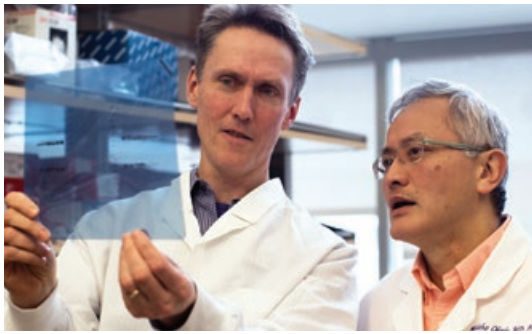
UCSF Neurological Surgery

2019 Annual Report

UCSF
University of California
San Francisco



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Dear Colleague:

I am thrilled to be sharing some of the clinical and research highlights from our Department in 2019. From a new blood test for concussion to the first demonstration of synthetic speech, there are fascinating stories from every subspecialty of neurosurgery.

UCSF has also again been ranked in the top three neurosurgery and neurology programs in the nation – and best on the West Coast – by U.S. News & World Report's 2019-20 survey of Best Hospitals, reflecting the outstanding dedication of our faculty and staff.

UCSF adult and pediatric neurosurgery clinics are available in Marin, Napa and Oakland to provide easy coordination with local physicians and convenient access for patients in those areas. Our spine specialists are also available to see patients at the new Berkeley Outpatient Center – a collaboration between UCSF and John Muir Health.

As always, thank you for allowing us to partner with you in the care of your patients.

Mitchel S. Berger, MD
Professor and Chair
Department of Neurological Surgery
Berthold and Belle N. Guggenhime Endowed Chair
Director, Brain Tumor Center

Brain Tumor Center

Steady Success in Identifying Genetic Drivers of Brain Tumors

Neuropathologist and molecular neuro-oncologist David Solomon, MD, PhD, is UCSF Health's director of Molecular Neuropathology, responsible for all genomic testing performed on brain and spinal cord tumors at UCSF Medical Center. His efforts have been instrumental in facilitating a molecularly integrated diagnostic scheme and enabling a precision medicine approach for the treatment of neuro-oncology patients.

"We hope that if we can determine the genetic alterations that are responsible for driving the different brain tumor types – as well as the cellular pathways that these genetic alterations deregulate to fuel tumor development – we can intervene with highly specific targeted therapies," says Solomon, whose research laboratory investigates the molecular pathogenesis of human brain tumors.

Solomon points out that the UCSF500 next-generation sequencing panel, which he oversees and which is one of the world's leading targeted panels for brain tumor diagnosis and therapy, has led to multiple precision medicine trials.

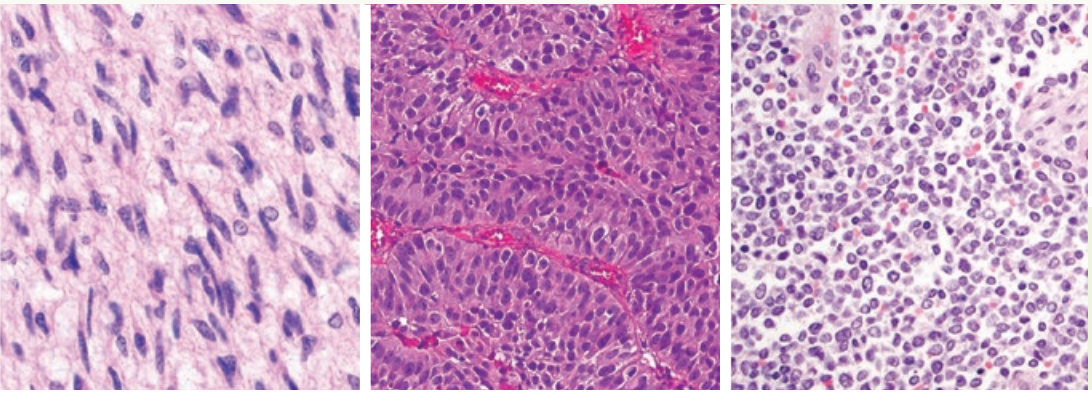
In one of these trials, clinicians analyze resected tumors using the UCSF500 panel, and a molecular tumor board will decide upon the best personalized targeted therapies, with a particular focus on combination therapies.

In fact, today the UCSF500 panel is now used to study the vast majority of brain tumors resected at UCSF, ensuring the most accurate diagnosis while also identifying potentially targetable mutations in the tumor and uncovering any type of germ-line mutation associated with increased cancer risk.

At the same time, the research continues on multiple fronts. Solomon's lab recently published an article in *Nature Communications* that explains how the STAG2 gene – which is commonly mutated in several human cancer types – plays an essential role in DNA replication, thus revealing new potential mechanisms for therapeutically targeting those glioblastomas harboring STAG2 mutations.

"This work not only helps individual patients, but it also builds our knowledge base about the fundamental mechanisms by which cancer develops and escapes standard treatment regimens, which will allow us to come up with new and better therapies," says Solomon.

Solomon's dedication to classifying and deciphering the molecular basis of the many distinct brain tumor entities – including in the last year chordoid glioma, ganglioglioma, spinal cord diffuse gliomas and radiation-induced gliomas – has led to his being part of the scientific team working to update the World Health Organization (WHO)'s Classification of Tumors of the Central Nervous System.



STAG2 is one of the most commonly mutated genes in (left to right) glioblastoma, bladder cancer, and Ewing sarcoma.

Mondal G, Stevers M, Goode B, Ashworth A, Solomon DA. A requirement for STAG2 in replication fork progression creates a targetable synthetic lethality in cohesin-mutant cancers. *Nat Commun.* 2019;10(1):1686.

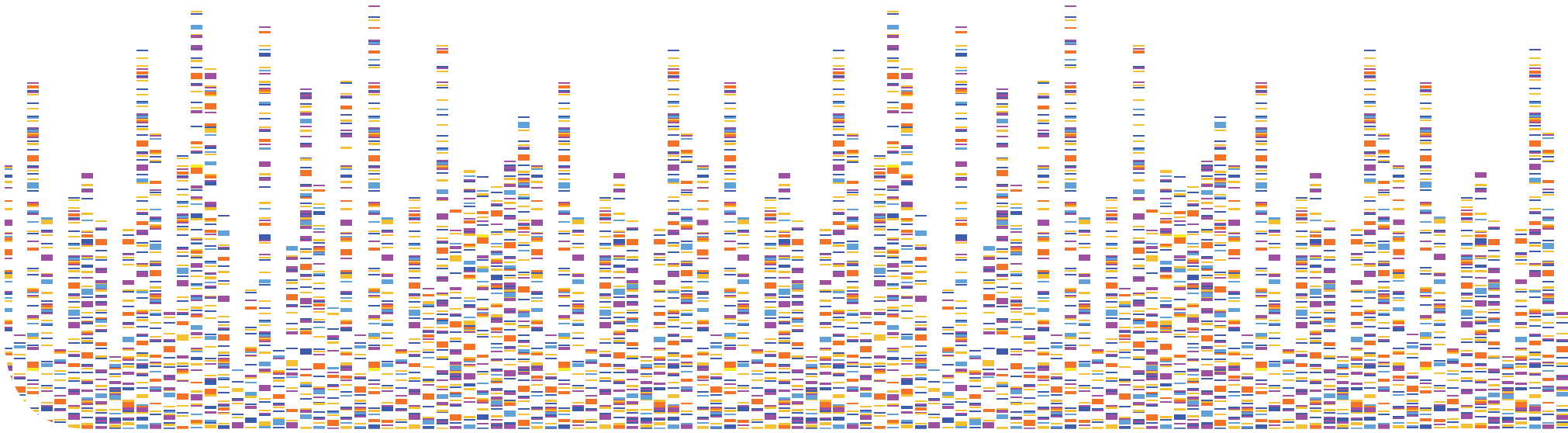
Precision Medicine Trial Offers Individualized Therapy Based on Tumor Genetics

In 2019, UCSF neuro-oncologist Jennifer Clarke, MD, initiated a pilot precision medicine trial for adult patients with recurrent glioblastoma. In the trial, 15 eligible participants undergo surgery as part of their standard of care, with tumor tissue collected for sequencing aimed at determining each tumor's gene expression profile. A multidisciplinary genomic tumor board reviews the profile and looks for FDA-approved drugs to determine any that may target the abnormalities found in the patient's tumors, such as overactive tyrosine kinases or growth factors. The tumor board then recommends an individualized regimen of up to four FDA-approved drugs.

Repurposing existing drugs is one way to more quickly offer alternative therapies to patients with life-limiting illness who may not be eligible for other clinical trials. A previous pilot study in 2014, run through the Ivy Foundation Early Phase Clinical Trials Consortium, demonstrated the feasibility of making the recommendation in a timely fashion but did not provide the actual drugs for treatment.

"With this new trial, we are excited to actually implement the individualized treatments, to start to assess the efficacy of this approach," says Clarke.

While the team is using the Clinical Laboratory Improvement Amendments (CLIA)-approved UCSF500 next-generation sequencing panel to create the profile and determine treatment, when adequate tissue is available, patients' tumors will also undergo whole-genome and RNA sequencing to assess whether this would change treatment recommendations. In addition, patients' tumor cells will be cultured and inoculated into organoids to generate patient-specific models for further testing.



Robust Clinical Trials Program Continues Its Growth

The world-renowned clinical trials program at the UCSF Brain Tumor Center continues to grow, offering an increasing array of promising treatment options for nearly any brain tumor patient, at any point in their cancer journey.

“Our trials cover the spectrum,” says Susan Chang, MD, director of the Division of Neuro-Oncology. “We have options for newly diagnosed or recurrent tumors, low-grade or high-grade tumors, as well as window-of-opportunity studies when a promising treatment modality becomes available.”

The center’s innovative approaches to forging connections between its clinical trials and basic research has helped it secure game-changing grants, including a P01 Program Project grant from the NIH that was renewed in 2019. “Noninvasive Metabolic Signatures to Improve Management of Molecular Subtypes of Glioma” consists of four integrated and synergistic projects and two cores, with the overall goal of identifying metabolic signatures associated with subgroups of glioma defined by various molecular characteristics. The plan is to integrate these signatures with multiparameter imaging strategies that assess spatial and temporal changes in individual patients during the course of their disease. The hope is that this will provide a more accurate characterization of tumor burden and response to treatment. Such projects keep UCSF at the forefront of advancing understanding of how to effectively treat and eventually cure brain cancers.

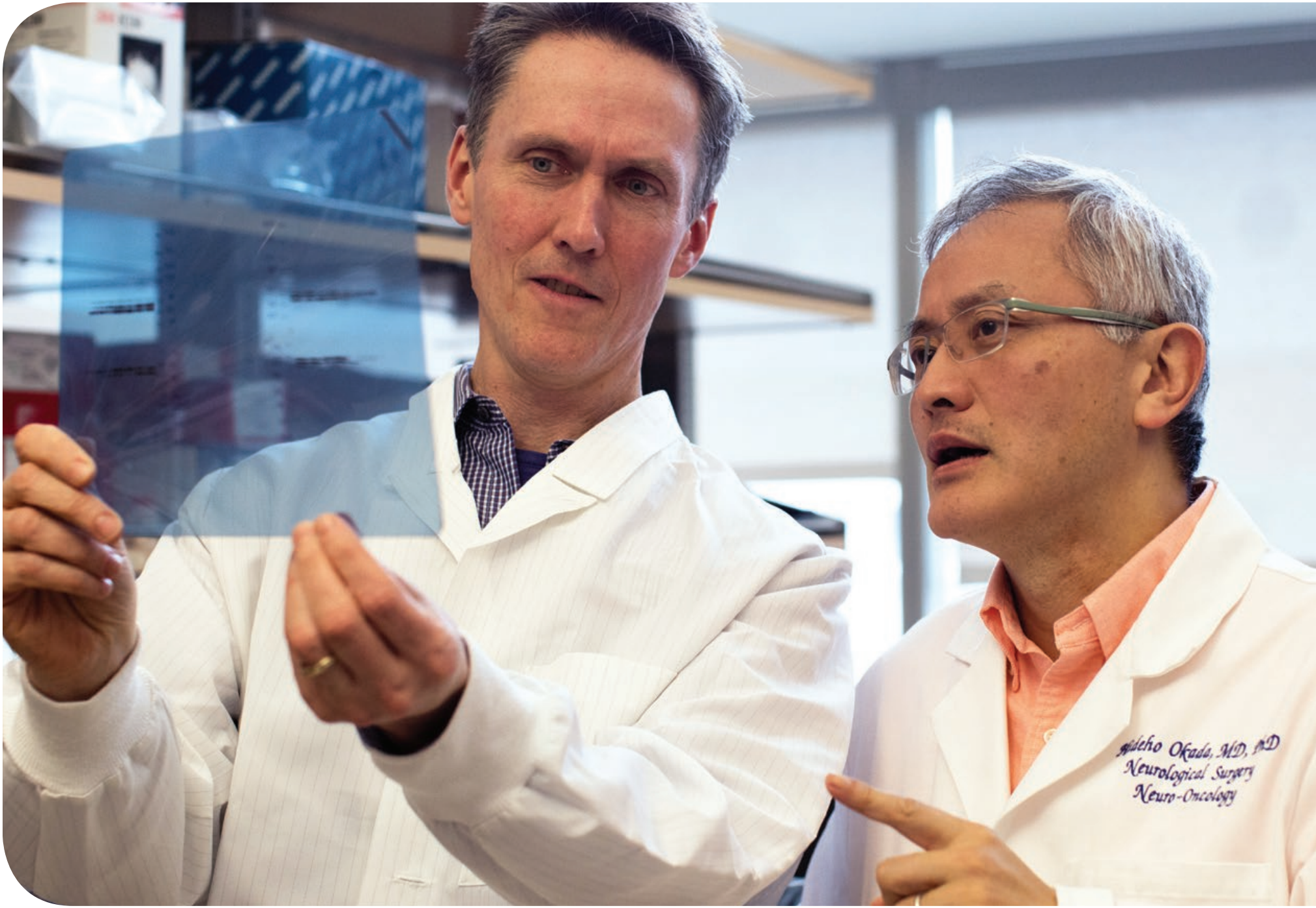
“The synergy and collaborations among our basic scientists and clinicians help us accelerate the development of exciting new treatments for our patients,” says Chang.

Among the most exciting:

- UCSF is one of only a few institutions offering a clinical trial of personalized treatment vaccines for low-grade glioma in adults, as well as pediatric gliomas like diffuse instrinsic pontine glioma (DIPG), as noted below.
- The clinical trials program offers a number of immunotherapies that involve engineered viruses or DNA plasmids, including oncolytic virus therapies. One of these oncolytic virus trials is testing a modified poliovirus directed against recurrent glioblastoma. Other trials are assessing treatments for glioma, DIPG, medulloblastoma and atypical teratoid/rhabdoid tumor (AT/RT) in children.
- There are several ongoing clinical trials investigating the use of immune checkpoint inhibitors, either alone or in combination with other therapies like radiation.

“The synergy and collaborations among our basic scientists and clinicians help us accelerate the development of exciting new treatments for our patients.”

- Susan Chang, MD


Hideho Okada, MD, PhD
Neurological Surgery
Neuro-Oncology

UCSF Researchers Awarded Competitive Grant to Fund Immunotherapy Studies

This year, Brain Tumor Center researchers Joseph Costello, PhD; Hideho Okada, MD, PhD; and Aaron Diaz, PhD, were awarded Brain Tumor Funders' Collaborative (BTFC) grants for two projects that highlight promising work on immunotherapy strategies. They will be among four teams splitting $3 million.

Researchers in the Costello and Okada Labs will use the grant to begin development of a personalized neoantigen-based immunotherapy trial for patients with low-grade glioma (LGG). Prior work, much of it from the Costello Lab, found that one complication in treating glioma is that the tumor cells develop different mutations over time, especially during the progression from LGG to HGG. Another complication that has vexed clinicians is that a mutation found in one tissue sample may not be representative of the entire tumor.

In response, the two labs have developed a 3-D immunogenomics approach that collects and analyzes samples across the tumor volume. Using this method at initial diagnosis and again at recurrence, researchers can identify neoantigens that are present throughout the tumor and persist over time. Such neoantigen targets may prove more successful than those currently found using single-sample analysis and, the researchers hope, will facilitate personalized vaccines for individual patients' tumors, especially LGG.

In the second project, UCSF researcher Aaron Diaz, PhD, is working with Gary Kohanbash, PhD, from the UPMC Children's Hospital of Pittsburgh, to investigate T-cell receptor (TCR) therapy for pediatric patients with HGG and DIPG.

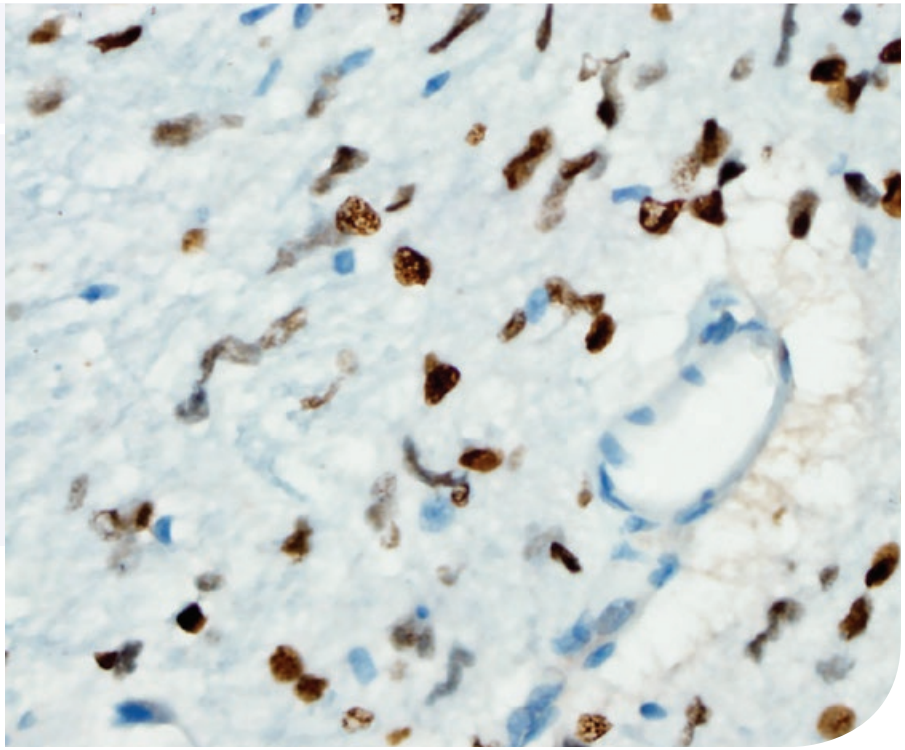
Although TCR therapy has been highly effective in some cancers, finding safe and effective TCRs for pediatric HGG and DIPG has been challenging. The Diaz and Kohanbash Labs have developed a novel approach for isolating viable TCRs from patient samples. By identifying the few T cells that successfully target the tumors, Diaz and Kohanbash can use single-cell RNA sequencing to determine the most promising TCR sequences. They will further assess isolated TCRs for tumor-specific killing capabilities in both cell culture and animal models. Validating these TCRs is a foundational step toward developing safe and effective TCR therapies for children with HGG and DIPG.

Okada Lab Partners to Create TCR Therapies for DIPG

The Brain Tumor Center's Hideho Okada, MD, PhD, is also leading a project aimed at advancing novel engineered TCR therapies for rare and currently incurable pediatric conditions with high mortality rates. Part of an exclusive licensing and research collaboration with Tmunity Therapeutics Inc., a private clinical-stage biotherapeutics company, the research will focus initially on DIPG.

To date, Okada has discovered and engineered a TCR that binds to and is selective for the H3.3K27M neoantigen, a mutation observed in more than 70 percent of DIPGs – and which had antitumor activity and limited toxicity in mouse models.

"We are excited to join forces with Tmunity to further study the potential of our TCR T cell as a therapy for DIPG," says Okada.



Immunostaining of pediatric brainstem glioma showing mutation in histone H3 variants (brown nuclear staining). This mutation – called the H3.3K27M mutation – has been identified as a tumor-specific antigen and UCSF is leading a clinical trial of a vaccine for children who are H3.3K27M-positive.

"All of us sitting in the same room and working on this problem together creates unique opportunities for improving patient outcomes."

- Joseph Costello, PhD

Loglio Consortium Update

In 2012, the family of Ashley and Alan Dabbiere created an LGG research collective called Loglio. With a primary focus on oligodendroglioma, a rare type of LGG, the consortium is based at the UCSF Brain Tumor Center. Joseph Costello, PhD, is the scientific principal investigator.

The Dabbieres' initial investment led to the discovery of a chemotherapy-driven hypermutation that can cause LGGs to recur and advance to an HGG, inspiring a series of additional investments from the Dabbiere family. To date, they have donated more than $15 million, yielding a steady stream of insights to improve clinical treatment of LGGs.

In 2019, as part of an effort to understand how LGGs and their treatment affect neurocognition, a group of UCSF neurocognitive researchers and clinicians – including some at the newly formed Sheri Sobrato Brisson Survivorship Program – assessed a variety of potential interventions that they hope will improve these patients' outcomes and their quality of life. The interventions included using the prehab setting to assess individual needs and then designing interventions for both before and after surgery to address those needs.

Costello says the effort highlights the value of the consortium's multidisciplinary approach. "All of us sitting in the same room and working on this problem together creates unique opportunities for improving patient outcomes," he says.

"We created a stealthy virus, a tumor-selective retroviral replicating vector (RRV),that integrates itself into a cancer cell's genome."

- Noriyuki Kasahara, MD, PhD

Virotherapy Shows Promise for Recurrent High-Grade Glioma and Beyond

Though oncolytic virotherapy is a concept that dates back to the early 20th century, in the modern era, it was largely ignored until the 1980s and '90s, when scientists began experimenting with viruses as effective delivery vehicles for emerging gene therapies.

Now UCSF Brain Tumor Center researcher Noriyuki Kasahara, MD, PhD, is developing a novel form of virotherapy that has shown such promising evidence of therapeutic efficacy in patients with recurrent high-grade glioma (HGG) that it received a "Breakthrough Therapy" designation from the Food and Drug Administration (FDA).

The therapy appears to solve the problem of virotherapies' cancer-fighting effects being short-lived due to the fact that most viruses that clinicians and researchers have used to date immediately start killing cancer cells when introduced into the tumor, but because the tumor suppresses the immune system – which protects viruses from being cleared – it becomes a race between the viruses killing cancer cells and the immune cells coming in to clear out the virus. When the immune cells successfully clear out the virus, their absence enables the tumor to regrow.

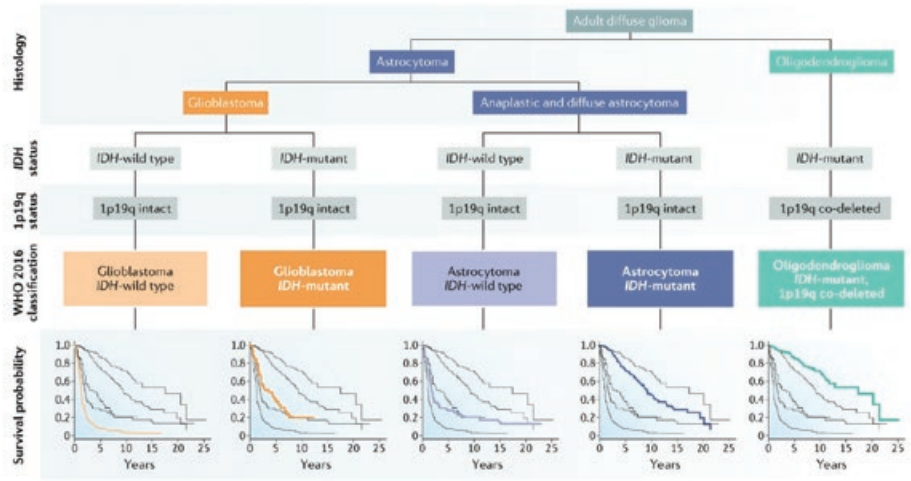
"We created a stealthy virus, a tumor-selective retroviral replicating vector (RRV), that integrates itself into a cancer cell's genome," says Kasahara. "Now every time the cancer cell proliferates, it has a copy of the virus in its own genome, enabling the virus to spread quietly through the tumor mass."

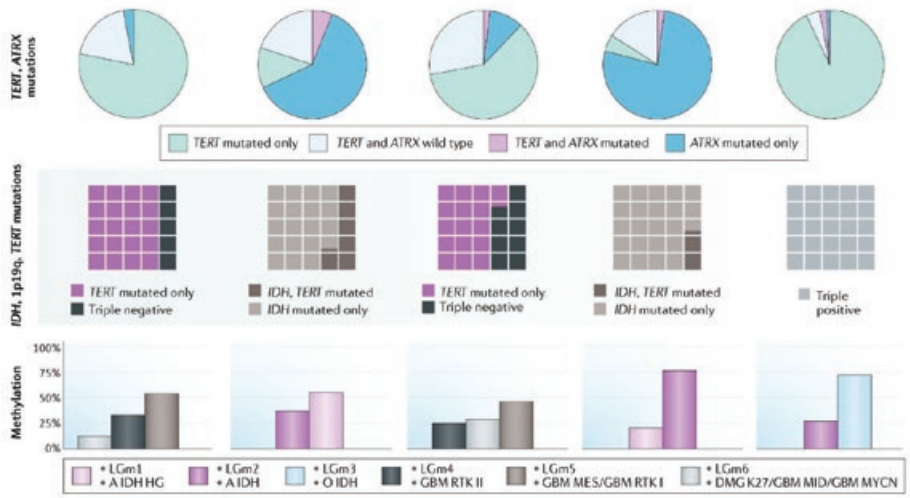
The retrovirus also contains a "suicide gene" that converts a nontoxic precursor compound, called a "prodrug," into an active chemotherapy drug, 5-FU. Once the tumor is nearly fully infected by the virus, patients take the prodrug as an oral medication, and that is converted into the chemotherapy drug – but only in the infected cancer cells. Since the virus' suicide gene uses the prodrug as the raw material to essentially force the infected cancer cells to manufacture the chemotherapy drug within themselves, this kills the tumor with few of the systemic side effects typically associated with 5-FU. In addition, a "bystander effect" occurs by which 5-FU leaking out of the dying cancer cells then kills immunosuppressive cells in the tumor microenvironment, thus activating antitumor immune responses.

After mouse models showed no evidence of tumor recurrence and clear evidence of immune system response, the therapy moved into human trials. Tocagen Inc. – a company Kasahara co-founded – has sponsored first-in-human multicenter clinical trials for this RRV suicide gene virotherapy. When a phase I trial confirmed that the therapy was well tolerated, suggested an immune-activating effect that was very targeted to the cancer cells and increased the median overall survival rate in a higher-dose cohort to 40 percent at 24 months, the therapy earned its Breakthrough Therapy designation. A phase II/III trial has treated 200 patients at 61 centers for recurrent HGG and appears to have replicated those kinds of results in a subgroup of those patients, but did not show a statistically significant difference overall.

"Phase III was supposed to keep patients on a high dose of the prodrug for one year, but unfortunately it appears that the majority of patients only stayed on the prodrug for two months. These results certainly underscore the need to develop even more potent virotherapy strategies that will work better and faster," says Kasahara.

In addition to this trial, Tocagen and Kasahara have begun efforts to test the therapy in other cancers, including newly diagnosed HGG, pediatric gliomas and medulloblastoma, and central nervous system (CNS)-metastatic breast cancer. He is also working in collaboration with radiation oncology, because 5-FU can enhance the effect of radiation therapy. Finally, Kasahara has received additional funding from the National Institutes of Health (NIH), the Department of Defense and the Alliance for Cancer Gene Therapy to develop new types of virotherapy vectors that, in combination with immunotherapies, can enhance their anticancer effects.


Histology
Adult diffuse glioma
Astrocytoma
Oligodendroglioma
Glioblastoma
Anaplastic and diffuse astrocytoma
IDH status
IDH-wild type
IDH-mutant
IDH-wild type
IDH-mutant
IDH-mutant
1p19q status
1p19q intact
1p19q intact
1p19q intact
1p19q intact
1p19q co-deleted
WHO 2016 classification
Glioblastoma IDH-wild type
Glioblastoma IDH-mutant
Astrocytoma IDH-wild type
Astrocytoma IDH-mutant
Oligodendroglioma IDH-mutant, 1p19q co-deleted
Survival probability
Years


TERT, ATRX mutations
TERT mutated only
TERT and ATRX wild type
TERT and ATRX mutated
ATRX mutated only
IDH, 1p19q, TERT mutations
TERT mutated only
Triple negative
IDH, TERT mutated
IDH mutated only
TERT mutated only
Triple negative
IDH, TERT mutated
IDH mutated only
Triple positive
Methylation
100%
75%
50%
25%
0%
• LGm1 • A IDH HG
• LGm2 • A IDH
• LGm3 • O IDH
• LGm4 • GBM RTK II
• LGm5 • GBM MES/GBM RTK I
• LGm6 • DMG K27/GBM MID/GBM MYCN

Updating the Classification and Known Causes of Brain Tumors

Biostatistician Annette Molinaro, PhD, of the Department of Neurological Surgery, and her colleagues Jennie Taylor, MD, MPH; John Wiencke, PhD; and Margaret Wrensch, PhD, published a 2019 article in *Nature Reviews Neurology* that provided a sweeping overview of the many advances that led WHO to reorganize its classification of adult diffuse gliomas.

"By better understanding glioma subtypes, we can help our patients make decisions about treatment," says Taylor.

The review reflects how understanding of glioma subtypes has expanded to include the molecular and genetic variants that can influence a tumor's development, prognosis and response to treatment. Until recently, there were few established causes for gliomas, but now – in part due to UCSF research – there are 25 inherited genetic variants known to increase the risk for the condition.

The majority of adult diffuse gliomas are now classified into the following five groups:

1. Glioblastoma, isocitrate dehydrogenase (IDH) wild-type (no mutation)
2. Glioblastoma, IDH mutation
3. Diffuse or anaplastic astrocytoma, IDH wild-type (no mutation)
4. Diffuse or anaplastic astrocytoma, IDH mutation
5. Oligodendroglioma or anaplastic oligodendroglioma, IDH mutation with 1p/19q codeletion

Molinaro and her colleagues provide a comprehensive overview of molecular features that are also associated with patient outcome and/or treatment response, including the following:

- *TERT* and *ATRX* mutations affecting telomere maintenance
- Tumor methylation profile
- Methylation of the *MGMT* promoter
- *CDKN2A* and/or *CDKN2B* deletion
- Histone H3.3K27M mutation

"Identifying a patient's unique tumor profile is critical not only for diagnosis and prediction of prognoses, but potentially for tailoring treatment to each patient's specific gene alterations," says Molinaro.

The review also highlighted novel ongoing research at UCSF into immunologic factors related to glioma development and prognosis. The large-scale retrospective and prospective epidemiological studies characterize peripheral immune profiles on the basis of archival DNA to assess how variation among patients' immune profiles impacts glioma risk.

Together, these findings combined with the discoveries of changes within the tumors provide a solid foundation for future research into why some people get glioma and what may be done to help reduce the risk of disease or death from this disease.

Figure on Page 10 adapted from: Molinaro AM, Taylor JW, Wiencke JK, Wrensch MR. Genetic and molecular epiedemiology of adult diffuse glioma. *Nat Rev Neurol*. 2019;15(7):405-417.

"By better understanding glioma subtypes, we can help our patients make decisions about treatment."

- Jennie Taylor, MD, MPH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Hyperpolarized MRI Opens New Diagnostic Possibilities

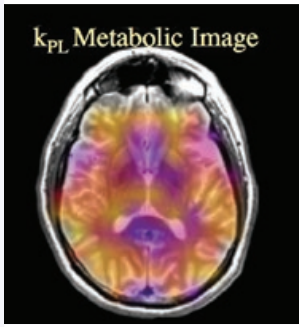
The UCSF Brain Tumor Center's Dan Vigneron, PhD, leads the Hyperpolarized MRI Technology Resource Center (HMTRC), which is funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and focuses on the development and dissemination of new advances in dissolution DNP (dynamic nuclear polarization) techniques and instrumentation, specialized data acquisition methodology, and analysis software for biomedical research.

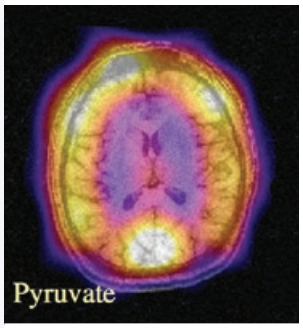
In 2019, the HMTRC developed new detectors and acquired new data using hyperpolarized carbon-13 MR to better understand tumor metabolism, including in the IDH mutation, one of the most important genomic alterations in lower-grade and secondary gliomas.

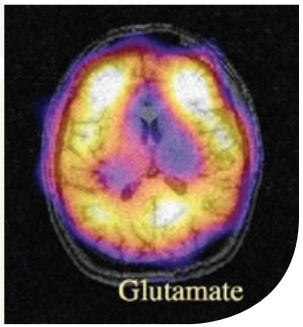
Hyperpolarized carbon-13 MR is a molecular imaging method used to monitor enzymatic conversions through previously inaccessible biochemical pathways. To date, it has shown exciting promise, and the HMTRC works collaboratively to develop new technology to advance the field.

At UCSF, the research advances by integrating the hyperpolarized imaging into the standard MRI exam for brain tumor patients. "It only takes a few minutes to change the software, inject pyruvate, and do the additional imaging," says Vigneron. "The new hardware coil allows us to do all of this without even having to switch the detector."

The result from the new imaging agent development is that researchers can now visualize tumor metabolism at two new positions, including where the IDH mutation occurs. "The first position enables us to look at lactate and bicarbonate; the other looks at the conversion to glutamine," says Vigneron. "This allows us to now identify the genotypic and phenotypic subtypes of these gliomas, which enables us to improve treatment selection, possibly detect recurrences earlier and benefit patient outcomes."



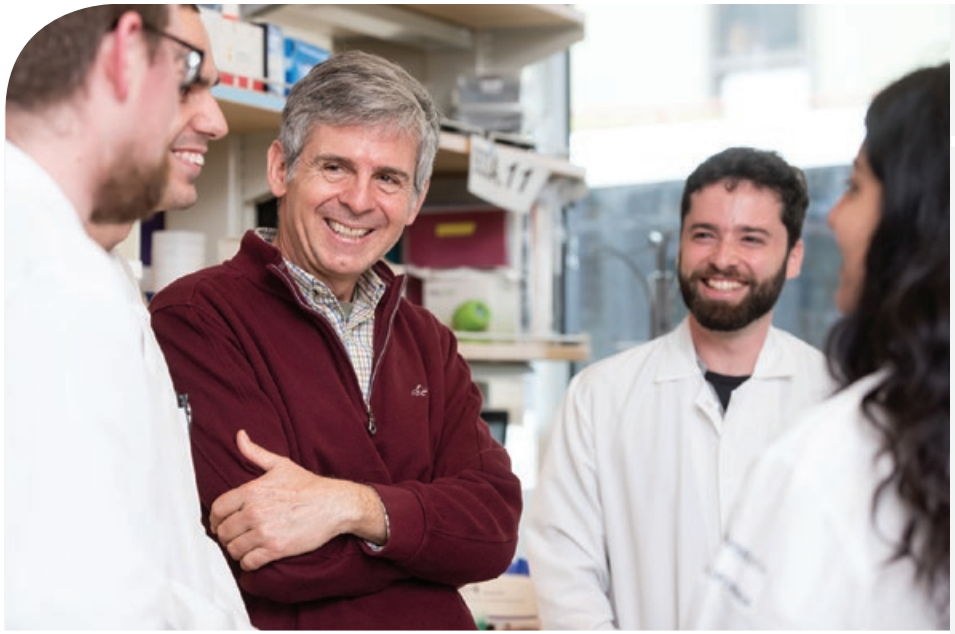




"This allows us to now identify the genotypic and phenotypic subtypes of these gliomas, which enables us to improve treatment selection, possibly detect recurrences earlier and benefit patient outcomes."

– Dan Vigneron, PhD

Brain Tumor Center imaging advances in 2019 include a new commercial MRI coil (top) developed with RAPID Biomedical Inc. that enables both high-quality anatomic images and biochemical measurements of hyperpolarized carbon-13 pyruvate-to-lactate (kPL) metabolism (second image from top). A new metabolic imaging agent (C2-pyruvate) was also developed and approved for human studies. This agent was shown to probe a new pathway of metabolism in normal volunteers (bottom two images) and could help advance brain tumor characterization.



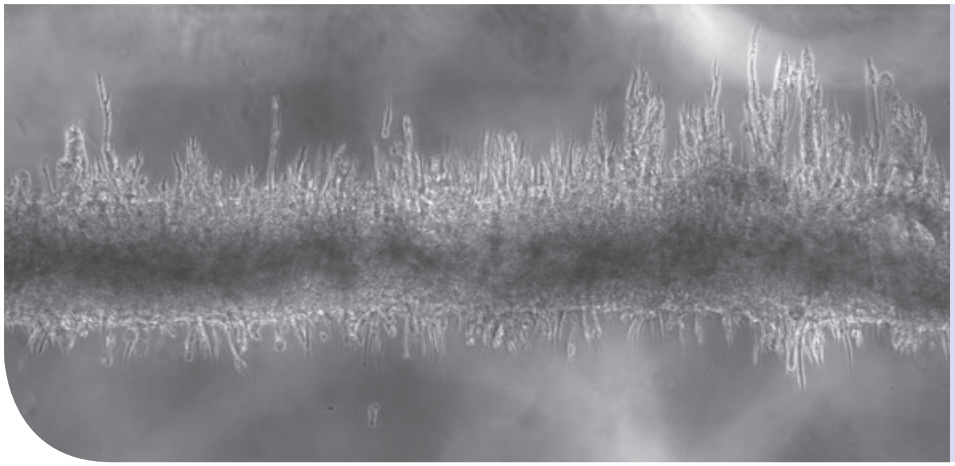
Researchers Find Mood Neurons Mature During Adolescence

Researchers in the lab of Arturo Alvarez-Buylla, PhD – the Heather and Melanie Muss Endowed Chair and professor of Neurological Surgery – have discovered that a mysterious group of neurons in the amygdala remain in an immature, prenatal developmental state throughout childhood. Most of these cells mature rapidly during adolescence, suggesting a key role in the brain's emotional development as the amygdala is a key center for emotional processing in the brain, but some of the cells stay immature throughout life, suggesting new ideas about how the brain keeps its emotional responses flexible.

In the study, published June 21, 2019, in *Nature Communications*, researchers examined postmortem human amygdala tissue from 49 human brains, ranging in age from 20 gestational weeks to 78 years. Using both anatomical and molecular techniques to classify individual neurons' maturity and function within neural circuits, they found that the percentage of immature cells in the paralaminar (PL) nuclei region of the amygdala remains high throughout childhood but declines rapidly during adolescence: From birth to age 13, the number of immature cells declines from approximately 90 percent to just under 70 percent, but by the end of adolescence, only about 20 percent of PL cells remain immature.

Sorrells SF, Paredes MF, Velmeshev D, Herranz-Pérez V, Sandoval K, Mayer S, Chang EF, Insausti R, Kriegstein AR, Rubenstein JL, Manuel Garcia-Verdugo J, Huang EJ, Alvarez-Buylla A. Immature excitatory neurons develop during adolescence in the human amygdala. *Nat Commun*. 2019;10(1):2748.

Engaging with the Cancer Tissue Engineering Collaborative



The lab of Manish Aghi, MD, PhD, is one of nine in the country selected to be part of the Cancer Tissue Engineering Collaborative – and the only one on the West Coast. With the support of a grant worth more than $2 million over five years, Aghi's lab works in collaboration with researchers at UC Berkeley to replicate the glioblastoma microenvironment, so they can model a tumor's progression in real human tissue. In 2019, all nine labs met at MIT to discuss shared challenges and future directions.

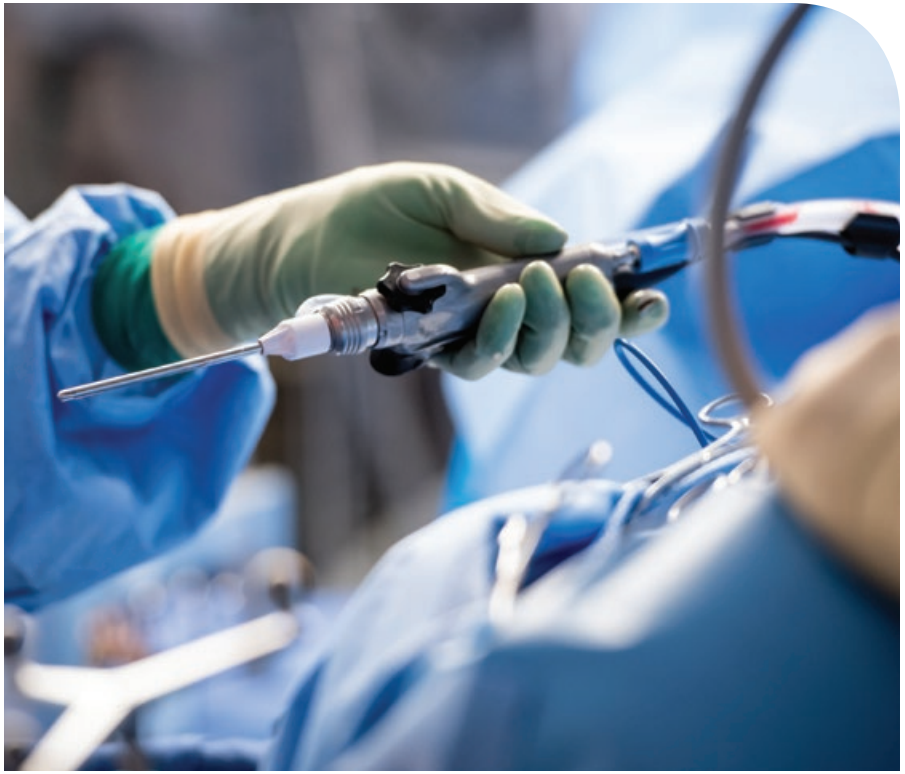
"Because targeting tumor progression in clinic has not worked very well to date, we believe this gives us a more rational approach to identifying targets," says Aghi.

Minimally Invasive Skull Base Surgery Provides a Wide Range of Treatment Options for Complex Lesions

At UCSF's California Center for Endoscopic and Minimally Invasive Skull Base Surgery, a range of surgical approaches are available for treatment of skull base tumors, sinonasal malignancies, and benign conditions like fibro-osseous lesions and optic nerve compression.

Minimally invasive skull base surgery often involves the use of endoscopes to operate through the nasal cavity to remove tumors or repair defects of the anterior skull and lateral skull base. This often avoids the larger facial incisions associated with traditional craniotomy approaches, and results in fewer complications, improved cosmesis, faster recovery, and reduced blood loss.

At UCSF, neurosurgeons and otolaryngologists have also developed two-surgeon techniques, often operating together, to achieve safe and efficient endoscopic dissection around critical structures.



Specialized Program in Research Excellence (SPORE) for Brain Tumors

UCSF's Brain Tumor Center SPORE program comprises four projects aimed at potential new therapies for glioblastoma. UCSF is home to the only brain tumor program to have been granted SPORE funding from the National Cancer Institutes for four cycles.

Each project is focused on speeding translation of novel diagnostics (blood markers and hyperpolarized C-13 imaging) and therapeutics (*TERT* promoter and 4EBP1 inhibitors) from the bench to the bedside:

Project 1

Blood immunomethylomic markers of outcome in glioblastoma patients

Project 2

Monitoring metabolism in GBM using hyperpolarized C-13 imaging and H-1 MRSI

Project 3

A New Therapeutic Target for *TERT* Promoter Mutant Glioma

Project 4

Targeting 4EBP1 in glioblastoma

New Faculty Member to Initiate Clinical Service for Patients with CNS Metastases

Neuro-oncologist Mariza Daras, MD, has joined the faculty at the Brain Tumor Center, in part to play a leading role in coordinating care for patients with CNS metastases.

Daras has spent the last six years at Memorial Sloan Kettering's Brain Tumor Center, treating primary tumors and metastatic disease. "One goal for me at UCSF will be to help medical oncologists provide more comprehensive care for people with CNS metastases by creating an infrastructure specifically for these patients, whose metastatic disease tends to have very specific characteristics," says Daras. "My role will be to tie together all the expert pieces available at UCSF into a dedicated consultative service that supports medical oncologists as they treat metastases involving the brain."

Daras will also work with medical oncologists and other expert UCSF specialties and resources to develop new clinical trials designed specifically for this group of patients.

"The goal is to personalize care," she says. "If we join forces for everything from preclinical modeling through collection of biospecimens and biobanking, perhaps we can offer more targeted approaches."

UCSF Neuro-Oncology Gordon Murray Caregiver Program Continues Its Growth

In 2019, the UCSF Neuro-Oncology Gordon Murray Caregiver Program focused its efforts on extending its support to patients and their families in the North Bay at MarinHealth Medical Center in Greenbrae and Queen of the Valley Medical Center in Napa. "We want to establish the program as the norm for all of our patients," says Susan Chang, MD, director of the program.

The program also held its annual event dedicated to caregiver well-being on Saturday, May 18. The focus this year was on strategies for fostering resilience through knowledge and self-compassion. "You may think you have to set aside your own needs as a caregiver, but the truth is, that's not sustainable," says Margaretta Page, RN, MS, nurse coordinator of the program.

The daylong event – provided at no cost to the nearly 30 caregivers attending, thanks to philanthropic donations – featured informational and emotional support sessions, as well as self-care activities like chair massages, and exercise and self-compassion workshops.

Talks from UCSF faculty and staff included information on how brain tumors affect patients and specific strategies for how caregivers can respond to things like behavior and mood changes.

Growth of Neurocognitive Service Enhances Brain Cancer Survivorship Program

As the Sheri Sobrato Brisson Brain Cancer Survivorship Program entered its second year, it has expanded its offerings for the growing numbers of brain cancer survivors.

Perhaps the biggest growth came in the program's neurocognitive consultation service. Led by neuropsychologist Christina Weyer Jamora, RN, PhD, the service provides comprehensive neuropsychological evaluation and treatment for patients whose cognition has been impacted by cancer and its treatment. Patients are referred to the clinic by their oncologist, ideally after completion of treatment. In its first 15 months, the clinic saw 90 patients and had nearly 350 patient visits.

"The evaluation helps to pinpoint areas of cognitive strength as well as areas of challenge, and leans into the strengths to support patients with compensatory strategies during their rehabilitation," says Program Manager Naomi Hoffer, MA, MCHES.

Weyer Jamora also works with caregivers to help them understand the compensatory strategies, the effects of treatment on their loved ones and how to explain the changes to children. The service is also contributing to advancing the science around neurocognitive strategies, by participating in research funded by the Loglio consortium (page 8).

"We are on the forefront of providing these types of services to brain tumor patients, and we are seeing improvements," says Hoffer. Patients have noticed. As one commented, "Dr. Jamora has really been a lifesaver for me in helping me cope with the changes in my thinking."

In 2019, the program also hired a dedicated nurse practitioner, who participates in the Cognitive Consultation Clinic but will also play a central role in the launch of a Survivorship Wellness Clinic. A weekly, on-site exercise-counseling program in the radiation oncology department provides a number of preventive benefits for patients.

Other additions include a speaker series for providers, a Living Well webinar series for patients, interviews with survivors to better understand their needs and showcase their stories on our website, a survivorship wellness manual and a series of "Living Well with Brain Cancer" patient education sheets.

Christina Weyer Jamora, RN, PhD

Naomi Hoffer, MA, MCHES

Will to Live

Nearly two years after surgery to remove an astrocytoma, Will Pearce finds strength in family, faith in the future, and a love for a life he didn't expect.

How was your experience recovering from brain surgery?

The first month was kind of a blur because there wasn't much I could do. Sometimes I had a thought, I knew what I was thinking, but I couldn't get it out. Or things would scramble in my head. And that was pretty normal for the first two or three months initially.

I got to a point after brain surgery where I was asking 'What if I never get better? What if I can't function like a normal human being?' And if that's where you land, then there's not a whole lot of fight left. I had to actually ask myself if I wanted to live. Because choosing to fight is the harder option. But that's ultimately what I chose.

How did you begin that fight?

The first step was relatively difficult. I just forced myself every morning to get up and take my dog for a walk. Which seems like not a big deal, but it was almost impossible. After a few weeks, it got easier and I added one minute of meditation in the morning. That was all I could handle. I'd do the walk, one minute of meditation, and that was kind of my day. Eventually the walks became miles of hiking and mediation went to 5 minutes, and then 10, and that's what I try to keep up now.

You don't go back to regular life anytime soon, and the reality is that you can't go back to the person you were before. Parts of my mind are different than they were before and I finally got to the point where instead of fighting to get back to where I was, I wanted to accept who I am now. I think that is the greatest form of recovery. To say 'You know what? My decrepit, debilitated self, I love.' That's the moment you get through it.

What other things do you think are helpful for going through this process?

Being honest with family and friends about how hard things are and asking for help. From the supporting spouse or caregiver position as well, it's very hard if you don't have help. Whether that's financial help or people bringing a meal, it's incredibly necessary to build an army.

As part of the Brain Tumor Center's Sheri Sobrato Survivorship Program, Dr. Christina Weyer Jamora focuses on neuropsychology and cognitive rehabilitation. How was your experience working with her?

Working with Chris is amazing. My profession is all mental, so she made my program about improving things that were important to me. And there is a lot of inspiration in seeing that you can get better. It was like training for a sport. We started with short meditations and reading short articles and built up gradually. She saw individually what I needed to get back to the intellectual level that I needed to function as an attorney and that was incredibly helpful.

How quickly were you able to return to work?

I went back to work after 10 months, which was earlier than was recommended, to be honest. But it was right for me and I'm glad I did, even if I had to get a little 'ahead of my skis.' The work with Chris definitely helped me to get back.

Were there other resources at UCSF you found helpful?

It was important to have a psychologist or a psychiatrist to talk with about the emotional stuff. For all patients going through this, both neuropsychology to improve mental status and psychology to improve emotional status are vitally important. I also had an outside psychologist, but was also connected with Jamie Cohen who is a therapist at UCSF specializing in cancer. In those sessions I could talk through my fears about life and mortality; that I may not get to see my grandkids. These are tough things to have to accept.

You had your second child this year, was that a big decision?

Yes, it was. But I can function, I can support a family, and after a lot of discussion, my wife and I decided to go for it. After everything we went through it's amazing to be on the other side, growing our family and learning how to live a happy life once again.

Pearce's Survival Strategy:

Be Honest and Build an Army:

"Tell your friends and family that this is going to be a nearly impossible year and ask for help. Once you do that, a lot of people will help you out. So the first thing is to build your army."

Have Faith in Your Future:

"You need to have faith that even though it's a hard battle, it's going to get better. It's not about religion, but if you don't have any faith that you're going to get through it, then you're not going to. And that matters a lot."

Embrace Change:

You aren't the same person, and that's ok. Learning to love and be comfortable with the person you are now and not try to fit back into the person you used to be is critical. Believe in yourself, grow that love for yourself and then fight for that."

Find Some Personal Space:

"For me, the early morning when I can make myself a cup of tea, relax for a minute, take my dog on a walk, do a mediation is vitally important. I need my friends and family and army behind me, but I also need a lot of personal space to work through the emotions, to work through my brain not working as well. To understand how to compensate for that. So that time is my sacred space every day."

California Center for Pituitary Disorders

Endoscopic Procedures Grow

The California Center for Pituitary Disorders continues to expand its use and application of multidisciplinary endoscopic endonasal procedures. The procedures have expanded to include removal of meningiomas and craniopharyngiomas. For larger tumors, the use of the endoscope has, in many cases, allowed patients to avoid undergoing a craniotomy.

Neurosurgeon Manish Aghi, MD, PhD, says that the visualization the endoscope makes possible opens the new possibilities and that, "By doing these types of cases together with otolaryngologists and orthopaedic surgeons, we reduce operative time and improve outcomes."

The result is improvements in patient satisfaction tied to reduced pain and reduced length of stay. "We do just shy of half of our endonasal procedures with the endoscope now, compared to 10 percent a decade ago," says Aghi.

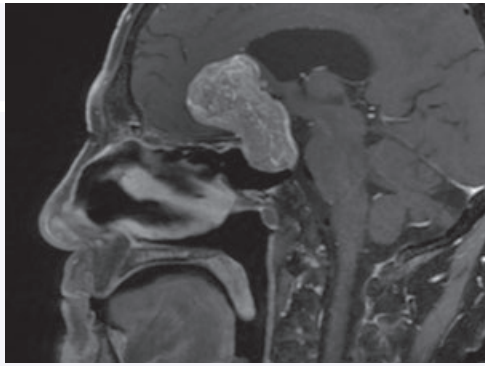
The case study below illustrates the advantages.

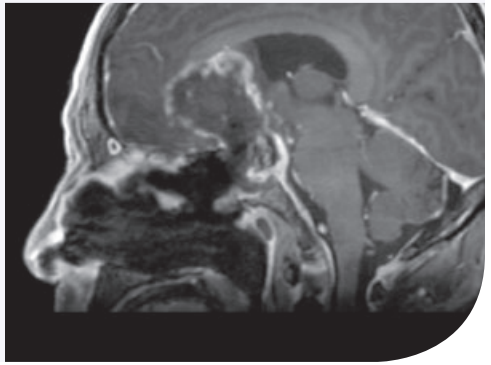
Case Study

A 74-year-old man hospitalized with pneumonia was found to be hyponatremic with low cortisol levels. He had a history of blindness in the right eye and now had progressive vision loss in the left eye, with central 20/100 acuity. An MRI scan revealed a 4.8-centimeter giant pituitary adenoma. Hormonal workup showed pan-hypopituitarism, and the man began cortisol replacement therapy, before being referred to the California Center for Pituitary Disorders.

There, specialized neurosurgery and neuroendocrine consultation led to a decision to move forward with surgery. Aghi and otolaryngologist Ivan El-Sayed, MD, undertook an endoscopic endonasal approach, using a 30-degree angled endoscope that enabled them to visualize the anterior extent of the tumor. While it extended from the sellar/suprasellar space into the frontal lobe, it did not grow along the bony tuberculum and planum of the anterior skull base. Instead, there was a cuff of frontal lobe below the anterior extent of the tumor. Aghi used the endoscope to clean out the anterior tumor without causing any trauma to the frontal lobe underneath the tumor.

The patient was hospitalized for a total of three days. His vision is slightly improved, and while he has needed levothyroxine, a thyroid replacement drug, to combat fatigue, his energy is expected to improve over the next few months as the empty resection cavity collapses over time, further decompressing the frontal lobes.





Brain and Spinal Injury Center

Blood Test Finds Concussions Missed by CT Scans

In a study published in August 2019 in *The Lancet Neurology*, researchers from the UCSF Brain and Spinal Injury Center (BASIC) tracked 450 patients with suspected traumatic brain injury (TBI) who had been admitted to one of 18 level I trauma centers throughout the nation. The patients, whose injuries were mainly attributed to traffic accidents or falls, all had normal CT scans, but a simple blood test found that many did, in fact, have TBI.

Within 24 hours of their accidents, the patients had their blood drawn to measure for glial fibrillary acidic protein (GFAP), a marker correlating to TBI. The study used a device by Abbott Laboratories called the i-STAT Alinity System, a handheld, portable blood analyzer, currently unavailable in the U.S., which produces test results in minutes. The researchers later confirmed the blood test results against MRI and found that 120 of these 450 patients (27 percent) had an MRI that was positive for TBI.

"Our earlier research has shown that even in the best trauma centers, patients with TBI are not getting the care they need," says Geoffrey Manley, MD, PhD, senior author of the study, co-director of BASIC and principal investigator of Transforming Research and Clinical Knowledge in TBI (TRACK-TBI). "Now we know that many of these patients with TBI are not even getting a diagnosis." This is particularly troubling given that nearly 5 million people a year present to emergency departments with a potential TBI.

To assess the accuracy of the blood test, researchers compared the results of the patients whose CT-negative TBIs were confirmed by MRI with those of a group of healthy participants as well as a cohort of patients with orthopaedic injuries. They found that the average protein value of the blood samples of patients with positive MRIs was 31.6 times higher than those with orthopaedic injuries and nearly 52 times that of the healthy participants. The protein was elevated even in the patients with normal MRIs, suggesting that the test may be sensitive to injury undetectable by MRI.

In the future, the blood test may help clinicians decide who can safely avoid a CT scan, with the advantage of not exposing patients to radiation from a CT, says first author John Yue, MD, of the UCSF Department of Neurological Surgery. Additionally, the blood test may be a useful tool for those patients in trauma centers and emergency departments whose symptoms may be altered by substance use.

"Patients with concussion may present as confused and disoriented, and may repeat themselves – symptoms that are similar in people with intoxication," says Yue. "With the blood test, we may be able to discern whether their symptoms are primarily due to brain injury and treat accordingly." Similarly, the test may also clarify diagnosis in patients with coexisting conditions or those who take medications that may impact speech and behavior.

"These blood-based biomarkers are the next step in the evolution of diagnosing and treating TBI," says Manley. "We are finding that not only are they more sensitive than CT in identifying TBI, but they may be more accurate than the current standard of MRI."

The study follows an earlier TRACK-TBI pilot study that found approximately 30 percent of concussion patients with negative CTs and positive MRIs had disability three months post-injury.

Yue JK, Yuh EL, Korley FK, Winkler EA, Sun X, Puffer RC, Deng H, Choy W, Chandra A, Taylor SR, Ferguson AR, Huie JR, Rabinowitz M, Puccio AM, Mukherjee P, Vassar MJ, Wang KKW, Diaz-Arrastia R, Okonkwo DO, Jain S, Manley GT; TRACK-TBI Investigators. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. *Lancet Neurol*. 2019;18(10):953-961.

TED Seed Project Gets FDA Qualification

In March 2019, the OsiriX CDE Software Module, developed by Esther Yuh, MD, PhD, and her TBI Endpoints Development (TED) Initiative Seed Project team, became only the third device to receive FDA qualification as a medical device development tool (MDDT), the first for TBI and the first biomarker test tool to receive this qualification.

The OsiriX CDE consists of a software module that provides a standardized way to mark and classify brain lesions using common criteria and to label abnormalities on MRIs. The FDA qualification means that the FDA has evaluated the tool and concurs with available supporting evidence that the tool produces scientifically and clinically meaningful measurements of data that can be used to help inform medical product development within the specified context of use. In turn, the OsiriX CDE can now be used to better identify eligible patients for enrollment in clinical trials for therapeutic medical devices intended to improve outcomes of mild TBI patients.

TRACK-TBI Completes 12-Month Outcomes Assessment

Having successfully enrolled and captured longitudinal, multimodal data on more than 3,000 participants – a staggering 20,000+ data points across clinical, physiologic, neurocognitive and behavioral, proteomic, genomic and neuroimaging domains – the TRACK-TBI initiative has completed its 12-month outcomes assessment. This accumulation of data has enabled the initiative to move the dial on TBI diagnosis, management and, ultimately, treatment.

Its work was made possible by funding from the National Institute of Neurologic Disorders and Stroke (NINDS), the Department of Defense, philanthropy from One Mind and support from numerous industry partners. The result is a TBI Knowledge Network that has generated, among other things, more than 50 publications in top-tier national and international journals.

"Our dedicated staff and faculty at the 18 study enrollment and analytic sites has done the hard work of listening to the sometimes miraculous, often tragic, but always touching stories we call data," says Geoffrey Manley, MD, PhD, BASIC co-director.

TRACK-TBI LONG Launches

TRACK-TBI Longitudinal (TRACK-TBI LONG), funded through a competitive grant from the National Football League Scientific Advisory Board, launched in May 2019. TRACK-TBI LONG will further advance understanding of TBI's natural history by extending follow-up of the original TRACK-TBI cohort by an additional year. This follow-up effort aims to collect longer-term data on the outcomes of those original TRACK-TBI participants who experienced a brain injury and to screen for a variety of neurodegenerative disorders.

Neurospinal Disorders

Advanced Equipment Complements Innovative Procedures

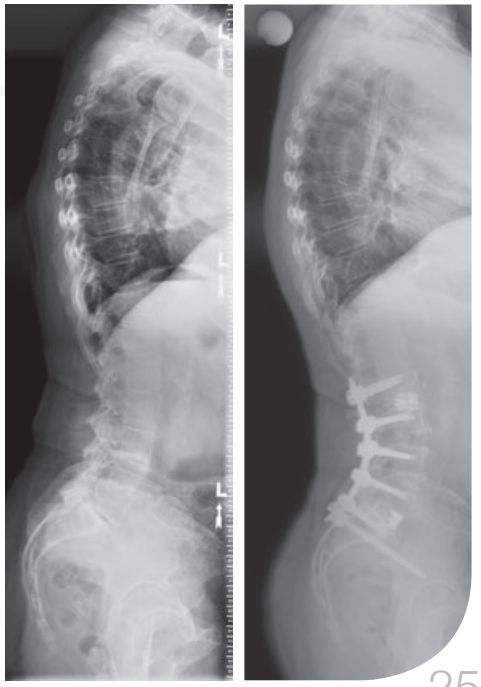
To complement the leading-edge procedures that neurospinal surgeons in the UCSF Department of Neurological Surgery perform, the department and medical centers made important investments in capital equipment, including an intraoperative CT scanner, two mobile CT scanners and a 3-D fluoroscopy unit.

The intraoperative scanner has been particularly helpful for awake fusions and minimally invasive scoliosis surgeries. Last year's report highlighted how neurospinal surgeon Praveen Mummaneni, MD, has been a leader in bringing awake decompressions and fusions to the West Coast. In April 2019, in *Neurosurgical Focus*, Mummaneni published a protocol for awake procedures, which described the use of liposomal bupivacaine in combination with a spinal anesthetic to allow for operative analgesia during an awake procedure for minimally invasive transforaminal lumbar interbody fusion (MI-TLIF).

"We are one of the first centers in the country doing awake minimally invasive posterior decompression and fusion procedures using the intraoperative CT scanner with navigation," says Mummaneni.

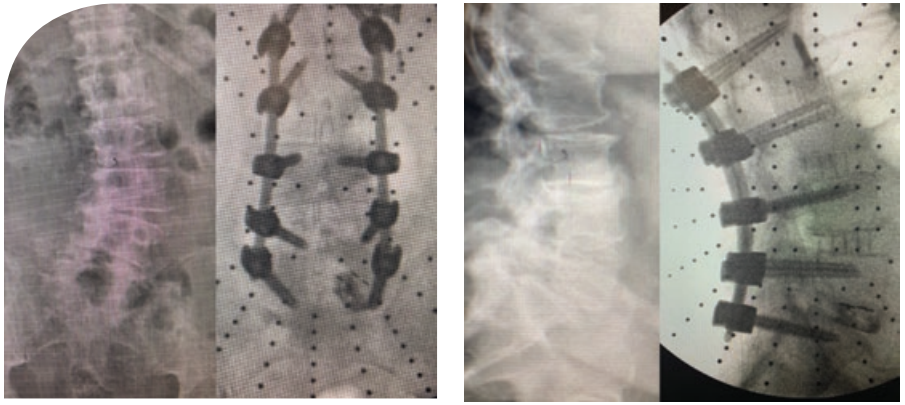
New Algorithm for Minimally Invasive Spinal Deformity Surgery

Neurosurgeons Praveen Mummaneni, MD, and Dean Chou, MD, together with the International Spine Study Group, have updated their algorithm for patient selection when considering a minimally invasive or open approach to treat adult spinal deformity. The algorithm (MISDEF2) was first published in 2014, but the update published this year in *Journal of Neurosurgery: Spine* takes into account new surgical techniques that have widened the pool of patients who may be candidates for minimally invasive procedures.



Example of MISDEF2 Class II deformity. This patient is a 70-year-old woman who presented with chronic low back pain and radiating pain into her legs as a result of lumbar spondylosis (preoperative imaging, left). After conservative measures failed, she underwent L3-S1 anterior lumbar interbody fusions and minimally invasive L2-S1 instrumentation, tolerating the procedures well (postoperative imaging, right).

Mummaneni PV, Park P, Shaffrey CI, Wang MY, Uribe JS, Fessler RG, Chou D, Kanter AS, Okonkwo DO, Mundis GM, Eastlack RK, Nunley PD, Anand N, Virk MS, Lenke LG, Than KD, Robinson LC, Fu KM; International Spine Study Group (ISSG). The MISDEF2 algorithm: an updated algorithm for patient selection in minimally invasive deformity surgery. *J Neurosurg Spine*. 2019;25:1-8.



Pre- (left) and post-op (right) AP xrays showing correction of degenerative scoliosis using robotic assistance and minimally invasive approach.

Robot-Assisted Surgeries Expand

Another equipment improvement for neurospinal procedures arrived this year in the form of a robot.

“We are now doing some robot-assisted cases, which can improve accuracy and lead to reduced complications and better patient outcomes,” says neurospinal surgeon Lee Tan, MD, who trained on these procedures during his fellowship. At UCSF, he has used the robot for minimally invasive single-level and multiple-level spinal fusions, and says it can also be used effectively for open procedures as well.

“It’s more accurate than using navigation only, because the robotic arm gives you the entry point and trajectory, so there is less variability for screw insertion,” he says.

Advances in Managing Cervical Deformity

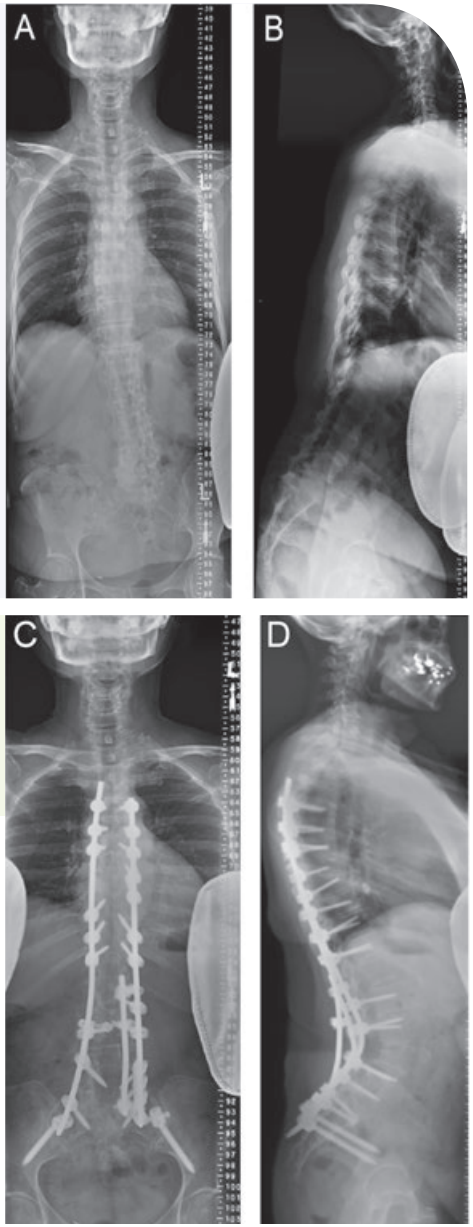
Surgical correction of severe cervical deformity is associated with higher complication rates than most other spine procedures, especially when surgeons have less experience.

In a study published in the May 2019 issue of *Journal of Neurosurgery: Spine*, Ames and his colleagues looked at whether the use of neuromonitoring could reduce neurological morbidity for these procedures. The article found that while interoperative neuromonitoring is an important component, complication rates remained high. But the study also stated there may be reasons for further study, including the finding that performing osteotomies at the upper thoracic levels has a lower risk for nerve injury than doing these procedures in the lower cervical spine or at T1 or T2.

The Value of PSO Experience Explained

Neurospinal surgeon Christopher Ames, MD, has done more than 400 pedicle subtraction osteotomies (PSOs) and this year turned that experience into an article in the *Journal of Neurosurgery: Spine*.

Historically, three-column PSOs have been associated with a high rate of complications relative to other procedures because PSOs require large cuts through the spinal canal and spinal column itself. In his article, Ames tracked his own complication rate over the past 12 years and found it came down from a starting point of 15 percent to 20 percent to about 4 percent today, with the downward trend beginning after approximately five years of experience. Other important factors in keeping complications down include being part of a center experienced with the procedures and one that works in a multidisciplinary way, with everyone involved with the management of these complex patients, from orthopaedic surgeons through ICU and rehabilitation personnel.



Lau D, Deviren V, Ames CP. The impact of surgeon experience on perioperative complications and operative measures following thoracolumbar 3-column osteotomy for adult spinal deformity: overcoming the learning curve. *J Neurosurg Spine*. 2019;25:1-14.

Preoperative and postoperative radiographs of a representative patient with rheumatoid arthritis who underwent T4-pelvis instrumentation and fusion with PSO at L4. Preoperative standing long-cassette radiographs demonstrate significant sagittal imbalance. Anterior/posterior imaging (A) indicates a coronal imbalance of 3.7 cm. Lateral imaging (B) demonstrates global sagittal imbalance, with a sagittal vertical axis (SVA) of approximately 13.5 cm, LL 38°, PI 66°, and PT 18°. The patient had not undergone prior instrumentation for deformity. Postoperatively, standing long-cassette radiographs demonstrate improvement of sagittal balance. Anterior/posterior imaging (C) indicates good coronal alignment. Lateral imaging (D) demonstrates improvement in sagittal plane balance, with a postoperative SVA of 0 cm, LL 70°, and PT 22°. Figure originally published in: Dalle Ore CL, Ames CP, Deviren V, Lau D. Perioperative outcomes associated with thoracolumbar 3-column osteotomies for adult spinal deformity patients with rheumatoid arthritis. *J Neurosurg Spine*. 2019;30(6):822-832.

Vascular Neurosurgery

Hybrid Operating Room a Boon for Patients

The undisputed highlight of 2019 for vascular neurosurgery was the performance of the first several neurosurgery cases in UCSF's new state-of-the-art hybrid operating room, which allows for angiography and performance of both open and endovascular techniques.

"Previously, patients undergoing microsurgical clipping for an aneurysm would have had to wait one or more days, undergoing another round of sedation for the postoperative angiogram," says Adib Abla, MD, chief of Vascular Neurosurgery. "Now it can be done during the same procedure."

The robotic angiography system creates a 3-D image of the aneurysm to visualize blood flow, allowing surgeons to assess the success of the operation prior to closing the skull. As such, patients don't have to return for a second procedure, in part because the surgeons can adjust the clip more than once by doing multiple intraoperative angiograms if needed.

"Doing all this at the same time is an enormous plus for patients," says Abla. "In the future, for the most complex cases, we expect to be able to do open bypass and endovascular coiling at the same time."

"Previously, patients undergoing microsurgical clipping for an aneurysm would have had to wait one or more days, undergoing another round of sedation for the postoperative angiogram. Now it can be done during the same procedure."

- Adib Abla, MD

Two Procedures Expand Patient Options

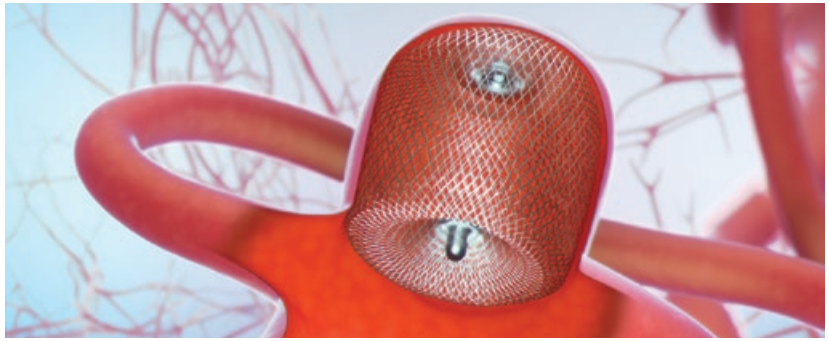
Neurovascular surgeons have long hoped for an alternative to completing endovascular angiograms and coiling through the femoral artery to avoid its risk of potentially life-threatening bleeding, as well as the inconvenience of patients having to lie flat for several hours.

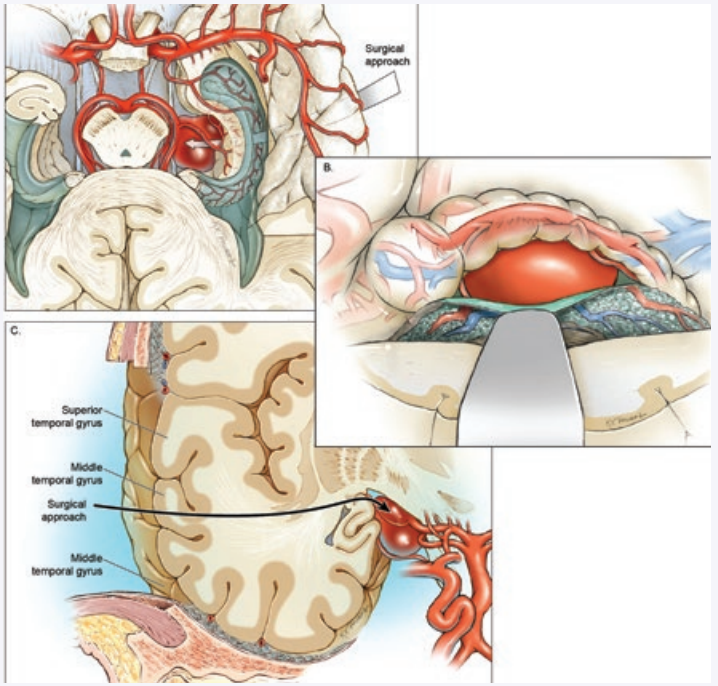
Now, using specially designed catheters and micro coils, surgeons can approach a brain aneurysm by coming through the radial artery in the wrist. "This is now our first-line approach for coiling," says Abla. "Patients are more comfortable – they love it – and the risks of bleeding and transfusion are considerably reduced when compared to going through the femoral artery."

Another procedure vascular neurosurgeons at UCSF are now using involves MicroVention's Woven EndoBridge (WEB) Aneurysm Embolization System for wide-neck intracranial aneurysms.

"This is for a relatively small patient population, but this system allows us to endovascularly treat the wide-neck brain aneurysm without a stent and without antiplatelet meds," says Abla. Instead, surgeons run a permanent nitinol self-expanding mesh spherical implant into the sac of the intracranial aneurysm and then detach it from the catheter. The goal is to disrupt blood flow entering the aneurysm and help promote thrombosis.

"The trick is to properly size each implant individually, based on the size of the aneurysm," says Abla.



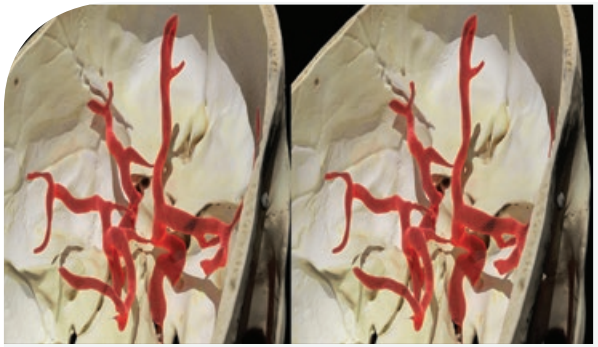
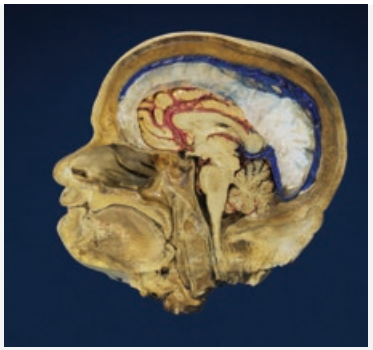
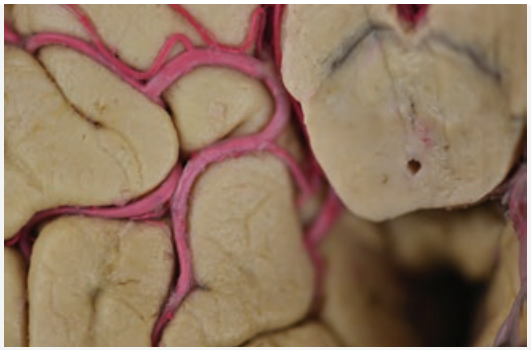
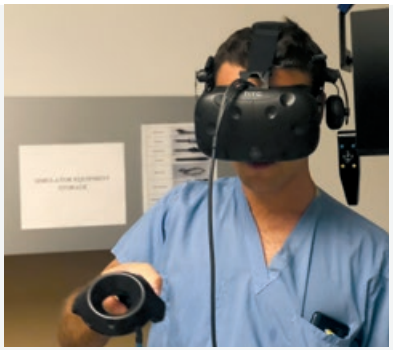


Resident Publishes Paper in British Journal of Neurosurgery on Transchoroidal Approach for Ruptured Aneurysms

Neurosurgical resident Caleb Rutledge, MD, published a paper on April 22, 2019, in the *British Journal of Neurosurgery* describing a new approach for a hyperplastic anterior choroidal artery – a vascular anomaly where the anterior choroidal artery supplies the posterior cerebral artery territory.

The case study described a subarachnoid hemorrhage from a hyperplastic anterior choroidal artery with tandem fusiform aneurysms. The patient underwent a temporal craniotomy and transcortical transventricular transchoroidal-fissure approach for clip reconstruction.

Rutledge C, Jonzzon S, Winkler EA, Hetts SW, Abla AA. Transcortical transventricular transchoroidal-fissure approach to distal fusiform hyperplastic anterior choroidal artery aneurysms. *B J Neurosurg*. 2019: 1-5. doi:10.1080/02688697.2019.1594691.

Skull Base and Cerebrovascular Laboratory Expands Its Impact

According to Roberto Rodriguez Rubio, MD, director and principal investigator of the UCSF Skull Base and Cerebrovascular Laboratory, 2019 was a time to take the lab's 3-D virtual reality (VR) modeling – used for both surgical simulation and education – far beyond UCSF.

For one, Rodriguez Rubio traveled to Costa Rica and the Philippines to share the lab's work with local residents and neurosurgeons through hands-on workshops. In addition, via publications related to the use of 3-D immersive technologies for neuroanatomy education, the creation of the UCSF Surgical Neuroanatomy Collection (the first open-access atlas using 3-D scanning techniques and VR models) and a TED-style talk at the annual conference of the Association of Medical Illustrators, the work is helping to enhance understanding of how to navigate the delicate anatomy of the brain and the skull base while dealing with complex pathologies.

"It's not easy to acquire the skill set of doing this type of navigation – it requires a lot of time – and sharing our 3-D dissections complements the anatomy lab, so people can gain more realistic experience," says Rodriguez Rubio. "The publications and travels are an evolution of what we've been doing to advance surgical knowledge, so we can improve our ability to treat and care for patients."

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Pain and Peripheral Nerve Disorders

Targeted Muscle Reinnervation for Limb Amputations

UCSF has begun offering targeted muscle reinnervation (TMR) for patients with limb amputations. In this surgical procedure, neurosurgeons can redirect the ends of severed nerves from an amputated limb, via nerve grafts or transplants, into a nearby muscle that has otherwise lost function.

Once the residual nerve ends are transferred to the target muscle, they can begin to regenerate axons, and the muscle can often be trained to move a myoelectric prosthetic device using electromyographic signals.

TMR has the added advantage of significantly improving postoperative neuroma pain that can occur after amputation. If not redirected, the ends of severed nerves can sprout axons that grow into the skin and create neuromas, leading to pain at the amputation site and sometimes making it difficult to wear a prosthetic that creates friction against the neuroma.

TMR requires a multidisciplinary team that includes plastic surgeons, neurosurgeons, physical medicine and rehabilitation specialists, and experts in orthotics and prosthetics. At UCSF, patients have the benefit of this team working together at one hospital.

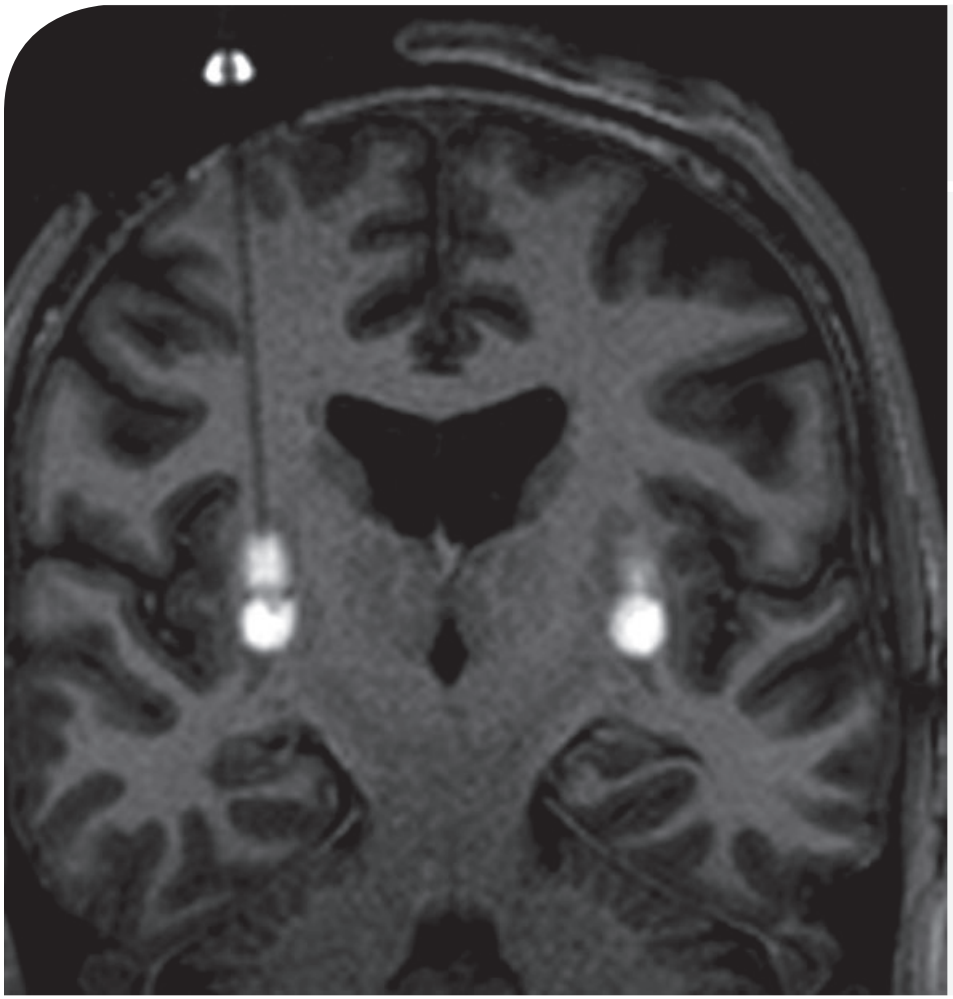
Clinical Trial Evaluating Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome

UCSF is participating in the TARGET Post-Approval Study to evaluate dorsal root ganglion stimulation for the treatment of complex regional pain syndrome (CRPS) types I and II.

CRPS affects the arms, legs, hands or feet and is usually the result of trauma or injury to the affected limb. The FDA-approved system for dorsal root ganglion stimulation includes an implantable neurostimulator, its leads and an external device that monitors the stimulator and leads and adjusts the stimulation settings.

"This treatment is likely most effective for patients with very focal pain in one limb, such as the knee, the foot or the abdominal area," says Line Jacques, MD, chief of peripheral nerve and pain surgery. "For instance, we have a patient on this study who had injury to a small sensory nerve after getting a knee replacement that was beyond repair."

Patients will be followed for two years, at which point Jacques and her colleagues hope to see modified neural chemistry of the spinal cord and brainstem that will alleviate pain for these patients.



Gene Therapy Shows Promise for Parkinson's Treatment

In a study published in the May 2019 issue of the *Annals of Neurology*, a UCSF research team described a phase I gene therapy trial in which 15 patients got as much as three hours of extra medication efficacy without the involuntary muscle movements known as dyskinesia. The patients were also able to decrease their Parkinson's medication by up to 42 percent, depending on the amount and the dose of the gene therapy that was infused.

Neurosurgeon Paul Larson, MD, was senior author on the study, which highlighted the inaugural use of intraoperative MRI-guided monitoring to deliver the gene for AADC – the primary enzyme that converts levodopa to dopamine – via a benign virus. Krystof Bankiewicz, MD, PhD, of the UCSF Department of Neurological Surgery developed the surgical technique.

The patients, who were aged between 40 and 70, were divided into three groups of five people. The first two groups received the same concentration of gene therapy, with the second group receiving twice the volume of the infusion, enabling a broader coverage of the putamen. The third group received three times the concentration as the other groups and the same volume as the second group. While the study was aimed primarily at assessing safety, patients were able to reduce levodopa in all three groups.

"A phase II study of this gene therapy was recently launched, and that study will allow us to better understand the safety and effectiveness of this treatment," says Larson, who is chair of the trial's surgical core.

Christine CW, Bankiewicz KS, Van Laar AD, Richardson RM, Ravina B, Kells AP, Boot B, Martin AJ, Nutt J, Thompson ME, Larson PS. Magnetic resonance imaging-guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease. *Ann Neurol*. 2019;85(5):704-714.

Another Step in Adaptive DBS

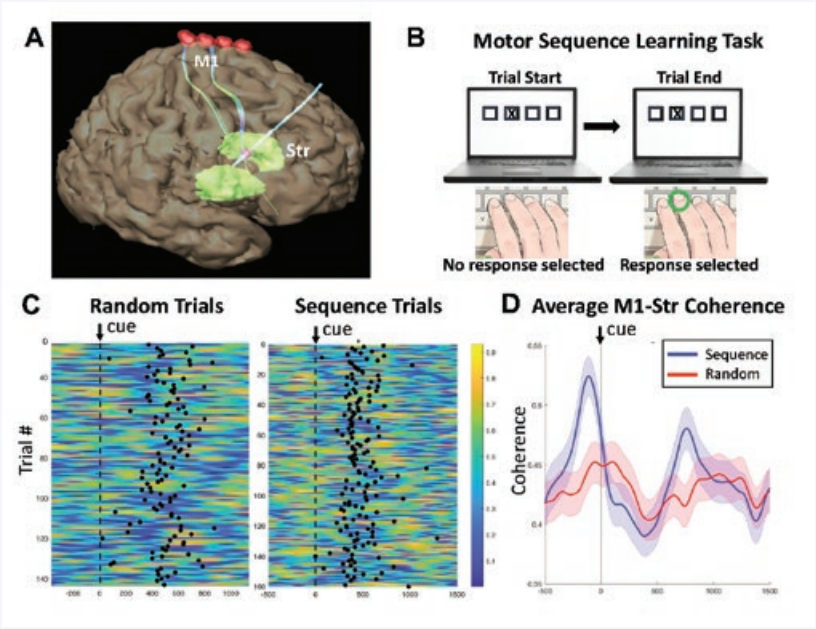
As highlighted in last year's report, neurosurgeon Philip Starr, MD, PhD, has been implanting deep brain stimulation (DBS) devices with neural sensing to test their ability to address the symptoms of Parkinson's disease and dystonia. His team is testing "adaptive" DBS, in which neurostimulation settings are automatically adjusted based on sensing of brain signals.

This year, Starr became the first in the world to implant Medtronic's Summit RC+S, a newer investigational device with a neural sensing system that uses internal controls to auto-adjust but also streams wirelessly to an external computer, enabling extensive hours of brain recordings and allowing surgeons to manually adjust settings.

"The recordings are important for the study, because understanding the signals via the wireless streaming allows us to better understand the patient's brain signaling and further personalize the stimulation," says Starr.

To date, the team has discovered that certain brain signatures indicate when patients are moving well or not moving well. In practice, this enables clinicians to better program the algorithms for auto-adjusting in response to those signatures – and because they can communicate wirelessly with the patient's internal computer, the clinicians can make the algorithm adjustments remotely.

"It's a game-changing device that we have pioneered with five patients here – four with Parkinson's and one with dystonia – and we are helping other centers get started with it," says Starr.



3-D reconstruction of patient implanted with a subdural electrode (red) overlying the motor cortex (M1) and a DBS electrode (blue) with the top contact (pink) in the striatum (Str, green). Tractography showing fibers projection from sensorimotor areas to the striatum.

Schematic of sequence learning task design. A cue appears in one of 4 positions on a screen and the subject is asked to press the key that corresponds to the cue position on a keyboard. Cues can appear in random positions or in a sequenced order. Improvements in reaction time between sequence and random trials is a measurement of motor learning.

Single trial coherence in the 8-12 Hz frequency band between motor cortex and striatum during all random trials (left) and sequence trials (right). Cue presentation is noted by the dotted line (time 0) and black dot represents response selection. Warmer colors indicate higher coherence. The reaction time (time between cue and response selection) is shorter for sequence trials. There is also increase coherence around the time of cue presentation.

Averaged 8-12 Hz frequency band coherence for all random (red) vs sequence (blue) trials. There is increased coherence prior to cue presentation during sequence trials, suggestive of changes associated with sequence learning. Shaded areas represent mean standard error.

Improving Rehabilitation or Movement Disorders: A Conversation with Doris Wang

Doris Wang, MD, PhD, joined the UCSF Department of Neurological Surgery in 2018. Her research lab has received an NINDS K12 grant, and she also has the support of a Burroughs Wellcome Fund Career Award for Medical Scientists.

What is the primary focus of your research?

My research investigates the brain activities involved with motor skill learning – attaining skills through repeated practice – in the context of Parkinson's disease, and how we can use neurostimulation to improve motor learning in Parkinson's and other neurodegenerative disease. We know that Parkinson's patients can learn new motor skills, but less efficiently than a healthy individual does. I am trying to understand the underlying neural signals that contribute to that learning process, because there has not been much study of this in humans to date. My hope is that if we can identify those neural signals, then we might be able to use these signals to drive brain stimulation to enhance them and improve motor skill learning.

What is the status of the work?

We are working with several Parkinson's patients who are already participating in a study on the use of a bidirectional DBS device capable of recording brain signals in addition to providing therapeutic stimulation. Patients are asked to perform various tasks of motor learning involving either the upper or lower limbs, and we record from the cortical and subcortical brain structures to see whether there is a correlation between increases in brain signal strength and improvement in motor performance.

In a few patients, we've seen increases in low-frequency brain activity associated with performance improvement, which is similar to what we've seen in the animal literature. Once we feel confident we've identified biomarkers associated with learning, the next step would be to see if we can increase this activity by stimulating the cortical and subcortical structures during specific times of motor learning. But we are not quite there yet. We need to confirm that these changes occur in a greater number of patients and, of course, develop stimulation based on the strength of these signals, which is not a trivial task. But if this work is successful – if we learn the pathways of learning a new skill and internalizing it – we believe it has the potential to be useful information for any type of rehabilitation.

Can We Use DBS to Treat Severe OCD?

Years ago, neurosurgeon Paul Larson, MD, began studying whether DBS can be effective for patients with obsessive-compulsive disorder (OCD). The arrival at UCSF of psychiatrist Moses Lee, MD, PhD, and Katherine Scangos, MD, PhD, has enabled this clinical and research program to resume.

The therapy is reserved for patients with severe OCD for whom medications and cognitive behavioral therapy have not been effective. Larson implanted a DBS device in a patient with OCD this year, and a clinical trial involving multiple faculty members is in the works.

Pediatric Neurosurgery

PNOC's Growth Opens New Trial Settings

The Pacific Pediatric Neuro-Oncology Consortium (PNOC), led by UCSF, expanded dramatically in 2019.

"This was a global expansion," says neurologist Sabine Mueller, MD, PhD, PNOC's project leader. "We onboarded in Australia and Canada and opened our first site in Europe, in Zurich, Switzerland. In 2020, Tata Memorial Hospital in Mumbai, India, will join PNOC as well."

She says the rationale is simple: Treatment of pediatric brain tumors has to be based on specific subtypes, many of them rare. To do complete trials in a timely manner, there is a need to expand the access area for the PNOC trials, a development that also creates richer scientific collaborations and enables clinicians to bring new therapies to children outside of the U.S. The PNOC expansion coincided with the development of a number of new trials on top of its 15 active trials.

In one, PNOC has a pilot study underway for pediatric patients with newly diagnosed high-grade glioma (HGG), in which Mueller and her colleagues will treat up to 44 children and young adults in the PNOC network. The researchers will analyze samples of tumor to identify its gene expression profile and then will match any genetic alterations with existing targeted therapies or investigational new drug (IND) study agents that block the growth of cancer by interfering with the molecular targets that drive progression.

"We have learned a lot about the molecular makeup of high-grade gliomas in recent years, and we recognize that their heterogeneity means that a blanket treatment approach fails to reach most patients," says Mueller. "We hope that this personalized strategy may lead the way to lifesaving treatments for children with high-grade gliomas."

Another trial in development – a collaboration with Hideho Okada, MD, PhD – will exploit the histone H3.3K27M mutation, which is present in 80 percent of diffuse gliomas that occur in midline structures of children. PNOC has completed enrollment in a vaccine-based strategy against this mutation and is currently analyzing outcome data. But latest results from Okada's laboratory have shown that this mutation can most likely also be targeted with a T cell-based therapy approach, which has shown great promise in other tumor types. "We are working on a protocol with the Parker Institute [for Cancer Immunotherapy] to develop an H3.3K27M T-cell receptor," says Mueller.

Yet another trial in the works is an international, adaptive clinical trial for diffuse midline gliomas. "We are developing a clinical trial protocol, with multiple arms, where we will use evidence from multiple labs to bring the best combination therapies forward," says Mueller. "Initially, our main concern is if drugs are really getting into the tumor of these devastating diffuse midline gliomas [DMGs]. If we get a negative on drug penetration, we will close that arm." The other key focus of this program – referred to as DMG-ACT – will be to offer combination therapies at each stage of the disease (newly diagnosed, recurrent as well as at time of first progression). This trial setup is unprecedented for pediatric diffuse midline glioma.

Another key focus of PNOC is the integration of functional and quality-of-life measures in all of its clinical trial protocols. Mueller says, "It is critical for us as doctors to understand how our therapies impact function as well as quality of life in our patients. This data has not been consistently collected for some of the tumor types, but is urgently needed. Disease control cannot be the only measure of how we judge our therapies."

Using Advanced Imaging to Better Inform Pediatric Neurosurgery

Jarod Roland, MD, is a pediatric neurosurgeon who treats children with a wide variety of neurological conditions, including brain and spinal cord tumors. His research seeks a better understanding of how brain networks adapt and react to changes caused by tumors, epilepsy or other conditions.

What do you see as the more important recent developments in pediatric neurosurgery?

I would say the advancement of techniques and technologies that enable less invasive cranial procedures. Stereo-electroencephalography (SEEG) is one such example that has recently seen tremendous growth in the United States for neurosurgical treatment of refractory epilepsy. This is driven partly by advanced robotics for precise placement of SEEG leads, as well as improved imaging, like MRI and CT angiography, which helps avoid critical blood vessels when placing electrodes.

Also, pediatric neurosurgeons are discovering that a variety of conditions, such as some epilepsy and tumors, can be treated very well by laser interstitial thermal therapy (LITT), with much less pain, minimal blood loss and shorter hospital stays. LITT is made possible by several technologies, one of which is advanced MRI-based imaging techniques. I believe advanced imaging and other noninvasive or less invasive diagnostic technologies will continue to drive the field forward. Faster sequences and smarter computer algorithms for MRI acquisition mean less need for sedation to obtain routine imaging. Advances in functional imaging are also rapidly developing and will mean improvements in surgical planning and personalized medicine, such that the best treatment is decided based on data from the individual patient as opposed to extrapolation of data averaged from a larger population.

How are those advances connected to your own research?

One of the ways to describe how the brain functions is to think about it as a collection of networks and nodes of a network that interact over time. We now have tools like functional MRI (fMRI) that measure signals from the entire brain noninvasively, allowing us to better understand these networks. I want to figure out how our neurosurgical procedures like resections and functional disconnections affect these networks and how the brain responds. Kids' brains have a remarkable plasticity that allows them to tolerate these procedures remarkably well, and even reorganize the way the brain works to overcome some deficits. So my plan is to study functional networks before and after surgery to understand how the brain is reorganizing, in the hope that it can better inform how we should perform surgery. One of the benefits of resting-state fMRI in this clinical setting is that we can obtain data while patients are undergoing routine MRI scans to decrease the onus placed on the patient.

Craniofacial Clinic Offers Comprehensive Care Across Two Hospitals

The integration of the Craniofacial Clinic across both UCSF Benioff Children's Hospitals allows the clinic's complex patients to benefit from increasingly well-coordinated and timely diagnosis, counseling and treatment provided by a multidisciplinary team of dedicated craniofacial specialists.

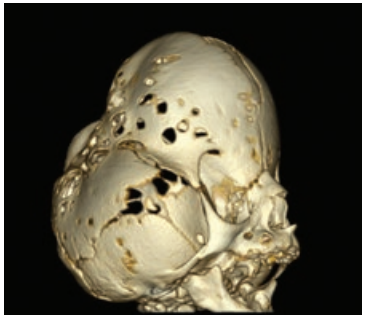
Now a single, unified practice offers fully comprehensive care for patients with conditions affecting the developing face and head, whether they occur before birth or are acquired after birth, such as from trauma or tumors. That care combines the most advanced diagnostic, surgical and therapeutic techniques with respectful and compassionate team care. Multidisciplinary panels confer on the best approach for each individual patient.

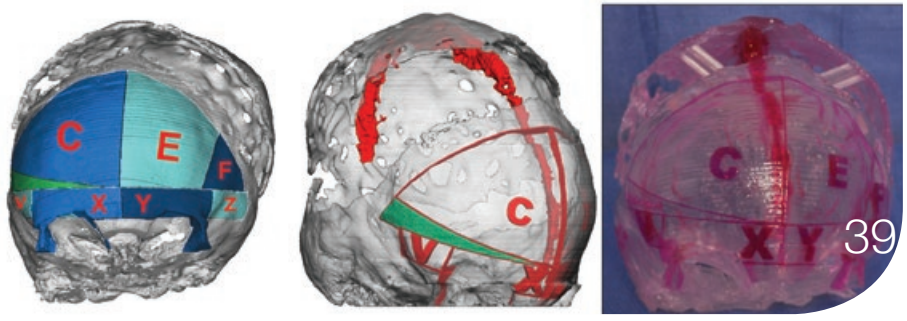
On the diagnostic front, the latest addition is the use of a virtual reality theater that enables surgeons to visualize all the folds in the bone, so they can do more precise surgical planning for the most difficult cases.

Surgical techniques include minimally invasive procedures, using tiny incisions and endoscopes for faster recoveries, less blood loss and equal or better results. For patients with more severe deformities, the surgeons rely on time-tested open procedures for reshaping the cranial vault and/or the latest implantable devices, including distractors and springs that reshape the skull over time.

In addition, because not all craniofacial abnormalities require surgery, the comprehensive craniofacial practice includes full-time prosthetic experts who design tailor-made helmets that correct head shape over several weeks in the outpatient setting.

Social workers are also part of the team, because most of these conditions affect an individual both medically and socially. "We work hard to address both the medical and social challenges these patients and their families face," says neurosurgeon Kurtis Auguste, MD.





Left: 3-D reconstruction of a complex craniosynostosis case assists with surgical planning. Right: Virtual and 3-D printed models of surgical repair.

Epilepsy

UCSF Pioneers Neurostimulation Technologies for Epilepsy

Leading advances in the field of neurostimulation, the UCSF Epilepsy Center is widely considered a center of excellence in pioneering novel therapies for patients with epilepsy.

With medically refractory patients representing approximately one-third of all epilepsy cases, the design and improvement of nonmedical approaches remains a priority. Such strategies include neuromodulation therapies like vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS).

“There is increasing evidence that neurostimulation, among other approaches, can approximate the same types of results as traditional open surgeries and, so, are very valuable options for long-suffering patients,” says UCSF neurosurgeon Edward Chang, MD.

Vagus Nerve Stimulation

VNS is currently approved by the FDA for patients with medically refractory or drug-resistant epilepsy. VNS involves implantation of a device that resides under the skin at the neck and chest, and delivers regular pulses of electrical stimulation to the vagus nerve.

Clinical studies show significant reduction of seizure frequency in patients implanted with VNS. Although the exact mechanism of action remains unclear, VNS is thought to work by affecting areas of the brain receiving input from the vagus nerve, which ultimately may modulate neuronal networks involved in seizure onset and propagation.

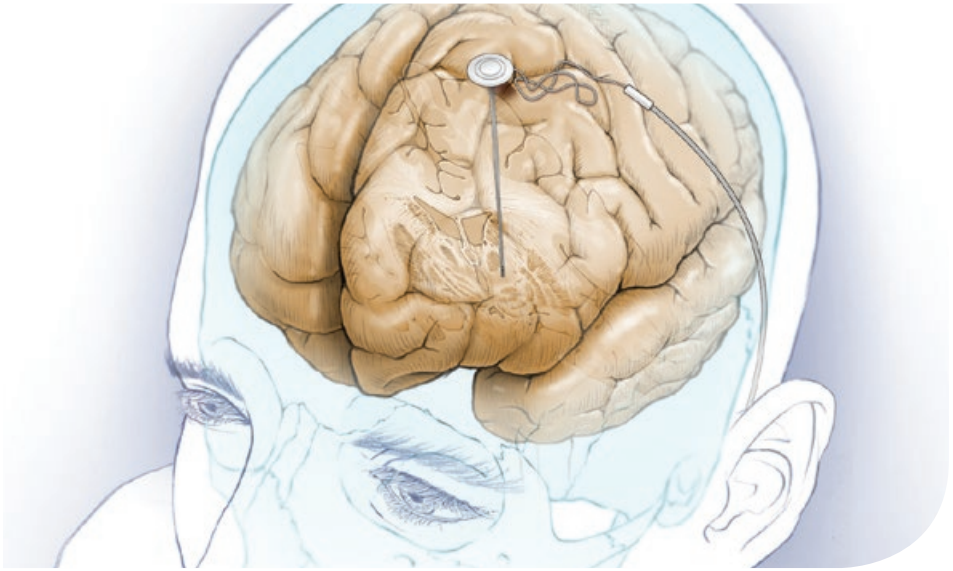
In 2018, UCSF was among the first centers to adopt the latest VNS device, LivaNova's SenTiva Model 1000, for clinical use in patients with epilepsy.

Deep Brain Stimulation

More widely known for its use in treating Parkinson's disease, DBS involves the placement of a neurostimulator device that applies electrical stimulation to specific targets in the brain. In the case of treating epilepsy, stimulation of the anterior nucleus of the thalamus is associated with significant reduction in seizure frequency.

The UCSF Epilepsy Center was among the first in the country to contribute to the SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) clinical trial (NCT00101933), which led to FDA approval of thalamic DBS for medically refractory epilepsy.

"The first patient who received thalamic DBS at UCSF, outside of a clinical trial, was implanted in 2018," says UCSF neurologist Vikram Rao, MD, PhD. "Since then, we've led the way in transitioning use of DBS from experimental therapy to clinical use for epilepsy."



“This past year, we implanted our 50th patient with RNS,” says Rao. “In the past decade, we’ve seen considerable advances in neurostimulation therapies, and it’s had enormous impact – especially for medically refractory patients who previously had no other options.”

- Vikram Rao, MD, PhD

Responsive Neurostimulation

UCSF is among the world leaders in the use of RNS, in which an implantable device detects seizure-related electrical activity in the brain and responds immediately by delivering imperceptible levels of electrical stimulation to prevent seizures before they start. The UCSF Epilepsy Center was one of the first centers on the West Coast to offer RNS, and remains among the top five centers by volume for this therapy.

“RNS works well for patients with seizures arising from more than one region in the brain, or from a region that can’t be safely removed by surgery,” says Chang. “Thanks to optimal patient selection, advanced surgical expertise and high-quality outpatient follow-up care, including a dedicated RNS clinic, our RNS patients have had an average seizure reduction of 80 percent. This surpasses the 48 percent to 66 percent seizure reduction reported in long-term clinical trials.”

UCSF is involved in a five-year post-approval study that follows patients implanted with the NeuroPace RNS System to evaluate the long-term effectiveness of the device. Rao’s research group has also leveraged data from NeuroPace devices in seminal work that identified cycles of electrical activity patterns that predict seizure risk.

“This past year, we implanted our 50th patient with RNS,” says Rao. “In the past decade, we’ve seen considerable advances in neurostimulation therapies, and it’s had enormous impact – especially for medically refractory patients who previously had no other options.”

Deepening Understanding of Rare Epilepsies

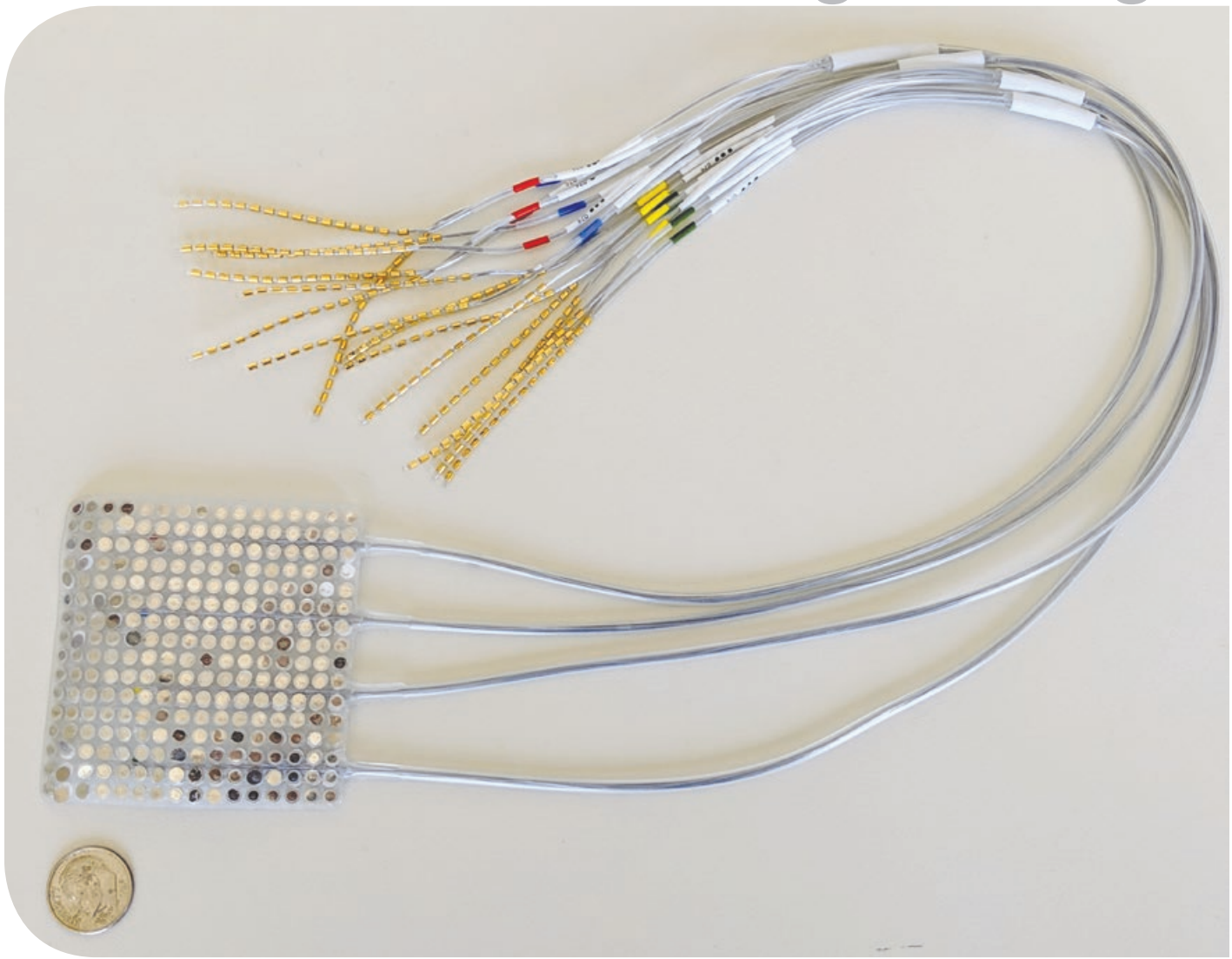
The lab of Scott C. Baraban, PhD, had an eventful year in its efforts to push forward understanding of rare genetic epilepsies.

An August 2019 publication in *Brain Communications* stems from Baraban's groundbreaking work with zebrafish. Dravet syndrome is a life-threatening, early-onset epilepsy that is not well controlled by existing antiepileptic drugs. Baraban's paper describes his lab's discovery of three clemizole analogues with serotonin (5-HT) receptor binding that demonstrated powerful antiepileptic activity. Supported, in part, by the UCSF Catalyst Program, the work involved designing and synthesizing 28 novel analogues of clemizole, obtaining receptor binding affinity profiles and performing in vivo screening in an scn1lab-mutant zebrafish model that exhibits Dravet syndrome clinical features.

"Kids with Dravet are usually on multiple medications but still experience hundreds of seizures a day and, sometimes, sudden death," says Baraban. "Yet these genetic epilepsies are so rare that they do not generate a lot of drug development." A company that grew from Baraban's zebrafish work (Epygenix Therapeutics) is currently involved in preclinical studies to further develop these therapeutics, and findings like the one above generate targets that could be applicable for a number of these intractable epilepsies.

Griffin AL, Jaishankar P, Grandjean J-M, Olson SH, Renslo AR, Baraban SC. Zebrafish studies identify serotonin receptors mediating antiepileptic activity in Dravet syndrome. *Brain Commun*. 2019;1(1):fcz008. doi:10.1093/braincomms/fcz008.

Center for Neural Engineering and Prostheses



"I'm proud that we've been able to bring together expertise from neuroscience, linguistics and machine learning as part of this major milestone toward helping neurologically disabled patients."

- Gopala Anumanchipalli, PhD

In an April 2019 issue of *Nature*, neuroscientists in the lab of neurosurgeon Edward Chang, MD, described a state-of-the-art brain-machine interface they created, which generates natural-sounding synthetic speech by using brain activity to control a virtual vocal tract – an anatomically detailed computer simulation including the lips, jaw, tongue and larynx. While the study was conducted in research participants with intact speech, the technology could one day restore the voices of people who have lost the ability to speak due to paralysis and other forms of neurological damage.

Chang, who has been studying how the brain produces and analyzes speech for over a decade, says, "For the first time, this study demonstrates that we can generate entire spoken sentences based on an individual's brain activity. This is an exhilarating proof of principle that with technology that is already within reach, we should be able to build a device that is clinically viable in patients with speech loss."

Gopala Anumanchipalli, PhD, a speech scientist, and Josh Chartier, a bioengineering graduate student in the Chang Lab, led the study, which builds on another, in which the pair described for the first time how the human brain's speech centers choreograph the movements of the lips, jaw, tongue and other vocal tract components to produce fluent speech.

"The relationship between the movements of the vocal tract and the speech sounds that are produced is a complicated one," Anumanchipalli says. "We reasoned that if these speech centers in the brain are encoding movements rather than sounds, we should try to do the same in decoding those signals."

Detailed mapping of sound to anatomy allowed the scientists to create a realistic virtual vocal tract for each participant that could be controlled by their brain activity. This comprised two "neural network" machine-learning algorithms: a decoder that transforms brain activity patterns produced during speech into movements of the virtual vocal tract, and a synthesizer that converts these vocal tract movements into a synthetic approximation of the participant's voice. In the future, this approach could not only restore fluent communication to individuals with severe speech disability, the authors say, but also reproduce some of the musicality of the human voice that conveys the speaker's emotions and personality.

"We're quite good at synthesizing slower speech sounds like 'sh' and 'z' as well as maintaining the rhythms and intonations of speech and the speaker's gender and identity, but some of the more abrupt sounds like 'b's and 'p's get a bit fuzzy. Still, the levels of accuracy we produced here would be an amazing improvement in real-time communication compared to what's currently available," says Chartier.

Now, the researchers are experimenting with higher-density electrode arrays and more advanced machine-learning algorithms, which they hope will improve the synthesized speech even further. The next major test is to determine whether people who can't speak could learn to use the system without being able to train it on their own voice and to make it generalize to anything they wish to say.

"People who can't move their arms and legs have learned to control robotic limbs with their brains," says Chartier. "We are hopeful that one day people with speech disabilities will be able to learn to speak again using this brain-controlled artificial vocal tract."

"I'm proud that we've been able to bring together expertise from neuroscience, linguistics and machine learning as part of this major milestone toward helping neurologically disabled patients," says Anumanchipalli.

Anumanchipalli GK, Chartier J, Chang EF. Speech synthesis from neural decoding of spoken sentences. *Nature*. 2019;568(7753):493-498.

Extension

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The UCSF Department of Neurological Surgery's community extension program continues to partner with hospitals throughout the Bay Area to provide local surgical expertise for brain and spine disorders. For cases that require special equipment or expertise, the patients still have access to UCSF's San Francisco campus. Patients also benefit from the department's many clinical trials and leading-edge research.

The team at Marin General Hospital demonstrates why this is such a boon for patients. There, three full-time UCSF faculty neurosurgeons – Tarun Arora, MD, Catherine Miller, MD, and Keith Quattrocchi, MD, PhD – work together to provide the full spectrum of spine care, trauma surgery for both brain and spinal injuries, and complex brain tumor surgeries. In the next few years, they hope to also build a neurovascular and movement disorder service.

"Offering these services locally keeps us in touch with the primary care physicians and enables them to continue to be involved with their patients' care," says Arora, director of the community extension program. "Patients appreciate being able to receive care from their UCSF neurosurgeon close to their support systems, family and their primary care physician."

He adds that when necessary, patients still have access to that extremely specialized care at UCSF Helen Diller Medical Center at Parnassus Heights.

"Patients appreciate being able to receive care from their UCSF neurosurgeon close to their support systems, family and their primary care physician."

- Tarun Arora, MD

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