Dear Colleague:

In your hands is the annual report from the Department of Neurological Surgery at UCSF, showcasing some of the recent clinical and research achievements made by our faculty. It has been an exceptional year for scientific discovery and we continue to be at the forefront of developments in patient care, technology, and the realization of personalized medicine.

What may particularly stand out is the progress we are making in extracting clarity from the chaos of big data. At the Brain and Spinal Injury Center, a team led by Adam Ferguson, PhD, is applying topological data analysis to a database of hundreds of preclinical spinal cord studies to identify patterns that may serve to improve translational research (page 24). In the Brain Tumor Center, Aaron Diaz, PhD, is using machine learning to solve the problem of heterogeneity in gliomas combined with interactions of the tumor microenvironment in an individual patient. And in the Spine Center, neurosurgeon Christopher Ames, MD, is using predictive analytics to vastly improve our predictions of success or failure of surgery for patients with adult spinal deformity (page 45).

In our operating rooms, we continue to find ways of making surgeries safer and less invasive for our patients. From defining safer surgical routes to insular gliomas (page 6) to new techniques for cerebrovascular bypasses (page 26) and minimally invasive spine surgeries (page 49), UCSF neurosurgeons continue to optimize the procedures in their fields of specialty and train others in new techniques.

Finally, I am proud to note that we have moved up to number four on U.S. News & World Report’s roster of best neurology and neurosurgery services in the nation and continue to be first on the West Coast. On behalf of my colleagues in the Department, we look forward to another year of partnering with you in the care of your patients.

Sincerely,

Mitchel S. Berger, MD
Professor and Chair,
Department of Neurological Surgery
Berthold and Belle N. Guggenheim Endowed Chair
Director,
Brain Tumor Research Center
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| | David Rowitch, MD, PhD | William Weiss, MD, PhD | Kyle Walsh, PhD |
| | Johnn Wiencke, PhD | Margaret Wrensch, MPH, PhD | Shichun Zheng, PhD |
The UCSF Brain Tumor Center offers specialized surgical procedures for benign and malignant brain tumors. All patients are evaluated in a multidisciplinary conference and treatment plans are tailored for each patient's specific needs. Using modern techniques such as diffusion tensor imaging and tractography, intra-operative speech and motor mapping, image-guided surgical systems, and intraoperative tumor fluorescence displays, high rates of complete and near-complete tumor removal are accomplished.

Neurosurgeons at UCSF have special expertise in awake speech mapping surgery for insular tumors and those in dominant language hemisphere. There is also an active research program investigating the functional connectivity of speech and seizure foci related to tumors.

Benign tumors such as meningiomas, schwannomas, and pituitary adenomas are managed by integrated surgical programs with a complementary research effort. Meningiomas are the most common primary brain tumor and occur over the cranial vault and along the skull base. The surgical team at UCSF has operated on more than 2,000 meningiomas since 1992 and published many guidelines on surgical and nonsurgical management for these tumors.

UCSF also has one of the largest experiences with skull base tumors in the United States. Multi-modality treatment plans for patients with skull base tumors are designed with our colleagues in the Departments of Otolaryngology – Head and Neck Surgery, Radiation Oncology, Plastic Surgery and Neuro-ophthalmology. Vestibular schwannomas are not all treated with radiosurgery and many require microsurgery as a definitive or first step in treatment.

Neurosurgeon Michael McDermott, MD, specializes in meningiomas, acoustic neuromas, and complex tumors of the skull base. Here he uses intraoperative neuronavigation software to ensure the safest surgical trajectory.

Fluorescence-guided tumor resection enhances surgeons’ ability to remove infiltrative tumor cells

For patients with low-grade or high-grade glioma, a greater extent of resection can increase survival, making precise brain mapping a critical component of surgery for these tumors. In 2012, UCSF became the first institution on the West Coast to offer surgery using 5-aminolevulinic acid (5-ALA) as an investigational new drug. The drug is taken orally before surgery and causes fluorescent porphyrins to accumulate in malignant gliomas, enabling surgeons to visualize them under fluorescent light and revealing areas of infiltration outside defined margins of the tumor. This year, UCSF neurosurgeons published their initial results from a prospective phase 2 study, demonstrating that ALA can be a useful adjunct when combined with mapping to safely remove as much tumor as possible. But the study’s authors, led by Mitchel S. Berger, MD, caution that while intense fluorescence is a good indicator of tumor presence and can guide surgeons to areas of infiltrated tumor, low or absent fluorescence does not correlate well with absence of tumor.

Defining Safer Surgical Routes to Insular Gliomas

Brain tumors growing in the insula, in close proximity to important vascular structures and areas of the cerebral cortex that control speech and motor function, pose a significant surgical challenge. UCSF Chair of Neurological Surgery, Mitchel S. Berger, MD, is known for his pioneering work devising brain mapping strategies to remove as much of the tumor as possible without injuring critical functional regions of the brain. In 2010, he and former UCSF neurosurgical resident Nader Sanai, MD, devised the Berger-Sanai zone classification system that divided the cortex into four quadrants that could allow them to predict the extent of resection that would be possible depending on which quadrant the tumor fell into.

A study led this year by Berger and surgical anatomist Arnau Benet, MD, set out to validate the Berger-Sanai zones by analyzing 244 procedures involving 218 patients with insular gliomas treated at UCSF. They were able to show that the zones accurately predicted both the extent of resection achieved and rate of complication. By using these zones to analyze an insular glioma, brain tumor surgeons can have more confidence in preparing their patients for risks of surgery.

In a related study, Berger, Benet, and their colleagues compared the surgical corridors most often used to access insular gliomas: the transcortical and transylvian corridors. To date there has been little evidence demonstrating a benefit of one over the other, but by carefully analyzing each approach in a surgical anatomy laboratory, the authors were able to show that the transcortical approach is superior for achieving a greater extent of resection, but intraoperative subcortical mapping is essential to ensuring that functional and language areas are protected.
On November 8, the UCSF Neuro-Oncology team joined Voices Against Brain Cancer for their second annual run/walk to raise funds for brain tumor research. The nonprofit organization honored Susan Chang, MD, Jennie Taylor, MD, Jennifer Clarke, MD, Charlotte Huie, RN, BSN, Nadia Javed, and Avelina Gomez at the event. As part of their mission to advance scientific research, Voices Against Brain Cancer provides generous grants to neuro-oncology research at UCSF and other institutions across the United States.

Neuro-Oncology Team Honored for Best Patient Care

For the eighth consecutive year, the division of neuro-oncology has received the highest patient satisfaction ratings of any outpatient care team at the UCSF Medical Center, earning them the 2015 Hall of Fame Award. Questionnaires administered by the independent company Press Ganey consistently score patients’ satisfaction with brain tumor care and treatment above 97%. The dedicated group of physicians, nurses, and staff that make up the neuro-oncology team have won the award every year since it was established in 2008.
Brain Tumor Clinical Trials

The Brain Tumor Center aims to improve survival for adults with brain tumors through clinical trials that test novel agents and strategies based on basic and translational research.

The clinical service consists of neuro-oncologists, neurosurgeons, radiologists, pathologists, radiation oncologists, nurses and support staff who are involved in the development of investigator-initiated clinical trials or trials developed in collaboration with the NIH, tumor consortiums, and industry. The Brain Tumor Center conducts approximately 10-20 such trials at one time.

**Newly Diagnosed Glioblastoma**

**Phase I Study of AZD1775 (MK-1775) with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma**

**Description:** A multi-center consortium study testing the addition of AZD1775 to initial treatment. It is being added to radiation along with temozolomide (Arm 1), or to adjuvant temozolomide after radiation (Arm 2). If it is safe in both these groups, then it will be added both during and after radiation (Combination Arm).

**Phase 2 Study to Evaluate the Clinical Efficacy and Safety of MEDI4736 in Patients with Glioblastoma**

**Description:** A multi-center phase II study testing MEDI4736 with 3 arms for different patient populations. Cohort A combines MEDI4736 with radiation in patients with newly-diagnosed, MGMT-unmethylated glioblastoma. Cohort B treats patients with recurrent, bevacizumab-naive glioblastoma with MEDI4736 alone, and Cohort C treats patients with recurrent, bevacizumab-refractory glioblastoma with both MEDI4736 and bevacizumab.

**A071102: A Phase II/III Randomized Trial of Veliparib or Placebo in Combination with Adjuvant Temozolomide in Newly Diagnosed Glioblastoma with MGMT Promoter Hypermethylation**

**Description:** This randomized phase II/III trial studies how well temozolomide and veliparib work and compare them to temozolomide alone in treating patients with newly diagnosed glioblastoma. Veliparib is poly(ADP-ribose) polymerase (PARP) -1 and -2 inhibitor with chemosensitizing and antitumor activities which may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Questions about patients’ participation in the following clinical trials can be directed to our New-Patient Coordinator at NeuroOncNewPtCoord@ucsf.edu.
A Randomized Phase III Open Label Study of Nivolumab versus Bevacizumab and Multiple Phase 1 Safety Cohorts of Nivolumab or Nivolumab in Combination with Ipilimumab Across Different Lines of Glioblastoma

Description: This trial adds nivolumab to radiation and temozolomide for the treatment of newly diagnosed glioblastoma. Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death one (PD-1) receptor on activated T-cells.

Phase I Ipilimumab and/or Nivolumab in Combination with Temozolomide in Treating Patients with Newly Diagnosed Glioblastoma or Gliosarcoma

Description: This phase I trial studies the safety and best dose of ipilimumab, nivolumab, or both in combination with temozolomide in treating patients with newly diagnosed glioblastoma. Ipilimumab and nivolumab may block tumor growth in different ways.

Glioblastoma - First Recurrence

A Phase I Study Evaluating the Safety and Pharmacokinetics of ABT-414 for Subjects with Glioblastoma Multiforme Incorporating Amendments 1, 2, 3 and 4

Description: ABT-414 targets cancer cells by combining both a chemotherapy drug (MMAF) with an antibody directed against the epidermal growth factor receptor (EGFR). This combination in a single drug is called an antibody drug conjugate (ADC). As an ADC, ABT-414 is designed to be stable in the bloodstream and to release the potent chemotherapy agent only inside targeted cancer cells.

Glioblastoma - Multiple Recurrences


Description: A multi-center, cooperative group trial on which patients undergo surgical resection of recurrent glioblastoma, from which an autologous vaccine is made. If resection and vaccine synthesis are successful, patients are randomized to vaccine with concurrent bevacizumab, vaccine alone followed by bevacizumab at second progression, or bevacizumab alone.

Phase 2 Study to Evaluate the Clinical Efficacy and Safety of MEDI4736 in Patients with Glioblastoma

Description: A multi-center phase II study testing MEDI4736 with 3 arms for different patient populations. Cohort A combines MEDI4736 with radiation in patients with newly diagnosed, MGMT-unmethylated glioblastoma. Cohort B treats patients with recurrent, bevacizumab-naive glioblastoma with MEDI4736 alone, and Cohort C treats patients with recurrent, bevacizumab-refractory glioblastoma with both MEDI4736 and bevacizumab.

NCCTG Study N1174 – Phase I/Comparative Randomized Phase II Trial of TRC105 plus Bevacizumab versus Bevacizumab in Bevacizumab-Naïve Patients with Recurrent Glioblastoma Multiforme

Description: A randomized phase I/II trial that examines the tolerability and efficacy of anti-endoglin monoclonal antibody TRC105 when given together with bevacizumab. Monoclonal antibodies, such as anti-endoglin monoclonal antibody TRC105 and bevacizumab, may find tumor cells and help kill them.
A Phase II, Multicenter, Open-label Study of BGJ398 in Patients with Recurrent Resectable or Unresectable Glioblastoma

Description: This is an open-label non-randomized, multicenter, phase II study of BGJ398 administered to adult patients with confirmed GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2 or 3.

A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme

Description: SL-701 is an enhanced immunotherapy designed to activate the immune system to attack tumors by targeting multiple epitopes.

A Pilot Trial Testing the Feasibility of Using Molecular Profiling to Guide an Individualized Treatment Plan in Adults with Recurrent/Progressive Glioblastoma

Description: This study uses a treatment approach based on each patient’s tumor genomic profiling consisting of whole genome sequencing, exome analysis, and RNA sequencing as well as predictive modeling. The current study will test the feasibility of a specialized tumor board assigning a treatment plan within 35 calendar days of obtaining tumor tissue.

Study of Convection-Enhance Delivery, Image-Assisted Delivery of Liposomal-Irinotecan in Recurrent High-Grade Glioma

Description: This is a dose-toleration study designed to investigate and determine the maximum tolerated dose of nanoliposomal irinotecan in adults with recurrent high-grade glioma when administered directly into the tumor using a process called convection-enhanced delivery with real-time imaging.

Glioblastoma, Recurrent - Phase I Studies

A Phase I Dose Escalation Study of Hypofractionated Stereotactic Radiotherapy with Bevacizumab in the Treatment of Recurrent Malignant Glioma

Description: This is a two-institution study to evaluate the safety of escalating doses of hypofractionated radiation when combined with bevacizumab in the treatment of focally recurrent grade III or IV glioma.

Phase I Safety Study of VAL-083 in Patients With Recurrent Malignant Glioma

Description: A bi-functional alkylating agent, VAL-083 crosses the blood brain barrier and alkylates and crosslinks DNA, which ultimately leads to a reduction in cancer cell proliferation. In addition, VAL-083, does not show cross-resistance to other conventional chemotherapeutic agents.

A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-414 for Subjects with Glioblastoma Multiforme Incorporating Amendments 1, 2, 3 and 4

Description: ABT-414 targets cancer cells by combining both a chemotherapy drug (MMAF) with an antibody directed against the epidermal growth factor receptor (EGFR). This combination in a single drug is called an antibody drug conjugate (ADC). As an ADC, ABT-414 is designed to be stable in the bloodstream and to release the potent chemotherapy agent only inside targeted cancer cells.

Grade III Glioma

Study of Convection-Enhance Delivery, Image-Assisted Delivery of Liposomal-Irinotecan in Recurrent High-Grade Glioma

Description: This is a dose-toleration study designed to investigate and determine the maximum tolerated dose of nanoliposomal irinotecan in adults with recurrent high-grade glioma when administered directly into the tumor using a process called convection-enhanced delivery with real-time imaging.

Low-Grade Glioma, Newly Diagnosed

PI3K/mTOR Pathway Activation Selected Phase II Study of Everolimus (RAD001) with and without Temozolomide in the Treatment of Adult Patients with Supratentorial Low-Grade Glioma

Description: Single-institution, phase II study testing everolimus in patients with newly diagnosed, low-grade glioma, utilizing molecular characterization to assign patients to treatment with everolimus alone or with combined everolimus/temozolomide.
Neurosurgeon and pituitary disorder specialist Manish Aghi, MD, PhD recently led a study defining risk factors for headaches among patients undergoing pituitary surgery.

Headaches in Patients with Pituitary Disorders: Risk Factors and Predictors of Improvement

Headaches are a common complaint in the general population — 22% of women and 11% of men are estimated to suffer from them. While not as familiar, lesions of the sellar and parasellar region are also relatively common, but they are usually not symptomatic and often go undetected throughout life. Studies of cadavers and healthy volunteers give us an incidence that ranges from 1.7% to 27% in the general population. When the two occur together, it is difficult to determine whether the headaches are caused by the lesion or if the two are occurring coincidentally. The prevalence of headaches is higher among patients with pituitary lesions than it is in the general population, and headache is often the symptom that leads previously undiagnosed patients to a physician in the first place.

But there is not always a direct correlation and rates of headache improvement after surgery have not been evaluated in large cohorts.

This has important implications for counseling patients with pituitary lesions who have headaches but no other indications for surgery. “While we can be sure that symptoms like visual deficits and endocrine dysfunction are related to the tumor, evaluating a patient whose only complaint is headache is much more complicated,” says neurosurgeon Manish Aghi, MD, PhD. Aghi led a recent study at the California Center for Pituitary Disorders that analyzed 961 patients treated over five years to determine factors that may predict whether headaches will improve following...
surgery. Just over a third of all patients in the study suffered from headaches and 73% of those patients described it as their primary symptom.

Headache was most common in patients with pituitary apoplexy (84%), followed by Rathke’s cleft cysts (60%), hypophysitis (50%), craniopharyngiomas (46%), and pituitary adenomas (28-29%). Women and younger patients were also more likely to present with headaches.

Most patients with headaches improved after surgery, but improvement was frequently delayed (11% reported improvement at 6-week follow-up and 53% reported improvement at 6-month follow-up). Patients with headache as their chief complaint, patients undergoing complete removal of their tumor, and patients with a shorter history of headache were more likely to experience postoperative improvement. Surprisingly, the size of the tumor or cyst was not a variable associated with headaches.

“Our finding that complete removal was associated with headache improvement and that headache improvement can take up to 6 months to occur will be important for endocrinologists and neurosurgeons to be cognizant of,” says Aghi.

To address these issues prospectively Aghi and his team are putting in place a clinical trial involving structured questionnaires like the Headache Impact Test (HIT-6) given before and after surgery, intraoperative measurements of pressure within the pituitary gland, and blood biomarkers to better identify patients whose headaches could be attributable to their pituitary tumor or cyst.

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**Expertise + Experience**

Physicians at the California Center for Pituitary Disorders are among the most experienced in the nation. The high volume of patients we see each year translates into better outcomes. Our cure rates are above 90% and our complication rates are 7 times less than the national average for pituitary surgery.

Sophisticated diagnostic tools and state-of-the-art microscopic and endoscopic surgical approaches are tailored for each patient. Our team focuses on ensuring that patients understand all aspects of their disease and treatment options so that they are part of the decision-making process in their own care.

| 247 | >1500 |
| Surgeries for Pituitary Disorders | Outpatient Visits |
Genetic Markers Provide Better Brain Cancer Classification

A team of scientists from UCSF and Mayo Clinic has shown that using just three molecular markers will help clinicians classify gliomas – the most common type of malignant brain tumors – more accurately than current methods.

The study, published by New England Journal of Medicine, reported that based on the presence or absence of each marker, 95 percent of gliomas fall into one of five distinct groups, which vary in terms of median survival times and other characteristics.

Currently, malignant gliomas are classified based on the appearance of biopsy samples under the microscope, and their grade, or degree of aggressiveness, with grade II being the least aggressive and grade IV the most.

The three markers are a mutation in the region that promotes expression of the gene TERT, which expresses telomerase, an enzyme that helps keep cancer cells alive by protecting structures called telomeres; a mutation in the genes IDH1 or IDH2, referred to collectively as IDH mutation; and a combined mutation that deletes parts of chromosome 1 and chromosome 19.

The study authors analyzed genetic and clinical data from 1,087 malignant glioma patients and 11,590 healthy controls from Mayo Clinic, UCSF and The Cancer Genome Atlas, a program of the National Cancer Institute.

The scientists found that among grade II and III tumors, 29 percent were “triple positive,” showing all three markers. Patients with these tumors had a median survival time of 13.1 years. Five percent had both TERT and IDH mutations, and had a median survival time similar to triple positive tumors. Forty-five percent had IDH mutation only, and a median survival time of 8.9 years. Seven percent of tumors were triple negative, with none of the mutations, and had a median survival time of 6.2 years. The 10 percent of tumors that only had the TERT mutation were associated with the shortest median survival time – 1.9 years.

Wrensch suggested that once these or similar molecular markers are accepted by clinicians as part of the classification system, “it may make a great deal of difference in treatment approach for individual patients.”

She said that under the current system, “someone with a grade III glioma, for example, may not have been treated as aggressively as someone with a grade IV. But now, if you determine that it’s a TERT-mutated-only tumor, there is more confidence that it will behave more like a grade IV tumor and could be treated more aggressively.” In contrast, said Wrensch, “a grade III tumor that only has an IDH mutation might be treated less aggressively. Glioma treatments can be very toxic, so it’s important to know how aggressive treatments need to be.”

The researchers found that among patients with grade IV tumors, age at diagnosis was a more important predictor of survival than molecular subgroup, with younger patients having a better chance of surviving longer than older patients. “We don’t know why that is yet,” said Wrensch. “It might have something to do with the immune system or with telomere maintenance, but we are studying these questions. This study provides a new foundation.”

At UCSF, co-lead authors of the study are Annette M. Molinaro, PhD and Kyle M. Walsh, PhD; the other UCSF co-senior author is John K. Wiencke, PhD. At the Mayo Clinic, co-lead authors of the study are Jeanette E. Eckel-Passow, PhD and Daniel H. Lachance, MD; the Mayo Clinic co-senior author is Robert B. Jenkins, MD.

This story was written by Elizabeth Fernandez and first appeared in the UCSF News Center on June 10, 2015 (www.ucsf.edu/news).
Visualizing Tumor Metabolism to Follow Treatment Response

One of the most important recent findings in brain tumor biology has been a mutation in the gene coding for isocitrate dehydrogenase-1 (IDH1). Tumors with mutations in the IDH1 gene tend to occur in low-grade gliomas and are associated with longer survival times for patients, serving as a positive prognostic factor. The mutation also affects cellular metabolism, which can be measured with sophisticated imaging technologies, such as hyperpolarized $^{13}$C MR spectroscopy (MRS).

$^{13}$C MRS approaches to detect metabolites that are only produced in tumor cells (called oncometabolites) have been developed at UCSF, including a method to measure 2-hydroxyglutarate (2HG), which is produced only in mutant IDH1 cells. Monitoring a tumor's metabolism could give clinicians a measure of how a tumor may be responding to a given treatment. When a patient receives a drug and 2HG levels drop, for example, it may indicate a response to therapy.

An especially exciting aspect of this technology is that changes in metabolism happen much faster than changes that can be measured with standard imaging methods, giving patients and their doctors the opportunity to switch therapies early in the course of treatment if no change in metabolism is detected.

The correlation between changes in 2HG levels and treatment response is being tested in an ongoing clinical research project at UCSF. But one caveat to measuring 2HG is that it occurs in very small quantities and changes are not always easy to detect. In a new study published this year in Cancer Research, investigators at the Brain Tumor Research Center, led by Sabrina Ronen, PhD, have identified additional metabolites that may be able to serve as surrogates for the presence of IDH-mutated tumor cells.

The study showed that the entire cycle of pyruvate metabolism is altered in the presence of an IDH1 mutation, and $^{13}$C MRS could follow changes in the flux of pyruvate dehydrogenase between normal cells and glioma cells. A reduction in the metabolism of hyperpolarized pyruvate into hyperpolarized glutamate was found to be a characteristic of IDH1 tumor cells, and one that could be more easily measured than the presence of 2HG.

Using $^{13}$C MRS to gain information about an individual tumor's biology is a relatively new clinical technique and UCSF is one of a handful of institutions in the United States developing the technology to help guide treatment decisions for brain tumors. As we discover more about the way individual mutations alter cellular metabolism, more oncometabolites will likely emerge to tell us which treatments a tumor is likely to respond to, and possibly what alternative pathways it uses to recur after an initial response to one type of treatment.


The uncontrolled growth seen in cancer cells is partially attributed to the fact that their chromosomes do not lose telomeres—the critical caps of chromosomes required for cell replication. Telomeres are maintained by the enzyme telomerase, which is normally only expressed in stem cells and is controlled by the genes TERC and TERT, among others. These genes are turned off when the cell differentiates into a somatic cell. In cancer cells, reactivation of the TERT gene extends the cells’ telomeres, stabilizing their chromosomes and allowing them to replicate and survive longer than normal cells.

The reactivation of TERT has been linked to highly recurrent mutations in the gene’s promoter region, which are found in approximately 85% of glioblastoma and oligodendroglioma tumors, as well as many other cancers. Collaborating with Jun Song, PhD and a team of researchers at the University of Illinois at Urbana-Champaign, BTRC investigators, led by Joseph Costello, PhD, have now uncovered the mechanisms by which these common mutations result in elevated TERT expression.

The team’s findings, published this year in *Science*, identifies the transcription factor GABP as selectively binding to the mutated promoter sequences; GABP does not recognize the normal promoter sequence, which is why it does not activate TERT expression in normal cells. Costello and his colleagues also showed that GABP recognizes and binds the mutant TERT promoter in tumor cells from four cancer types: glioblastoma, melanoma, hepatocellular carcinoma, and bladder urothelial carcinoma. Costello and lead author Robert Bell, PhD, are now determining whether inhibition of the transcription factor would decrease TERT expression or result in selective cancer cell death.

UCSF Scientists Uncover Previously Unknown Function of a Genetic Mutation Found in Many Cancers

Cells with aberrant telomeres

TERT promoter mutations are found in many forms of cancer, enabling cell survival and replication. A new study has identified the transcription factor that binds to the mutated promoter region, giving oncologists an exciting new target for cancer therapy.
Q: How did you first get involved in volunteering overseas?
A: It probably goes back to 2003, when I was working as a resort nurse in the town of Zihautanejo. I found myself most engaged doing rounds at the local clinics and hospital with the Mexican physicians.

Q: Where have you been?
A: In 2013, I visited Bangkok, Thailand, where I was invited to round with the local general surgeon at a large public teaching hospital. In 2014, I traveled to Thimphu, Bhutan to develop the country’s first hydrocephalus program for the Department of Neurosurgery at the National Referral Hospital. And for the past two years, I have provided primary health care services to underserved populations at remote villages in Mexico.

Q: What was your most memorable trip?
A: This past summer I spent two weeks providing nursing education at the Sihanouk Hospital for Hope in Phnom Penh, Cambodia.

Q: Had you ever been there before? What were your first impressions?
A: This was my first trip to Cambodia, and I was extremely impressed both with the generosity of the staff and their dedication to providing services to the poorest of the country’s citizens. The staff was completely reliant on international volunteers to achieve their personal learning objectives. During my stay, I met medical professionals from Switzerland, Ireland, and Germany. The staff nurses were eager to learn both through classroom instruction and by including me in patient care through their daily routines on the wards.
Q: How were the facilities? Were you well prepared?
A: The facilities were basic but clean. Much of the equipment had come from donation through the USAID program. Most of it was from decades past, but still worked, and the staff was creative with the resources they had. I was able to bring with me a large donation of requested supplies from MedShare. For lesson plans, I knew I wouldn’t be able to develop my teaching plans until I was on site and able to assess the needs of the hospital and the specialized patient population. I prepared my lectures in the evenings for the following day.

Q: What was the day-to-day activity like?
A: The mornings were spent working one-on-one with the nurses on the medical and surgical wards and in the ER. The afternoons were spent providing classroom instruction to a group of nurses on a range of topics that they requested and were important for their learning. These included talks on mobilization, deep vein thrombosis and pulmonary embolism, hydrocephalus, brain tumors, and stoke.

Q: What skills did you teach the other providers and families?
A: I taught them about the importance of mobilization, pressure ulcer prevention techniques, and postoperative management of surgical patients. I also instructed them on a range of neurological conditions, which they had very little exposure to previously. These topics were well received and generated a lot of discussion within the group. I also talked to the nurses about the importance of being assertive in certain instances and how best to advocate patient needs with their physician colleagues.

Q: What did they teach you?
A: I learned a great deal about how to maximize resources when little is available. Due to staffing limitations and cultural practice, family members are at the bedside at all times providing essential care related to activities of daily living, including bathing, feeding, positioning, and personal hygiene. Involving the family and teaching them how to care for their ill family member from the time of admission left a lasting impression.
Q: What types of illnesses did you typically see?
A: The range of illnesses I attended to included HIV-AIDS, alcoholism, tuberculosis, tetanus, sepsis, breast cancer, and stroke.

Q: How were patients with neurosurgical conditions treated?
A: The sister hospital [to Sihanouk Hospital for Hope] that provides fee-for-service care is able to provide limited neurosurgery services. But they do not have MRI equipment or operating room microscopes so the majority of patients with resources travel to Thailand to obtain neurosurgical services. They have the capability to perform simple craniotomies and they perform some spine surgeries.

Q: You helped to establish the first hydrocephalus program in Bhutan. What was involved in getting it off the ground and how has it impacted patients there?
A: I began by writing grant proposals to solicit necessary equipment and supplies, such as shunt passers and ventricular-peritoneal shunts. At the hospital in Thimphu, I instructed the nurses in the operating rooms about how to use the equipment and instructed the nurses on the ward about how to care for the patients postoperatively. Previously, patients who required a shunt had to travel, along with their families, to India to be treated. The cost of this critical procedure was born by the Bhutanese government.
Q: How is the care paradigm different across the regions you’ve visited?
A: In Bhutan and Cambodia, both Buddhist societies, the view on death and illness is very different than western culture. Treatment is often sought first from traditional healers, and the hospitals are often viewed as a place of last resort for medical care. The health care model provides limited access to primary care services, so diseases that could otherwise be treated or prevented are often diagnosed only in their late stages. Once released from the hospital, patients generally return home to be attended to by family members, as there are no skilled nursing care facilities.

Q: What do you see as the biggest barrier to delivering care to underserved populations in developing countries?
A: It is difficult to maintain a presence at a particular location and ensure that practices continue to follow recommendations once a volunteer medical professional departs. It is also very difficult to understand what work has already been done and where it was left off. Ongoing coordination of these programs would be highly beneficial.

Q: What was the most rewarding aspect of your work abroad?
A: Teaching local providers standard practices that will hopefully endure and be passed along to others is very rewarding. I’m a firm believer in the metaphor of teaching people how to fish rather than just offering one.

Q: What was the most surprising thing you learned?
A: In Cambodia, I was surprised to see how young the medical staff was at the hospital, including senior physicians. As explained to me, this was due to the large number of professionals, including doctors, who were killed by the Khmer Rouge during the country’s genocide in the 1970s. The country is still rebuilding itself and as a result many opportunities for mentorship in the medical profession exist.

Q: What’s the next stage of developing your volunteer network?
A: Based on the groundwork I have laid in Bhutan and Cambodia, the UCSF Department of Neurological Surgery has an open invitation to return to these locations. The neurosurgeons there are excited to host us in order to learn from our innovative techniques. Personally, I would like to establish a working relationship with a medical facility close enough to sustain an ongoing presence and partnership. This could be in a country in the Caribbean or Central America that has limited access to neurosurgical care.

Q: What would you tell other health care workers looking to get involved in international medical training or relief programs?
A: Just do. You can start off small with a short trip. If you need to, use your vacation time. You will find it extremely rewarding.

Q: Where is your dream vacation?
A: A trip from Namibia to Botswana, serving local villages along the way.

Teaching local providers standard practices that will hopefully endure and be passed along to others is very rewarding. I’m a firm believer in the metaphor of teaching people how to fish rather than just offering one.
The newly rebuilt Zuckerberg General Hospital in San Francisco features state-of-the-art neurotrauma resources. Image courtesy of Zuckerberg General Hospital.
Newly Redesigned Zuckerberg San Francisco General Hospital and Trauma Center Gives State-of-the-Art Treatment to Patients with Brain and Spinal Cord Injuries

On November 21, 2015, a ribbon-cutting ceremony to celebrate the rebuild of San Francisco’s only Level 1 trauma center drew city officials, hospital staff, patients, and hundreds of San Francisco residents. Renamed the Mark Zuckerberg and Priscilla Chan San Francisco General Hospital and Trauma Center in honor of a $75 million donation from Mark Zuckerberg and Priscilla Chan, the new trauma building has an expanded neuro ICU, including state-of-the-art neuromonitoring equipment and 3T MRI scanners.

With the new trauma center will come expanded efforts toward prospective data collection on spinal cord injuries – a complex group of conditions that remain poorly understood. With more data, clinicians and researchers at UCSF and Zuckerberg General Hospital hope to be able to better predict outcomes for patients and develop new therapies. They are particularly interested in documenting the effects of acute care delivered within the first few hours of injury on short-term and long-term outcomes.

The relative rarity of spinal cord injuries and their heterogeneous nature make it difficult to study them at any one institution, even those with high volumes of trauma patients. Sanjay Dhall, MD, director of spinal cord injury program, is leading a new network of trauma centers across California to coordinate clinical trials for patients suffering from these rare conditions. “We hope that by combining and standardizing data collection across the state, research on spinal cord injury will catch up to the progress that has been made with traumatic brain injury,” says Dhall.

UCSF’s neurotrauma experts, led by Geoffrey Manley, MD, PhD, were also involved in developing the Best Practices in the Management of Traumatic Brain Injury. Released in January 2015 by the American College of Surgeons the new guidelines are based on the most recent evidence-based medicine. The Zuckerberg General Hospital was the first hospital in the nation to receive Joint Commission certification in traumatic brain injury in 2011, highlighting the hospital’s leading expertise in this area.

The Zuckerberg General Hospital is also home to the UCSF Department of Neurological Surgery’s Brain and Spinal Injury Center, which is engaged in translational neurotrauma research. This year the multidisciplinary Center received over $5 million in research funding to advance programs aimed at defining and treating the entire brain and spinal cord injury spectrum.

“We hope that by combining and standardizing data collection across the state, research on spinal cord injury will catch up to the progress that has been made with traumatic brain injury,” – Sanjay Dhall, MD
A Look at the Practice of Increasing Blood Pressure in the Acute Setting of Spinal Cord Injury

Existing Treatment Paradigm

It has long been accepted that extended episodes of hypotension following spinal cord injury lead to worse outcomes. Hypotension may contribute to secondary injury through decreasing blood flow and perfusion, leading to ischemia and impairing neurological recovery. The standard of care in the acute setting of spinal cord injury is to raise the patient's mean arterial blood pressure (MAP), usually by administering a vasopressor, to a level of 85-90 mm Hg for seven days.

However, support for this practice comes primarily from class III evidence and animal models, and despite the high costs of implementing it, there have been no rigorous comparative studies to determine whether or not it has a significant beneficial effect. The recommendation for 85-90 mm Hg is derived from a small group of uncontrolled, underpowered studies and may even be considered somewhat arbitrary. Nevertheless, current guidelines issued by the American Association of Neurological Surgeons and Congress of Neurological Surgeons (last updated in 2013) still advise increasing MAP as a standard part of aggressive medical treatment for spinal cord injury.

High-frequency Physiologic Data Correlates Blood Pressure and Recovery

In a recent study of 74 patients treated at San Francisco General Hospital between 2005 and 2011, researchers at the Brain and Spinal Injury Center found new evidence to support current guidelines. Bedside monitors for patients with acute spinal cord injury measured blood pressure in 1-minute intervals while patients were in the ICU.

Correlating these high-frequency measurements with outcome, the researchers found that patients whose blood pressures averaged in the target zone of 85 or above did indeed have better outcomes on the American Spinal Injury Association Impairment Scale (AIS). However, even for patients whose average MAP was maintained, there were periods were it dipped as low as 40 mm Hg, highlighting the inherent difficulty in keeping MAP above 85 mm Hg in this patient population.

Interestingly, the positive effect of raising blood pressure began to diminish after two to three days. The group of patients with greater than 1 AIS grade of improvement also had the fewest hypotensive episodes in the first 24 hours compared with other time points. Therefore, it may be more important that MAP is maintained as close to the target zone as possible in the first two to three days of treatment rather than achieving a high average over seven days.

Does the type of vasopressor matter?

In a separate study, BASIC investigators looked at complication rates among patients with acute traumatic central cord syndrome according to which vasopressor was used to increase their blood pressure following injury. The most commonly used vaspressors are dopamine and phenylephrine. For most groups of patients analyzed, there was no difference in outcome related to the choice of vasopressors, with the exception of patients over 55 years who received dopamine. Their complication rate was significantly higher than patients in the same age range who received phenylephrine.
This could mean that dopamine may not be the best choice for elderly patients in the acute spinal cord injury setting and BASIC investigators advocate that future clinical trials for spinal cord injury include separate analyses of patients with acute traumatic central cord syndrome, taking into consideration choice of vasopressor.

Is there an ideal blood pressure range?
The laboratory of Michael Beattie, PhD, and Jacqueline Bresnahan, PhD, has been studying rodent models of spinal cord injury for over 30 years. While focusing on standard outcome measures of functional recovery, they also meticulously recorded data on other physiological characteristics such as weight, behavior, bladder function, and appetite. These details had been stored in research notebooks dating back to the early 1990s until bioinformatics expert Adam Ferguson, PhD and postdoctoral fellow Jessica Nielson, PhD breathed new life into them with topological data analysis (see page 24).

In their initial analysis of rats with thoracic spinal cord injuries, the biggest predictor of outcome was, perhaps unsurprisingly, severity of injury. However, another predictor of poor outcome was hypertension at time of surgery; rats with the highest MAP had the worst outcomes.

This result implies that while avoiding hypotension in patients does correlate with better neurological recovery, there may be an optimal range of MAP that has not yet been defined.


An exciting report from the UCSF Brain and Spinal Injury Center, published this year in *Nature Communications*, described how topological data analysis (TDA) can be used to mine thousands of preclinical studies and transform massive amounts of data into useful insights.

TDA is an analytics tool that combines unsupervised pattern detection with visual networks. That is, it can very quickly apply multivariate analysis to large swaths of predictor and outcomes data and display the findings simultaneously in a color-coded map of clustered, individual outcomes. The map represents what the investigators describe as the syndromic space of spinal cord injury and it can be explored for answers to a wide variety of hypotheses.

“It’s giving us the ability to answer questions we didn’t even know to ask at the time the original experiments were being performed,” says Jacqueline Bresnahan, PhD, principal investigator at BASIC.

Earlier this year, principal investigator Adam Ferguson, PhD, and postdoctoral scholar Jessica Nielson, PhD, took TDA for a spin through data from a model of combined brain and spinal cord injury that was developed in the BASIC laboratory of Bresnahan and Michael Beattie, PhD.

Bresnahan and Beattie had found that when the two injuries were contralateral, rats experiencing contusions in both brain and spinal cord had worse neurological deficits than those with an injury in only one area or the other. But surprisingly, rodents with ipsilateral brain and spinal cord injuries had better forelimb function than rodents with only spinal cord injuries or sham brain surgery.

Using TDA to re-analyze the outcomes of the animals in the study, Ferguson and Nielson generated a map that depicted the same result. Only this time, the effect size of the result was shown to be much larger because TDA was able to combine more endpoints than a univariate analysis. This began highlighting the powerful potential of TDA to turn long-held hunches derived from smaller studies into compelling evidence. It also raised the possibility that it could be used to detect important results that may have been missed in other studies simply because they weren’t sufficiently powered to detect a meaningful change in outcome.

This proved to be the case when Ferguson and Nielson turned the TDA lens onto the Visualized Syndromic Information and Outcomes for Neurotrauma SCI (VISION-SCI) repository – a huge set of raw data derived from hundreds of preclinical studies of spinal cord injury. After generating a visual network, they noticed nodes within the topology representing animals with the worst outcomes for functional recovery but not necessarily the worst injuries, and they began investigating why these outcomes were worse than expected.
The subset of animals making up those nodes turned out to be subjects in a preclinical drug trial, which was not included as a predictor in generating the visual network. The trial tested minocycline, methylprednisone, and a nontherapeutic control in small groups of rats with cervical spinal cord injuries. Both the minocycline and methylprednisone groups actually had more tissue damage at the injury epicenter than was seen in controls, and methylprednisone also significantly reduced motor neuron sparing. The study was never published because the therapeutic effect of both drugs was negative.

The importance for the BASIC researchers was that this showed that TDA could identify a drug effect, even with very small sample sizes, and could potentially extract important, unpublished results. “This demonstrates proof-of-concept that large-scale data-sharing coupled with modern analytical tools can deliver insights about the precise limits of therapeutic reproducibility in CNS disorders,” says Ferguson.

Despite thousands of preclinical studies, we still have a limited understanding of the disease process that occurs with CNS injury and few treatment options. And while TDA could be a big step forward for the field, the collaboration between basic scientists and clinicians at BASIC will ultimately be crucial to realizing its potential. The translational research championed at UCSF gets the answers from preclinical models into the hands of health care providers who can use them to design better clinical trials and therapies. This integration may be especially critical for conditions like spinal cord injury, where the sample size of patients is very small. Without this partnership and the high volume of trauma patients seen by UCSF physicians at Zuckerberg San Francisco General Hospital, it would take much longer to apply these findings to clinical use.

Patients with giant intracranial aneurysms or large skull base tumors can experience intracranial arterial occlusion that requires a bypass from an extracranial or intracranial donor artery to restore adequate blood flow. Standard extracranial-intracranial procedures can be invasive, requiring cranial, cervical, and limb incisions to link a high-flow artery (either the common carotid artery or external carotid artery) to the intracranial intracerebral artery. Grafts are typically constructed from the saphenous vein or radial artery, but the caliber and wall thickness of these vessels do not match the recipient vessels.

Director of the Skull Base and Cerebrovascular Laboratory, Arnau Benet, MD, and Chief of Vascular Neurosurgery Michael Lawton, MD, have been exploring the use of the internal maxillary artery (IMA) as an alternative arterial donor. Its closer proximity to the cranial base would require a shorter graft to the recipient artery than is required with the standard approach, improving patency of the graft and flow. But the deep, narrow surgical window in the infratemporal fossa and lack of reliable landmarks made the existing procedure to expose and harvest the IMA difficult to perform and still required a second skin incision to connect the interposition graft.

Using surgical simulation techniques in cadaver specimens, Benet's group found that they could bypass blood flow from the IMA to the middle cerebral artery (MCA) using a different approach through the middle cranial fossa. They used a modified superficial temporal artery graft that could maintain the high flow of both
“The anatomy of the brain has been completely described. But the surgical use of that anatomy is limitless.”

–Arnau Benet, MD, Director of the UCSF Skull Base and Cerebrovascular Laboratory


Jae Seung Bang, MD, is an associate professor in the Department of Neurosurgery at Seoul National University Bundang Hospital in Korea. He specializes in cerebrovascular surgery and is one of 25 visiting scholars who have come to UCSF this year to learn advanced techniques from Chief of Vascular Neurosurgery, Michael Lawton, MD. Here Bang talks about his experience with the Department of Neurological Surgery’s observer program and what he plans to bring back to his practice.

Q. Why did you choose to come to UCSF to observe?
A. Because of Professor Lawton. I think he is the best cerebrovascular neurosurgeon in the world. I wanted to be able to watch his operations and learn more from his surgeries. He is so famous in the cerebrovascular neurosurgical field that every vascular neurosurgeon in the world knows his name and his books, Seven Aneurysms and Seven AVMs.

My senior professor Hee Won Jung, the previous president of SNU hospital, was the first visiting doctor who came to UCSF Neurological Surgery (from 1988 to 1989) and several of his pupils have now also visited. But all of the previous visiting doctors from SNU have been brain tumor surgeons; I am the first vascular surgeon from SNU.

Q. What procedures were you the most interested in learning about before you came?
A. Cerebrovascular bypass surgeries and difficult aneurysm clipping surgeries.

Q. Which procedure has been the most helpful to observe since you have been here? Is it the same as what you were expecting?
A. Yes, it is. Watching and learning Dr. Lawton’s bypass surgeries and clipping surgeries have been the most helpful to me. His surgical skill is amazing, but he also has good decision-making ability.
Q. Would you recommend the program to other neurosurgeons? If so, what are some of the strengths of the program that stood out to you?

A. Of course! I strongly recommend this UCSF observing program.

Professor Lawton’s operating skills and decision-making abilities are amazing! I think his skill is the world’s best. He is also very relaxed and not puzzled in the operating room whenever he is faced with difficult surgical situations (generally, surgeons tend to be very nervous when they are faced with difficult situations), so all of the operating room personnel like him. He always kindly replies to our questions about operations, so many foreign doctors respect him.

There are many established conferences and lectures. The Thursday programs (case conferences, grand rounds, neuroscience lectures) have been especially beneficial to me.

Dr. Arnau Benet Cabero’s 3D neuroanatomy lecture series is the best of the best. His lectures have awakened me to posterior fossa and temporal bone anatomy. His attitude is also amazing.

The operating room personnel, neurosurgical residents and fellows, and academic staff are very welcoming and make transitioning to UCSF easy. When I go to an operating room, circulating nurses and engineers are friendly and positive, which allowed me to adapt myself to UCSF rapidly.
For thousands of patients with medically intractable epilepsy, surgery offers the best option for a chance at freedom from disabling seizures. But the success of surgery depends on precise localization of the “epileptogenic zone” – the region and extent of cortical brain tissue that needs to be removed to prevent further seizures.

In their daily practice, co-directors of the Seizure Disorders Surgery Program Robert Knowlton, MD, and Edward Chang, MD, interpret a complex battery of tests and neuroimaging results to determine whether patients are candidates for surgery. “So many more patients could be permanently free of their seizures,” says Chang. “But for some patients, finding the source of seizures requires the use of advanced diagnostic techniques that are not available everywhere.”

Electroencephalography is the principal test to characterize brain activity related to seizures, but its spatial resolution is intrinsically low. Without corroborating evidence from brain imaging, patients are frequently dismissed as unsuitable candidates for surgery or must undergo costly and invasive tests using electrodes implanted in the brain. Even when resorting to invasive tests, without prior imaging that can help to estimate where the seizures are most likely originating, the likelihood of successful surgery is significantly reduced.
Advances in brain imaging, especially high-resolution MRI, have greatly improved diagnostics by revealing lesions that can be implicated as the cause of seizures in patients with focal epilepsy. This type of imaging serves as a simplified and reliable surgical evaluation tool and can successfully predict outcomes.

About half of patients with focal epilepsy, however, have no lesion detected with MRI. Even when an abnormality suspicious for an epileptogenic lesion is present, it is often too subtle to be diagnostically conclusive or to guide surgical decision-making. Evaluating subtle lesions is also subjective and dependent on a great amount of expertise, which is not available to many patients.

Positron emission computed tomography (PET) scans can be helpful for detecting abnormal brain metabolism in patients being evaluated for epilepsy surgery, particularly those with inconclusive MRI results. However, PET scans are challenging to read, and the expertise needed to provide a diagnostically reliable interpretation is rare even in academic and other highly specialized medical centers.

With the goal of developing a clinician-friendly tool for evaluating patients with epilepsy, researchers led by Knowlton and postdoctoral scholar Ho Sung Kim, PhD, are using advanced computing analysis methods to exploit measurable features in both MRI and PET that can detect “true” lesions and abnormalities. These quantitative methods employ data-driven computer algorithms to provide this unique added information.

“Historically, these types of advances have been relegated to research environments to forward understanding of disease attributes and mechanisms in groups of patients,” says Knowlton. “Unfortunately, this work rarely makes it into the clinical environment where such advances could help care for patients.”

One reason that neuroimaging research can be difficult to translate into widespread use is the lack of fidelity and rigor of image data acquisition and management outside of a research laboratory. The UCSF research team, led by Knowlton, aims to change this by demonstrating the validity of diagnostic results using standard patient scans and control data. Their ultimate goal is to develop common and reliable imaging practices, which are less dependent on rare expertise, to ensure that more patients who would benefit from epilepsy surgery are identified and offered a surgical treatment option.

Research MRI at 7-Tesla magnetic field strength reveals evidence of focal cortical dysplasia (box) missed on 3T MRI interpretation, but accurately discovered with quantitative MRI and PET classifier analysis. Images courtesy of Ho Sung Kim, PhD.
Taking large libraries of existing FDA-approved drugs, the laboratory of Scott C. Baraban, PhD, employs high-throughput screening to quickly identify compounds with the ability to block seizures. The Baraban lab screens drugs in larval zebrafish mimicking genetic forms of epilepsy, which have surprisingly significant genetic similarity to humans. Unlike cell-based in vitro screening assays, the in vivo zebrafish model maintains the complex neural networks that are disturbed in various types of epilepsy, making results more likely to be correlated with actual therapeutic outcomes.

The first stage of the screening process tracks the fish's behavior—high-velocity locomotor movements are a reliable indicator of convulsions and all of the epileptic fish start out experiencing these movements. If a drug is able to stop the convulsions and is not toxic, it moves on to a second phase of testing with electrophysiological recording. Just like recording brain activity in humans, the Baraban lab uses microelectrodes placed in the forebrains of agar-immobilized zebrafish to record local field potentials and determine which of the drugs that restore locomotion are doing so by silencing the underlying neural networks.

Using this strategy in 2013 to screen 320 available compounds, Baraban’s group identified clemizole as being able to block seizures in a zebrafish model of Dravet syndrome—a devastating form of pediatric epilepsy that is highly resistant to current antiepileptic drugs and causes severely delayed development, cognitive deficit, and bouts of uncontrolled status epilepticus. Clemizole had not previously been known to have antiepileptic activity, and the lab is currently working toward additional preclinical proof-of-principle and safety data with this compound.

Most recently, the Baraban lab screened a new panel of 1000 existing compounds in the Dravet syndrome model and initially found 20 that blocked seizure behavior in the zebrafish. Four of the initial 20 candidates moved on to the second phase of evaluation and one was found to be a true antiepileptic. The drug, dimethadione, was previously known to have anti-seizure activity and has been prescribed to patients.

As the screening is blinded, identification of a drug currently indicated for seizures shows that the phenotype-based antiepileptic drug screening is a promising strategy for identifying drugs suitable for evaluation in patients. Another benefit of the in vivo model is that it can also quickly identify those that would be too toxic to consider, without having to apply testing in higher mammals, such as rodents. The overall strategy to use zebrafish to mimic specific human forms of epilepsy, and then rapidly identify potential therapeutic compounds using these zebrafish, offers an example of how precision medicine may evolve in the coming years.

UCSF scientists have discovered a possible mechanism for how deep-brain stimulation (DBS), a widely used treatment for movement disorders, exerts its therapeutic effects. Few medical treatments show results as rapid and dramatic as those seen with DBS, in which surgically implanted devices deliver electrical pulses to inner brain structures involved in movement. In most Parkinson’s disease (PD) patients who receive the treatment, symptoms of slow movement, tremor, and rigidity sharply diminish soon after the stimulation device is activated, and quickly return if the device is turned off.

But surprisingly, there has been very little understanding of precisely why and how DBS works so well – a lack of knowledge that has held back efforts to further improve the therapy. Despite the great success of DBS, some significant problems remain. Customizing the stimulation delivered by DBS devices for each patient to maximally reduce symptoms is challenging and time-consuming. And a minority of patients never obtains the full benefit their physicians expect. With a better understanding of how DBS acts on brain circuits, researchers hope to address these shortcomings and make DBS an even more effective treatment.

The new research, published online in *Nature Neuroscience*, reveals that DBS keeps PD symptoms in check by reducing excessive synchronization of brain activity in the motor cortex, a region on the outer surface of the brain that governs movements of the body.

“This therapy is becoming widespread for many brain disorders aside from movement disorders, including psychiatric conditions such as depression, but no one knows how it works,” says Philip Starr, MD, PhD, the Dolores Cakebread Chair in Neurological Surgery and senior author of the new study. “This is a significant step in answering this question on the level of brain networks, not just addressing where you’re actually applying the stimulation in the brain.”
Previous research led by Coralie de Hemptinne, PhD, a postdoctoral fellow in Starr’s laboratory, laid the groundwork for the new study. In 2013, de Hemptinne, Starr, and colleagues reported in the *Proceedings of the National Academy of Sciences* that a measure of synchronized rhythmic activity in the brain, which normally varies with movement or other behaviors, is excessively high in the cortex in PD.

In that paper, the team hypothesized that this lockstep synchronization of brain circuits in PD thwarts the flexibility the brain requires to plan and execute movements, and that DBS might work by decoupling activity patterns in the motor cortex.

In the new work, “since we had found this excessive synchrony in PD patients, we decided to see if there’s a relationship between that synchrony and symptoms, and whether synchrony is lessened when symptoms are improved by DBS,” says de Hemptinne, first author of the *Nature Neuroscience* paper. “We measured synchrony in the motor area of the brain before, during, and after DBS, and while the patient was resting or engaged in a movement task in which they had to reach and touch a computer screen.”

During surgery on 23 patients with Parkinson’s disease in whom permanent DBS electrodes were being surgically implanted, the UCSF team slid a temporary strip of six recording electrodes under the skull and placed it over the motor cortex. As in the prior research, recordings of neural activity showed excessive synchronization of activity rhythms in the patients.

As the name of the therapy implies, the ends of the stimulating leads of DBS devices are placed in a structure deep in the brain known as the subthalamic nucleus (STN), which is part of a “loop” of neural circuitry that includes the motor cortex on the brain’s surface. When the DBS device was activated and began stimulating the STN, the effect of the stimulation reached the motor cortex, where over-synchronization rapidly diminished. If the device was turned off, excessive synchrony re-emerged, more gradually in some patients than others.

DBS surgery generally takes about six hours, and during the middle of the procedure patients are awakened for testing of the device and to ensure that the stimulating lead is properly placed in the STN. During this period the researchers asked 12 of the patients to perform a reaching task in which they had to touch a blue dot appearing on a computer screen. Importantly, says Starr, recordings revealed that DBS eliminated excessive synchrony of motor cortex activity and facilitated movement without altering normal changes in brain activity that accompany movements.

“Our 2013 paper showed how Parkinson’s disease affects the motor cortex, and this paper shows how DBS affects the motor cortex,” says Starr. “With these two pieces of information in hand, we can begin to think of news ways for stimulators to be automatically controlled by brain activity, which is the next innovation in the treatment of movement disorders.”

Because in these experiments the recording strip had to be removed before the end of surgery, recording data was collected over a relatively short time. To broaden opportunities for research, Starr and his team have collaborated with medical device company Medtronic on a new generation of permanently implantable DBS devices that can record activity in the motor cortex while delivering stimulation to the STN.

Five UCSF patients have been implanted with these new devices, and all data they collect can be uploaded for research during follow-up visits, de Hemptinne said, which will bring an even deeper understanding of how DBS reshapes brain activity.

“Now we can try to find even better correlations between DBS and symptoms, and we can even look at the effects of medications,” says de Hemptinne. “This new ability to collect data over a longer time course will be very powerful in driving new research.”

Other UCSF researchers taking part in the work were postdoctoral fellow Nicole Swann, PhD; Jill L. Ostrem, MD, professor of neurology; Elena Ryapolova-Webb, now a graduate student at UC Berkeley; Marta San Luciano, MD, professor of neurology; and Nicholas Galifianakas, MD, MPH, assistant professor of neurology. The research was funded by the Michael J. Fox Foundation for Parkinson’s Research and by the National Institutes of Health.

*This article was written by Peter Farley and first appeared in the UCSF News Center on April 13, 2015 (www.ucsf.edu/news).*
Combining Cell Transplants or Gene Therapy with Deep Brain Stimulation for Parkinson’s Disease

Deep brain stimulation (DBS) for Parkinson’s disease can manage symptoms such as tremor, stiffness, and slow movement by providing electrical stimulation to areas of the brain involved in motor control. But as the underlying disease progresses, DBS becomes less effective and ultimately insufficient to manage symptoms.

There are currently no treatments that can halt or slow the degenerative nature of Parkinson’s disease. However, gene therapy and cell transplantation to replace the dopamine-producing neurons that die off as the disease progresses are two strategies that researchers continue to explore. While both have been tested in historical trials with little success, newer iterations of these therapies use cells and gene therapy vectors of better quality, which scientists have engineered to address previous failures.

Advancements in biological delivery strategies are also overcoming previous shortcomings related to injecting cells into the central nervous system. This year a study led by UCSF neurosurgeon Daniel Lim, MD, PhD, reported on the use of radially branched deployment combined with interventional MRI to deliver cells. Published in Molecular Therapy, the article described successful delivery of human embryonic stem cell–derived dopaminergic neurons into swine striatum.

By monitoring the infusion in real time, surgeons can ensure that a sufficient amount of infusate covers the target area of the brain, which was not possible with previous methods using preoperative images to guide direct injections. With the radially branched deployment, cells can be delivered at multiple points along a single tract of brain penetration, expanding the area of coverage without incurring the risks associated with multiple brain penetrations.

Despite the promise of novel biological therapies, it can be difficult to justify urging patients to enroll in clinical trials when an existing therapy, in the form of DBS, has been proven to alleviate symptoms. In an article published this year in Movement Disorders, specialists at UCSF suggest that future trials of novel cell transplant or gene therapies may be combined with DBS to overcome ethical concerns, as well as financial constraints of clinical trials.

Many patients with Parkinson’s disease who are candidates for DBS are likely to also be candidates for an experimental biological therapy. By randomizing patients to either a control group that receives only DBS or a treatment group that receives both DBS and an experimental therapy, all patients will receive benefit from DBS and an invasive sham procedure can be eliminated. Cell or gene therapies can be infused during the same procedure as for implantation of DBS leads, and as DBS is an established, reimbursable procedure, the costs for performing the trial may be lowered.

The authors also suggest that because DBS and medications work to address symptoms and biologics and gene therapy work to address the underlying disease mechanisms, it is possible that neuromodulation and biologics could enhance one another, producing an additive effect.
Cervical spinal cord stimulation can be used to treat many types of chronic refractory pain, including complex regional pain syndrome or cervical radiculopathy that results from a failed back surgery. But there have been few studies examining whether the risks of complication outweigh the potential benefits of the procedure, which needs to be tailored to a select patient population.

Case reports and small series have indicated that rates of spinal cord injury, the most severe potential complication, are relatively low. But with small studies come a danger of under-reporting the actual risk and there has been a need for a more comprehensive analysis to be able to accurately counsel patients seeking surgery.

Analyzing over 2000 outcomes for cervical spinal cord stimulation entered into a national U.S. database, chief of peripheral nerve surgery Line Jacques, MD, and neurosurgery residents Andrew Chan, MD, and Ethan Winkler, MD, found that although the risk of spinal cord injury was higher than previously reported, it was still only 0.5%. Rates of neurological, medical, and general perioperative complications were also relatively low (1.1%, 1.4%, and 11.7%, respectively).

“After collecting this data, spinal cord stimulation may be a good option for carefully selected patients because the complication rate is low and it gives them another option that may help alleviate their pain,” said Jacques.

First author of this study, Andrew Chan, MD, was given the Charlie Kuntz Scholar award from the Congress of Neurological Surgeons when the results were presented at the organization’s 2015 annual meeting.

Peripheral nerve syndromes make up a complex group of disorders. Often misdiagnosed because of incomplete diagnostics or symptoms that overlap with similar conditions, they can go untreated for years and significantly affect quality of life.

At UCSF, cutting-edge imaging techniques can quickly identify sources of compression that can be alleviated with surgery. Delays in treatment for patients who are good surgical candidates can result in irreversible nerve damage and untreatable pain, so it can be helpful for patients with symptoms of neuropathy to be evaluated for surgery soon after conservative therapies fail.

UCSF’s world-renowned neuroradiology team uses magnetic resonance neurography (MRN) to reveal otherwise invisible features of the nerve’s anatomy. While the technology has been in use since the early 1990s, only recently has it become robust enough to accurately confirm sources of nerve compression and provide a valuable adjunct to electrophysiology and physical exam. Newer MR sequences like STIR, SPAIR, and steady-state with 3D volumetric acquisition provide better fat suppression and greater structural detail than ever before.

Diffusion tensor imaging is also used at UCSF, giving physicians pictures of the nerve fascicles, which can be used to differentiate among nerve tumor types or to assess the likelihood of spontaneous axonal regrowth following nerve injury.

MRN can be particularly useful in diagnosing rare conditions like neurogenic thoracic outlet syndrome (nTOS), which results from compression of the brachial plexus anywhere along its span from the thoracic outlet to the axilla. Like many other compression syndromes, including disputed TOS, it results in pain in the neck, shoulder, arm, and hand. While patients with disputed TOS have no clear source of compression and derive little benefit from surgery, patients with nTOS can experience a dramatic improvement once the source of compression has been identified and the brachial plexus has been decompressed.

The additional diagnostic information given by newer imaging technologies not only allows for a more confident diagnosis and better decision-making, but it also allows the surgical team to tailor surgical procedures more accurately. Mapping a source of compression or injury with MRN and DTI can greatly increase the preservation of nerve function and the safety margin of any surgical intervention.


Representative images showing compression between the anterior and middle scalene muscles. A: Coronal STIR-weighted MR neurogram shows increased signal and expansion in the C-6 nerve root as it enters the interscalene space (arrow). B: Coronal STIR-weighted MR neurogram shows increased signal in C-7 and C-8 nerve roots as they enter the interscalene space. C: MR tractography shows impression (arrows) of the scalene muscle (red band on tractography) on C-6 as it enters the interscalene space and on C-8 where it is compressed by scalene muscle. The tract size is decreased distal to the site of compression. D: Intraoperative photo demonstrates the decompressed C5–8 nerve roots, the upper trunk (white vessel loop), and the phrenic nerve (red vessel loop) after anterior scalenectomy and neurolysis.
Stacy Wong, NP, Provides Continuity of Care for Patients with Peripheral Nerve and Pain Disorders

Stacy Wong is a nurse practitioner in the Department of Neurological Surgery at UCSF. She obtained her bachelor’s degree from the Duke University School of Nursing in North Carolina and later pursued her master’s degree from the UCSF School of Nursing, specializing in acute care. Before joining the Department of Neurological Surgery in 2011, Wong worked as a registered nurse on the neurological surgery transitional care unit at the UCSF Medical Center.

Wong has recently become a dedicated nurse practitioner in the Peripheral Nerve and Pain Program, working with Chief of Peripheral Nerve and Pain Surgery Line Jacques, MD. She serves as a link with patients’ primary care physicians and provides technical support for any implanted devices that may be used to control pain. Wong enjoys the continuity of care she can provide for her patients throughout their experience at UCSF. Her main focus is to educate, advocate, and counsel her patients on what to expect before, during, and after surgery.
In 2012, a missense mutation in the histone 3 variant H3.3 was discovered in biopsies of pediatric brainstem glioma. Dubbed the K27M mutation, the amino acid lysine (K) is substituted with methionine (M) at the position 27 of H3.3. It has since been estimated that nearly 70% of diffuse intrinsic pontine gliomas harbor the mutation.

For immunologist Hideho Okada MD, PhD, the discovery of the K27M mutation represents a much-needed breakthrough in therapy for brainstem tumors. In the field of immunotherapy, it’s a rare representation of a tumor-specific antigen—a targetable mutation specific only to cancer cells and not normal cells. This characteristic is critical for avoiding dangerous autoimmune reactions.

Another feature of the K27M mutation that makes it an ideal target is that it appears to be spread out throughout the entire tumor and not just a few cells within the tumor mass. This makes it more likely that the immunotherapy could wipe out most, if not all, of the tumor.

With grant support from the V Foundation for Cancer Research and the NIH, Okada and his colleagues are working to develop a therapy that transduces a patient’s own T-cells with the receptor for the K27M mutation, priming them to recognize and attack the mutated tumor cells.
Four New Institutions Join the Pacific Pediatric Neuro-Oncology Consortium

In 2012 the Pacific Pediatric Neuro-Oncology Consortium (PNOC) was formed as a network of 11 children’s hospitals offering cutting-edge clinical trials for children with brain tumors. Based at UCSF, PNOC’s mission has been to leverage advances in personalized medicine strategies to offer new hope for children with malignant disease. In 2015, the consortium grew to 15 hospitals that are home to over 90 specialists in pediatric neuro-oncology care and research.

The four new institutions that joined in 2015 are: Dana-Farber Cancer Institute, Nationwide Children’s Hospital, St. Louis Children’s Hospital, and Ann and Robert H. Lurie Children’s Hospital of Chicago.

For information about PNOC and how to refer patients for clinical trials in their area, visit pnoc.us.

PNOC Clinical Trials Open for Enrollment

- A pilot trial testing the feasibility of using molecular profiling to guide an individualized treatment plan in children and young adults with newly diagnosed diffuse intrinsic pontine glioma
- Phase II study of everolimus for recurrent or progressive low-grade gliomas in children
- Safety and phase 0 study of vemurafenib, an oral inhibitor of BRAF\textsuperscript{V600E}, in children with recurrent/refractory BRAF\textsuperscript{V600E}-mutant glioma

Chief of Pediatric Neurological Surgery, Nalin Gupta, MD, PhD, is an investigator with the Pacific Pediatric Neuro-Oncology Consortium and helps to develop new clinical trials for malignant brain tumors.
The Pediatric Brain Tumor Foundation Institute at UCSF

The Pediatric Brain Tumor Foundation (PBTF) and UCSF have been long-time partners in the search for a cure for childhood brain tumors. UCSF is one of three PBTF Institutes in the nation, and this investment in our research laboratories funds several innovative research projects.

Four new projects are investigating the origins of pediatric brain tumors, new treatment strategies, and how to reduce late effects of radiation therapy after it has been used to successfully manage tumor growth. The PBTF Institute grant also funds critical core resources used by all researchers, including cell lines, animal models, and a tumor tissue bank.

On October 10, 2015 members of the Pediatric Brain Tumor Center at UCSF were proud to participate in the Pediatric Brain Tumor Foundation’s annual Starry Night 8.5K walk/run to raise funds for research and family services. Starry Night’s San Francisco’s Hero Award honored Chair of Neurological Surgery, Mitchel Berger, MD and the UCSF Benioff Children’s Hospital Child’s Life team.

Current PBTF Institute Research Projects

The oligodendrocyte developmental methylome to characterize progenitors for pediatric glioma (Investigators: Arturo Alvarez-Buylla PhD and David Rowitch MD, PhD)

Targeting tumor-associated inflammatory cells to ameliorate radiation-induced cognitive changes (Investigators: Nalin Gupta MD, PhD and Susan Rosi, PhD)

Personalized treatment strategies for DIPG (Investigators: Sabine Mueller MD, PhD, Nalin Gupta MD, PhD, and Joseph Costello, PhD)

Targeting Wnt-driven angiogenesis in pediatric glioma (Investigators: David Rowitch MD, PhD and William Weiss MD, PhD)
Deep Brain Stimulation for Pediatric Movement Disorders

UCSF is home to one of the nation’s most experienced surgical teams for deep brain stimulation to treat pediatric dystonia and movement disorders – approximately 60 cases have been performed. The team includes neurosurgeons, neurologists, neuropsychologists, and clinical nurse specialists who work to provide excellent clinical care to children suffering from movement disorders and to improve their quality of life.

Deep brain stimulation can be used to treat both primary and secondary dystonia and rarer diseases like essential tremor and juvenile Parkinsonism. It can be used to treat patients who are not helped by medications or who cannot tolerate the severe side effects of medications. It is possible that surgical intervention could give life-long control over movement disorders.

The UCSF Benioff Children’s Hospital at Mission Bay has a specialized surgical suite to accommodate the ClearPoint platform, which is ideal for children. ClearPoint, developed at UCSF, allows deep brain stimulation leads to be implanted under direct visualization while patients are under general anesthesia inside an MR scanner. Traditional methods of implantation require patients to be awake, which can be difficult for children.

Two case series for deep brain stimulation in children have been published by the UCSF team in *Journal of Neurosurgery: Pediatrics*. The second series, published in 2014, reported results using the ClearPoint platform and demonstrated outcomes that were equal to the best results for awake deep brain stimulation lead implantation.

New Gene Therapy Trial for Children with AADC Deficiency

Aromatic L-amino acid decarboxylase (AADC) is an enzyme involved in the synthesis of neurotransmitters. Patients with the rare genetic disorder known as AADC deficiency have mutations in the *DDC* gene that affect the production of AADC, preventing the conversion of the chemicals L-dopa and 5-hydroxytryptophan into dopamine and serotonin.

As a result, children suffer from a variety of symptoms including developmental delay, autonomic dysfunction, cognitive disabilities, and severe movement disorders resembling dystonia or Parkinson’s disease.

In a new gene therapy trial funded by the NIH, UCSF investigators will infuse adeno-associated viral vector carrying the AADC gene (AAV2-AADC) into the putamen of children with AADC deficiency. By increasing the expression of AADC in the brain, physicians hope that the severity of patients’ symptoms will be reduced and their quality of life will improve.

While this gene therapy strategy has been previously employed with direct injection with some success, the UCSF trial will use convection-enhanced delivery to cover a larger volume of brain tissue than can be achieved with direct injection. The injection will also be visualized in real time on intraoperative MR images to ensure that the correct dose covers the target area.

A trial of the AAV2-AADC gene therapy for adults with Parkinson’s disease began enrollment in 2014, and successful preliminary results provided a basis for extending the therapy to AADC deficiency. The trial for children will open for enrollment in the spring. For more information, contact Nalin Gupta, MD, PhD at Nalin.Gupta@ucsf.edu.
Hunting for Seizures in Children: Neurosurgeons Succeed by Casting Smaller Nets

The Pediatric Epilepsy Surgery Service has a powerful new tool in the fight against pediatric epilepsy: stereoelectroencephalography (stereo-EEG). Using this newer technology, epileptologists and neurosurgeons are able to study epileptic patients, pinpoint the source of their seizures, and generate treatment plans, all while minimizing surgical risk.

Epilepsy specialists ask the same question for all of their patients: where are the seizures coming from? To answer this, many tests are employed including electroencephalograms (EEGs), MRIs, positron emission tomography (PET) scans, and others. In some cases, more invasive maneuvers are necessary to study the brain and this often is accomplished with small electrodes that are implanted with a surgery. “Sometimes, pictures and scalp recordings are just not enough,” explains Kurtis Auguste, MD, Director of the Pediatric Epilepsy Surgery Service at UCSF Benioff Children's Hospital at Mission Bay. “When we reach that limit to our understanding, we begin to think about a surgical procedure to ‘listen’ to the brain directly.”

The traditional surgical approach to study seizure activity in challenging cases is to implant indwelling electrodes on the surface of the brain. Rows of small electrodes are placed together in sheets called grids or in smaller, linear arrangements called strips and then are placed on the brain. To provide access, surgeons must create an incision along the scalp and a window in the skull called a craniotomy. This surgery has been used for decades and has been considered the gold standard for the most difficult-to-treat epilepsy patients. It requires a second surgery to remove the electrodes and resect the seizure focus. Each surgery also requires several hours to perform and carries with it a small risk of bleeding, infection, and injury to brain tissue. Finally, as with any surgery, there can be incisional pain. “We’ve always done well with keeping our kids comfortable after brain surgery,” says Auguste, “but we’re always looking for better ways to do things.”

Stereo-EEG is the most recent addition to the pediatric epilepsy armamentarium. It collects the same information as grids and strips, but does so by using electrodes arranged in a fine wire called a ‘depth electrode’ instead of on sheets or strips. “The depth electrodes are really no bigger than a few strands of hair when you look at them,” says Auguste. “And the incision we use to place one is just over a millimeter so there’s barely any hair shaved. It’s really quite remarkable.”

The electrodes are strategically placed into regions of interest that are candidates for the source of the patient’s seizures. To achieve this level of precision, the epilepsy surgery team uses stereotactic MRIs and computer software to isolate potential targets for the placement of depth electrodes. “All of the preoperative
data we have on a patient goes into the planning and decision-making,” says Auguste. From that data, a unique surgical plan is generated for depth electrode placement in each patient. The added benefit of stereo-EEG depth electrodes is that surgeons can now access deeper areas of the brain safely, in ways not possible with traditional grids and strips.

Auguste likens the choice between stero-EEG and standard techniques to fishing. “We can obviously take a boat, travel out to sea, cast a large net and reel it in. We’ll catch more fish than we can possibly eat but look at all the time we’ve wasted. Plus, we’ll probably collect unwanted things,” he says. “With stereo-EEG, we’re spearfishing. We see the biggest, juiciest fish right there at the shore. We catch only what we need without the waste.”

As with any neurosurgical procedure in children, the priority is always safety. A drawback of traditional multi-stage grid and strip procedures has always been the invasive nature of larger incisions, larger craniotomies, and exposure of cerebral cortex that turned out not to be the source of seizures. With each updated technique, surgeons are focused on accomplishing more with less. Stereo-EEG represents the newest advance in that continuum. It has allowed surgeons to avoid implanted grid and strip surgeries altogether. For patients who still go on to need the traditional approach, the information collected with stereo-EEG helps minimize the size of planned craniotomies and exposure of cortex.

“There may always be a role for traditional grid and strip surgeries in pediatric neurosurgery,” says Auguste. “Our recommendations are always tailor-made to the needs of the individual. But our hope is that more and more children will benefit from this minimally invasive approach whenever possible.”

“We’ve always done well with keeping our kids comfortable after brain surgery, but we’re always looking for better ways to do things.” – Kurtis Auguste, MD, Director, Pediatric Epilepsy Surgery Program
Perhaps the single most important question physicians get from their patients is whether or not a treatment will work. Unfortunately, the answer is not always straightforward. A procedure may have a dramatic effect on one patient but do nothing to ease the pain of another with the same illness.

“You can examine the literature and quote patients a number based on averages in case series and your experience,” says Christopher Ames, MD, co-director of the UCSF Spine Center. “You also can apply factors such as age or smoking habits. But that doesn’t tell you a whole lot about an individual patient and how these things may interact to affect outcome.”

Predictive analytics has long been used to predict the behavior of individual consumers in industries such as finance and insurance, guiding everything from marketing campaigns to loan practices. But until recently, it has seldom been used by doctors to guide treatment decisions. With rising health care costs and increasing pressure to narrowly define the population that will benefit from an expensive procedure, however, that has begun to change.

Estimating outcomes in health care is usually done using odds ratios and regression analyses. These familiar statistical methods rely on a set of control data to confirm or refute a specific hypothesis. Predictive modeling, on the other hand, uses computational methods to identify patterns in large data sets that can be applied to individuals.
Can a Computer Program Predict Your Chance of Having a Major Complication During Spine Surgery?

Over the last year, Ames, who specializes in surgery for adult spinal deformity, began investigating how predictive analytics could be used to better predict outcomes for his patients. Currently, 27.5 million elderly people in the U.S. live with some degree of spinal deformity, and with a growing aging population that number will likely increase to 60 million by 2050.

In studies that measure patients’ improvement on scales of functional ability and pain, surgery undoubtedly benefits adults with spinal deformity as a group. But some patients do not improve, suffer major unforeseen complications, or do worse after surgery. A recent study conducted by the International Spine Study Group compared the outcomes of patients who had severe structural deformity but little disability prior to surgery with the outcomes of patients with minimal deformity but severe disability. Surprisingly, there was no difference in Oswestry Disability Index (ODI) scores or neck disability. “This was a very interesting result,” says Ames. “What other factors are contributing to good or bad outcomes at the level of the individual patient?”

UC San Diego medical student Justin Scheer worked with Ames to develop five different bootstrapped decision trees that analyzed variables related to demographics, surgical data, quality of life, and imaging. They applied the model to the outcomes of patients registered in the International Spine Study Group database to see if it could predict ODI Score; development of proximal junction kyphosis; and major complications.
The ODI is a validated, self-administered questionnaire that is one of the primary tools used to measure pain and disability among patients with back pain and spinal disorders. Using 43 clinical variables for 198 patients, the model was able to predict with 86% accuracy whether a patient would reach a minimally important difference on the ODI scale after surgery. The investigators noted that the 11 variables revealed to be most important for prediction were largely not modifiable by surgery, indicating that baseline patient characteristics were the most important factors for reaching a meaningful change in disability score.

Proximal junction kyphosis and proximal junction failure are among the more common complications following surgery for spinal deformity, and patients with these complications can require a second surgery to restore sagittal balance. Current literature puts the risk for proximal junction kyphosis following adult deformity surgery as high as 40%. As with ODI scores, the new predictive model was used to analyze 2-year follow-up data from 510 patients and was 86% accurate in identifying those who would develop proximal junction kyphosis or failure.

The risk for major complication during spinal deformity surgery ranges from 14% to 58%, and there are no validated predictive models for determining which patients will have complications. Using data from 558 patients, Scheer, Ames, and their colleagues at the ISSG identified 20 variables from an initial 45 that could be combined to predict with 87.6% accuracy the risk of intraoperative and perioperative complications.

### Top 11 Predictors of Improvement in Oswestry Disability Index Score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Predictor Value</th>
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<tbody>
<tr>
<td>Gender 1</td>
<td>SRS-Schwab Coronal curve type</td>
</tr>
<tr>
<td>SRS-Schwab Coronal curve type</td>
<td>Number of interbody fusion levels</td>
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<tr>
<td>Age</td>
<td>Maximum Cobb angle (&lt;30 deg, 30-60, &gt;60)</td>
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<tr>
<td>BMI</td>
<td>Coronal C7 plumbline distance</td>
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<tr>
<td>Revision surgery (yes/no)</td>
<td>Pelvic tilt (PT)</td>
</tr>
<tr>
<td>At least 1 comorbidity (yes/no)</td>
<td>Mismatch between pelvic incidence and lumbar lordosis (PI-LL)</td>
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<tr>
<td>Number of comorbidities</td>
<td>Thoracic kyphosis (T2-T12)</td>
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<tr>
<td>Charlson comorbidity index</td>
<td>C7 sagittal vertical axis (SVA)</td>
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<tr>
<td>Race</td>
<td>T1 spino-pelvic inclination (T1SPI) 7</td>
</tr>
<tr>
<td>Depression (yes/no)</td>
<td>T1 pelvic angle (T1PA) 9</td>
</tr>
<tr>
<td>Osteoporosis (yes/no)</td>
<td>Oswestry Disability Index (ODI)</td>
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<td>Physical Component Score from SF36 (PCS)</td>
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<tr>
<td>ASA grade 8</td>
<td>Mental Component Score from SF36 (MCS)</td>
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<td>Smoker (yes/no)</td>
<td>SRS Activity 2</td>
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<td>Upper-most instrumented vertebra</td>
<td>SRS Pain 10</td>
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<tr>
<td>Lower-most instrumented vertebra</td>
<td>SRS Appearance</td>
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<td>Number of posterior levels fused</td>
<td>SRS Mental</td>
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<td>Decompression (yes/no)</td>
<td>SRS Satisfaction</td>
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<tr>
<td>Number of decompression levels</td>
<td>SRS Total 11</td>
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<td>Smith-Peterson osteotomy (yes/no)</td>
<td>Back pain numerical rating scale 3</td>
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<tr>
<td>Number of Smith-Petersen osteotomies</td>
<td>Leg pain numerical rating scale</td>
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<tr>
<td>3-column osteotomy PSF/VCR (yes/no)</td>
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Point-of-Care Application

The next step for bringing the new predictive model to clinical care will be to validate it with more data. In 2015, the Scoliosis Research Society awarded Ames a $50K grant to conduct a 2-year prospective, multicenter validation study with data from a European health care database. The award will also be used to validate what Ames has named a frailty index – a new index of over 90 variables that can gauge a patient’s fitness and help identify those who are most likely to benefit from surgery.

While their current analyses have already brought forth exciting results, Ames and Scheer say that increased accuracy can be had with more sophisticated neural network models, which are applications of machine learning that can analyze complex interactions. Ames emphasizes that it is the interaction of variables that is most important for increasing the accuracy of a prediction for an individual patient.

Applying predictive analytics to patient care has powerful implications for a wide range of public health issues, ranging from health insurance to informed consent. In the future, Ames predicts that the models can be deployed in real-time on handheld mobile devices in the clinic to provide an immediate assessment of risk and better counsel patients. The models can also be applied at the hospital level to predict the likelihood of repeat surgeries or time needed in the ICU.

“We will eventually be able to say ‘at this hospital, with this surgeon, and your patient profile, these are the odds of success or complication,’” Ames says. “No question, it’s the future.”
UCSF neurosurgeons Praveen Mummaneni, MD, and Dean Chou, MD, have pioneered minimally invasive surgical techniques for a number of spinal pathologies. Over the past several years they have been using a technique they call the ‘mini-open transspinous approach’ to remove tumors at the thoracolumbar junction. These tumors are still almost exclusively removed via laminectomy—a procedure that involves removing part of the vertebrae, large incisions, and significant tissue destruction.

Their transspinous approach, initially published in 2011 with former neurosurgery resident Daniel Lu, MD, uses an expandable tubular retractor that can be maneuvered through a 3- to 4-cm incision. The
primary goal of this approach is to avoid unnecessary damage to ligaments and musculature, preserving as much of the normal anatomy as possible. This year, Mummaneni and Chou published one of the largest comparisons (51 patients) of transspinous minimally invasive vs open surgery for intradural-extramedullary tumors.

Intradural-extramedullary tumors are those that form within the dura mater but outside the spinal cord itself. They are relatively benign and slow growing, usually meningiomas or nerve sheath tumors, and patients may have symptoms such as back and leg pain for many years before a diagnosis is made. Patients undergoing laminectomy generally have good outcomes, with minor risks. But Chou and Mummaneni were looking for away to avoid the tissue trauma and eliminate any postoperative instability for these patients.

“At the thoracic-lumbar junction, removing too much bone with a laminectomy can lead to junctional instability and kyphosis,” says Mummaneni. “Spinal instability and damage to tissue in this area can also lead to adjacent segment degeneration, eventually requiring fusion.” A later need for fusion may be especially burdensome for younger patients who wish to have active lives for many years to come.

In the 2015 study, co-authored by Kunal Raygor, MD, and Khoi Than, MD, patients undergoing open resection lost more than twice the amount of blood than patients undergoing minimally invasive surgery, indicating that the need for blood transfusion may be lower with the smaller operations. Otherwise, there were no significant differences in outcomes or complication rates between the two groups, demonstrating that the minimally invasive approach is as good a procedure as the traditional laminectomy.

In addition to less blood loss, minimally invasive spinal procedures have been shown to correlate with lower infection rates in large, multi-institutional analyses, and may also be more cost effective. But the strongest indication for this type of surgery may be patient preference. “One of the most frequent questions I get from my patients is whether or not I can offer them a minimally invasive surgery,” says Chou. “Most people don’t want to undergo a major surgery if we can offer the same results with a minimally invasive procedure.”
UCSF participated in a large, multi-center review, conducted by the International Spine Study Group, of over 400 patients who underwent either minimally invasive or open surgery for adult spinal deformity. The results, presented at the 2015 meeting of the North American Spine Society, showed that patients undergoing minimally invasive procedures experienced significantly less blood loss and shorter recovery periods in the intensive care unit. The shorter hospital stays also correlated with a reduction in costs.

Multi-center Study Demonstrates Benefit of Minimally Invasive Surgery to Correct Spinal Deformity

At UCSF, neurosurgeons use lateral approaches and percutaneous instrumentation to correct scoliosis. “Not all patients need huge operations that open the entire back to correct scoliosis,” says Dean Chou, MD. “For many patients with mild to moderate deformity we can perform the same correction with a few small incisions that don’t strip the back muscles.”

New Minimally Invasive Specialist Joins the Team, Provides Surgical Outpatient Procedures for Spinal Disorders

This year, Aaron Clark, MD, PhD joined the Neurospinal Disorders Program. Clark recently completed a fellowship in minimally invasive spine surgery at the Semmes-Murphey Neurologic and Spine Institute in Memphis, Tennessee. The main focus of his practice is to provide minimally invasive outpatient procedures for lumbar/cervical herniated discs and lumbar/cervical stenosis. In addition to minimally invasive procedures, Clark specializes in lumbar fusion surgery.

“It is exciting to offer UCSF patients minimally invasive spinal operations at our newly renovated Mount Zion Outpatient Surgery Center,” says Clark. “These operations provide excellent outcomes with smaller incisions, less tissue damage, and less post-operative pain compared to traditional operations. Patients I am treating with minimally invasive microdiscectomies, laminectomies, and foraminotomies have consistently been going home on the same day of surgery.”

Clark earned his medical and postdoctoral degrees from the Medical College of Virginia. He is a graduate of UCSF’s neurological surgery residency program, where he developed his interest in spine surgery and began publishing research on spinal oncology, spine biomechanics, spinal deformity, and intraoperative neurophysiological monitoring during spine surgery.

Not all patients need huge operations that open the entire back to correct scoliosis” – Dean Chou, MD

“It is exciting to offer UCSF patients minimally invasive spinal operations at our newly renovated Mount Zion Outpatient Surgery Center” – Aaron Clark, MD, PhD