UCLA Registry Helps Researchers and Physicians to Better Understand Dwarfism

The world’s largest registry for skeletal disorders, based in UCLA’s Department of Orthopaedic Surgery, continues to play a critical role in the diagnosis, management and etiology of patients with dwarfism, as well as providing an invaluable tool for researchers seeking to develop better treatments. The International Skeletal Dysplasia Registry was established in 1970 at Cedars-Sinai Medical Center and then moved to UCLA in 2013. It now has more than 20,000 cases, providing a treasure trove of DNA, cell lines, radiographs and medical records that have led to a better understanding of the genetic and biologic
First dissolvable cardiovascular stent available at UCLA

UCLA is now offering the first bioabsorbable stent approved by the U.S. Food and Drug Administration to patients with coronary artery disease requiring coronary stenting. After the stent resorbs, the vessel regains normal vasomotor function, while late complications that can occur with metallic stents are eliminated.

Limb-sparing surgery for rare bone cancers

Limb-sparing surgery avoids amputation by removing only the tumor and a small portion of the surrounding soft tissue. Over 90 percent of bone sarcoma cases can be surgically managed by limb-sparing surgery.

Study analyzes radiotherapy, surgery for very aggressive prostate cancer

A retrospective analysis by researchers at UCLA’s Jonsson Comprehensive Cancer Center has concluded that high-dose radiation therapies may be as effective as radical prostatectomy for treating very aggressive prostate cancer.

Placement and removal of inferior vena cava filters

While inferior vena cava filters can effectively prevent blood clots from traveling to the heart and lungs, the FDA recommends their removal as soon as protection from blood clots is no longer needed.

Clinic treats male-factor fertility issues

Male-factor fertility problems play a role for about half of all couples having difficulty getting pregnant. When properly identified, most male-factor fertility problems can be overcome, and couples can often succeed in initiating a pregnancy.

To download these and other clinical advances at UCLA Health, go to: uclahealth.org/clinicalupdates

News from UCLA Health

Discovery Could Lead to New Insomnia Treatments

UCLA scientists have found evidence that a gene outside the brain controls the ability to rebound from sleep deprivation. The discovery could lead to greatly improved treatments for insomnia and other sleep disorders that do not involve getting a drug into the brain.

uclahealth.org/sleepbiology

Combination Therapy Could Provide New Treatment for Ovarian Cancer

UCLA researchers have pinpointed a combination therapy that may be effective for up to 50 percent of women with ovarian cancer.

uclahealth.org/combotherapy

Virtual Reality Unlocks Mysteries of Memory

A study by UCLA researchers is the first to blend virtual reality with a surgically implanted prosthesis to reveal what happens in the brain when people create memories.

uclahealth.org/mysteryofmemory

Conscious Sedation a Safe Alternative for Heart-valve Procedure

UCLA scientists have found that conscious sedation is a safe and viable option to general anesthesia for people who are undergoing transcatheter aortic-valve replacement.

uclahealth.org/conscioussedation
Synthetic-Cartilage Implant Offers Relief from Great Toe Arthritis

The first synthetic cartilage approved by the U.S. Food and Drug Administration for the treatment of great toe arthritis appears to be highly effective in relieving pain while retaining motion for patients who suffer from the debilitating condition, according to a UCLA orthopaedic surgeon who treats patients with the new implant.

Great toe arthritis (hallux rigidus) involves the gradual loss of cartilage around the joint at the base of the big toe, causing swelling and reduced function. “This can become very painful, limiting the patient’s ability to participate in physical activities,” says Joan R. Williams, MD, who specializes in foot and ankle injuries. Great toe arthritis affects an estimated 45 percent of patients older than 70 — though it can start as early as young adulthood. Patients typically present with stiffness and pain, and in some cases with a bump at the site.

In the past, the surgical approach to treating great toe arthritis typically involved fusing the joint responsible for the pain. While effective in addressing the discomfort, that treatment has a major drawback. “It’s not ideal for patients who want to retain motion in their great toe, which is necessary for activities like running and jumping,” Dr. Williams notes. Toe-joint replacement procedures also have had problems. When the replacement fails, there tends to be substantial bone loss. Attempting fusion at that point results in poorer outcomes and higher complications than fusion without the replacement, Dr. Williams explains.

The Cartiva implant, which the FDA approved last year, is a polymer device that is designed to have similar properties as articular cartilage. When inserted into joints, it resurfaces the metatarsal head. “This has an excellent survival rate at five years, which is the longest outcome study we have at this point,” Dr. Williams says. “It has been very effective in relieving pain while retaining motion for patients.”

Dr. Williams notes that patients with large cartilage lesions often are not candidates, nor are patients with gout. Other than that, the implant can be beneficial for those who find that their great toe arthritis is interfering with their quality of life, particularly after they have failed to get relief from nonsurgical options, such as orthotics and anti-inflammatory drugs. “Fusion still is an option for patients who can’t benefit from the implant, or for those who aren’t that active and don’t need to retain motion in their toe for their quality of life,” Dr. Williams says. “But having this additional option is a major advance, particularly since we want our older patients to be able to stay active for as long as possible.”
Dwarfism

**STORY HIGHLIGHTS**

The International Skeletal Dysplasia Registry now has more than 20,000 cases, providing a treasure trove of DNA, cell lines, radiographs and medical records.

The findings have led to a better understanding of the genetic and biologic underpinnings of inherited disorders related to both short and large stature.

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**COVER STORY**

UCLA Registry Helps Researchers and Physicians to Better Understand Dwarfism

(continued from cover)

underpinnings of inherited disorders related to both short and large stature.

“When this registry was started, it was thought that dwarfism was just one or two disorders. Now we know that there are approximately 450 distinct forms,” says Deborah Krakow, MD, UCLA professor of orthopaedic surgery and genetics, co-director of the registry and chair of the Department of Obstetrics and Gynecology. “We have found the genes involved in 350 of these disorders — the most common ones — and are now trying to understand how these genetic defects affect cartilage, bone, tendon and muscle, and to use that deeper understanding to make a positive impact on patients.”

In addition to starting and building the registry, its founder, the late David Rimoin, MD, PhD, trained multiple generations of experts in the clinical and molecular aspects of very short and very tall stature, including Dr. Krakow, a geneticist who has a clinical service dedicated to patients with connective-tissue disorders; and Daniel H. Cohn, PhD, a UCLA geneticist who serves as the registry’s other co-director.

Individuals with dwarfism tend to develop chronic skeletal problems, including early-onset degeneration of the cartilage and bone typically associated with the elderly. Many become incapacitated by chronic pain in their back, knees and hips, and they are unable to walk long distances. Some develop visual problems, such as retinal detachment, pulmonary or auditory complications, and issues associated with the compression of their spinal cord at the back of the neck. They may be more prone to fractures. These disabilities can result in the need for wheelchairs or assisted motor devices, as well as increasing the risk for obesity and other complications associated with sedentary lifestyles.

“Our hope is to understand the cell biology and pathways that are perturbed, then direct therapeutics in a more evidence-based manner to improve patient outcomes.”

The ability to make a molecular diagnosis and understand the genetics of a patient’s disorder provides insights into the natural history and a roadmap for clinicians. “With radiographs and clinical information on all of these disorders in one place, we have a large enough cohort to know what we should anticipate or be concerned about, as well as what we should be working to prevent,” Dr. Krakow explains. “Our team, including our orthopaedic surgeons, works on skeletal issues such as correcting scoliosis and addressing any alignment issues that can improve the quality of life, as well as trying to avert long-term complications such as deafness, retinal detachment and respiratory problems.”

The UCLA experts also have provided guidance to families affected by dwarfism in their reproductive choices. “In some cases, these inherited disorders have the possibility of recurrence, and in others there is no such risk,” Dr. Krakow says. “Either way, the families want to know. Some have used the data showing that recurrence is a possibility to opt for in vitro fertilization.”

Dr. Krakow explains that there currently are several drugs in clinical trials for particular dwarfism subtypes that might improve height and, provide more room in the spinal

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This sagittal (from the side) T2-weighted MRI image of the lumbar spine shows exaggeration of the lumbar curve (lordosis) in addition to scalloping of the posterior vertebral bodies and spinal canal stenosis typically seen in achondroplastic dwarfism. Significant spinal stenosis is often a problem in patients with dwarfism that can become very symptomatic.

*Photo: Science Source*
column to prevent or reduce complications. Bisphosphonates are now given to patients with brittle bone disease to decrease the incidence of fractures. UCLA also is participating in a clinical trial to test whether drugs developed to treat osteoporosis also can reduce the risk of fractures in patients with rare bone-fragility disorders. Surgical treatments for certain dwarfism subtypes can lengthen limbs, though they have a high complication rate and are rarely performed. In addition, a growing number of start-up companies are targeting molecular pathways to increase bone growth and the health of the cartilage in ways that could combat long-term osteoporosis, scoliosis and other conditions associated with short stature.

With archived tissues and DNA for many of the disorders, as well as mouse models for some of the diseases, the UCLA researchers are able to test treatment strategies in the laboratory. “Our hope is to understand the cell biology and pathways that are perturbed, then direct therapeutics in a more evidence-based manner to improve patient outcomes,” Dr. Krakow says. The UCLA group also works with families, physicians and researchers throughout the world to classify skeletal disorders radiographically, histologically and genetically, and collaborates with those seeking material on a rare disease to help to solve new disorders.

Dr. Krakow says that the experience of UCLA’s team in the diagnosis and management of these rare disorders provides much-needed clarity for patients about the genetics and natural history of their condition. The group includes subspecialists in pediatrics, internal medicine, neurosurgery, ophthalmology and pulmonology, as well as orthopaedic surgery and plastic surgery. “We have assembled a high-quality team,” Dr. Krakow says. “We are extremely committed to providing these patients with the best possible care.”
Tailoring Sarcoma Care to Meet the Needs of the Patient

Each year, physicians diagnose approximately 10,000 soft-tissue sarcomas and 3,000 bone sarcomas in the United States. These cancers tend to be complex, with many subtypes, and they are very aggressive. “It’s important not to overlook or mistake a lump or mass as benign when it actually is malignant,” says Francis J. Hornicek, MD, PhD, chair of the UCLA Department of Orthopaedic Surgery.

The diagnostic process involves imaging studies and a preoperative tissue diagnosis confirmed frequently by image-guided core needle biopsy. If the tissue is found to be malignant, staging studies are conducted to determine the extent of the disease and to provide guidance for the patient’s care. But Dr. Hornicek notes that in some cases, physicians who suspect a lump is benign will perform an unplanned excision, failing to take the surrounding normal tissue — an important step in sarcoma care to ensure that tumor cells aren’t left behind. “That’s why whenever there is any doubt, it is best to send the patient to a center with experience treating high volumes of sarcoma cases,” he says.

When a finding is determined to be malignant, there are many advantages to a team approach, says Susan V. Bukata, MD, an orthopaedic oncologist with the UCLA Sarcoma Program. “It’s about knowing exactly where to take the biopsy, how much material to take, and what to send to the pathologist to make sure you’re getting the right diagnosis,” Dr. Bukata says. “It’s about having that pathologist available while you’re taking the biopsy to make sure you’ve provided adequate material. It’s about having an integrated team, including people who do the patient evaluations, interpret the imaging, perform the biopsies and evaluate the pathology. It’s about looking at the patient holistically.”

Dr. Hornicek notes that there are more than 100 types of sarcomas. “Subtypes have different molecular alterations, and those genetic alterations produce varying proteins that affect the cancer cells’ abilities to recur locally and demonstrate different patterns of metastasis, which makes it very important to understand each individual sarcoma,” he says. The treatment protocol and sometimes prognosis also is guided by the pathology report. “If it’s a high-grade tumor, there is more of a chance of it spreading to another location or metastasizing, and we would consider chemotherapy in the management of those higher-grade tumors.”

“If a patient wants to be able to play soccer after we’ve removed the tumor in his or her leg, we might use a different reconstruction option than if that patient says he or she just wants to be able to take a five-minute walk down the beach.”

STORY HIGHLIGHTS

A center with experience treating high volumes of sarcoma cases is often the best option for physicians to send patients.

An integrated team approach provides advantages for a malignant sarcoma diagnosis, including comprehensive treatment plans that ensure the patient is looked at holistically.
Dr. Hornicek says, “These tumors might also have a higher incidence of local recurrence, so we may want to include radiation therapy to decrease local recurrence.” Patients whose disease has already metastasized — most commonly to the lungs in patients with sarcoma — are likely to be offered chemotherapy initially. This pattern of metastases is different than in the more common carcinomas.

The treatment approach for soft-tissue sarcomas is very different from the approach to bone sarcomas, Dr. Bukata adds. “Soft-tissue sarcomas can develop in the muscles, fat and nerves, and sometimes in the joints, but they don’t specifically involve the bone,” she explains. These patients often are treated with radiation, and in some cases chemotherapy, prior to surgery. Bone sarcomas are almost always treated with chemotherapy, and in some cases with radiation, both before and after surgery.

For bone sarcomas, the surgery typically involves taking out the cancerous area of bone and performing reconstruction. “Oncologists are trained to kill the cancer, but orthopaedics is a quality-of-life field,” says Nicholas Bernthal, MD, chief of UCLA’s Musculoskeletal Oncology Service. “For those of us who are orthopaedic oncologists, we have really pushed the field in the last several years to pay greater attention to how content patients are after the reconstruction. If a patient wants to be able to play soccer after we’ve removed the tumor in his or her leg, we might use a different reconstruction option than if that patient says he or she just wants to be able to take a five-minute walk down the beach.”

On the scientific end, the sarcoma team is moving closer to personalized approaches to treating patients — for example, taking part of the material from the biopsy and studying the effect of potential therapies in the laboratory so that if patients have a recurrence or other adverse outcome, the team will have insights into what drug will be best for them. “It used to be that we really had only one shot against sarcomas,” Dr. Bernthal says. “Now, with targeted and immunotherapies, we are able to gain access to the newest drugs for second- and third-line therapies, and we have seen some very promising results.”

Properly Treating Sarcoma Requires Experience and a Comprehensive Approach

UCLA has one of the three largest sarcoma centers in the country, performing approximately 600 surgeries a year. The high volume allows UCLA to offer a large number of clinical trials; typically, more than a dozen are active at any given time.

But it is not just the volume that’s important. “In sarcoma care, each specialty is critical to getting the patient from diagnosis to cure,” says Noah C. Federman, MD, director of the UCLA Pediatric Bone and Soft Tissue Sarcoma Program. “Having all of the specialists working together as equals in the care of these patients not only is ideal, but necessary to provide true comprehensive care for patients.”

Diagnosing sarcomas is challenging for several reasons, notes Scott D. Nelson, MD, chief of musculoskeletal pathology. With so many subtypes, “you can’t just look at the slides and make the correct diagnosis. Communicating regularly with the team of surgeons, oncologists, radiologists and radiation therapists is the best way to make sure you are factoring in all of the imaging studies and clinical history you need to ensure accuracy and give the treating physicians the confidence to go forward with the therapy,” he says.

Navigating all of the specialties needed to diagnose and treat a sarcoma can be challenging in any medical environment, and ensuring that the team is in constant contact is often difficult. At UCLA, “we pride ourselves in making the care of these sarcoma patients seamless,” Dr. Federman says. Patients who are referred to the group are almost always seen within 24-to-48 hours, and each week, approximately 30 physicians meet to review every active case. Together, the team — including representatives from pediatric oncology, medical oncology, radiation oncology, surgical oncology, orthopaedic oncology, musculoskeletal radiology, interventional radiology and musculoskeletal pathology — reaches a consensus on the diagnostic and therapeutic plan, which is ultimately presented to the patient.

The contact among team members is not confined to the weekly meetings. “We are constantly texting, calling and going into each other’s office to discuss cases,” Dr. Nelson says. “My office is next door to an orthopaedic oncologist and a pediatric oncologist. That’s very unusual.”

This seamless multidisciplinary approach leads to improved patient satisfaction, the UCLA sarcoma team members say, both because the diagnostic and treatment process is expedited and because patients see that decisions about their care are being made in a rigorous and coordinated manner. “I would hesitate to operate on a patient whose case hasn’t been presented at our multidisciplinary conference, because of how often I get feedback from other members of the team that leads to a revised strategy,” says Fritz C. Eilber, MD, director of UCLA’s Jonsson Comprehensive Cancer Center Sarcoma Program. “I tell my patients that I can take their tumor out, but what they are really benefiting from is the power of this large group of sarcoma-specific physician-scientists. It’s irreplaceable.”
After a distinguished career spent on the East Coast, why did you elect to come to UCLA?

UCLA has a fantastic national and international reputation, with its hospitals ranked among the best by U.S. News & World Report. The Department of Orthopaedic Surgery has been very strong over the years and is historically well-known for certain clinical services, such as arthroplasty, hand surgery, sports medicine, sarcoma and pediatric care. Basic-science research and translational efforts at UCLA orthopaedics are considered to be equally prestigious. My intention is to build on the strong foundation that my predecessor, Dr. [Jeffrey] Eckardt, created. I aim to grow the department in all of the different subspecialties; to continue to build its reputation locally, nationally and internationally; and to align with the mission of UCLA Health to deliver the highest-quality care, conduct groundbreaking research, and offer the best education and training to medical students, residents, fellows and other faculty locally and beyond.
What do you see as the major challenges for the field of orthopaedic surgery?

If you look at all of the forecasts, much of what we do is being shifted to the outpatient setting, with more procedures being done in ambulatory-care centers and fewer being done inpatient at large hospitals. This requires a restructuring. As care becomes more distributed, the challenge is to maintain cohesion within the department even as we are moving to these outside facilities. It is important to maintain that cohesion because only by operating as a team can we successfully adapt to the changes in health care while incorporating technological advances into our practice at the same time as we are striving to keep costs down. It’s a significant challenge, and one that requires a team approach. The leadership at UCLA supports this approach.

Beyond working as a team, how do you deal with this challenge of advancing technologies and rising costs?

That’s where we’ve seen a lot of effort focused on looking at approaches like bundling and total medical expenditures for chronic problems such as arthritis of the knee, as we are doing at UCLA. You might, for example, develop a center to address knee problems that spans from childhood through adulthood. Orthopaedics is one of the few fields that touches all age groups, and it also touches on almost all the other fields within the health care system. This presents us with unique opportunities to affect many lives through these types of initiatives.

What are the department’s research priorities?

We are fortunate to be strong in clinical research, translational research and basic science research, and the advantage is that these can complement one another. One of the areas where we’re finding more and more useful information is in studying patient outcomes and looking at the experience of patients — their quality of life and how they view their experience going through our system. That is very important and something we will continue to focus on. All of our basic-science research projects under the direction of Dr. John Adams have a translational aspect or focus to them. We hope to have significant impact on the management of many human diseases related to the musculoskeletal system.

What do you imagine the field will look like in five-to-10 years?

In orthopaedics, there are many different implants that are used in the spine, in arthroplasty, in hip and knee replacements, and even in oncology. With these, we replace certain bones with metal or plastics. With many of the new biologics and the work that’s being done with stem cells, there’s a great desire to use the patient’s own cells to reproduce some of these devices. You might, for instance, create a scaffolding around which you would develop a bone, or some other means to treat the patient using biologics as opposed to utilizing the devices we have now. There also continues to be a move toward minimally invasive surgery in many areas of orthopaedics, such as spine surgery and arthroplasty. Robotics will be used in these efforts. I think we will see more improvement in these techniques, and with that, decreased lengths of hospitalizations.

What should referring physicians know about the UCLA Department of Orthopaedic Surgery?

We offer the complete portfolio of cases, from the simplest to the most complex, within all of the orthopaedic subspecialties. That’s a unique capability: to have a place where people are skilled at something as simple as carpal tunnel release but that also performs hand transplants. It also is extremely valuable to be part of an institution where there is so much expertise outside of our specialty. If a patient has comorbidities, such as cardiovascular issues, even a relatively simple procedure can become complex. If a transplant patient is going to need a knee replacement, the actual surgery might not be that complicated, but certainly the management of the patient perioperatively will be. Having the wide range of experts in orthopaedics coupled with the broad access to experts in other fields is something you only really find at a top medical institution.

Francis J. Hornicek, MD, PhD
The partnership between UCLA Health and the Los Angeles Lakers, which now is in its second year, provides faculty in the Department of Orthopaedic Surgery’s sports-medicine program with a unique experience as team doctors for one of the world’s most recognizable sports franchises. This relationship has benefits beyond the professional court; it informs the care that UCLA’s orthopaedic-surgery specialists provide to their broader population of high school and college athletes, as well as to weekend warriors.

Under the partnership announced in August 2016, UCLA orthopaedic surgeons and sports-medicine physicians serve as the in-game health providers for the team’s players and oversee all aspects of care off the court, including the assessment and management of injuries, rehabilitation and guidance in the players’ return to activity.

As the physicians for UCLA’s intercollegiate athletic teams, the specialists of the sports-medicine program have plenty of experience treating elite athletes. But there are significant differences when working with an NBA team. “These are athletes who have a relatively small window of time in which they will perform at a peak level,” says Daniel Vigil, MD, an associate clinical professor in UCLA’s departments of orthopaedic surgery and family medicine who serves as associate head team physician and director of primary care for the Lakers. “As a result, there is a lot of pressure to stay healthy.
and to be able to return to the court as safely and quickly as possible from any injuries. It’s our job to help them do that.”

One of the major differences in working with the NBA team is the expediency with which the evaluations take place, notes David R. McAllister, MD, professor of orthopaedic surgery and chief of the sports-medicine program, and head team physician for the Lakers. “Because these are multimillion-dollar professional athletes, everything is very time-sensitive,” Dr. McAllister explains. As part of his role, he attends every Lakers home game; if a player potentially has an injury, Dr. McAllister conducts an immediate medical evaluation, ordering X-rays or an MRI so that within hours he has all of the information needed for a firm diagnosis and determination of what treatment, if any, is needed. “So much is riding on these players’ health,” Dr. McAllister says. “They can’t work without being healthy, or without knowing.”

Another major difference is the intensity of the rehabilitation from an injury or after surgery. “Unlike most of us, for these players their number-one responsibility is getting better, and they have no other job to go to,” Dr. McAllister says. “So they spend many hours doing rehab, with their own physical therapist and a team of athletic trainers who will respond immediately to our instructions.”

Kristofer Jones, MD, assistant professor of orthopaedic surgery and assistant team physician for the Lakers, points out that rehabilitating professional athletes from injuries carries special challenges. “With recreational athletes, you can often modify their activities to avoid reinjury. But for people who rely on their musculoskeletal health for their livelihood, that’s not an option,” he says.

Working with elite athletes also is instructive on issues of biomechanics, Dr. Jones adds. The Lakers have begun using wireless GPS systems to monitor players during workouts. “By tracking players over time and analyzing what kind of load they are putting on their bodies, we can identify when chronic fatigue issues may come into play, because the fatigue manifests in poor biomechanics. That puts the athlete at risk for injuries like hamstring or quad strains and ankle sprains,” Dr. Jones says. “And by looking at abnormal biomechanics in high-level athletes, we can translate the same principles to our recreational athletes, who may be at even higher risk for these types of injuries.” The relationship with the Lakers also has reinforced lessons about nutrition — such as the importance of sufficient vitamin D and calcium for preventing joint injuries — that Dr. Jones applies in his everyday practice.

“With elite athletes, we learn about the effects of intensive training, and we can then translate that to our weekend warriors,” says Sharon Hame, MD, professor of orthopaedic surgery, who works with professional athletes with hip-related ailments. “We learn about overuse injuries, and we can take the protocols that they use to train effectively and adjust them to an appropriate level for the casual-athlete level.”

Seeing the positive impact of the intensive rehabilitation efforts practiced by elite athletes also underscores the importance of assisting the general patient population in accessing tools that can help them be successful. “As orthopaedists and sports medicine physicians, we’re lucky in that most of our patients are highly motivated to return to exercising,” Dr. Hame says. “For our weekend warriors, we need to push to make sure they are getting the support that they need.”
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