Innovative imaging technology effectively measures disease severity in rare neurodegenerative disorder

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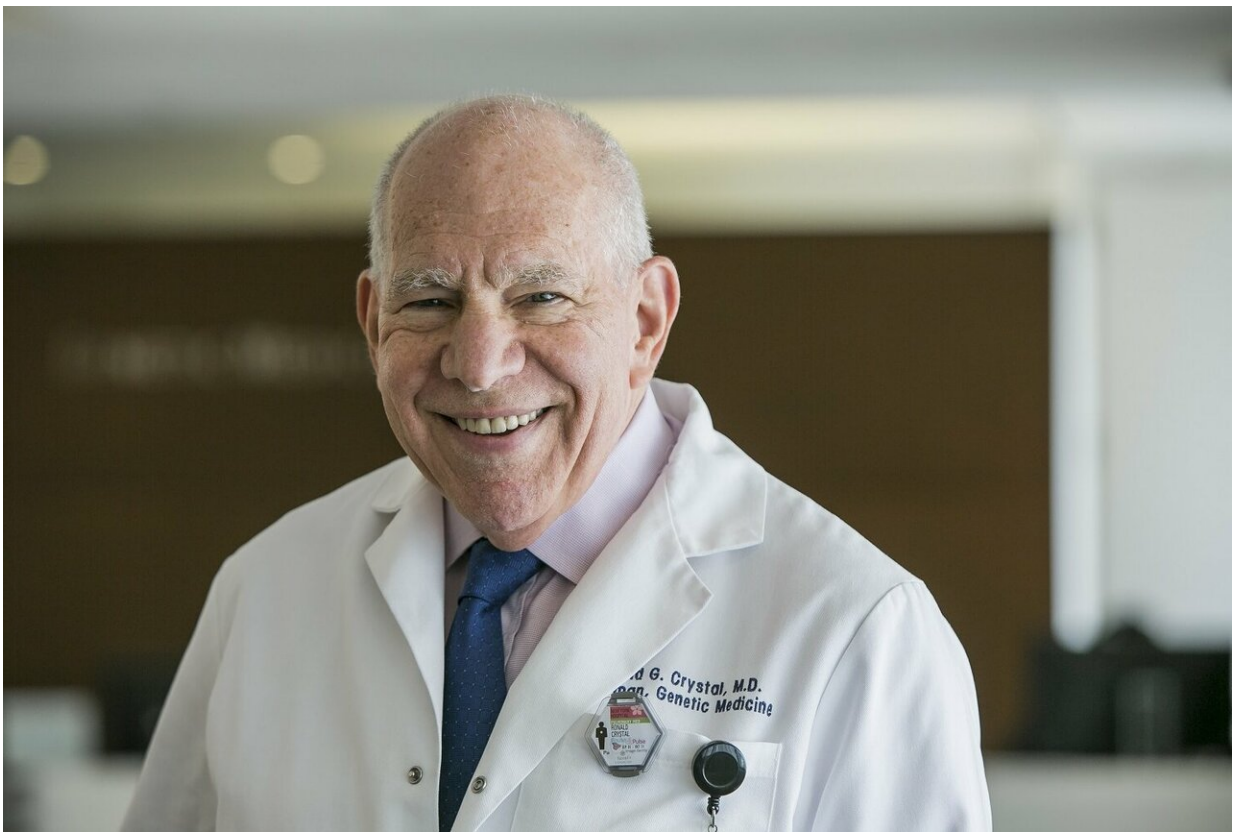

Dr. Ronald Crystal. Credit: Jesse Winter

A rapid, non-invasive eye exam that uses innovative imaging technology effectively measures the severity of disease in patients with a rare

neurodegenerative disease called Friedrich ataxia, according to a study by Weill Cornell Medicine, Weill Cornell Medicine-Qatar and NewYork-Presbyterian researchers. The results suggest that the exam, known as corneal confocal microscopy (CCM), could be a rapid and sensitive tool for assessing patients in the clinic and act as a biomarker in clinical trials testing new therapies for the disease.

The paper, published in the Dec. 21 issue of the *Annals of Neurology* and online Oct. 7, provides compelling evidence for using CCM to assess the degeneration of corneal nerves in patients with Friedrich ataxia, a disease that affects the nervous system and causes increasing muscle movement problems, immobility and premature death. CCM produces high-resolution images of thin layers of corneal tissue, allowing investigators to measure nerve fiber density, length and branch density. The test takes a few minutes and requires a couple of drops of anesthetic in each eye before the pictures are taken. By contrast, current clinical assessments involve a series of evaluations to assess muscle movement and neurological performance and take much longer to complete.

"The corneal nerves are a window into the health of the nervous system," said senior author Dr. Ronald Crystal, chairman of the Department of Genetic Medicine and the Bruce Webster Professor of Internal Medicine at Weill Cornell Medicine. Dr. Crystal is a paid consultant for Adverum, a biotechnology company that partially supported this study. "The fact that our results align so well with the gold standard clinical evaluation tools, the Friedrich's Ataxia Rating Scale (FARS) and the Scale for the Assessment and Rating of Ataxia (SARA) and the underlying genetics provides strong evidence that CCM is an efficient and accurate tool we should add to our diagnostic techniques."

Friedrich ataxia affects an estimated one in 50,000 people in the Caucasian population, with onset typically beginning between the ages of 10 and 15. It is an inherited autosomal recessive disorder, meaning that a

person must inherit two abnormal frataxin genes, one from each parent, to develop the disease. This genetic abnormality causes increasingly impaired muscle coordination over time. Those diagnosed with the disorder typically require a wheelchair about 10 years after signs and symptoms appear, and most die in their late 30s. The symptoms include the loss of coordination of gait, hand, and eye movements, slurred speech, uneven weakness in muscles of the limbs, sensory loss, wasting of the optic nerve, abnormal thickening of the heart muscle, and diabetes. The disease is diagnosed through clinical and neurologic evaluations, followed by genetic testing.

For the study, Dr. Crystal, who is also a pulmonologist at NewYork-Presbyterian/Weill Cornell Medical Center, and colleagues at Weill Cornell Medicine, including lead author Dr. Odelya Pagovich in New York and co-senior investigator Dr. Rayaz Malik in Qatar, a pioneer of CCM, used the technology to examine the corneal nerves of 23 patients with Friedrich ataxia and 16 people without the disease. Patients with Friedrich ataxia had a significantly lower number of nerve fibers and shorter nerve lengths compared with people without the disorder.

The researchers compared the CCM test results with data from the current clinical assessment tools and genetic testing. The CCM results correlated with disease severity, age of disease onset and diagnosis, FARS and SARA scores, and genetic test results. For six of the 23 patients with Friedrich ataxia who were still ambulatory, the CCM results also correlated with gait abnormalities observed in walking tests. The strong correlation with existing assessment tools suggests that CCM could act as an accurate biomarker for the disease.

Currently, there are no available treatments for Friedrich ataxia. Recently, however, biotechnology companies have been testing experimental therapies in early-stage clinical trials and evaluating patients' responses with standard clinical assessments. Integrating CCM

as a biomarker into future clinical trials could help researchers identify responders more quickly, optimize doses, and save valuable time in the drug development pipeline.

"As a rapid, non-invasive diagnostic test, CCM may serve as an effective therapeutic endpoint for measuring outcomes in future studies for Friedrich ataxia and potentially other neurological diseases such as Alzheimer's disease," Dr. Crystal said.

More information: Odelya E. Pagovich et al. Corneal confocal microscopy: Neurologic disease biomarker in Friedreich ataxia, *Annals of Neurology* (2018). DOI: 10.1002/ana.25355

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