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Closing the Gap Between Bench and Bedside Research for Early Arthritis Therapies (EARTH):

Report From the AOSSM/NIH U-13 Post–Joint Injury Osteoarthritis Conference II

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Abstract

This report summarizes the 2010 AOSSM/NIH (American Orthopaedic Society for Sports Medicine/National Institutes of Health) U13 Post–Joint Injury Osteoarthritis II Conference to include the discussion concerning potential study cohorts, assessment considerations, and research priorities. There was strong consensus and enthusiasm for approaching the development of disease-modifying treatments for osteoarthritis through study of “pre-osteoarthritic” cohorts, particularly human subjects under 30 years of age following acute anterior cruciate ligament injuries. Clinical study of acute treatment strategies initiated within a few days after injury will need development of recruitment pathways and short-term proof-of-concept outcome measures that are specific to the intervention being studied. For example, measures of joint inflammation can be used in short-term prospective randomized controlled trials to determine whether an anti-inflammatory intervention was effective in decreasing early inflammation. These short-term clinical trials will need to be followed by longer-term evaluation of the clinical cohorts for joint and cartilage degeneration to determine if the acute intervention affected later development of osteoarthritis. Research priorities were identified in several disciplines, particularly regarding development and validation of quantitative imaging, biomechanics, and biomarker measures of joint structure, composition, and function that predict the accelerated development of osteoarthritis. Systematic study of posttraumatic osteoarthritis is anticipated to advance understanding and treatment of all forms of osteoarthritis.

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Osteoarthritis (OA) is the most common joint disease and is a leading cause of disability worldwide.³ The physical impairment from OA of a single lower extremity joint is equivalent to that reported for major life-altering disorders such as end-stage kidney disease and heart failure.⁴³ The causes of OA are not well understood. However, joint trauma is a leading etiologic factor.^{2,3}

Intra-articular fracture, joint dislocations, and other joint injuries commonly treated by orthopaedic surgeons such as anterior cruciate ligament (ACL) tear can lead to altered mechanical loading and accelerated degeneration of a previously healthy joint to early disabling OA.¹ Anterior cruciate ligament transection and meniscal injury in several animal models have long been used in laboratory studies of chondroprotective and disease-modifying treatments for OA. However, human clinical studies with similar goals have primarily evaluated cohorts with radiographic signs of OA (Table 1). Radiographic changes occur long after articular surface breakdown and after significant cartilage loss and other joint changes. As such, human clinical trials of substances and strategies shown to be chondroprotective in the laboratory have not shown similar results in human subjects without sufficient remaining healthy cartilage to restore or to protect. Critical gaps between laboratory and clinical investigations represent major barriers to effective bench to bedside clinical translation of promising new treatments that may delay or prevent the onset of OA. To this end, the study of the development and modulation of post-joint injury osteoarthritis is important for advancing both understanding and clinical treatment not only of posttraumatic OA but of all forms of OA.

AMERICAN ORTHOPAEDIC SOCIETY FOR SPORTS MEDICINE (AOSSM) POST-JOINT INJURY OSTEOARTHRITIS CONFERENCE GOALS

The AOSSM/NIH U-13 Post-Joint Injury Osteoarthritis II was convened as a think-tank conference to address the primary gaps between laboratory and human clinical studies of cohort characteristics and assessment methods. The study group was tasked to develop recommendations for a possible Early ARthritis Therapies (EARTH) multicenter clinical study initiative involving human subjects without substantial joint degeneration but who are at risk for rapid progression of OA because of joint injury. The goal of EARTH would be to evaluate acute interventions following severe joint injuries such as ACL tear or intra-articular fractures as strategies to delay or prevent the onset of posttraumatic OA. The underlying hypotheses are that joint injury initiates a series of events resulting in more rapid joint degeneration that culminates in early disabling OA, and that early intervention prior to the development of irreversible changes may modify the disease course. The gap between the current clinical and research capabilities in conducting a study of this nature and the desired goal of being able to perform effective randomized clinical trials of new treatment strategies to delay or prevent joint degeneration following joint injury would identify potential research priorities.

This conference was a logical follow-on to the momentum generated from the initial AOSSM/NIH R-13 Post-Joint Injury Osteoarthritis Conference held in December 2008 (see Appendix 1, available in the online version of this article at <http://ajs.sagepub.com/supplemental/>), which resulted in development of recommendations for future directions in new areas of cooperative research that could improve the translation of basic research into patient care. This initial conference brought together orthopaedic

surgeons and rheumatologists, clinical and basic scientists in OA and cartilage research, and scientists and representatives from industry (Appendix 1). This multidisciplinary conference resulted in a marked increase in awareness, interest, and funding opportunities for studying the acute events following ACL injury as a potential human clinical model of early degenerative joint disease potentially amenable to disease-modifying treatments (NIH [National Institutes of Health] Challenge Grant RC1: 03-AR-101).

Following the lecture and small group think-tank format of the initial conference, the current conference brought together approximately 70 attendees (see Appendix 2, available online). Invited speakers were selected from the portfolio of projects and programs in joint injury and posttraumatic OA funded at the NIH R01 or higher level by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The speakers, moderators, and discussion team leaders included prominent orthopaedic surgeons, rheumatologists, radiologists, clinical scientists, imaging scientists, biologists, biomechanicians, experts in joint kinematics, and biochemists. Ten early career young investigators were selected by a multidisciplinary panel. This document constitutes a summary of the conference and discussion groups.

This conference summary is not intended for use as a guideline for specific studies. Rather, this summary of the discussions focused on identifying clinical cohorts and assessment methods among experts spanning related clinical and scientific disciplines forms a valuable springboard for future individual and collaborative studies to advance the development of early treatment strategies to delay the onset of posttraumatic OA.

AOSSM POST-JOINT INJURY OSTEOARTHRITIS II CONFERENCE SUMMARY

The focus of the conference was defined as an exploration of the current feasibility, potential design, and candidate outcome measures that could be used if a multicenter human randomized clinical trial comparing different treatment strategies to alter the acute events following joint injury were to be initiated within the next year.

By working toward this goal, attendees determined several areas where current state of the art may not yet fully support multicenter randomized clinical trials. Knowledge shortfalls were particularly apparent in respect to quantitative measures of the early structural, biochemical, and functional events following acute joint injuries.

Consequently, there was considerable interest expressed for prospective, long-term observational studies of the early events following joint injury similar to the Osteoarthritis Initiative (OAI) to first understand the natural history before formulating and studying interventions. These goals could be achieved through synergizing with existing individual and multicenter studies as well as filling gaps with new proposals. Current multicenter studies of outcomes following ACL reconstruction such as the Multicenter Orthopaedic Outcomes Network (MOON), led by Spindler, provide information on the natural history of the ACL-reconstructed knee. Lohmander presented an elegant series of long-term observational studies showing that ACL and meniscus injuries, particularly in combination, led to a high incidence of radiologically apparent and symptomatic OA within a decade or 2 of injury.^{25,26} Through analysis of military databases, Ficke showed that joint pain and arthritis was a leading cause of early separation from the Army.³⁶

Reporting on comprehensive bench to bedside work involving posttraumatic OA following intra-articular fractures, particularly of the ankle, a joint otherwise relatively unaffected by OA, Buckwalter highlighted the inciting role of the joint injury, the role of injury severity,

post-joint injury instability and incongruity, and patient factors such as age in the progression to joint degeneration and OA. He also outlined the multiple ways in which study of post-joint injury OA can advance understanding for the development and progression of all forms of OA. Clinical and laboratory data from a single-center project studying the early structural changes to articular cartilage following ACL and meniscus injury led by Chu highlighted the importance of improving stratification of cartilage injury severity in identifying individuals who can potentially benefit from chondrorestorative treatments. Both Buckwalter and Lotz presented experimental data supporting a potential for acute treatment strategies to modify some of the early pathologic events.²⁸ While comprehensive multicenter natural history data are lacking for a variety of joint injuries, the existing data presented on ACL and intra-articular fracture outcomes support the clinical significance and current relevance of the conference goals and hypotheses.^{45,49}

Through achieving conference goals of evaluating the feasibility and developing criteria and assessments for randomized human clinical trials to evaluate acute intervention strategies following joint injury, attendees determined that not all questions pertinent to advancing clinical treatment in this area can be or must be answered by randomized controlled trials. Evidence-based medicine has been defined by David Sackett, the modern pioneer in this field, as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.”⁴² Sackett further clarifies in this succinct editorial that it “is not restricted to randomized trials and meta-analysis.” General examples provided by Sackett pertinent to current research priorities identified by conference participants for the study of post-joint injury osteoarthritis include: “To find out about the accuracy of a diagnostic test, we need to find proper cross sectional studies of patients clinically suspected of harbouring the relevant disorder, not a randomized trial. For a question about prognosis, we need proper follow up studies of patients assembled at a uniform, early point in the clinical course of disease.”

Experimental Design

In an era of financial constraints and anticipated flat-to-declining federal research funding levels, focused and efficient study designs leading to development of effective new clinical treatments were emphasized. Given the multifactorial nature of the OA disease process, Felson introduced the concept of a factorial design where the effects of more than 1 factor and interactions between factors can be more efficiently evaluated than study designs evaluating 1 single factor at a time. An intervention study designed in this fashion would also generate natural history data through analysis of the untreated control group, provided the sample size is large enough. Additional ideas to improve the efficiency of the overall research effort include nested cohorts of subjects undergoing specialized evaluations in imaging, biomechanics, or biomarker assessments that are uniquely available at some participating centers.

Attendees emphasized that the specific study populations and assessment methodologies selected will need to fit the particular research question and the intended therapeutic strategy. For example, efforts to reduce chondrocyte loss acutely following joint injury will likely have a much shorter time frame for recruitment than studies of rehabilitation strategies or the effects of different surgical interventions on joint kinematics.

Study Populations

Several potential clinical cohorts were identified for the study of “early osteoarthritis,” defined as populations who do not yet meet the classic criteria for OA defined based on radiographic changes of joint-space narrowing, osteophytosis, subchondral bone thickening, and subchondral cyst formation. Rather, patients have joint pathologies placing them at

increased risk for accelerated development of OA. These populations include the post-ACL-injured knee, individuals with meniscus tears, soldiers with combat injuries, and patients with intra-articular fractures.

The primary potential study groups discussed during this AOSSM conference were the ACL and meniscus-injured cohorts. There is potential overlap between the ACL- and meniscus-injured cohorts. Data from the MOON study show that approximately 50% of ACL tears are accompanied by meniscus tears and that the meniscus injury is hypothesized to lead to worse outcomes.⁴⁵ This hypothesis is supported by the systematic review of the literature on outcomes following ACL injury by showing that meniscus tear with ACL injury markedly increased the incidence of radiographic OA.³⁸ Conference attendees also stressed the importance of separating the degenerative meniscus tear population from that of traumatic meniscus tears occurring as part of the ACL tear–joint injury complex or through other high-energy knee injuries not involving the ACL. Considerable interest was placed on the degenerative meniscus tear population as a separate study group that can help define some of the earlier structural and metabolic events leading to eventual development of radiographically apparent OA.

Anterior Cruciate Ligament Tear Cohort—For the study of acute interventions following ACL injuries, enrollment within 1 week of injury was considered ideal, with enrollment within 3 months considered generally acceptable depending on the proposed intervention. Concerning potential ACL tear cohorts, attention was paid during the discussions to factors such as age, presence, and type of meniscus and articular cartilage injuries, medial collateral ligament tear, tears of the other primary knee ligaments and associated structures, timing of ACL surgery, and non-operative management. To reduce potential confounders, the consensus was to exclude individuals with prior injury or surgery to the index knee, individuals with inflammatory arthritis or major medical comorbidities requiring chronic medication, and knees with injuries beyond ACL, meniscus, and cartilage pathologies such as multiligament-injured knees. Tibiofemoral mechanical alignment, patellofemoral alignment, and body mass index were considered important to record but not as criteria for exclusion. The specific inclusion/exclusion criteria would be dependent on the clinical question matched to appropriate study design for the proposed intervention.

A consensus emerged on target age range from skeletally mature to 30 years of age for acute ACL tear cohorts. This range would potentially be most similar to laboratory studies involving animal models. Data from the MOON study shows increasing joint degeneration in patients over 30 years of age (personal communication, Kurt P. Spindler, MD). From a cartilage biology standpoint, skeletal maturity to 30 years of age was identified as a range during which human articular cartilage retains a higher metabolic activity level than after age 30.³⁰ The subchondral bone and calcified cartilages about the growth plates continue to turn over into the late teens in females and the early twenties in males.³⁴ Examination of actual practice patterns of applicants for board certification and recertification by the American Board of Orthopaedic Surgery (ABOS) show a median age of 25 years for individuals undergoing ACL reconstruction with a mode of age 16 for females and of age 17 for males (personal communication, William E. Garrett, MD). Based on these data, the age range of skeletally mature to age 30 years was described as biologically optimal and clinically feasible for studies in which examining the effects of trauma on a previously healthy joint is important.

The need for cohorts and assessments tailored to the research question was an important and recurrent discussion point. For example, laboratory studies show substantial chondrocyte death within hours to days following impact injuries to articular cartilage.^{7,46} Several recent in vivo studies also suggest that early administration of chondroprotective agents is more

effective than delayed administration.^{15,17} This means that a clinical treatment study of this type would potentially require recruitment within a few hours to a few days after injury, potentially before full evaluation of the subject and the joint injury could be completed. The treatment under investigation would potentially be undertaken prior to a decision on the need or timing of surgical reconstruction. This type of study may require an acute “proof of concept” outcome measure that would take place prior to any reconstructive surgery that is matched to the research question (eg, a therapy designed to reduce inflammation would result in more rapid resolution of joint effusion and a reduced concentration of biomarkers of inflammation 2 weeks after the intervention). Other studies evaluating the effects of surgical or rehabilitative interventions on biomechanic or kinematic outcomes would permit a longer time frame after injury for recruitment into proof-of-concept studies. These short-term randomized controlled trial study cohorts would need to be followed by longer-term studies using measures of joint and cartilage degeneration to determine whether the intervention altered the later development of OA.

Another major factor for consideration relates to the timing and the need for operative intervention, which represents a second biologic insult to the knee. For the acute intervention type of study discussed, where the decision for reconstructive surgery may not be known at the time of intervention, operative treatment may be performed acutely, in a delayed fashion, or not at all. As such, the timing and presence of surgery would be important variables in longer-term study of the treatment arms using structural, biochemical, and biomechanical measures to evaluate the longer-term effects of the intervention on joint degeneration. In order to permit adjusted analyses, discussants emphasized the importance of consistency and documentation in the study design with attention paid to the length of time between injury and surgery, description of the ACL surgery, and that the postoperative rehabilitation protocol be standardized, measured, and recorded. A standardized approach for arthroscopic documentation of articular cartilage and meniscus pathology was also considered important. While it is ideal for the ACL surgery to be done using similar techniques, this is difficult to achieve when multiple surgeons at multiple sites are involved. Variables in tunnel position, graft tension, and surgical technique result in differing kinematics and the potential for altered biomechanical loading.⁶ Consideration may be given to use of a kinematic assessment as a functional outcome measure for the ACL reconstruction that would be independent of specific surgical technique. In general terms, ACL reconstructions performed within 3 months of injury can be classified as acute. The date of reconstruction then becomes time zero for follow-up evaluations.

Degenerative Meniscus Tear Cohort—An alternative clinical study cohort for early disease-modifying therapies was defined as individuals between 30 and 50 years of age with symptomatic meniscus tears arising from low-energy trauma undergoing arthroscopic partial meniscectomy who have minimal radiographic signs of OA (ie, no joint-space narrowing). Advantages include higher prevalence of degenerative meniscus tear than ACL tear and the potential for more rapid disease progression, thereby shortening the length of time needed to show evidence for disease modification. Clinical practice data collected by the ABOS on surgeries performed by orthopaedic surgeons seeking initial board certification consistently show that the most commonly performed procedure is arthroscopic partial meniscectomy. The procedure itself provides an opportunity for comprehensive joint assessment of cartilage, meniscus tear, and other intra-articular structures by conventional arthroscopy, examination of the articular cartilage using newer techniques such as arthroscopic optical coherence tomography,⁵ and synovial fluid sampling and synovial biopsy in addition to radiographs and MRI examination. Limitations include that the time of meniscus tear may be uncertain and that underlying OA is common. Because of significant overlap with individuals further along the continuum of joint degeneration who already have clinical OA, careful definition of the acceptable radiographic changes for the study group is considered

essential. While there was general agreement this cohort represents a “pre-osteoarthritic” cohort, this group was also considered to potentially show more heterogeneity in disease state than the acute ACL tear cohort, with patients frequently presenting after either low-energy trauma such as a misstep off a curb or with no identifiable trauma.¹⁹ Nevertheless, this cohort offers the possibility of studying a variety of interventions including but not limited to medications, intra-articular injections, mechanical modifying devices, rehabilitation, activity modification, and weight loss. Intervention outcomes can be assessed using patient-reported outcomes in the short term and improved or delayed structural progression to OA in the longer term.

Assessment Considerations

Individual sessions were held to address patient-reported outcomes and related factors, imaging outcomes, measurement of joint kinematics, and biochemical biomarkers. The major factor limiting effective clinical evaluation of acute intervention strategies was the lack of validated quantitative metrics of acute and short-term changes to articular cartilage and other joint structures such as the meniscus that predict later development of radiographic OA. Patient-reported outcomes are insensitive to early changes to joint structure and function.²⁰ The current Food and Drug Administration standard for evaluating disease-modifying strategies for OA is radiographic joint-space narrowing.¹¹ Because radiographic joint-space narrowing may take several years to develop in clinical cohorts such as young human subjects following acute ACL injuries, development and validation of quantitative methods to directly image and assess joint structures such as meniscus and articular cartilage were considered important for the study of early intervention strategies in these types of joint injury cohorts. While several promising quantitative imaging assessments and new ideas for kinematic and biochemical assessments were presented, validation of these techniques through systematic human clinical study represents critical research priorities to support EARTH clinical trials.

Patient-Reported Outcomes and Patient-Related Factors

There are currently several ongoing multicenter studies of ACL- and meniscus-injured patients, including the NIH-funded MOON³² and METEOR²⁷ studies that use primary validated patient-reported outcome tools and databases that are identical in several aspects with multiple clinical sites trained on the use of the forms. The ongoing MOON study presented by Spindler has generated important new information through multicenter study of outcomes following ACL reconstruction. Through his experience leading METEOR (Meniscal Tear in Osteoarthritis Research), Katz highlighted the need to use validated assessment methods and to take into account floor and ceiling effects. There are also large cohorts of knee OA subjects in the NIH-sponsored MOST (Multicenter Osteoarthritis Study)³⁵ and OAI³⁹ studies presented by Felson and Kwoh, respectively. To facilitate future comparison of clinical outcome data on studies with similar cohorts, there was substantial support for using a common set of core outcomes tools from these studies as appropriate to the research cohort and questions of a new study.

Specific for the assessment of acute knee injury patients, there was general agreement on use of the International Knee Documentation Committee (IKDC) Subjective Knee Form and the Knee Injury and Osteoarthritis Outcome Score (KOOS) as primary outcome measures. The KOOS and IKDC form were compared and contrasted with other instruments by Irrgang, who also discussed the concepts of minimal clinically important difference (MCID) and minimal detectable change (MDC).^{12,16} For the relatively young and healthy individuals typical of the population undergoing primary ACL reconstruction, the Short Form-12 was considered sufficient as a general measure of health status. Collection of basic demographic information, consisting of age, sex, knee alignment, body mass index, and racial/ethnic

information, were also uniformly supported. Documentation of activity level using a validated instrument was considered critically important. This has been performed using the Tegner, Noyes, and Marx instruments, with the Marx scale for athletically oriented subjects being utilized in MOON and MARS (Multicenter ACL Revision Study).

Use and documentation of a standardized rehabilitation program was considered important, with recognition that the rehabilitative protocols and compliance with the rehabilitation program could themselves be the research topic.⁹ Other outcome measures to consider include economic cost utility analysis with the EuroQol EQ-5D, a validated preference-based utility measure. Other suggested measures included quadriceps strength, joint effusion, return to work, preinjury activity level, and costs. In an analysis of the Johnson County OA cohort, Jordan reported on race-related differences in OA disease, suggesting the potential importance of genetic factors. Consideration of collection of blood for future genetic analyses was proposed.

Imaging Outcomes

Conference presenters discussed the use of radiographs, morphologic and quantitative MRI, as well as novel technologies such as optical coherence tomography on the articular cartilage and other joint structures, particularly the subchondral bone. The current Food and Drug Administration standard for imaging outcomes of potential disease-modifying treatments for OA continues to be assessment of radiographic changes.¹¹ Using fluoroscopy to guide positioning for radiographic examinations, Beynon showed measurable changes to tibiofemoral joint-space widths on flexion weightbearing radiographs 4 years following acute ACL injury. Through direct imaging of articular cartilage using standard morphologic MRI, Potter showed that 100% of acute ACL-injured knees had chondral injuries, particularly to the posterolateral tibial plateau. There was consensus on the critical need to establish more sensitive imaging standards and measurement techniques that improve on gross observation of radiographic joint-space narrowing used with the various grading systems such as the Kellgren-Lawrence grade for assessment of earlier changes leading to the development of OA.

There has been much interest in high-resolution quantitative MRI of articular cartilage to evaluate changes to subsurface matrix components of proteoglycan and collagen. The more commonly known quantitative MRI techniques include dGEMRIC (delayed gadolinium-enhanced MRI of cartilage), T1rho, and T2 mapping. Gold summarized several current and emerging quantitative MRI techniques, while Majumdar focused on MRI T2 and T1rho changes following ACL injury. In broad terms, dGEMRIC and T1rho are considered to be sensitive to proteoglycan content and measurement of T2 relaxation time to be sensitive to collagen architecture, with dGEMRIC considered the best validated of the 3.²¹ Limitations of dGEMRIC for multi-institutional application include the need for delay after injection prior to imaging, as well as recent concerns regarding the safety of gadolinium compounds. Both T1rho and T2 mapping show a degree of overlap and both are likely sensitive to changes in water content. Emerging quantitative MRI include Na MRI for assessment of proteoglycan content, as well as ultra-short echo time (UTE) and UTE-T2* mapping for improved evaluation of deep tissue to include the subchondral bone junction. These modalities show promise for continued study. Early human clinical UTE-T2* maps of articular cartilage and other joint tissues obtained in human subjects shown by Chu⁴⁸ and by Potter indicate clinical feasibility of this novel quantitative MRI technique for studying injured joints.

Although evidence for reproducibility in longitudinal and multicenter studies has been shown by several groups, quantitative MRI techniques require expertise in sequence optimization, quality control, scan acquisition, segmentation, and data analyses that are

technique-dependent and time-consuming. These potentially limit widespread application of quantitative MRI technologies in a multicenter clinical study. MRI T2 mapping is a component of the NIH-funded multicenter OAI and is considered to have had the widest usage to date of the quantitative MRI techniques for evaluation of articular cartilage that do not involve the use of contrast agents. A recent study shows the potential for consistency of MRI T2 mapping data acquired using magnets from different manufacturers at different clinical sites.³³ Conference attendees stressed, however, the need for a dedicated and experienced imaging team with consistent hardware, software, and quality control standards across sites to obtain meaningful imaging data.

On the question of ability to show structural change ahead of radiographic changes, there was general agreement that standard MRI using a cartilage-sensitive sequence can show cartilage fissuring, delamination, and focal loss as verified by arthroscopy.⁴¹ Standard MRI also shows bone edema patterns, subchondral bone changes such as sclerosis and impaction, synovitis, meniscal, and other soft tissue joint pathologies that frequently escape radiographic detection.⁵⁰ Interest was expressed in the use of MRI for short-term quantitative evaluation of synovitis with the idea that changes to synovium may be a measurable treatment outcome following an acute biologic intervention. Quantitative measurement of synovitis, however, may require use of contrast.¹³ While several scoring systems for standard MRI such as WORMS (Whole Organ Magnetic Resonance Imaging Score) and BLOKS (Boston Leeds Osteoarthritis Knee Score) have been used,^{10,29} there was general agreement that development and validation of a more specific scoring system with improved grading of joint tissues such as meniscus and ligaments commonly involved in joint injuries and early joint degeneration was needed. Use of MRI as primary imaging outcome measures will also require attention to whether metallic fixation is used close to the tissues being assessed, such as the articular cartilage.

There was also discussion on short-term changes to quantitative MRI metrics such as MRI T2 mapping. Although longitudinal MRI T2 map values can be detectable for individuals within 6 months to 1 year,²⁴ changes within study cohorts such as the OAI have been more difficult to discern. In a study of ACL-injured human subjects, Chu showed that intraoperative optical coherence tomography–detectable subsurface changes predicted prolongation of MRI T2 relaxation times suggestive of progressive degeneration as early as 6 months after ACL reconstruction. Both Chu and Majumdar highlighted the increase in ability to detect subsurface matrix changes potentially indicative of early disease and disease progression afforded by regional and laminar quantitative MRI assessments of articular cartilage.^{4,5,14} Continued research into the use of new imaging technologies to improve earlier diagnosis and stratification of cartilage and joint injury severity were considered to be critically important research priorities.

The current widely available imaging outcome measures include weightbearing radiographs inclusive of a flexion weightbearing view obtained using a standardized technique such as the SynaFlexer (Synarc Inc, Boston, Massachusetts) knee positioning frame and phantom, or fluoroscopy. A careful arthroscopic examination of the chondral surfaces in all 3 compartments should be performed and recorded by the surgeon using an accurate, consistent, and reliable assessment system. Standard MRI using a high-resolution 2-dimensional fast-spin echo and a 3-dimensional structural sequence such as DESS (dual-echo steady state) or a fat-suppressed T1-weighted SPGR (spoiled gradient-recalled echo) should be obtained using a higher field strength 3-T system by research teams with experienced and dedicated imaging personnel.

Research priorities include development and validation of a joint injury–appropriate scoring system for standard MRI by follow-on expert panels, translational human clinical study of

new quantitative MRI and other imaging technologies for improved diagnosis and staging of cartilage/meniscus injury and early joint degeneration, and cross-platform and cross-site validation of MRI technologies. Additional longitudinal studies using quantitative MRI techniques are necessary to provide a basis for the expected changes in relaxation time occurring over time in patients predisposed to OA, such as following ACL tear. To be academically sustainable for investigators and economically sustainable for funding agencies and industry, attendees emphasized the critical research priority of establishing quantitative imaging biomarkers that can show joint changes within 6 months to 2 years of the index injury that are predictive of later development of radiographically apparent OA, but not be constrained by the relatively insensitive imaging metrics of radiographic changes.

Kinematic Outcomes

Distinct motion pattern changes occur following joint injury. Andriacchi showed regional differences in cartilage biology and cartilage microarchitecture and how changes to contact areas following ACL injury can potentially overload areas unaccustomed or maladapted to the new loading conditions.^{8,44} He further showed the articular cartilage to be vulnerable to kinematic changes with these effects greater in the medial compartment than in the lateral compartment. This concept was used to support the idea that joint kinematics may predict later development of OA in a site-specific manner.

It remains unclear whether interventions ranging from rehabilitation to ACL reconstruction improve the altered kinematics observed following ACL injury. Tashman showed that use of advanced biplanar fluoroscopy for arthrokinematic assessment of dynamic joint function after injury and intervention can show articular contact pathways in near real-time under realistic loading conditions such as walking, running, and jumping.⁴⁷ This technology affords the potential for evaluating the degree to which a particular ACL reconstruction restores an altered motion pattern and for visualizing areas of stress concentration with different gaits and motions. Currently, the expertise and technologies for this type of assessment are available at select centers, although interest and capability are expanding.

In a multicenter study of service academy cadets, Padua used standard video cameras combined with a relatively simple assessment method to evaluate jump-landing movements using standard video cameras and showed similar altered movement profiles of cadets with prior ACL injuries and cadets who did not have ACL tears at the time of testing but who then subsequently tore the ACL.⁴⁰ Collection of this type of gross movement pattern data may be useful in studies of rehabilitation strategies as a direct outcome measure and in the development of screening tests for high-risk movements that could either predispose an individual to reinjury or to more rapid progression of OA. The Young Investigator presentation by Hart suggested a potential role of neuromuscular inhibition in joint degeneration.

Conference attendees recognized the importance of mechanical and kinematic contributions to the development of early OA following joint injury. Interest was expressed in developing and validating a kinematic test akin to a cardiac “stress test” to identify joints at risk of either injury or OA. Similar to collection of activity level and rehabilitation results such as strength and range of motion, it was considered important to have quantitative measures of joint function for comprehensive outcome assessment. Discussants determined that knee adduction moment could be measured and recorded at 6-month follow-up in a standard gait laboratory and that gait measures such as the adduction moment should be considered within the scope of “biomarkers” for risk of OA progression. A more comprehensive kinematic and kinetic assessment could be additionally considered at 2-year follow-up when graft incorporation is likely to be complete.

Biomarker Outcomes

The OA Biomarker Global Initiative (OABGI), which arose in 2004 as a partnership between the Osteoarthritis Research Society International (OARSI) and the Arthritis Foundation, has increasingly focused, beginning with the 2009 meeting, on biomarkers of earlier preradiographic disease to include acute changes following joint injury.²² This was the first of 3 NIAMS U-13–funded workshops addressing OA biomarker development also jointly sponsored by the Arthritis Foundation, the Orthopaedic Research Society, and the AOSSM. While speakers at the current AOSSM Post–Joint Injury OA Conference II characterized the human clinical biomarker investigations following acute joint injury as “nascent,” substantial progress in organizing the existing OA biomarker field was reported. Work groups from the global initiative (OABGI) have identified candidate OA biomarkers supported by published data that are commercially available for further study.³⁷ A new foundation for the NIH study to evaluate biomarkers from this list using samples from the OAI is planned. While the recently held second NIAMS U-13 OABGI workshop focused on genetics and genomics, the third and final workshop of the series is planned for spring of 2012 and will examine the combined role of “Imaging and Biochemical Biomarkers.”

Conference presentations highlighted the early developmental nature of the new focus on the acutely injured joint as well as the importance of clinical and imaging metrics of disease stage and severity. Presentations from awardees of the NIH Challenge Grant 03-AG-109 “Biomarkers of Persistent Damage After Acute Joint Injury” based biomarker data analyses upon stratification of structural disease using imaging assessments. Martin and colleagues based their human biomarker study upon a novel CT-based evaluation of the severity of ankle fractures⁴³ and highlighted the importance of a corroborative measure of OA for biochemical biomarker studies. This was echoed by Gibson, who showed preliminary analysis of serum micro-RNA isolated from biomarker samples obtained from the Canadian Pro-Knee (Prospective Study of Patients With Knee Injuries),²³ a multi-institution study inclusive of annual standard MRI scored using WORMS. Benefiting from a relatively uniform group of thoroughbred race horses, McIlwraith showed the predictive value of serum biomarkers for stress fracture risk but similarly emphasized the need for a corroborative imaging standard such as a bone scan for clinical decision making.³¹ Given the potential for diurnal, age, and other factors unrelated to injury and disease that potentially affect biochemical biomarkers, the importance of inclusion of structural and other clinical information in the validation process cannot be overemphasized.

There was general agreement that biospecimens for biomarker analyses should be collected and stored for potential future analyses in studies of the acutely injured joint where imaging, clinical, and other outcomes assessments are planned. A need for development and/or dissemination of guidelines for clinical blood, urine, and synovial fluid sample collection and storage was determined. Procedures for blood and urine collection have been established for the OAI and are available for reference (www.oai.org). Because of the early nature of research into acute human joint injuries and that biospecimen collection requirements will vary depending on the research question, there was no consensus as to specific collection time points.¹⁸ Rather, for patients undergoing surgery, convenient time points for biospecimen collection could correspond with the surgery itself and standard follow-up visits. This could potentially include day of surgery, initial follow-up (typically 1–2 weeks), 6 weeks, 3 months, and 6 months postoperatively, 1 year, and annually thereafter depending on study questions and resources.

Biomarker research priorities identified at the meeting include improved definition of the continuum of cartilage disease, including study of age-related changes to cartilage turnover, and establishing criteria for “normal” cartilage as well as stages of preradiographic disease. There was general recognition and agreement of the need for biochemical biomarker studies

to be correlated with structural changes and imaging evaluations of disease state and severity. Improved staging of early, preradiographic disease through identification and validation of sensitive and predictive biochemical and imaging biomarkers was again determined to be a critical research priority. Conference attendees agreed that clinical study of early treatment strategies is dependent on identification of methods to diagnose and stage early joint degeneration.

SUMMARY OF RESEARCH PRIORITIES IDENTIFIED

Several priority areas for further research to facilitate development of strategies to optimize healing or functional recovery after joint injury were identified. There is a need to define appropriate populations for further study, so that nested cohorts can be identified for study at institutions that have the unique capability to carry out specialized evaluations in imaging, kinematics, or biomarker assessments. One of the principal factors limiting further rigorous study is the lack of validated quantitative measures of cartilage structure and composition that predict the later development of OA. Continued development and validation of quantitative imaging and biochemical assessment techniques are critical research priorities. There is also a compelling need to advance understanding of how mechanical joint injuries lead to joint degeneration, and to define the roles of acute joint damage and post-joint injury incongruity and instability as etiologic factors leading to development of OA. A relatively overlooked area has been identification of the rehabilitation strategies that can optimize healing following injury or surgery. Rehabilitation specialists with expertise in measuring joint function and neuromuscular performance should be included in multidisciplinary approaches to the study of posttraumatic OA. This will contribute to the development of validated measures of knee kinematics to provide quantitative measures of joint function. Another critically important area is to identify biochemical markers that reflect changes in not only articular cartilage but also other relevant joint tissues such as subchondral bone and synovium. Once identified, such markers should be correlated with structural changes and imaging evaluations of disease severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1Differences Between Laboratory and Clinical Study^a

Laboratory Animal Study	Human Clinical Study
Young, healthy	Elderly, comorbidities
Disease onset known	Disease onset unknown
Acute inciting event	Chronic/advanced disease
ACLTx, meniscectomy	Idiopathic
Cartilage present	No or little cartilage
Laboratory assessments	Clinical assessments
Histology	Radiographs
Biomechanics	Subjective patient-reported outcomes
Biochemistry	Functional outcomes
Cellular/molecular	

^a ACLTx, anterior cruciate ligament transection.