only neurosurgery, but also radiation oncology. At Mayo Clinic, we value the shared expertise and interdis-

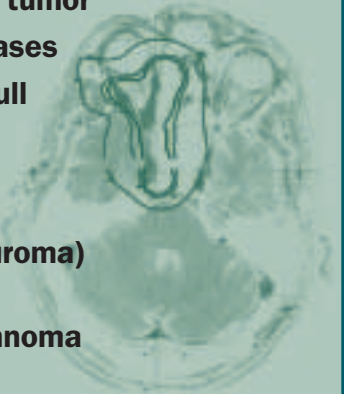
ciplinary integration.”

Cooperation extends throughout the team. As Dr Pollock says, “Our nurses work like patient caseworkers, each one assigned to a given patient. Our nurses are enthusiastic and experts in keeping patients comfortable. The colorful notes of thanks from patients on the corkboard in the waiting area are not in the database but are a valued testament to the care patients receive.”

The entire team is looking forward to the new equipment—to improved patient comfort, shorter treatment sessions, and the opportunity to offer treatment to patients with conditions not previously addressed by radiosurgery.

Conditions Commonly Treated With Stereotactic Radiosurgery

- Arteriovenous malformation
- Dural arteriovenous fistula
- Primary brain tumor
- Brain metastases
- Malignant skull base tumor
- Vestibular schwannoma (acoustic neuroma)
- Other cranial nerve schwannoma
- Meningioma
- Pituitary adenoma

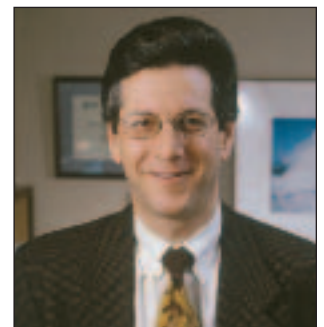


Parkinson Disease: Pathways to Prevention

Mayo Clinic researchers are changing concepts about the molecular basis for Parkinson disease (PD) and generating new ways of identifying those at risk before the disease strikes.

Risk detection is only part of the story. As Demetrius (Jim) M. Maraganore, MD, a Mayo Clinic Rochester neurologist, says, “We’re developing methods at Mayo that not only predict but also prevent the disease.” Charles H. Adler, MD, PhD, a neurologist at Mayo Clinic Arizona and chair of the Division of Movement Disorders across Mayo’s 3 sites, adds, “By the time someone devel-

ops the classic signs of PD, we know that anywhere from 60% to 80% of their dopamine-producing nerve cells have degenerated. If we can identify individuals at risk before they develop clinical signs, we might be able to intervene to



Charles H. Adler, MD, PhD



Demetrius (Jim) M.
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prevent the disease or slow its progression.”

PD is the second most common degenerative disease of the nervous system after Alzheimer disease. Dopaminergic therapies can reduce tremor, rigidity, and bradykinesia but cannot prevent disease progression. As PD progresses, drug doses often must

be increased, elevating the risk of debilitating adverse effects. Deep brain stimulation in appropriately selected patients can reduce the need for medication, but neither surgical procedures nor dopaminergic drugs address the nonmotor complications of PD (see sidebar). Physicians know that despite their best efforts to provide quality care, their patients’ condition continues to deteriorate, year after year.

Across its Arizona, Florida, and Minnesota campuses, Mayo Clinic’s integrated research in genetics and predictive biomarkers of PD is generating new possibilities for early detection and intervention, and, ultimately, for prevention. Some recent findings are reviewed below.

New Findings in the Molecular Mechanisms of PD

Like many complex diseases, PD does not have a single cause. Rare gene mutations account for about 10% of cases (familial PD). In the other 90% of cases (sporadic PD), multiple genetic and environmental factors combine to influence risk, age of onset, severity, and disease course. Uncovering the genetic factors contributing to PD has provided an understanding of disease mechanisms and insights to disease prevention.

Findings From Single Genes

Although causal gene mutations are rare, as Zbigniew K. Wszolek, MD, notes, “Each gene discovery helps us understand the mechanism of the disease and identify potential drug targets. Rare gene mutations uncover a cell’s dysfunction, and if you understand that, you can begin to envision possible treatments to remedy that dysfunction.” Dr Wszolek is a neurologist and clinical director of the Morris K. Udall Parkinson’s Disease Research Center of Excellence at Mayo Clinic Jacksonville. For the past 20 years, he and his colleagues have been on the hunt for genes that cause PD in families.

Ten years ago, Mayo Clinic was instrumental in the discovery of mutations in the *MAPT* gene (formerly known as the *tau* gene) as a cause of familial frontotemporal dementia. Common variations in

The 4 Cardinal Signs of PD

- Resting tremor
- Bradykinesia
- Rigidity
- Postural instability

Additional Features

- Asymmetry and favorable response to levodopa therapy
- Nonmotor complications that are not controlled by dopaminergic therapy
- Dementia
- Depression
- Dysautonomia
- Sleep disturbance



the *MAPT* gene have since been associated with PD. Two years ago, in collaboration with an international team, Dr Wszolek, Matthew J. Farrer, PhD, director of the Genetic Core of the Udall Center, and their colleagues identified mutations in the *LRRK2* (leucine-rich repeat kinase 2) gene as a cause of PD in approximately 2% of sporadic cases and in 10% to 40% of familial cases, accounting for as many as 20,000 of the 1 million PD cases in the United States. Kinase-inhibiting drugs, developed previously, are now being investigated as a preventive treatment in mutation carriers. *LRRK2* mutations may have much to tell us about sporadic as well as familial cases of PD. Such was the case with the *SNCA* (alpha-synuclein) gene.

The Alpha-Synuclein Story—From Identification to Intervention

The initial gene mutations in the *SNCA* gene were reported by scientists at the National Institutes of Health in 1997, but the mechanism by which the mutations contributed to PD was unclear. In 2003, collaborative work across Mayo’s 3 sites found that the cause of PD in an Iowa family, the Spellman-Muenter kindred, which



Zbigniew K. Wszolek, MD

had been studied for more than 80 years, was a multiplication mutation of the *SNCA* gene, resulting in overproduction of the alpha-synuclein protein. The Mayo discovery solidified evidence that elevated levels of alpha-synuclein play a key role in all cases of PD. Alpha-synuclein is the primary protein constituent in Lewy bodies, the neuronal cytoplasmic inclusions that are the pathologic hallmark of PD. While the mutations as seen in the Iowa family are rare, Dr Maraganore, Dr Farrer, and their international collaborators demonstrated that common variations in the *SNCA* gene predispose to PD, via the same mechanism of overexpression of the gene, across populations worldwide.

In light of these discoveries, researchers at Mayo Clinic, led by Drs Farrer and Maraganore, are working with a pharmaceutical company to develop a therapy to reduce alpha-synuclein levels via the synthesis and delivery of small ribonucleic acid compounds that interfere with the transcription of the gene in targeted tissues (RNAi therapy). The team has demonstrated efficacy of the therapy in cultured cells, laboratory mice, and primates. Dr Maraganore believes they are only a few years away from US Food and Drug Administration approval for a phase 1 clinical trial and states that the therapy “may benefit not just rare families with PD, but any patient with or at risk for PD worldwide.”

Common Gene Variants in the Population: Findings From Whole Genome Studies

Because rare gene mutations cause only a small fraction of PD as it occurs in the general population, Dr Maraganore and Mayo Clinic colleagues, including biostatistician Timothy G. Lesnick, MS, have been studying common gene variants called “single nucleotide polymorphisms” (SNPs), across the entire human genome. Their whole genome association study was the first of its kind for any neurologic disorder and provided an unbiased look at the entire genome for common genetic factors predisposing to PD. High-throughput technology made such an endeavor possible. By 2005, a total of 200 million genetic tests had been completed on 1,550 individuals—half with PD and half without PD.

Twelve gene variations or genetic loci were highlighted by the genome association study. The most important finding was related to a gene called *SEMA5A* (semaphorin 5A). Remarkably, it mapped to the cri du chat region of the genome. Cri du chat syndrome is a classic genetic disorder of brain development. What did it have to do with PD? Dr Maraganore and his team inferred from the *SEMA5A* gene’s association with cri du chat syn-

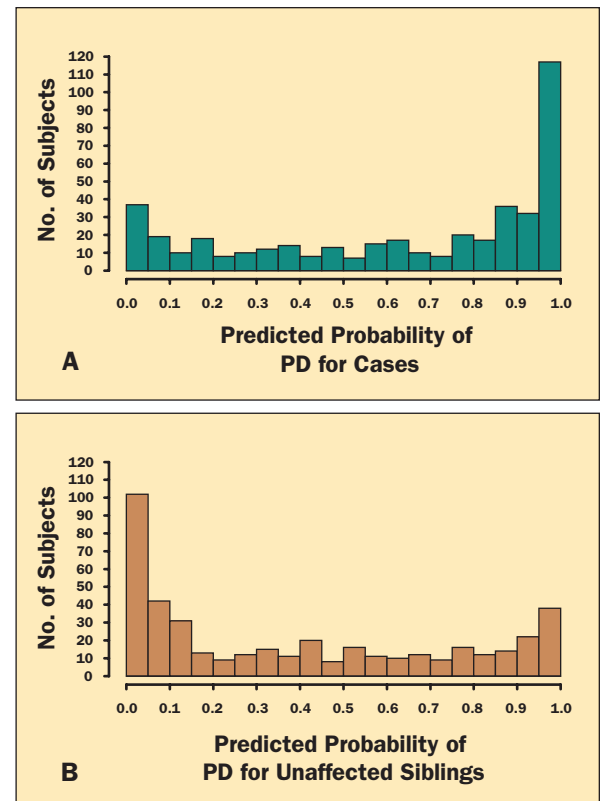


Figure 1. Axon guidance pathway models predict PD susceptibility. Bar charts show predicted probabilities of PD in cases (A) and unaffected siblings (B). A perfect fit would have all predicted probabilities for cases equal to 1 and all predicted probabilities for unaffected siblings equal to 0. A model with no explanatory value would have histograms that were indistinguishable.

drome that the gene is critical to a number of processes, including neurogenesis, and this led them to study the axon guidance pathway.

The Axon Guidance Pathway and PD: A Shift From Single Genes to Genomic Pathways

The axon guidance pathway guides axons from cell bodies to their target destinations via a complex array of chemical signals. Semaphorin 5A repels axons so that, for example, axons that should normally ascend ipsilaterally are prevented from crossing contralaterally.

At least 128 proteins contribute to the complex outgrowth, repulsion, and attraction of axons and constitute the axon guidance pathway. The same proteins also maintain and repair axons across the life-span. By looking at all the genes in this common biologic pathway, rather than at individual, unrelated genes or simple gene combinations, the Rochester team identified a constellation of common gene variations (SNPs) that can make people 90 times more susceptible to PD. Importantly, their findings explained as much as 70% of the cause of

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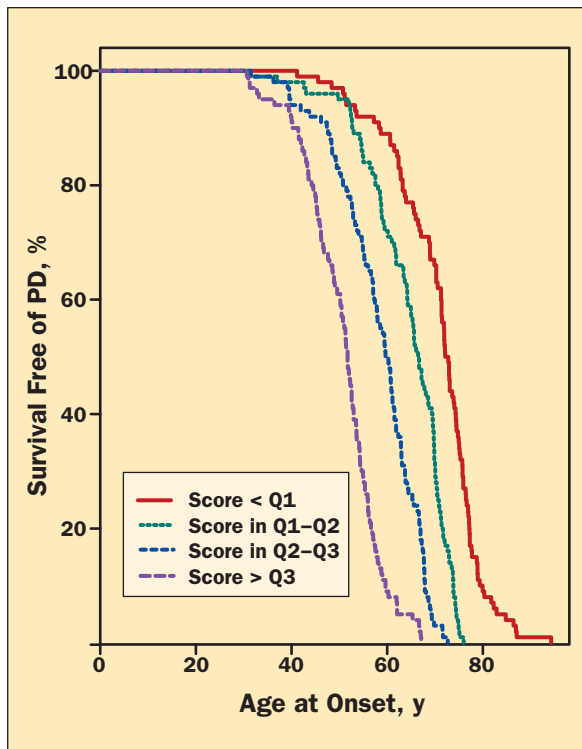


Figure 2. Survival free of PD. Categorized risk scores from a proportional hazards model are presented. The model clearly differentiates between cases with early age at onset and those with late age at onset. Cases generating the long-dashed (purple) line were predicted to be at highest risk for early onset of PD, followed by the medium-dashed (blue), short-dashed (green), and continuous (red) lines, respectively. Since only cases were included, all the lines end at 0% surviving free of PD. Q1 refers to the first quartile risk (25th percentile), Q2 refers to the second quartile risk (50th percentile, or median), and Q3 refers to the third quartile risk (75th percentile). The risks are determined by the hazards ratio (Cox proportional hazards model).

PD within the several hundred subjects that they studied. Not only were they able to predict who would get PD, but at what age they would have symptom onset (Figures 1-3; reprinted from Lesnick TG, Papapetropoulos S, Mash DC, et al. A genomic pathway approach to a complex disease: axon guidance and Parkinson disease. *PLoS Genetics* Vol. 3, No. 6, e98 doi:10.1371/journal.pgen.0030098). They are now planning brain imaging studies of the anatomy of axon tracts in a sample of their subjects with and without PD, and with and without the high-risk axon guidance pathway genetic trait.

Dr Maraganore speculates that their axon guidance pathway findings may shift the focus of environmental research in PD from late adulthood to fetal development; perhaps maternal health and fetal exposures influence brain wiring and contribute to PD decades later. He also notes that their

axon guidance pathway discoveries may share a common disease mechanism with alpha-synuclein, a protein that is important in synapse formation and axonal sprouting and repair.

The focus on genomic pathways rather than single genes represents a shift in the study of complex disease. In fact, it is possible that a large number of neurologic conditions may be related to gene variations in the axon guidance pathway. Dr Maraganore and his team are pursuing additional breakthroughs.

Early Detection: Biometric Tests of PD

In addition to predictive genetic tests, the team of PD researchers at Mayo Clinic in Arizona is developing biometric tests to detect PD before its cardinal symptoms and signs emerge.

Mayo Clinic Arizona is part of a 6-institution consortium, led by Dr Adler, studying a cohort of elderly individuals that includes 800 living subjects and 950 subjects who have come to autopsy. These individuals are part of the Brain and Body Donation Program at Sun Health Research Institute. The study subjects undergo extensive screening that includes annual physical examination, neuropsychological testing, and laboratory blood work, as well as screening measures of olfaction, bowel motility, autonomic dysfunction, and sleep disorders. The Arizona group is also develop-

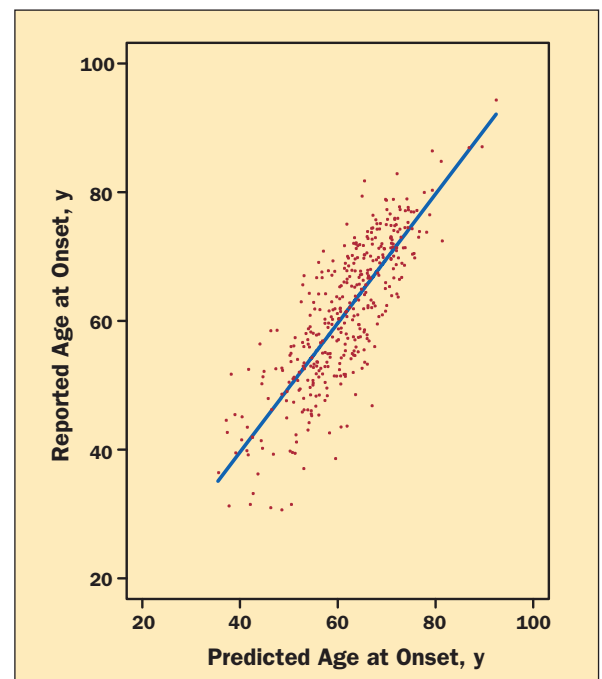


Figure 3. PD predicted and reported age at onset. Points indicate reported individual values, and the blue line represents perfect agreement. The fairly tight elliptical pattern of points reflects a good fit and high correlation. The fit appears equally good from the minimum to maximum reported age at onset.

