



BRIGHAM AND
WOMEN'S HOSPITAL

NEUROLOGY AND NEUROSURGERY ADVANCES

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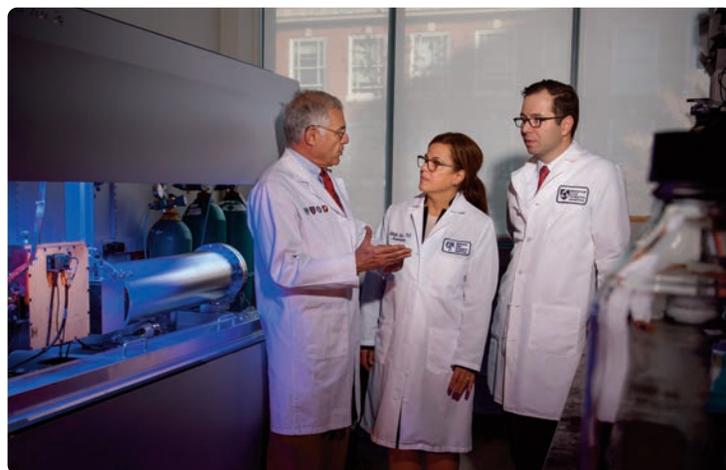
New Visualization Technique Delineates Pituitary Adenomas for Precise Surgical Resection and Preservation of the Pituitary Gland

In the Surgical Molecular Imaging Laboratory at Brigham and Women's Hospital (BWH), led by Nathalie Agar, PhD, researchers have developed a new visualization technique using matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI) to aid neurosurgeons in delineating small pituitary tumors.

Clinical Need Drives Innovation

Microadenomas, including many associated with Cushing syndrome, are often not visible on preoperative magnetic resonance imaging (MRI), making exact location difficult. In addition, discriminating pituitary tumor from normal pituitary gland to define the boundaries of these tumors during surgery, even with advanced intraoperative imaging tools, is extremely challenging. Current methods to detect hormone levels do not fit the time restraints of surgery.

"The result can be incomplete resection or the removal of normal pituitary tissue," said Edward R. Laws, MD, surgical director of the Pituitary and Neuroendocrine Center at BWH. "Our goal in each patient's case is to completely remove the tumor while preserving function of the pituitary gland, so we have a real clinical need to address these issues."



Neurosurgeon Edward R. Laws, MD (*left*) – with Nathalie Agar, PhD (*center*) and Sandro Santagata, MD, PhD (*right*) of the Surgical Molecular Imaging Laboratory at BWH – employs a new technique developed by researchers in the laboratory that uses MALDI MSI to aid in delineating small pituitary tumors.

Examining Large Molecules

Dr. Laws, Dr. Agar, and BWH neuropathologist Sandro Santagata, MD, PhD, collaborated with a team in the Surgical Molecular Imaging Laboratory to develop a test designed to assess the distribution of pituitary hormones, including prolactin, growth hormone, adrenocorticotrophic hormone, and thyroid stimulating hormone levels in pituitary tissue.

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New Visualization Technique Delineates Pituitary Adenomas for Precise Surgical Resection and Preservation of the Pituitary Gland...

continued from front cover

"We have been studying mass spectrometry-based techniques that evaluate smaller molecules for use during the surgical resection of other brain tumor types and have demonstrated the tests' clinical usefulness," said Dr. Agar. "Our team developed this test to analyze much larger molecules with very high specificity in order to visualize the hormone levels found in pituitary tumors, as compared with normal pituitary tissue."

In a proof of concept study published in August 2015 (*Proc Natl Acad Sci U S A.* 2015 Aug 11;112(32):9978-83.), they analyzed six non-pathological (NP) human pituitary glands and 45 hormone secreting and non-secreting (NS) human pituitary adenomas using MALDI MSI. The team found that it is possible to determine the peptide and protein hormone composition of pituitary tumor resection samples in less than 30 minutes, making it feasible to use the test for near-real-time detection and delineation of pituitary tumors for intraoperative surgical decision making. The team anticipates beginning clinical study of the new test within the year among patients undergoing surgery for small pituitary tumors.

Expert Evaluation and Treatment

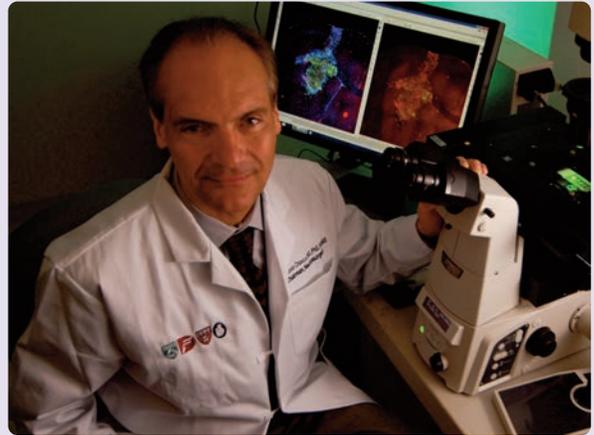
A multidisciplinary team in the Pituitary and Neuroendocrine Center at BWH, including neuroendocrinologists, neurosurgeons, neurologists, neuro-radiologists, neuro-ophthalmologists, neuropathologists, radiation oncologists, neuro-oncologists, psychiatrists, and others, delivers expert evaluation and treatment for hundreds of patients each year. Throughout his career, Dr. Laws has performed nearly 6,000 pituitary procedures and has pioneered new approaches designed to preserve the pituitary gland. An early adopter of the 3D endoscope, Dr. Laws has performed more than 600 3D endoscopic transsphenoidal pituitary procedures with preservation of the pituitary gland in more than 96 percent of patients.



Nathalie Agar, PhD
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E. Antonio Chiocca, MD, PhD, FAANS, Elected President of the Society for Neuro-oncology

E. Antonio Chiocca, MD, PhD, FAANS, chair of the Department of Neurosurgery and co-director of the Institute for the Neurosciences at Brigham and Women's Hospital, has been elected president of the Society for Neuro-oncology for a two-year term (2015-2017).

Dr. Chiocca's research interests include glioblastoma; the role of microRNAs in the process of a tumor's growth and invasion of the brain; and how medications can be used to stop tumor cells from metastasizing and migrating throughout the brain.

The Harvey W. Cushing Professor of Neurosurgery at Harvard Medical School, Dr. Chiocca was also recently selected as part of Newsweek Health's 2015 list of Top Cancer Doctors in the U.S.

Access to our Neurology and Neurosurgery Services

At Brigham and Women's Hospital, our specialists are available for timely consultations and will work with you to develop treatment plans for your patients. Our Physician Liaison Tom Anderson can provide direct assistance with patient referrals and consultations. Tom can be reached at (617) 582-4760 or tanderson0@partners.org.

Novel Multiple Sclerosis Studies Define Predictors of Prognosis to Personalize Treatment for Patients

Neurologists at Brigham and Women's Hospital (BWH) are using data captured by devices (such as sensors and smartphones), biologic profiling, clinical imaging, and neurologic examinations, in research studies designed to pinpoint factors that may determine an individual's course of disease and to tailor treatment options that have not been previously available to patients.

"Our goal is to individualize care for each MS patient, but we don't currently have any reliable way to predict which patients will respond to a specific treatment, as well as which patients have disease that will progress quickly and requires aggressive therapy," said Howard L. Weiner, MD, Director of the Partners Multiple Sclerosis Center and Co-director of the Ann Romney Center for Neurologic Diseases at BWH. "By compiling vast amounts of new information, combined with existing data from our ongoing studies, we are developing a deep phenotyping of the MS patient, enabling us to gain an understanding of this disease in a way that we've never been able to achieve in the past."

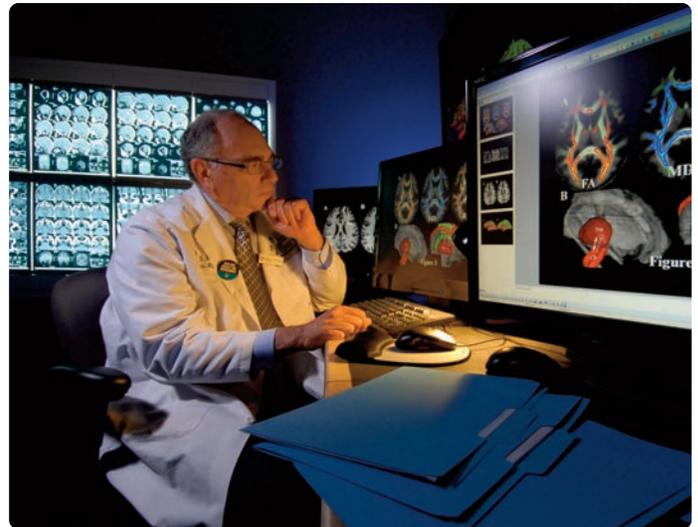
Collaboration Uses Wearables to Enable Robust Measurements

Dr. Weiner and BWH neurologist Tanuja Chitnis, MD, are principal investigators of the SysteMS study, collaborating with experts at Google and Biogen to determine new biologic, physiological, environmental, and behavioral factors that influence a patient's experience with MS as the disease progresses. This study of 2,000 MS patients incorporates details related to physical and neurological examinations, magnetic resonance imaging (MRI), and molecular assays, along with data generated by wearable miniaturized sensors designed by Google to continuously measure patients' movement, activity, and vital signs. Biologic profiling includes genetic information, immune activity, and other information derived from blood, urine, saliva, and stool samples. Multidimensional analysis of the datasets will be performed using a customized platform designed by the life sciences team at Google to identify factors associated with disease severity and progression. Researchers at Biogen will help to test new hypotheses and provide rapid feedback to quickly advance new findings.

"A great benefit from this study is being able to start an individual MS patient with the most effective therapy from the very beginning of the treatment for the disease, eliminating a lot of the trial and error that comes with the wide range of medications for MS," said Dr. Chitnis.

Feasibility Demonstrated in Study in Use of Smartphone Platform

A recent one-year smartphone study in MS, led by BWH neurologist Philip De Jager, MD, PhD, studied 38 participant pairs



BWH neurologist Howard L. Weiner, MD, Director of the Partners Multiple Sclerosis Center, is leading a team of researchers that is investigating the use of data captured by devices, biologic profiling, clinical imaging, and neurologic examinations to tailor treatment options for multiple sclerosis.

(MS and cohabitant) between 18 and 55 years-of-age. Illustrating several novel features of a smartphone platform, the study demonstrated the feasibility of utilizing a smartphone platform to gather useful passive and active performance data at high frequency in an unstructured manner in the field. The study was recently accepted for publication in *Neurology* and will appear in 2016.

"The daily capture of a participants' functioning in their own home environments offers us the ability to assess the participant's average performance the course of the year, as well as look at other study aspects, such as response accuracy and speed," said Dr. De Jager.



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NEUROLOGY AND NEUROSURGERY NEWS

Research Team Uncovers Mechanism Underlying Familial Alzheimer's Disease

Jie Shen, PhD, who leads the Alzheimer's and Parkinson's disease research in the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital (BWH), and her team have spent decades studying the function of presenilin genes and the effects of mutations in these genes in the development of Alzheimer's disease.

The Presenilin Hypothesis

Dr. Shen's earlier investigations brought into question widely held beliefs that presenilin mutations increase presenilin and gamma secretase activity, leading to the overproduction of beta-amyloid. She found that genetically suppressing presenilin and gamma secretase activity in pre-clinical models caused Alzheimer's-like neurodegeneration. In 2007, she published a paper in *PNAS*, together with a colleague at Massachusetts General Hospital, describing a theory that a loss of presenilin function may be the primary cause of neurodegeneration and dementia in familial Alzheimer's disease (FAD).

Specially-designed Models

For their most recent study, the team generated pre-clinical models with FAD-associated presenilin-1 mutations knocked in to the gene, representing how they are expressed in human patients with the particular mutation (*Neuron*. 2015 Mar 4;85(5):967-81.). The mutations included one that is common among patients with FAD, and one that is rare among FAD pa-

tients. The models in which a single presenilin-1 gene was mutated showed deficiencies in learning and memory compared with control models.

Result of the Loss of Presenilin Function

Production of beta-amyloid within the brains of these models was reduced, however the ratio between the peptide forms was changed and proportionally more plaque-associated beta-amyloid 42 was generated. Examinations of the brains of the models with the FAD mutation showed the same synaptic dysfunction and age-associated neurodegeneration seen in the brains of patients with Alzheimer's disease.

"We were able to clearly show that the presenilin-1 mutations cause a loss of presenilin function and gamma secretase activity that result in neuron loss," said Dr. Shen. "From a clinical standpoint, the study suggests that strategies that enhance, rather than inhibit, gamma secretase should be investigated as potential therapies for patients with FAD."

Access and Information

For a consultation, more information on our neurologists and neurosurgeons, or to refer a patient, please call our helpful and experienced referral coordinators at (617) 732-9894 or email bwhreferrals@partners.org.



Reisa A. Sperling, MD, Receives \$100,000 Prize for Alzheimer's Research

Reisa A. Sperling, MD, director of the Center for Alzheimer's Research and Treatment at Brigham and Women's Hospital and professor of Neurology at Harvard Medical School, received the 2015 Potamkin Prize of \$100,000 for Research in Pick's, Alzheimer's, and Related Diseases from the American Academy of Neurology and the American Brain Foundation. The Potamkin Prize honors both Dr. Sperling and Peter Davis, PhD, of the Feinstein Institute for Medical Research, for their work in helping to advance the understanding of Alzheimer's. Dr. Sperling's research focuses on identifying the earliest Alzheimer's disease changes in the brain, even before any symptoms present themselves. She leads the A4 Study, an NIH funded clinical trial in over 1,000 clinically older individuals, which is aimed at preventing the memory loss of Alzheimer's disease.



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