



Mount
Sinai

Department of Otolaryngology

Head and Neck Surgery

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FEATURED STORY

**Tumor Invades;
Surgeons Do Not**

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Eric Genden, MD

Established in 1890 as one of the first ear, nose, and throat services in the country, Mount Sinai's Department of Otolaryngology – Head and Neck Surgery continues its innovative spirit in all facets of patient care, research, and education. This past year has been an exciting one, replete with accomplishments and groundbreaking endeavors.

Throughout 2016, our faculty challenged the boundaries of tumor cell dormancy, advanced immunotherapy for patients diagnosed with HPV-related oropharyngeal cancers via a clinical trial with Advaxis, and explored the role of extranodal extension (ENE) in small metastatic lymph nodes. We also forged the use of 3D technology for skull base surgery (Surgical Theater) and oral and maxillofacial surgery (Virtual Surgical Planning). And, Satish Govindaraj, MD, Chief of the Division of Rhinology and Skull Base Surgery and Vice Chair of Clinical Affairs, launched the first ever CME-accredited “On Demand” course on coursera.org, “Acute and Chronic Rhinosinusitis: A Comprehensive Review.”

Additionally, our faculty has expanded, and we have introduced the Mount Sinai Robotics Institute in conjunction with other departments at the Mount Sinai Health System. The Department of Otolaryngology – Head and Neck Surgery is home to the largest robotic surgery program for head and neck oncology in the nation, and we continuously research how to reduce complications and perfect this surgical technique. We also launched our second CME-accredited Coursera course in the fall – “HPV-Related Oral and Throat Cancer: What You Need to Know” – which teaches primary care physicians, otolaryngologists, other health care professionals, and patients the basics of the HPV epidemic and how to diagnose and treat HPV-associated oropharyngeal cancers.

Amid these achievements and this growth trajectory, each member of our team keeps in mind that listening to our patients and effectively communicating with our referring physicians remain indispensable tools, trumping any technology. We are unwavering in our commitment to our patients, faculty, and referring physicians and are excited about how technology, bench-to-bedside research, and training will propel this field of medicine into the near and distant future. ■

Cancer in Small Nodes

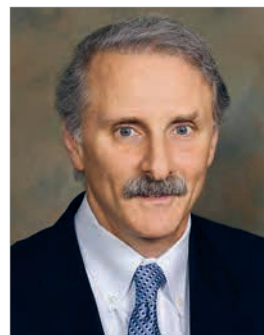
Study Questions Traditional Diagnostic Rule

A study by Mount Sinai researchers suggests that the traditional way of gauging the danger of thyroid cancer—based on the size of metastatic lymph nodes—may not be correct.

The researchers examined extranodal extension (ENE), an established prognostic indicator of more virulent disease in thyroid cancer patients. A common presumption in thyroid cancer management is that small-lymph-node metastases do not indicate aggressive disease, and that ENE occurs only in metastatic lymph nodes that have reached a critical size. However, a team of pathologists and researchers, led by Mark Urken, MD, Chief of the Division of Head and Neck Oncology at the Department of Otolaryngology – Head and Neck Surgery at Mount Sinai Beth Israel, found no previous studies that had investigated the relationship between the size of these lymph nodes and the presence of ENE. Our multidisciplinary research group conducted a retrospective study that compared the prevalence of ENE in metastatic nodes with the diameter of the node in order to clarify the relationship between metastatic lymph node diameter and the risk of ENE.

A thorough review of the pathology in 1,126 metastatic lymph nodes from 171 thyroid cancer patients who had been operated on by a single surgeon at Mount Sinai Beth Israel from 2004 to 2015 was conducted. We evaluated histological features that included primary tumor histopathology, number and size of metastatic lymph nodes, and the presence of ENE in each node. One hundred seventy-three (15.4 percent) of the 1,126 lymph nodes demonstrated ENE. Lymph nodes manifesting ENE ranged from 1.5 to 44.0 mm in size. Increased lymph node size had a statistically significant association with ENE status.

However, the results showed that a significant percentage of even small metastatic lymph nodes exhibited ENE. ENE had been previously established as a negative prognostic factor associated with further lymph node metastases, distant metastases, biochemically incomplete response to therapy, and higher rates of disease-related death. This study has prompted a reevaluation of protocols in the Department and nationally, and plans are under way for future studies to further elucidate the prognostic significance of small metastatic lymph nodes manifesting ENE relative to larger nodes with the same adverse feature. ■



*Mark Urken, MD,
Chief of the Division
of Head and Neck
Oncology at the
Department of
Otolaryngology – Head
and Neck Surgery at
Mount Sinai Beth Israel*



Alfred Marc Iloreta, MD, performs a transnasal endoscopic surgery to remove patient James O'Shaughnessy's trigeminal schwannoma.

Tumor Invades; Surgeons Do Not Technology Aids Removal of Complex Schwannoma

James O'Shaughnessy's journey to The Mount Sinai Hospital began with ear problems. He had a persistent sensation that his right ear was blocked with wax, but it did not get better. He went to Kevin Braat, MD, an ear, nose, and throat doctor at ENT and Allergy Associates, a Mount Sinai affiliate on Long Island, who said it looked like there was fluid trapped behind his eardrum. Dr. Braat placed a tube through the eardrum to drain the fluid in order to give James some relief, but suggested he obtain a referral from his primary care physician to a head and neck surgeon to further explore the issue.

"A couple of weeks later, I got hit in the head at the welding shop where I work," Mr. O'Shaughnessy says, "and I knew right away it was a severe concussion. The impact of the rod that hit me was so acute, it created swelling on my right temple. I went to a hospital where it was verified that I had a concussion, but they also said I had a trigeminal schwannoma located near the brain at the base of my skull."

The hospital advised Mr. O'Shaughnessy that it was not urgent to address the trigeminal schwannoma, so it wasn't until a few months later that he returned to Dr. Braat, who placed a more permanent stent in his ear and strongly suggested that he visit Eric Genden, MD, Chair of the Department of Otolaryngology – Head and Neck Surgery and Co-Director of the Skull Base Surgery Center at Mount Sinai.

"I met with Dr. Genden, who relayed to me that this type of tumor would never stop growing. He said the tumor was funneling out of the brain and into my sinus cavity, and the risk was that it could actually expand inside my brain," Mr. O'Shaughnessy says.

"Dr. Genden had a great demeanor and was so confident; it appeared to me that he and his team had done numerous tumor-removal surgeries. He then introduced me to a skull base surgeon, Alfred Marc Iloreta, MD, of Mount Sinai's Skull Base Surgery Center, who is incredible and easy to speak with. When I left, I was calm about having surgery at Mount Sinai and felt good about my treatment path, which was a lot less invasive than I expected."

Highly Complex Tumor, Advanced Technology, and No External Incisions

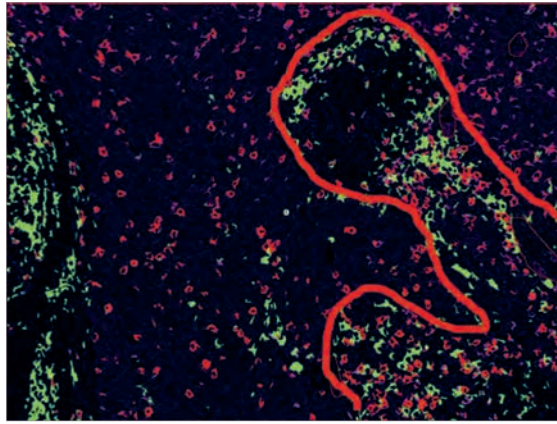
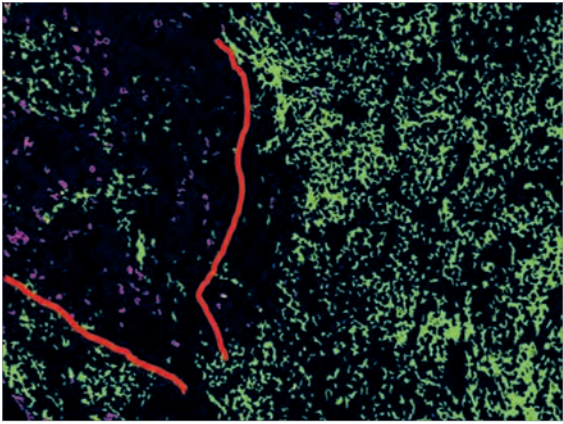
Mr. O'Shaughnessy's tumor was large—almost eight centimeters—and was located in a complex and difficult-to-access space, surrounded by the blood vessels that supply the brain and nerves that innervate and control the eye, as well as the face.

"Traditional approaches to remove this tumor include large incisions that would expose parts of the brain and even dismantle and remove the bones of the face and jaw," Dr. Iloreta explains. "In his case, we were able to combine our experience removing tumors using advanced technology, including optical endoscopes, high-definition cameras, and intraoperative neuro-navigation, to completely remove his tumor via a minimally invasive approach."

Dr. Iloreta employed a novel technology called Surgical Theater to reconstruct the tumor three dimensionally both for preoperative planning and for use during the surgery. Typically, this innovative mapping of a tumor has been used by neurosurgeons alone or in collaboration with head and neck surgeons, but this case marked the first

Continued on page 6

After surgery, a patient gets a nice surprise: waking up to find no external incision.



(Left) An HPV-related tumor is outlined in red under fluorescent microscopy. (Right) Red-cell infiltration after administration of the Advaxis vaccine. These cells represent infiltrating tumor-immune lymphocytes.

HPV Cancer Drug Gets a Trial

Therapy Targets Two Types of Immune Cells

The Head and Neck Cancer Research Program at the Icahn School of Medicine at Mount Sinai (ISMMS) is conducting a novel phase II trial to investigate the treatment of human papillomavirus (HPV)-related head and neck cancer with Axalimogene filolisbac (AXAL), a *Listeria monocytogenes* (Lm)-based immunotherapy treatment developed by Advaxis. This clinical-stage biotechnology company is developing multiple cancer immunotherapies based on its proprietary Lm Technology™. Mount Sinai was selected by the company as the initial clinical site because of the Department of Otolaryngology's long-standing clinical experience with TransOral Robotic Surgery (TORS) and with managing patients with HPV-related cancers, as well as because of its more than 20 years of research experience.

Brett Miles, DDS, MD, FACS, a head and neck cancer robotic surgeon, is the Site Principal Investigator of the Advaxis Window of Opportunity Trial for ISMMS, and Andrew Sikora, MD, PhD, is the Study Chairperson and Co-Director of the Head and Neck Cancer Program at the Baylor College of Medicine in Houston, Texas (the coordinating site for the trial). They work closely with Marshall Posner, MD, Medical Director of the Head and Neck Oncology Center and Associate Director of the Center for Personalized Cancer Therapeutics at The Tisch Cancer Institute. Together they collaborate with a team of researchers who are currently investigating the safety and efficacy of the vaccine.

How AXAL Works

AXAL is a live-attenuated Lm vector system that secretes an antigen-adjuvant protein (Lm-LLO) targeting HPV. It is

undergoing clinical trials for three potential indications: phase III for invasive cervical cancer, phase II for head and neck cancer, and phase II for anal cancer.

Advaxis has two additional immunotherapy products in human clinical development: ADXS-PSA for prostate cancer and ADXS-HER2 for HER2-expressing solid tumors. In addition, Advaxis and Amgen are developing ADXS-NEO, a preclinical investigational cancer immunotherapy treatment designed to activate a patient's immune system to respond against the unique mutations, or neoepitopes, identified in his or her tumor. Clinical application is expected in 2017.

Advaxis Trial Highlights

- AXAL is administered prior to standard-of-care TORS resection of the cancer in appropriate patients.
- The Mount Sinai Health System has enrolled eight study patients and three observational control patients.
- While it is very early in analysis of this trial, the preliminary data suggest systemic and intratumoral immune activation and enhanced antitumor immunity.

The FDA-funded trial of AXAL will continue to accrue patients at ISMMS while a second trial site is being added at the Baylor College of Medicine. Once a sufficient number of patients has been accrued and specimens have been collected, the study team will have an unparalleled opportunity to understand immune mechanisms activated by the immunotherapy and its potential to become a therapeutic approach for patients with HPV-related head and neck cancers. ■

Investigating immunotherapy as a supplement to robotic surgery for head and neck cancers.

Resecting Larynx, Restoring Voice

Complex Procedure Rebuilds Glottis and Trachea

Anna Balint lost her voice, but not from straining it. She fell in her home and broke her neck, and subsequently underwent surgery at a local hospital. During the procedure, an anesthesiologist damaged her voice box, and she awoke unable to speak after a tracheostomy. For months, Mrs. Balint communicated by writing on paper everything she wanted to say.

In March 2016, she was referred to Mark Courey, MD, Chief of the Division of Laryngology for the Mount Sinai Health System. He told her that she would require surgery, but he was confident he could restore her voice.

“When Mrs. Balint came to see me, she had a complicated multilevel airway stenosis involving her posterior glottis, subglottis, and trachea,” Dr. Courey notes. “At the level of the subglottis, the obstruction was complete. I performed a primary cricotracheal resection. I removed the involved anterior portion of her cricoid ring and the top three tracheal rings. Then I resected the scar from the posterior commissure and advanced a flap of posterior tracheal wall tissue to cover the exposed cricoarytenoid joints.”

Dr. Courey cut the tracheal rings in a step-like manner and used them to reconstruct the anterior cricoid ring. “Because I was uncertain of how successfully the advancement flap would relieve the posterior glottis

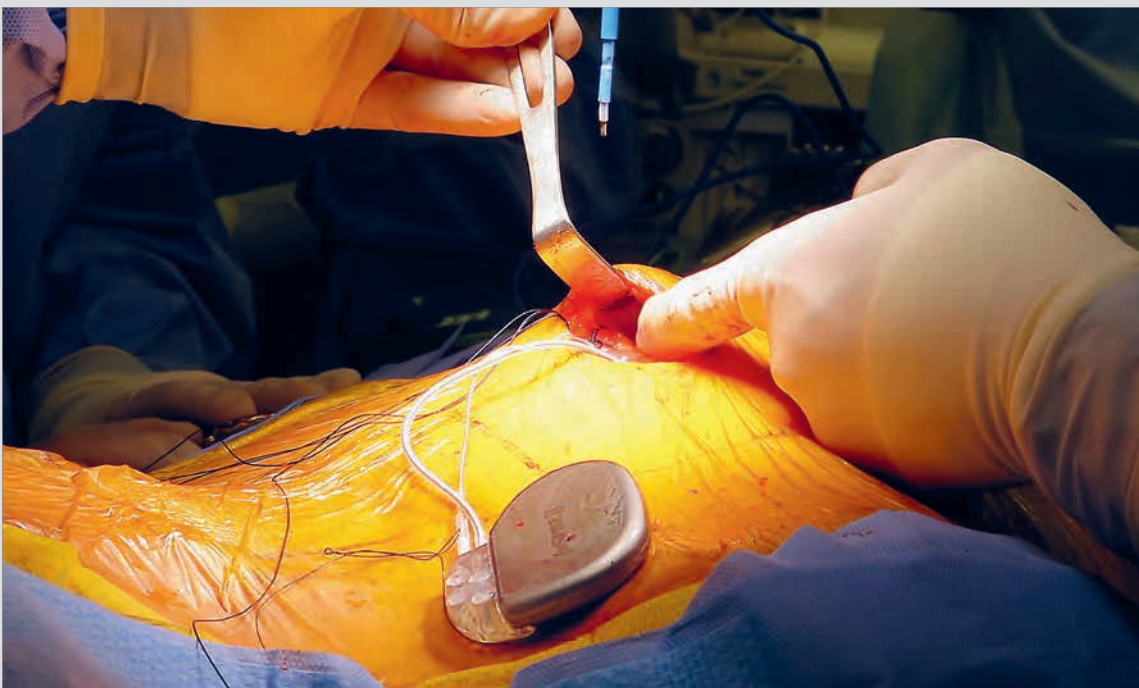


Anna Balint with Mark Courey, MD

stenosis, I created a permanent tracheostomy below my anastomotic line. The skin was advanced down to the trachea to create a skin-lined tract. This also had the benefit of taking tension off of her tracheal suture line.”

As soon as Mrs. Balint was out of surgery, she started to speak. Two months later, Dr. Courey removed her tracheostomy tube and closed her stoma. “I was free and so happy I could speak to my family,” Mrs. Balint recalls. “Dr. Courey is the only one who knew how to correct my voice. I am thrilled that I found him.” ■

Inspire Therapy at Mount Sinai



The Inspire Therapy implant is offered at Mount Sinai Beth Israel and The Mount Sinai Hospital as an alternate treatment for those with sleep apnea who cannot comply with CPAP. Peter Schectman, a patient who received the first implant at The Mount Sinai Hospital, had an excellent outcome—resolved snoring and respiratory events—with one of the lowest therapeutic amplitudes on record, just weeks after starting to use the device. “I have truly benefited from the Sleep Surgery Program at Mount Sinai,” he said.

Keeping Cancer Dormant

Therapy Would Reprogram Cells Left After Treatment

Cancer cells frequently remain in the body after initial treatment for the disease. To prevent recurrence, we need to identify drugs that will prevent these cells from ever growing again.

Julio Aguirre-Ghiso, PhD, Professor of Medicine (Hematology and Oncology), Otolaryngology, and Oncological Sciences, has identified a nuclear receptor as a master regulator of a program of cancer-cell dormancy. This gene, named NR2F1, allows cancer cells to enter dormancy and remain in this state for later awakening, which results in lethal metastatic growth.

Continuing this work, the Aguirre-Ghiso team and Maria Soledad Sosa, PhD, an Assistant Professor of Medicine (Hematology and Oncology) at the Icahn School of Medicine at Mount Sinai, have identified a new drug that activates NR2F1. In doing so, Dr. Aguirre-Ghiso and his team were the first to use data from dormancy models to design a therapy for cancer that taps into the mechanisms of dormancy.

The Aguirre-Ghiso team proposed that the reprogramming of cancer cells into a dormant state could be a way to prevent recurrences. They discovered specific agonists that activate NR2F1, which induces cancer cell dormancy.

Combining the NR2F1 agonist with a DNA demethylating agent (5-aza-C) that allows for NR2F1 expression and with agonists of the retinoic acid receptors (AM580, AM80, or BML) might allow restoration of dormancy. This depends on the production by dormant cells of BMP7 and TGFb2 signals that are strong dormancy inducers. Combining the NR2F1 agonists with MEK1/2 inhibitors might further enforce dormancy induction. The goal is to treat patients with such drugs in the adjuvant setting to prevent recurrences by inducing the reprogramming of cancer cells into dormancy or making the cells function as they do in normal tissue.

The Partnership for New York City has selected this research for the Partnership Fund's BioAccelerate NYC Prize. This is an exceptional opportunity to expand these researchers' discovery and translate their findings into clinical applications. ■



Julio Aguirre-Ghiso, PhD, and graduate student Kathryn Harper

Tumor Invades *continued from page 3*



Alfred Marc Iloreta, MD, left, with patient James O'Shaughnessy

time Surgical Theater was used solely by head and neck surgeons in the operating room, according to its manufacturer. "Before even meeting Mr. O'Shaughnessy, we were able to model and simulate the approach to the tumor and felt very confident that we would remove the entire mass with minimal impact."

Because of where the tumor was located, Dr. Genden initially told Mr. O'Shaughnessy that the surgeons might need to make incisions in both his gum line and outside his jaw. "To my surprise, when I awoke, I had no external incision at all," Mr. O'Shaughnessy recalls. Following the eight-and-a-half-hour surgery on April 29, 2016, he felt his face and said, "I don't even feel the external incision." That is because there wasn't one. The surgeons operated inside his mouth and alongside his jaw from the inside, without ever making the external incision. Mr. O'Shaughnessy stayed in the hospital only on Friday night and Saturday, and then on Sunday he was able to return home to continue his recovery.

"The nurses in the recovery room—I have never met people like that in my life," Mr. O'Shaughnessy says. "They were incredible. To watch them and the help they gave me was amazing. They were so nice and always had smiles on their faces."

"As for Drs. Genden and Iloreta, I don't even know where to begin," he adds. "I never felt stress speaking with them because they were so confident and easygoing about the surgery. The fact that they can focus for that many hours and use this incredible technology is amazing."

Upon arriving home, Mr. O'Shaughnessy felt fine and took painkillers for three weeks. "I had some bleeding for a few days, but I was talking and swallowing fine. The first days were filled with a lot of soup, shakes, and soft foods," he recalls. It took about four weeks for him to return to his daily routines. Now he is back to work, exercising four days a week, and paddleboarding.

"This whole journey was a wakeup call, because I was working long hours, six days a week. I certainly look at life differently now. I don't sweat the small stuff anymore, and I am so much happier with life! I can't praise or recommend The Mount Sinai Hospital enough. The doctors, nurses, and friendly staff were all amazing! I have a feeling of euphoria and am absolutely grateful to Mount Sinai for it." ■

Modeling Surgery in Advance

Imaging and 3D Help Doctors Plan and Patients Understand

For patients requiring complex correction of craniofacial and oncologic deformities and orthognathic surgeries, precise treatment planning is of the utmost importance. At Mount Sinai's Division of Oral and Maxillofacial Surgery, we utilize a digital X-ray system and cone beam technology to determine exact diagnoses and obtain three-dimensional models for surgical treatment planning. This radiographic technology then enables our surgeons to use virtual surgical planning (VSP) to plan various procedures. Additionally, we use 3D printed models of the jaw, particularly for jaw-reconstruction procedures, which help us adapt plates and contour the bone flaps in the operating room.

Since 2008, Mount Sinai has been at the forefront of employing VSP—closely collaborating with a Belgian company, Materialise NV, that provides specialized planning software and 3D physical models used in surgical planning, as well as the medical know-how and input to devise surgical workflows. Our team is one of only a handful across the nation planning advanced oral and maxillofacial surgery cases in daily practice. We use Mimics® Innovation Suite, a computer program made by Materialise that helps surgeons accurately plan a procedure using a computer-generated model. This technology can be applied to the placement of dental implants, advanced jaw-repositioning procedures (orthognathic surgery), repair of congenital deformities, and jaw reconstruction requiring sophisticated bone grafting and microvascular transplants. The use of VSP is becoming routine for complex oral and maxillofacial surgeries at the Mount Sinai Health System.

Upon obtaining each patient's imaging, the physician creates a cephalometric analysis using the software program, and 3D virtual models are rendered. The goal is to simulate the planned surgical movements on the 3D model, based on a preop analysis and individualized problem list. The software is quite intuitive and user friendly, showing the segmented objects in different colors. After the planned movements are made on the 3D computer rendering, plastic surgical cutting guides are fabricated using a 3D printer, allowing us to execute the plan in the OR. We use occlusal guides during surgery to ensure the precise repositioning of the jaws.

In the case of mandibular reconstruction, a 3D virtual model of the jaw is created. Using a virtual resection plane tool, a new object is then crafted consisting of the jaw segment that needs to be removed due to the tumor invasion. Then we use the CT scan of the patient's fibula—from which a segment of bone will be used in jaw reconstruction—to create precise cuts to restore the jaw to the same form as prior to surgery. Again, plastic resection



Daniel Buchbinder, MD, DDS

and cutting guides are printed and used in the OR to execute the planned surgical procedure.

Patients appreciate the communication and clarity offered with VSP, because they can visualize exactly what is going to happen during surgery. “Physicians can draw a sketch on a piece of paper to explain the procedure to patients,” says Daniel Buchbinder, MD, DDS, Chief of the Division of Oral and Maxillofacial Surgery at the Mount Sinai Health System. “But when we show patients a 3D rendering of their own jaw with the tumor and the proposed surgical plan for removal, it puts the entire procedure into perspective.”

Other patient benefits include:

- More individualized care
- Less operating time (VSP eliminates up to 45 minutes in reconstruction cases and several hours of orthognathic preop planning)
- Fewer intraoperative “surprises”
- More predictable and better outcomes, because the guides enable surgeons to double-check the planned operative movements.

Led by Vincent Carrao, MD, DDS, Chief of the Division of Oral and Maxillofacial Surgery at The Mount Sinai Hospital, our team conducted an outcomes study comparing the actual amount of maxillary anterior movement achieved in the OR to the VSP measurements that were predicted preoperatively. A retrospective analysis of 20 orthognathic cases over 18 months revealed a level of accuracy with a standard deviation for all of the procedures at 0.27 mm from the predicted value, confirming the accuracy of this method of surgical planning and the betterment of outcomes using it. ■

Plastic replicas made with 3D printers let surgeons decide precisely where to cut.



Icahn School of Medicine
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New York Eye and Ear
Infirmary of Mount Sinai



For you. For life.

QUICK FACTS

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

RANKED No. 1
AMONG PRIVATE MEDICAL SCHOOLS
IN TOTAL RESEARCH DOLLARS PER
PRINCIPAL INVESTIGATOR

\$290 MILLION
IN TOTAL NIH FUNDING

MOUNT SINAI HEALTH SYSTEM

7,100+
PHYSICIANS

THE MOUNT SINAI HOSPITAL
RANKED No. 15
NATIONALLY BY *U.S. NEWS &
WORLD REPORT*

4 MILLION
ANNUAL PATIENT VISITS

2016 OUTCOMES HIGHLIGHTS

43 PERCENT
REDUCTION IN C. DIFFICILE INFECTIONS

22 PERCENT
REDUCTION IN PATIENT SAFETY
INDICATOR INPATIENT HARM EVENTS
(Medicare patients)

2016 DEPARTMENTAL HIGHLIGHTS

LARGEST
HEAD AND NECK ROBOTIC SURGERY
PROGRAM IN THE NATION

RANKED No. 1
IN NEW YORK FOR OTOLARYNGOLOGY
BY *U.S. NEWS & WORLD REPORT*

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