Part of the 2017 UPMC Orthopaedic Surgery Highlights Report

UPMC
LIFE CHANGING MEDICINE

CARPAL TUNNEL DIAGNOSIS AND MULTIPLE LIGAMENT KNEE INJURY RESEARCH

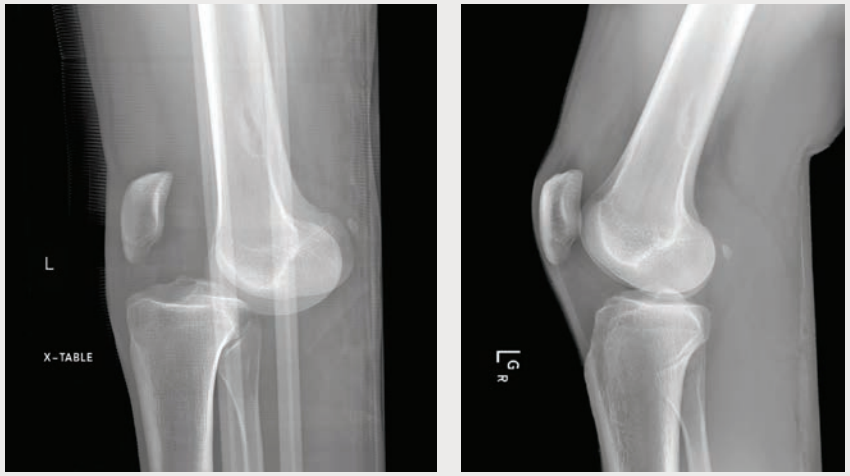
ОНТЯО


James J. Irrgang, PhD, PT
Volker Musahl, MD

IMPROVING OUTCOMES FOR **MULTIPLE LIGAMENT KNEE INJURIES**

In 2017, researchers from the Department of Orthopaedic Surgery were awarded a major new grant[1] (Contract Number: W81XWH-17-0073) from the United States Department of Defense (DoD) to study and determine optimal timing for surgery and rehabilitation of multiple ligament knee injuries (MLKIs). Officially titled the *Surgical Timing and Rehabilitation (STaR) for Multiple Ligament Knee Injuries (MLKIs): A Multicenter Integrated Clinical Trial*[2], the $4.5 million randomized trial is led by co-principal investigators **James J. Irrgang, PhD, PT**, professor and director of clinical research in the Department of Orthopaedic Surgery and chairman of the Department of Physical Therapy, and **Volker Musahl, MD**, associate professor and chief of sports medicine.

Current high-level evidence is scarce to nonexistent regarding when it is best to perform surgery and rehabilitation for cases of multiple ligament knee injuries to optimize outcomes and return individuals with an MLKI to, or as close as possible to, their preinjury level of activity and physical function. Most of the guiding principles used now are based on ACL reconstruction surgery, where early surgery and early rehabilitation after surgery is the standard of care. However, MLKIs are a much broader-spectrum, heterogeneous injury when considering what and how many different structures of the knee could be affected, and what kind of corrective surgery is required to repair the damaged tissues. These serious, complex, multidimensional injuries, while not exceedingly common in occurrence (the incidence in the general population is not exactly known but may be approximately 0.072 per 100 patient-years in civilians with orthopaedic injuries[3]), are quite devastating in their consequences. These injuries are often accompanied by significant nerve and vascular trauma, as well as fractures and injury to surrounding tendons and structures. MLKIs often are the result of high-energy trauma incidents, as well as high-impact sports such as football and other strenuous activities such as military training. MLKIs carry with them a range of potential postsurgical and rehabilitation complications. These include poor wound healing, arthrofibrosis, posttraumatic osteoarthritis, pain, and persistent joint instability, among other challenges.



Pre- and post-reduction multiple ligament knee injury x-rays.

Given the significant resources in time and costs of training and maintaining their active duty members, achieving better outcomes for individuals who suffer this type of injury is of significant concern for the DoD. For military personnel, return to duty at previous levels after sustaining an MLKI may be as low as 40 percent. In the civilian population, return to work at preinjury levels is on the order of 80 percent, however, this is dependent on the type of work the individual does. Furthermore, the time to return to preinjury activity level has not been studied.

This Study Will Address a Gap in the Literature

Why isn't there currently a good body of evidence to support the optimal timing of surgery and rehabilitation for these injuries? Dr. Musahl explains that it comes down to two main factors with these particular injuries. "If you examine the literature, it is very difficult to find studies that are prospective because of the severity of this injury and concomitant factors such as vascular and nerve injuries, open fractures, and head and poly-trauma. This makes it difficult to randomize patients in a study. This is why most of the studies done to date have been small in cohort size, and universally retrospective in nature."

This alludes to the second reason for a lack of clear-cut evidence for timing of treatment — the relative rarity of these injuries. "The only way that you can have a powerful enough study of this injury, because of the relatively low incidence coupled with the fact that we will necessarily exclude many patients from the trial because of concomitant injuries, is to design a multi-center trial," says Dr. Irrgang.

STaR Trial Participating Sites	Site PI
University of Pittsburgh (Lead Site)	James Irrgang, PhD
University of Pittsburgh - DCC	Charity Moore Patterson, PhD
Brown University	Brett Owens, MD
Health Partners Institute for Education and Research (Minneapolis, Minnesota)	Jonathan Cooper, DO
Hospital for Special Surgery (New York)	Anil Ranawat, MD
Keller Community Army Hospital (West Point, New York)	Matthew Posner, MD
Mayo Clinic (Rochester, Minnesota)	Bruce Levy, MD
Nova Scotia Health Authority – Queen Elizabeth Health Sciences Center	Cathy Coady, MD
San Antonio Military Medical Center	Travis Burns, MD
St. Michael's Hospital (Toronto)	Daniel Whelan, MD
TRIA Orthopaedic Center (Bloomington, Minnesota)	Bradley Nelson, MD
Tripler Army Medical Center (Honolulu, Hawaii)	Craig Bottoni, MD
University of Cincinnati	Brian Grawe, MD
University of Connecticut	Robert Arciero, MD
University of Kentucky Research Foundation	Darren Johnson, MD
University of Michigan	John Grant, MD
University of Minnesota	Jeff Macalena, MD
University of New Mexico Health Sciences Center	Robert Schenck Jr., MD
University of Texas Health Sciences Center at Houston	Christopher Harner, MD
University of Virginia	Mark Miller, MD
University of Washington (Seattle)	Albert Gee, MD
University of Western Ontario (London, Ontario)	Alan Getgood, MD
Walter Reed National Military Medical Center (Bethesda, Maryland)	Jeffrey Giuliani, MD
Washington University (St. Louis)	Matthew Matava, MD
William Beaumont Army Medical Center (El Paso, Texas)	Mark Pallis, MD

With a pilot grant from the DoD in 2015, that's exactly what Drs. Irrgang and Musahl accomplished: developing the protocols, assembling the sites and necessary analytical resources including an onsite data center and statistician, and eventually building a trial framework that the DoD has now funded in full to attempt to shed the necessary light on how best to treat these injuries.

Drs. Irrgang and Musahl have assembled a cohort of 24 United States Armed Forces entities and academic medical centers across the United States and Canada that will be participating in the trial and enrolling patients. **Andrew Lynch, PhD, PT**, assistant professor in the Department of Physical Therapy at the University of Pittsburgh, is serving as the qualified clinical investigator for rehabilitation in the study. Dr. Musahl is serving in that role from a surgical perspective. **Charity Moore Patterson, PhD**, professor in the Department of Physical Therapy, will serve as co-investigator and lead biostatistician for the study.

Study Aims and Details

The STaR Trial is comprised of two separate studies examining subpopulations of individuals with an MLKI and randomizing them into appropriate arms of the study based on injury criteria, timing of presentation, and concomitant injuries that would require or preclude early surgical treatment.

Photo depicting a current rehabilitation patient with a previously dislocated knee and multiple ligament injury.

The first aim of the study is to determine the combined effects related to the timing of surgery and rehabilitation on the amount of time it takes for enrolled patients to return to their preinjury status and activity. Individuals presenting for treatment within six weeks of surgery who are between the ages of 14 and 65 will be eligible for the study and will include both military personnel and civilians who have a multiple ligament knee injury. Individuals with a past history of knee reconstruction, or those who have associated vascular injury, polytrauma, or traumatic brain injury, will be excluded from participation.

Participants in the first study will be randomized into one of four groups:

- Early Surgery and Early Rehabilitation
- Early Surgery and Delayed Rehabilitation
- Delayed Surgery and Early Rehabilitation
- Delayed Surgery and Delayed Rehabilitation

"Our hypothesis at the start is that early surgery and early rehabilitation, and the combination thereof, will lead to better outcomes," says Dr. Musahl. "Early surgery sometimes enables us to repair structures that may not be possible to repair if there is a delay, because of early degeneration or retraction from connecting tissues. Using tissue grafts and anatomical reconstruction may also afford benefits in this regard. But we may find, too, that in some cases or variations of the injury, patients may benefit from a course of rehabilitation first — the concept of pre-rehab — in essence priming the musculoskeletal system for what is to come after surgery and during the postoperative rehabilitation phase, which for these injuries can be a year or more in duration."

> "The only way you can have a powerful enough study of this injury is to design a multicenter trials."
>
> *James J. Irrgang, PhD, PT*

The second aim of the study will seek to determine the effects of the timing of rehabilitation on the time to return to activity. Participants in this aspect of the study will have had an MLKI for which the timing of surgery cannot be randomized. These patients will be randomized into either early or delayed rehabilitation. Participants in this cohort also will have had an injury that precludes their randomization into surgery, or who for one reason or another have refused or declined randomization to surgery.

On the rehabilitation side, there exists little to no evidence at all about how best to rehabilitate these injuries after surgery. "They are just extensive injuries requiring detailed surgery. Typically, surgeons are concerned about progressing an individual too quickly lest they disrupt a repair or graft. This is why I think most individuals with MLKI do very little weight bearing and limited motion for the first four weeks postoperatively. However, when you review the evidence for ACL reconstruction, it overwhelmingly shows better outcomes with early weight bearing, strengthening, and range of motion exercises. The question then becomes: Can you apply those same principles to these more significant injuries and associated surgeries? The concern is that if we are too aggressive early on with rehabilitation, it could disrupt what was repaired, resulting in a knee that is too loose and unstable.

On the other hand, if we delay rehabilitation, particularly combined with early surgery, stiffness and a lack of range of motion may result. This is what we are trying to answer with the early versus delayed rehabilitation question," says Dr. Irrgang.

Approximate Return to Duty/Work at previous levels after sustaining an MLKI

40%	80%
Military Personnel	Civilian Population

A unique aspect of this study is the end outcome measure being evaluated. "We are really focused on the time to return to a preinjury level of activity. This will include, for example, participation in military activities, sports activities, and work. This has never really been looked at with knee injuries, even with ACL reconstruction. We don't have any solid evidence to answer this question of timing, so we are very excited to try and quantify this aspect in our study," says Dr. Musahl.

Randomization Stratification

Multiple ligament knee injuries present on a spectrum. They can present anywhere from a complete tear or rupture of two ligaments, the ACL and MCL for example, to a complete dislocation that results in tears of all four of the main ligaments with accompanying damage to cartilage, meniscus, and the like. "We think there is a big difference between tearing one cruciate ligament and some other ligament, or tearing both cruciate ligaments with or without additional damage," says Dr. Irrgang. To account for this spectrum in the study, randomization of participants will be stratified to help control the variability seen in these injuries. "Statistical analysis also will enter into the model of the injury classification to help adjust for these variances."

Laying the Groundwork for Future Research

While this new trial is just beginning, with patient recruitment set to start in the coming months, Dr. Musahl sees much potential for tangential, even department-wide, and new, related avenues of investigation in the future, such as how biologic applications or interventions may play a role and modulate responses to surgery and rehabilitation in cases of MLKI.

[1] *The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-14 is the awarding and administering acquisition office.*

[2] *This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Orthopaedic Research Program, under Award No. W81XWH-17-2-0073. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.*

> “Our hypothesis is that early surgery and early rehabilitation, and the combination thereof, will lead to better outcomes.”
>
> *Volker Musahl, MD*


HFL50
15-6f
2½
8ml

DIAGNOSING CARPAL TUNNEL SYNDROME WITH ULTRASOUND: BETTER, FASTER, AND COST-EFFECTIVE

Hand and upper extremity surgeon **John R. Fowler Jr., MD**, is not one prone to inflammatory remarks for their own sake; however, his advocacy for the use of ultrasound (US) is vocal and passionate, specifically when discussing the diagnosis of carpal tunnel syndrome (CTS) with US versus what has been used almost exclusively in the past — nerve conduction studies (NCS). "Nerve conduction studies definitely have their place, but the more research I conduct, the more I'm convinced it is not, except in limited circumstances, the most appropriate first line diagnostic for CTS," says Dr. Fowler.

Dr. Fowler's work over the last 10 years using, studying, teaching, and advocating for the use of ultrasound imaging to diagnose carpal tunnel syndrome is based in the evidence as much as it is in his unwavering and vocal passion to help patients by offering them a less invasive approach to diagnose their condition. "Less invasive is always good for any kind of test as far as patients are concerned, but the tests have to be reliable, predictable, repeatable, and accurate," says Dr. Fowler. Much of Dr. Fowler's work over the last decade and a half has been to prove the case for wider adoption of ultrasound as a first-line test for carpal tunnel syndrome through rigorous study and training.

Dr. Fowler first became interested in the use of ultrasound while in residency at Temple University. "We would see patients in clinic, refer them for nerve conduction testing, and half or more of these individuals would return without having gotten the test, due to a lack of appointment options and associated costs. The discomfort of the test itself likely also played a role in many of these cases. This got me thinking about what alternatives and options might be out there to diagnose these patients," says Dr. Fowler.

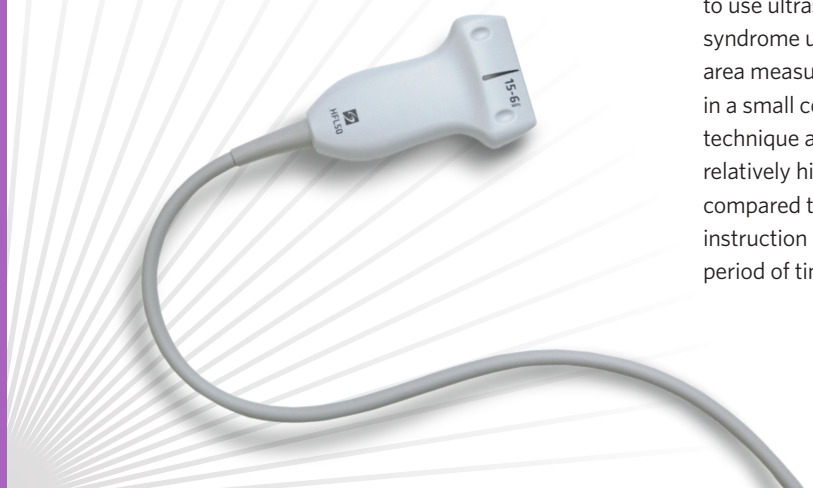
Further work as a surgical fellow at the University of Pittsburgh afforded Dr. Fowler the ability to use ultrasound for all manner of cases, allowing him to greatly increase his knowledge, skill, and accuracy with the technique by conducting nearly 1,000 ultrasound imaging procedures during his training. "This clinical work using a portable US machine at the Hand and Upper Extremity Center really became the impetus and basis for much of my early research."

Most of Dr. Fowler's research to date has worked to confirm and expand on past work by others that ultrasound is a very accurate test for carpal tunnel syndrome. In the right scenario, ultrasound has a similar — if not higher — sensitivity and specificity compared to nerve conduction studies. "A focus of my research now is to find ways to minimize the rate of false negatives and false positives," says Dr. Fowler. Part of Dr. Fowler's ongoing studies involves understanding whether or not the height, weight, and BMI of individuals matter in terms of their nerve size. "You would think that this would play a role, however, what we are finding is that the size of the individual has very little influence on their median nerve size, perhaps a millimeter or less in most cases."

Recent Research: Comparing US and NCS in Carpal Tunnel Syndrome

In 2016, Dr. Fowler and colleagues published findings of a study[1] designed to assess the correlation, if any, between cross-sectional area measurements of the median nerve via ultrasound imaging with the motor/sensory latencies of the nerve measured with NCS in patients with suspected carpal tunnel syndrome. This blinded, prospective study examined 87 suspected cases of CTS. Dr. Fowler's study showed a positive correlation between NCS and US (91 percent) in study participants, as well as similar levels of sensitivity and specificity between each testing modality (83 percent and 94 percent, respectively).

Other work by Dr. Fowler involves pre- and postsurgical correlations between findings in diagnostic tests. "If you look at the literature for NCS, you will find that even after the surgery, follow-up testing does not quite show a return to normal, despite the patient feeling 100 percent better and being pain free. We're not sure why that is, but perhaps we can correlate those findings on ultrasound of the median nerve," says Dr. Fowler. At present, Dr. Fowler has assembled a database of more than 500 patients who have had preoperative ultrasound, with 150 of those individuals having had a postoperative, follow-up ultrasound. Analysis is underway between these two patient cohorts to see if the improvements in a patient's nerve cross-sectional areas correspond with their symptoms, or lack thereof.



Another study in progress is examining if there is a way, using ultrasound, to predict how long it will take patients to recover depending on the severity of their carpal tunnel syndrome.

Training a New Generation of Ultrasound Users

Dr. Fowler is actively involved with education, specifically related to the use of ultrasound in orthopaedic surgery, but more generally as well with medical students. As assistant dean for medical student research, Dr. Fowler was instrumental in creating a new musculoskeletal educational program for second year medical students at the University of Pittsburgh in collaboration with **MaCalus V. Hogan, MD**.

Additionally, for the last several years, Dr. Fowler and colleague **Tom Hughes, MD**, have conducted an ultrasound pre-course at the annual meeting of the American Association for Hand Surgery. The six-hour course provides education and training on ultrasound for orthopaedic surgeons, and is offered as a separate registration course.

Some of Dr. Fowler's education with ultrasound imaging has fed recent research projects. Published in 2017, Dr. Fowler's paper[2] in the journal *Hand*, along with coauthors **Jared Crasto, MD**, and **Michael Scott, MD**, sought to quantify to what degree and within what timeframe an individual could be successfully trained to use ultrasound to detect the signs of carpal tunnel syndrome using ultrasound and nerve cross-sectional area measurements. "Surprisingly, this study showed, in a small cohort, that individuals are able to learn the technique and measure the correct structure — with relatively high degrees of success and accuracy compared to their baseline measurements prior to instruction and against the study controls — in a short period of time."

*Dr. Fowler discusses research findings with orthopaedic surgery resident **Chinedu Nwasike, MD**.*

> Nerve conduction studies definitely have their place, but the more research I conduct, the more I'm convinced it is not, except in limited circumstances, the most appropriate first line diagnostic for CTS.

John R. Fowler Jr, MD

About The Department of Orthopaedic Surgery

Founded in 1953 as a separate department of the University of Pittsburgh School of Medicine, the Department of Orthopaedic Surgery is committed to delivering the highest quality of diagnostic and therapeutic patient care to both adults and children for a diverse spectrum of orthopaedic disorders. To this aim, the department seeks to meet the needs of 21st century orthopaedic care not only by integrating the latest biological and technological advancements in orthopaedic science, but equally by leading the development of novel treatment modalities through distinguished basic science and clinical research programs. In addition, the Department of Orthopaedic Surgery seeks to be a leader in educating the next generation of orthopaedic surgeons through its residency and fellowship training programs, which include comprehensive, in-depth exposure to all specialties of orthopaedic care and advanced surgical experience.

Freddie H. Fu, MD, DSc (Hon), DPs (Hon)
Chairman

Centers of Excellence

- Adult Reconstructive Surgery and Musculoskeletal Oncology
- Concussion
- Foot and Ankle Surgery
- Hand, Upper Extremity, and Microvascular Surgery
- Orthopaedic Trauma
- Pediatric Orthopaedics
- Research
  - > Biomedical
  - > Clinical Outcomes
  - > Computer-assisted Surgery
  - > Kinematics
  - > Regenerative Medicine
  - > Stem Cell
- Spinal Surgery
- Sports Medicine and Shoulder Surgery

A Resource for You

UPMC Physician Resources delivers world-class physicians and free educational opportunities. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at **UPMCPhysicianResources.com/Ortho**.

References and Further Reading

Improving Outcomes for Multiple Ligament Knee Injuries

References

1 Surgical Timing and Rehabilitation (STaR) for Multiple Ligament Knee Injuries (MLKIs): A Multicenter Integrated Clinical Trial. Principal Investigator: James J. Irrgang. Award Number: W81XWH-17-2-0073. Integrated Clinical Trial Award.

2 Timing of Surgery and Rehabilitation to Optimize Outcomes for Patients With Multiple Ligament Knee Injuries: A Multicenter Clinical Trial. Principal Investigator: James J. Irrgang. Award Number: W81XWH-15-1-0655. Clinical Trial Development Award.

3 Lynch AD, Chmielewski T, Bailey L, Stuart M, Cooper J, Coady C, Sgroi T, Owens J, Schenck R, Whelan D, Musahl V, Irrgang J. The STaR Trial Investigators. Current Concepts and Controversies in Rehabilitation After Surgery for Multiple Ligament Knee Injury. *Curr Rev Musculoskelet Med*. 2017; 10: 328-345.

Diagnosing Carpal Tunnel Syndrome With Ultrasound

References

1 Pulikkottil BJ, Schub M, Kadow TR, Wang W, Fowler JR. Correlating Median Nerve Cross-Sectional Area With Nerve Conduction Studies. *J Hand Surg Am*. 2016; 41(10): 958-962.

2 Crasto JA, Scott ME, Folwer JR. Ultrasound Measurement of the Cross-Sectional Area of the Median Nerve: The Effect of Teaching on Measurement Accuracy. *Hand*. 2017; Epub ahead of print.

Further Reading

- Fowler JR, Hirsch D, Kruse K. The Reliability of Ultrasound Measurements of the Median Nerve at the Carpal Tunnel Inlet. *J Hand Surg Am*. 2015; 40(10): 1992-1995.
- Fowler JR, et al. Comparison of Ultrasound and Electro-diagnostic Testing for Diagnosis of Carpal Tunnel Syndrome. *J Bone Joint Surg Am*. 2014; 96: e148 (1-4).
- Fowler JR, Gaughan JP, Ilyas AM. The Sensitivity and Specificity of Ultrasound for the Diagnosis of Carpal Tunnel Syndrome. A Meta-analysis. *Clin Orthop Relat Res*. 2011; 469: 1089-1094.
- Fowler JR, Maltenfort MG, Ilyas AM. Ultrasound as a First-line Test in the Diagnosis of Carpal Tunnel Syndrome: A Cost-effectiveness Analysis. *Clin Orthop Relat Res*. 2012;
- Nerve Conduction Studies for Carpal Tunnel Syndrome: Gold Standard or Unnecessary Evil? Editorial. *J Orthopaedics*. 2017; 40(3): 141-142.

UPMC
LIFE CHANGING MEDICINE

200 Lothrop St.
Pittsburgh, PA 15213-2582

A $16 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than $900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 80,000 employees, more than 30 hospitals, 600 doctors' offices and outpatient sites, and a 3.2 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners on four continents. For more information, go to UPMC.com.

USNW505631 TS/AS/MP 02/18