Knee cartilage surgery: epidemiology, research methods and a proposal for improved surveillance

PhD thesis

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Abbreviations and definitions

ACI	Autologous chondrocyte implantation, refers to a surgical technique in cartilage repair
ACL	Anterior cruciate ligament
Clinical equipoise	The uncertainty to whether an intervention is beneficial
dGEMRIC	delayed Gadolinium-Enhanced Magnetic Resonance Imaging of cartilage
Effectiveness	Whether an intervention has effect in an uncontrolled, or real-life, setting, larger patient populations or different surgeons.
Efficacy	The effect of an intervention, or treatment, when measured under controlled settings, meaning the difference between two different techniques/instruments/medications excluding patient factors
External validity	Measures the generalizability of results from a study
FCD	Focal cartilage defect
Focal cartilage defects	Cartilage defects include a single or several focal lesions or it might constitute generalized degenerative changes within the knee. Focal lesions are either traumatic or non-traumatic and even degenerative, and some exist without causing symptoms. Cartilage injuries can be large or small, partial-thickness or full-thickness and localization might vary. They are believed to lead to a chronic osteoarthritic stage with pain and reduced function, despite demonstrated only in animal models.[1]
ICC	Intraclass correlation coefficient
ICRS	International Cartilage Repair Society
KOOS	Knee Injury and Osteoarthritis Outcome Score

K&L	Kellgren and Lawrence, refers to a radiological grading system of osteoarthritis
OAT	Osteochondral autograft, refers to a surgical technique in cartilage repair
LFC	Lateral Femoral Condyle
LTP	Lateral Tibial Plateau
MF	Microfracture, refers to a surgical technique in cartilage repair
MFC	Medial Femoral Condyle
MP	Mosaic Plasty, refers to a surgical technique in cartilage repair
MRI	Magnetic Resonance Imaging
MTP	Medial Tibial Plateau
NKLR	Norwegian Knee Ligament Register
NPR	National Patient Register
OA	Osteoarthritis
Phase-III-study	The drug/intervention is given to a larger population with an aim of confirming effectiveness and monitoring side effects. It is also comparable to other commonly known procedures at this stage, although without the gold standard comparison possible in an RCT.
Phase-IV-study	The drug/intervention is released to the free market and the effectiveness of long-term use, or long-term results, is monitored along with side effects.
PROMs	Patient reported outcome measures
ROI	Region of interest

Papers

Paper I

Engen CN, Årøen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. BMJ Open. 2015 Nov 30;5(11):e008423.

Paper II

Engen CN, Engebretsen L, Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. Cartilage. 2010 Oct;1(4):312-9.

Paper III

Engen CN, Løken S, Årøen A, Ho C and Engebretsen L. No degeneration found in focal cartilage defects evaluated with dGEMRIC at 12-year follow-up. Acta Orthop. 2016 Nov 24:1-9.

Paper IV

Engen CN, Årøen A, Engebretsen L. Development of a pilot cartilage surgery register. Manuscript, submitted to *BMC musculoskeletal disorders*.

Summary

Focal articular cartilage defects (FCDs) of the knee are identified in 20% of knee arthroscopies[2] and are affecting a large and severely troubled group of young, adult patients.[3] FCDs may subsequently lead to knee osteoarthritis (OA).[4-6] An obvious treatment goal is repair of the cartilage defect allowing patients to live their usual life and delay, or better still in the long run, avoid, joint replacement surgery. Existing treatments involve physical training, palliating surgical procedures, bone marrow–stimulating techniques and more advanced cartilage surgery. The results from clinical cohort studies and randomized controlled trials (RCTs) are conflicting, and no current gold-standard treatment exists. RCTs assess efficacy of interventions, but the effectiveness of cartilage surgery is unknown. Furthermore, cartilage surgery has not been compared to non-operative treatment under randomized and controlled conditions. In addition, the methodological quality of the majority of published studies is low. It is time for a comprehensive and standardized long-time follow-up of these patients, preferably through a register. However, there are some limitations and challenges that must be cleared out in advance.

The aims of the PhD-project were to outline epidemiological data of cartilage surgery in Norway and the external validity of RCTs. Furthermore, we studied the long-term effect of FCDs and biomarkers of early OA. Resolving these issues may lead to more standardized and less variations in treatment. Finally, we explored the prospects of a cartilage surgery register through a pilot.

The results show that cartilage surgery in Norway is common and there are large variations. The external validity in RCTs on cartilage surgery is low. There are currently difficulties with long-term follow-up as we are lacking reliable biomarkers. The results from this project support the establishment of a future cartilage surgery register, although the identified challenges must be continuously handled. Together with experiences from other registers, this project will serve as valuable information for optimizing the design of a potential cartilage surgery register.

Theoretical background

Epidemiology

Knee cartilage defects are well-known after the introduction of knee arthroscopy and MRI. Arthroscopic studies have shown that FCDs within the knee occur in 19-67% of patients with painful knees.[2;7-9] Knee cartilage defects also occur in healthy subjects,[7;9] and an MRI-study including healthy subjects

found that 37% had cartilage defects.[10] Increasing age and BMI are linked to increased prevalence and severity of cartilage injuries in healthy subjects.[7;11]

A systematic review found a prevalence of 36% in athletes examined by arthroscopy, MRI or both.[12] High-level sports are linked to increased incidence of cartilage defects, although most are asymptomatic.[13] Also asymptomatic collegiate basketball players were examined with MRI and 41% had abnormal cartilage signal or a focal abnormality.[14] None of the players had meniscal abnormalities. FCDs are commonly present in the general population, in subjects with knee pain and in athletes.

Impact on health system and society

A painful knee is a common reason for seeking medical assistance, and a report shows that nearly 14% of acute consultations within the primary health services in Norway constitute diagnosis affecting the musculoskeletal system and connective tissue.[15] Data available in Statbank provided by the Statistics Norway (SSB) illustrate that more than 10% of all consultations in the specialist health services constitute patients with musculoskeletal complaints. Lærum et al. estimates the yearly total costs for this group in Norway to be 70 billion NOK (10 billion USD), whereas the cost within specialist health services is 7.7 billion NOK. These numbers position this patient population as the most expensive patient group in Norway after psychiatric disorders.[16] Other studies have shown that musculoskeletal disorders cause 21% of all years lived with disability (YLDs) on a global scale.[17]

The population of patients with diseases or injuries within the musculoskeletal system is heterogeneous. Patients with cartilage defects are often young people early in their working career and many are competing in high-performance sports. They have increased risk of repeated periods of absence from work due to sick-leave and premature working disability. Knee symptoms in younger adults lead to not only physical impairments, but also a disrupted emotional and social life, and a different way of thinking about one's body and self.[18] Knee symptoms thereby influence recreational activities as well as work and social life. The young age of this patient population leads to a higher cumulative costs over the years.

FCDs increase the risk of OA.[5;6;19] The development of OA is gradual and includes increasing pain and stiffness and reduced joint function. Knee arthroplasty is not recommended for younger patients as the prosthesis has limited durability. The development of OA depends on genetics, age, gender

(higher risk in females), previous knee injury, local mechanical factors such as unfavorable axis or increased compression and stress from obesity or systemic factors.[20] Due to the disabling clinical picture and widespread disease, a major task for both physical health and socioeconomic costs is to delay or avoid the development of OA. Therefore, there may be a potential for larger savings if research is focused on the early stage of OA development, as FCDs are central risk and prognostic factors of knee OA.

What is cartilage, and what happens with injury?

The articular cartilage protects the intraarticular joint surfaces. It is of hyaline type and contains mainly water (around 70% of weight) and proteoglycans (3-10%) embedded in a collagenous framework (15-20%). It is normally 2-4 mm thick and an MRI-study found a mean average cartilage thickness of 2.28 mm in the weight bearing areas of the femoral condyles.[21]

The cartilage structure is important for proper joint function and it has the possibility of withstanding large amounts of load as well as providing low-friction movements throughout the lifespan of a person. The water molecules are held within a collagenous framework during loading. The smooth surface results from the superficial layer where the fibers are oriented horizontally. This layer has the highest potential of deformation during compression. The middle and deeper zone have less organized collagen with obliquely and perpendicularly oriented fibrils, withstand more effectively compression, have higher content of proteoglycan and lower content of water.[22]

When trauma, infection, fractures or degeneration causes disruption of the superficial layer, the homeostasis is changed and water molecules enters the cartilage layer uncontrolled from the synovial fluid. This disrupts the distribution of loading within the cartilage. The response to injury thereby depends on the affected layer of cartilage, whether it is damage to extracellular matrix (ECM) or cells without visible disruption of the joint surface and finally whether it is a chondral or an osteochondral defect. An osteochondral lesion may present itself either as an Osteochondritis Dissecans (OCD) in subjects with open physes or as an osteochondral fracture due to trauma in adults and older patients. OCD is a separate disease where a bony fragment separates from an otherwise normal vascular bone bed.

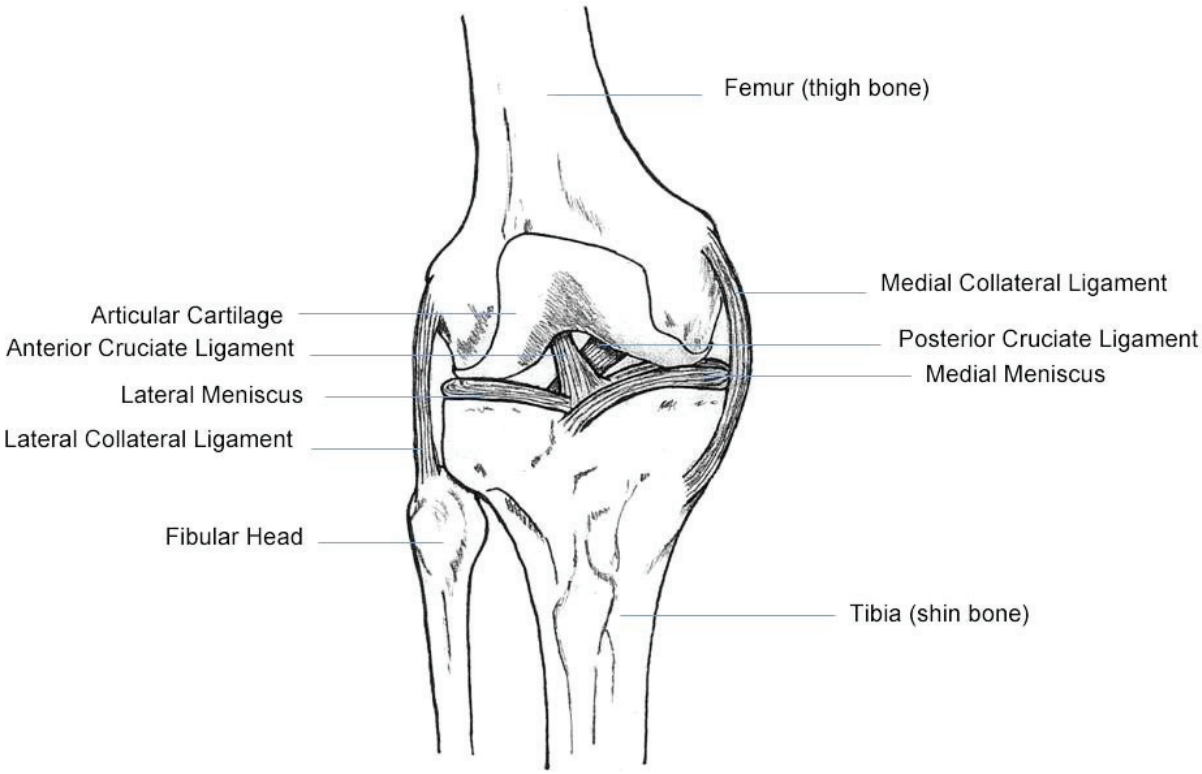

Figure 1 illustrates the anatomy of the human knee, including the articular cartilage. Adapted from Wikimedia Commons, with permission from Wikimedia commons (link: https://commons.wikimedia.org/wiki/File:Human_Knee_Anatomy.jpg).

Studies indicate that cartilage injury occurs after one single high impact or after several, repetitive smaller impact forces through joint instability or malalignment.[23;24] High-impact activity leads to increased degenerative changes.[25] The force and type of joint loading sufficient to cause cartilage injuries in humans is not fully understood. It is demonstrated that articular cartilage in donor knees can withstand impact loads up to 25 N/mm^2 (figure 2) without visible damage to chondrocytes or cartilage fissures.[26] Impact loads lead to a reduced content of proteoglycans in animal models, even in the absence of visible damages.[27]

1 N/mm^2 = 1 MPa = 1 000 000 Pa = 10 Bar
and
1 standard atmospheric pressure = 101325 Pa = 760 mm Hg

Figure 2 illustrates the relationships of pressure, represented by the tensile strength (newton per square meter).

Superficial cartilage defects do not heal. After 2 years the defects consist of rough and irregular surface both within the floor of the defect and the surrounding cartilage.[28] The mechanical shearing towards the area of the defect seems to induce degenerative changes. When the subchondral bone plate is affected, bleeding into the defect occurs. The bleeding supplies mesenchymal stem cells that initiate an inflammatory response. However, the repair tissue of the chondral part consists of a mixture of fibrous tissue and hyaline cartilage and normally does not fill the entire defect.[29]

An FCD may also lead to altered mechanical loading of the cartilage surrounding the defect. When an FCD occurs, the stress along the rim increases and the contact area adapts.[1] Guettler et al. studied the "threshold" defect size necessary to cause mechanical stress on the border of the defect.[32] This threshold is clinically important because it determines at what point the defect causes disruption of the adjacent cartilage and thereby provides a clinical implication of when to treat defects. They applied loading forces to cadaveric knees without defects and thereafter created increasingly larger osteochondral defects. They found that load was distributed properly through the meniscus in intact cartilage and with defects up to 8 mm in diameter. Lesions smaller than this did not affect the surrounding cartilage negatively, but when the defects had a diameter of 10 mm and above, rim stress was evident.

Table 1 summarizes some statements about FCDs and accompanying evidence.

What`s being said		*What research shows*
"FCDs may lead to joint damage and OA"		Approved in animal models for lesions over a threshold in size.[1;30] No studies in humans with healthy cartilage.
"Even small isolated defects lead to further degeneration"	-Cell death	Spontaneous repair occur in small lesions.[30;31]
	-Accelerated wear	A new layer of matrix is produced and present around a year after a controlled formation of small defects in rabbit articular cartilage.[28] Accelerated wear if >10 mm in diameter.[32]

This means that the surrounding cartilage and meniscus can adapt and protect the joint with defects up to 8 mm in diameter, but that surrounding structures

are affected with larger lesions. The mechanical loading depends upon defect size, depth and location within the joint. The study further noted increased stress on the medial femoral condyle (MFC), compared to the lateral femoral condyle (LFC). The intraarticular location, and whether the defect affects the weight bearing area, are important for further progress of these defects. Also, the depth of the defects is central as the penetration to the bone marrow ensures compounds for repair tissue. A defect also indirectly affects the subchondral bone so that calcification initiates and further degenerative changes with subchondral sclerosis occur.[33] To conclude, FCDs are considered progressive when present and over a certain size. They may lead to increased degeneration of both cartilage and bone.[11]

Natural history of FCDs

An isolated FCD may have an acute, chronic or acute-on-chronic onset. Approximately 50% of the patients present with a history of trauma.[34] The defects involve different depths of cartilage. FCDs occur at all ages, with gradually increasing degeneration with increasing age. The activity profiles of the patients vary from sedentary lifestyle to high-level athletes.

Articular cartilage lesions have limited capability of self-healing with normal hyaline cartilage.[30] Small defects might have some potential of spontaneous healing as it is demonstrated that 3 mm defects heal with hyaline or fibrocartilage in rabbit models.[31] Controlled FCDs develop into OA in animals.[4;30] but no such study is available in humans. Therefore, the link between an FCD and OA is not completely understood, and the penetration of the disease (which/how many patients will develop OA from their FCD) is not yet studied. It is believed that isolated FCDs eventually lead to OA.[6]

Some long-term observational studies on clinical outcome of non-operated, isolated FCDs in humans exist. Linden demonstrated that a clinically significant cartilage defect led to a higher incidence and to an earlier clinical onset of OA when compared to the general population.[35] Spahn et al. found that 30% of 115 patients with FCDs of the MFC were in need of arthroplasty 10 years after diagnosis.[36] These studies support the hypothesis of that FCDs lead to increased cartilage degeneration within the knee. However, the presence of an FCD may not lead to degeneration in all joints. A cohort of healthy subjects was examined with MRI at baseline and after 2 years by Wang et al.[6] They found that the mean cartilage defect score increased, although some patients had decreased scores (table 2). Another study performed MRI at baseline and after 2 years in a cohort of both children of

patients with total knee replacement (TKR) and randomly selected participants (mean age 45 years).[37] One third of these knees worsened while 37% actually had an improvement in cartilage defect score.

Table 2. Table adapted from Wang et al. The table illustrates the natural progression of cartilage defects over 2 years. For this purpose only baseline grade 3 and 4 were included in the table since these are the most clinically relevant defects. Of all FCDs scored as full-thickness lesions at baseline, 10 out of 22 (45%) regressed and had a lower score at follow-up, whereas 41% were no longer classified as full-thickness lesions. The grey-shaded windows are those defects with a similar or higher grade at follow-up. The authors discussed that the low number of full-thickness lesions in the cohort made ceiling-effects less likely to explain the negative association.

Baseline grade	*Follow-up grade at 2 years*				
	0	*1*	*2*	*3*	*4*
3 (n=14)	0	2	4	3	5
4 (n=5)	0	1	2	1	1

Widuchowski et al. studied patients with isolated untreated severe cartilage lesions (size 2-4 cm^2) 15 years after diagnosis, and found that clinical outcomes were comparable to the results following cartilage repair.[38] There were no statistically difference in the frequency of OA between injured and uninjured knee. Of the included patients, 39% had OA after 10-15 years, which is in the same range as the occurrence of degenerative changes after cartilage repair.[39;40] They concluded that isolated cartilage defects left with no treatment have limited influence on clinical outcomes and the development of OA. Another long-term study followed young, athletic patients after arthroscopic diagnosis (including 3 Pridie drillings and *occasional* cartilage shaving) of an isolated full-thickness FCD. The lesions were located in the weight-bearing area of the femoral or tibial condyles and were >1 cm in diameter whereas 70% were traumatic defects. They found that 92% of patients returned to pre-injury activity level and less than 50% had radiographic joint space narrowing (JSN).[41] A short-term study evaluated the feasibility of active rehabilitation in patients considered candidates for cartilage repair and found a significant improvement of knee Quality of Life subscale of Knee Injury and Osteoarthritis Outcome Score (KOOS) and the IKDC 2000.[42] These results imply that some patients may have a favorable result with a non-surgical approach. Thus, we still do not know if surgery actually is better than the natural development in preserving joint function after FCDs.

Which defects cause symptoms?

In a cohort of asymptomatic NBA players nearly half of the players had cartilage lesions in their knees.[43] All players with prior history of knee pain or mechanical symptoms were excluded. The localization of the defects was different from what is seen in symptomatic individuals. In clinical studies, the MFC and the patella are the most common localizations with around 50% of defects on the MFC, whereas the MFC was involved only in 10% of NBA-players. A systematic review found that 14% of athletes with FCDs were asymptomatic.[12] However, when these defects are symptomatic they seem to affect patients to the same degree as patients scheduled for total knee replacement for OA.[3]

Factors that need to be present for a defect to become symptomatic remain unknown. The different aspects of the defect itself might produce different intensities and types of symptoms. The articular cartilage has neither vascular nor nervous supply, and nerve endings are therefore not irritated until the subchondral bone is affected, meaning that there should be a full-thickness defect present in order for the defect to produce pain. Still some partial-full-thickness defects seem to cause similar symptoms. The threshold in size for symptoms to occur is unknown. Whether the defect is localized in the weight-bearing area is of clinical significance, as is the status of the surrounding cartilage.

FCDs often occur together with other types of injuries such as damage to the menisci, the ligaments, the joint capsule or intraarticular fractures. Medial meniscal tears and anterior cruciate ligament ruptures occur in 37% and 36% of cartilage injuries.[8] A focus in the literature has been cartilage injuries in combination with reconstructions of the anterior cruciate ligament (ACL). The long-term effects of isolated cartilage defects in ACL-reconstruction remains unresolved.[44;45] Studies have suggested worse prognosis with treating these patients with microfracture (MF) when compared to debridement or no treatment.[46]

To summarize, full-thickness defects larger than 2 cm^2 in the weight bearing area of the knee joint cause symptoms. However, the exact size for a defect to cause symptoms is not yet known. Some partial-thickness defects cause symptoms, as well as defects located outside the weight bearing area. This may be due to inflammatory mediators, for instance, matrix metallopeptidases (MMPs) through mitogen activated protein kinases, which influence the repair process after mechanical injury (animal models).[47;48] Inflammatory mediators are suspected to contribute to pain in knees with cartilage injuries, but their role is not fully understood.

Diagnostic challenges - arthroscopy, MRI and newer techniques

The findings from a clinical examination of a knee with an FCD are subtle and unspecific. A final and exact diagnosis is impossible without visualizing the defect. When diagnosed, the lesions are classified with different grading systems. In order to follow FCDs both with natural development and after cartilage surgery, it is necessary to have standardized grading systems. We also need biomarkers of early knee OA, as OA as an end-point requires long follow-up time.

The Outerbridge classification was previously widely used for arthroscopic assessment.[49] A study addressed the accuracy and reproducibility of the Outerbridge classification system for cartilage injuries in the knee by examining 3 cadaveric knees and found an overall accuracy rate of 68%.[50] Many sought a routinely assessment of size and location.[51] The International Cartilage Repair Society (ICRS) designed a standardized and simple classification system.[51] The system was developed to include enough information for long-term follow-up and allowing for prognostic evaluations of FCDs. It is the most widely used system. Other systems for classifying lesions on both arthroscopy and MRI exist. [52-56]

Both invasive and non-invasive procedures visualize FCDs. Although arthroscopy is the gold standard for diagnosing FCDs, there are obvious advantages of non-invasive techniques. Radiographs with Kellgren and Lawrence (K&L) protocol[57] is used for the development of OA. The method is not sensitive for FCDs or earlier degenerative changes, only for osteochondral defects with a visible bone-piece or lesions with substantial cartilage volume loss.[58] MRI detects soft tissue and is a potential tool for diagnosing and following FCDs within the knee. The advantage of MRI is that it is non-invasive and thereby allow better longitudinal follow-up of patients. MRI also enables a broader intraarticular evaluation, as opposed to histologic analysis. Additionally, not all defects are noticed on arthroscopy.[59;60] A non-invasive technique such as MRI is beneficial for subgroups of patients with FCDs undergoing an early non-surgical approach, for timing of surgical treatment and for detecting and following the lesions.

The MRI technique depends on how atoms react under the influence of a magnetic field. All atoms are oriented in one axis by an activated magnet and orients back to their original spin position when the magnetic effect is turned off. Different measures of time for the atoms to spin back result in values that are converted to a picture consisting of shades of grey. The grey-shaded

pictures represent the morphologic feature of the tissues dependent on the different MRI modalities, T1 and T2. Different tissues, and different parts of tissues, thereby yield different T1 and T2 values, dependent on how quickly the atoms spin back. A short T2 yields low signal and dark images in T2-weighted images, and a short T1 yields high signal, or bright images in T1-weighted images. The cartilage is bright in T2 and darker, although not completely dark, in T1. This means that different modalities are used according to what anatomical structure is studied. The most commonly used protocols for evaluating cartilage and FCDs are T2-weighted "fast-spin-echo" (FSE) (with or without fat suppression) and T1-weighted fat-suppressed (or water-selective excitation) spoiled gradient-echo (3D-GRE) image acquisition.[61;62] Fat-suppressed 3D-GRE has the advantage of yielding high signal intensity from cartilage and low from surrounding tissues, visualizing both thickness and surface. FSE-techniques yield low signal intensity from cartilage, whereas subchondral bone and joint fluid yields high signal intensity and the cartilage surface is visualized. The latter is also robust against artifacts in patients who have undergone previous knee surgery.

MRI gives objective and reproducible data on native cartilage and on cartilage repair tissue. The surface, signal intensity and homogeneity, subchondral lamina, osteophytes and effusion are evaluated. After repair, defect filling and integration can be evaluated. Some defects are too small to be detected[63;64] and conventional MRI is insensitive to how the surrounding cartilage reacts until gross morphologic changes occur. Although some studies have demonstrated good diagnostic accuracy, some have also demonstrated poor sensitivity. The diagnostic accuracy demonstrates large variations dependent on design and study population (table 3). The diagnostic accuracy of MRI may be satisfying when the correct technique is used.[65] The overall sensitivity for MRI is 0.74 (0.71-0.77) and specificity is 0.95 (0.94-0.95) when compared to arthroscopy, with a higher accuracy for high-grade lesions. A systematic review found that 1/3 of studies demonstrated correlation between MRI and clinical outcome and concluded that the reliability of MRI in predicting clinical outcome is lacking.[66] Additionally, it is not possible to evaluate the cartilage matrix in detail with conventional MRI-sequences. Therefore, many still rely on second-look arthroscopy. However, arthroscopy does not allow for an evaluation of deeper structures. Quantitative MRI (qMRI) allow for a detailed evaluation of different segments of the knee, including the content and quality of cartilage.

Table 3. The table demonstrates the sensitivity and specificity of different MRI-techniques.

MRI method	Author	Sensitivity / specificity
3D-GRE techniques	Tyrrell et al. (1988) [55]	36% (grade 1) and 100% (grade 2 and 3) / -
	Speer et al. (1991) [67]	15% (partial-thickness) and 41% (full-thickness) / -
	Disler et al. (1996) [63]	75-85% / 97%
	Spiers et al. (1992) [68]	18% / 100%
	Recht et al. (1993) [69]	96% / 95%
FSE-techniques	Potter et al. (1998) [70]	87-95% / 87-94%
	Bredella et al. (1999) [71]	94% / 99%
	Irie, Yamada and Inoue (2000) [72]	59.4% (grade 3) and 100% (grade 4) / -
Standard MRI	Disler et al. (1996) [63]	29-38% / 97%
	Figueroa et al. (2007) [73]	45% / 100%
MR arthrography	Kramer et al. (1994) [74]	85-87% / 100%

Early osteoarthritis

The primary changes towards a degenerated knee joint involve an interrupted cartilage structure, proliferation of chondrocytes and increased water content in the ECM. Fibrillation of the superficial layer and cracking of the matrix then occur before morphologic destruction of the cartilage. Lorenzo et al. looked at biochemical content in knees with normal cartilage, early OA and OA, and found increased relative amount of proteoglycans in early OA and an altered biochemical synthesis even in the absence of cartilage fibrillation.[75] The continuous degeneration ultimately leads to a destroyed joint and criteria for early OA are suggested.[76] To actually visualize "early OA" and identify these patients at risk of early TKR are important to implement early treatment strategies and increase future joint protection. Independent systems for sensitive evaluation of knee articular cartilage by MRI are developed, among which the most complete are the *whole-organ magnetic resonance imaging score* (WORMS)[77] and the *magnetic resonance observation of cartilage repair tissue* (MOCART).[78;79] The WORMS consist of several semi-quantitative

scores for different features for evaluating degree of degeneration within the knee. The quality after cartilage repair is evaluated by the MOCART system. Defect fill is considered to be the most important factor, and is demonstrated to correlate with clinical symptoms 2 years after MF,[80] and after MACT.[81] Also the cartilage surface, matrix thickness, volume and subchondral borders are visualized with MRI and the status following cartilage repair is evaluated with the same acquisition techniques as for native cartilage.

Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage

The altered composition of proteoglycans[82] with reduced GAG concentration ([GAG]) occur prior to cartilage loss.[22] A disrupted cartilage can also be evaluated with newer MRI-techniques which quantify the contents of cartilage and create a "biochemical image" to evaluate the cartilage quality.[83] The delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) is one of the newer techniques and detects areas with subtle changes even in the absence of morphological changes.[84;85]

GAGs, measured by dGEMRIC, correspond to the true [GAG] both biochemically and histologically.[86;87] The technique relies on the injection of a contrast agent that changes the relaxation rate and energy amount of cartilage. The dGEMRIC technique is validated for use in vivo,[88] for both hip and knee.[89;90]

T2 mapping

The T2 relaxation is increased in damaged cartilage.[91] T2 mapping is another method for quantifying biochemical content of cartilage. It is less time-consuming and does not require any contrast agents. For articular cartilage, the T2 relaxation time depends on the relationship between water content and collagen structure. The T2-mapping reflects water molecules and their interaction with surrounding collagen and macromolecules, thereby measuring the collagen component of ECM. It is therefore sensitive to altered hydration.[92;93]

Treatment and indication for treatment

Diagnosing FCDs can be challenging, as there are subtle symptoms and often additional injuries. This may lead to variations in both diagnosis and treatment. Improving function and symptoms and the long-term prognosis, to delay or

avoid, joint replacement surgery, are the goals when treating patients with FCDs. New surgical techniques have been developed since the first chondrocyte implantation in Sweden in 1994. Some treatment algorithms have been proposed (figure 3), based upon size and depth of lesion and age and level of activity of patient. But for the majority of this heterogeneous patient group with isolated FCDs, there is no known gold standard treatment. The role of physical training as treatment is not yet fully explored. Non-operative treatment generally consists of avoiding sports and weight bearing for 6 weeks in addition to a strict rehabilitation protocol with exercise under the control of an experienced physiotherapist. Intraarticular injections of Hyaluronic acid (HA) and platelet-rich-plasma (PRP) have an unclear role in the treatment of cartilage defects.[94] They are used more frequently in knees with cartilage degeneration or OA, although with still unresolved evidence.

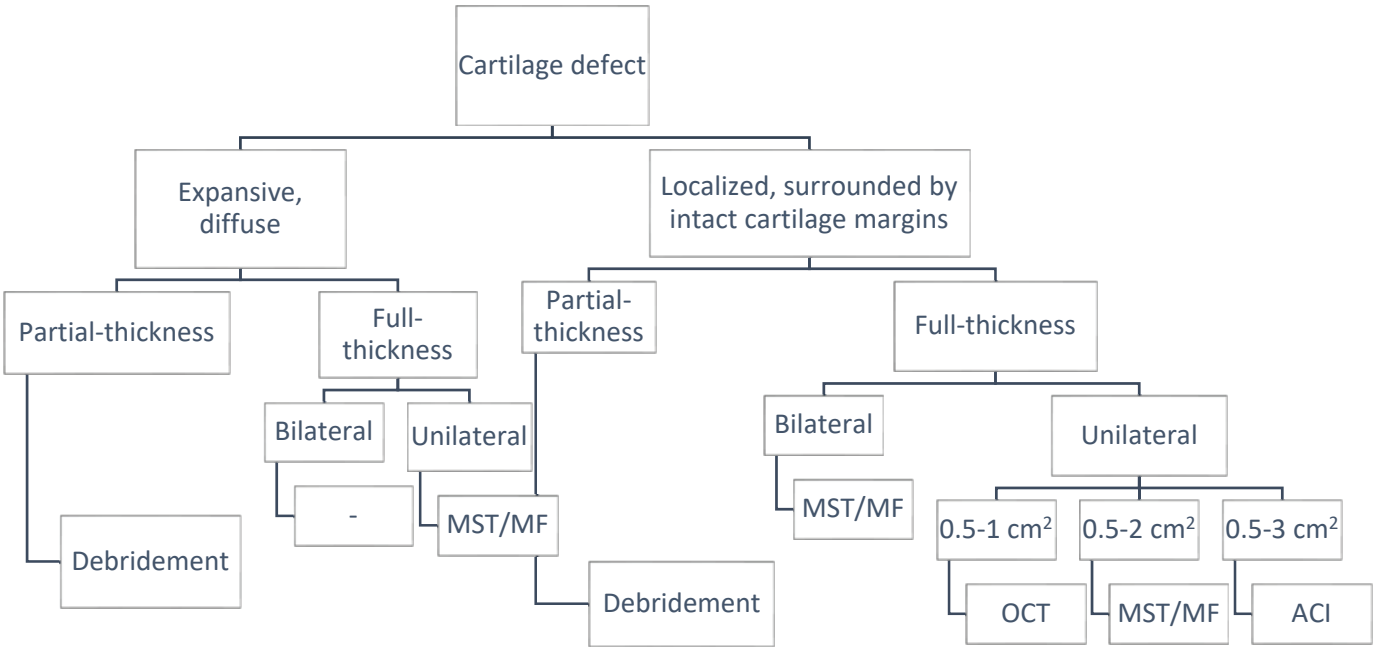

Figure 3 illustrates an example of a surgical treatment algorithm for FCDs. Figure adapted from Madry, Grün and Knutsen.[98] MST is an abbreviation for marrow-stimulating techniques, such as MF. MF or MP is mostly recommended for smaller lesions (less than 2 or 3.5 cm^2).

The treatment options concerning the depth of the defect have been non-operative treatment for ICRS grade 1 lesions. Prevention of progression is the main goal for grade 2 lesions, and simple debridement might reduce symptoms. Small (<1.5 cm^2) partial-thickness lesions are thought to be non-progressive.[95] More aggressive cartilage therapy is suggested for lesions

where more than 50% of the cartilage thickness is affected. Some algorithms suggest marrow-stimulating procedures and osteochondral autograft (OAT) for smaller defects, whereas autologous chondrocyte implantation (ACI) is recommended for larger defects.[96] A study comparing early cartilage repair of the knee with none or late cartilage repair showed better results for early cartilage repair in goats.[97] This supports early cartilage repair to prevent the cartilage from negative influence by the altered matrix metabolism. Delayed surgery in humans leads to increased development of OA.[34]

Non-operative therapy, active rehabilitation and training

The literature in non-operative treatment of FCDs mainly focuses on rehabilitation after surgery. However, many cartilage injuries are treated without surgery. Training has a positive effect on meniscal injuries when compared to arthroscopic surgery.[99] An identical study including randomization of active rehabilitation or training has not been performed for patients with FCDs. Training leads to neuromuscular effects with potential of modifying the loading of the joint. A study found increased GAG content after training.[100]

Still, morphological changes or changes in the biochemical status of cartilage are not demonstrated after 12 weeks of neither strength training or 12 months of high-intensity training.[101;102] Furthermore a study found a positive effect on bone but no effect on cartilage after progressively high-impact training in women aged 50-66 years.[102] The previously mentioned study evaluating the feasibility of active rehabilitation in subjects scheduled for cartilage repair showed a significant improvement of patient reported outcome measures (PROMs) after 2 years.[42] 64% of the patients postponed their surgery after 3 months of rehabilitation exercise. These findings support a further exploration of how non-operative treatment approaches affect the articular cartilage and the long-term prognosis. Exercise and activity modification are chondroprotective when knee OA is established.[103] Adjusted knee loading in well-adapted and highly trained extremities may reduce expected symptoms in some patients also with early degenerative changes and FCDs. We do not know yet how to identify patients who will benefit from training.

Prognostic factors in surgery

Single defects less than 4 cm^2 and located on the MFC are defined as *simple* lesions whereas larger defects on the MFC and defects located on the trochlea, tibia or patella together with multifocal defects are *complex*.[104]

Kissing lesions and early degenerative changes are considered to be salvage cases. Examples on prognostic factors are lesion etiology, size, depth, location, patient age, BMI, activity level and the different treatment modalities. The role of the depth is outlined in previous sections.

Age of the patient is highly relevant as certain surgical techniques should not be used in patients <50 years since there are demonstrated poorer results for older patients.[105] Other studies have identified better results for even younger patients.[40;106-108]

Location of the defects seems to affect the clinical presentation, treatment and prognosis. The location of an FCD is reported in accordance to the affected area and the ICRS have made a mapping system dividing the knee joint into 6 different parts; MFC, LFC, patella, trochlea, medial tibial plateau (MTP) and lateral tibial plateau (LTP). Most clinical studies report FCDs to be most common on the MFC and patella[7;8;34;70;109-111] or LFC[112] and uncommon on the tibia.[24] Lesions on the MFC have the best outcome after treatment in most studies.[41;107;113] The LFC is the most favorable one in others, although lesions occur more frequently here in younger patients.[114;115] Lesions on the femoral condyles show more improvement when treated with ACI than lesions on the patellae and trochlea.[116] Tibial lesions have poorer results and Mandelbaum have warned against using ACI and mosaic plasty (MP) on these defects.[24]

Size is an established prognostic factor in FCDs.[24] Lesions less than 2 cm^2 are classified as small, 2-10 cm^2 as moderate, and lesions more than 10 cm^2 as large. The size influence on the prognosis and small lesions on the femoral condyle have the best potential[41] whereas moderate and large lesions are more likely to develop into OA.[24] Recommendations of when to treat FCDs have ranged from 1.0 cm^2 to 1.6 cm^2.[110;117-119] Some utilize a cut-off at 4 cm^2,[40;120;121] whereas others suggest 2 cm^2 as the indication for cartilage repair.[106;120]

Based on size, there is no difference in clinical outcome in the natural history of FCDs in association with ACL-reconstruction (range 0.5 cm^2 to 6.5 cm^2).[122] However patients with sizes larger than 6 cm^2 have inferior results compared to patients with smaller defects 2-4 years after surgery for isolated FCDs.[123] Also, patients with lesions less than 2 cm^2 have a higher return-to-sports rate.[34]

Debut may be acute, chronic or acute on chronic. Approximately 40-50% of patients included in clinical studies have traumatic lesions.[110] The German Cartilage Registry includes degenerative lesions more frequently than

traumatic and posttraumatic lesions.[124] Acute lesions may have an increased potential for a good outcome, although no statistically significant difference between degenerative and other lesions was found after osteochondral allografting.[125] Acute injuries are also more common in younger patients, which is an individual prognostic factor. A systematic review of ACI and a clinical study on MF found that young patients with a short duration of symptoms do best.[80;126] Longer time periods from debut until treatment seems to worsen the outcome, as previously demonstrated for delayed ACL-surgery.[127]

Previous surgery is present in 20-28% of patients.[2;128] However, up to 83% and 94% of patients have prior surgery to the index lesion performed, including diagnostic arthroscopy.[110;129] Previous surgery with bone marrow stimulating techniques may complicate the current treatment as the subchondral bone plate is disrupted. In a study population where 37% had prior cartilage surgery, previous surgery was not identified as a poor prognostic factor.[130] Also, previous surgery did not seem to influence the 3 year clinical outcome in a register study on ACI.[131] Other studies have demonstrated the opposite, previous surgery seems to yield a poor outcome with the use of Hyalograft C autograft as only 7% of patients operated on primary indications experienced graft failure versus 81% of the patients operated for secondary indications.[132] ACI after previous marrow-stimulating techniques yields poorer results than ACI as a first-line treatment.[104;133] Also, prior surgery correlate negatively with return to sports after MF.[34]

Increasing age,[134] low activity level,[135] and high BMI[80] are negative prognostic factors for cartilage repair. In a cohort of athletes treated with MF, they found size to be a more important prognostic factor than age.[113] The best results are achieved in young patients,[34;120] with a single lesion less than 2 cm^2 on the MFC.[136;137] Patients with an acute history of trauma and a short period of symptoms prior to treatment and no previous surgery have better results.[34;120;135] However, there is still insufficient knowledge about the importance of each parameter`s role for the prognosis. Many of these factors are identified through RCTs, which is not suited for that purpose. A large, unbiased prospective cohort enables a more comprehensive evaluation of the prognostic factors.

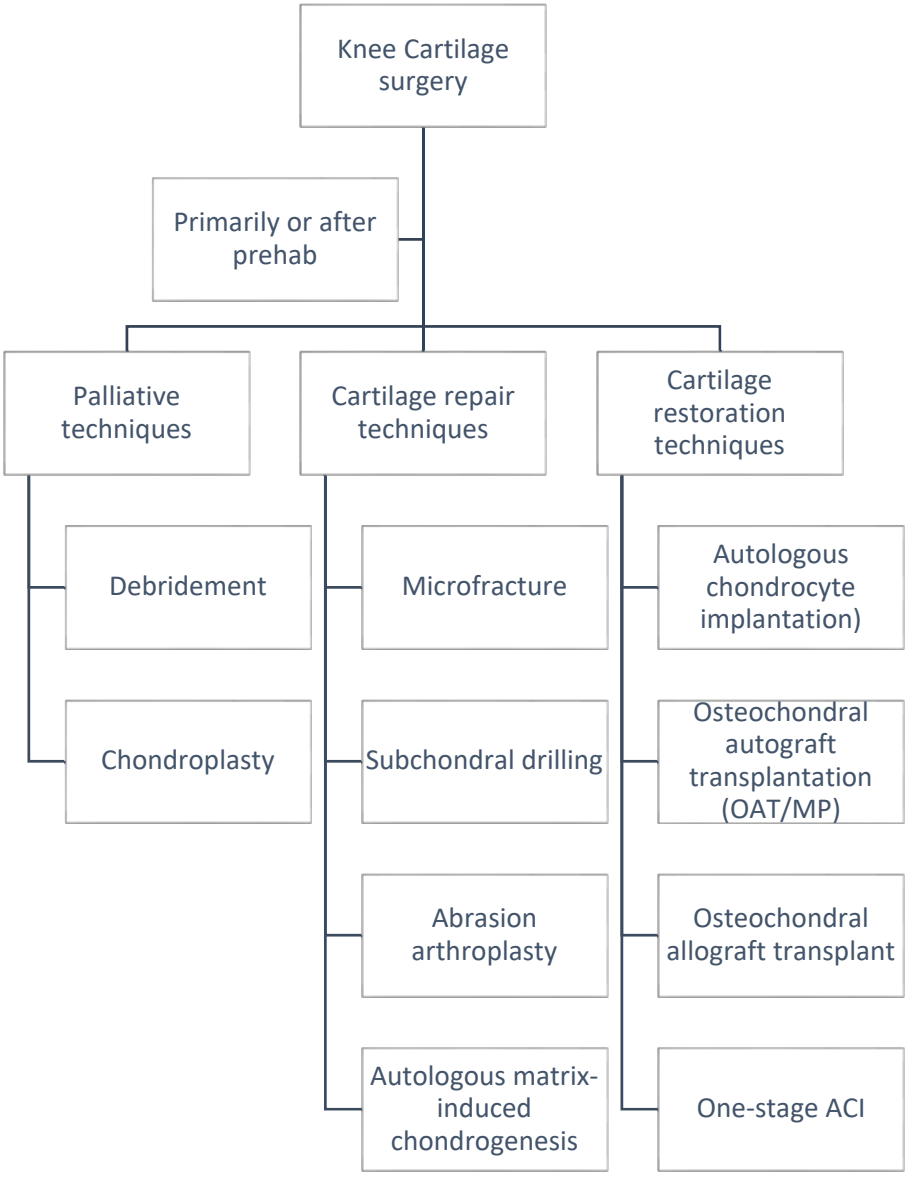

Figure 4 illustrates an overview of the existing treatment modalities.

Surgery

Several different surgical techniques exist and they can be divided into 3 groups based on their role as palliative, reparative or restorative techniques (figure 4). There is a general agreement that symptomatic full-thickness defects larger than 2 cm^2 in an otherwise stable and healthy knee could be treated with cartilage surgery. Good results from clinical studies support surgery for defects over this size, however we are not aware of any original research supporting cartilage surgery over non-surgical treatment. Some of the smaller lesions are operated and some larger lesions undergo non-operative treatment. In this section, I will first present the commonly used

surgical techniques together with some clinical results, mainly from cohort studies, before a summary of the existing evidence with results from RCTs.

Palliating techniques

Palliative techniques include chondroplasty, debridement or smoothening of the defect. The defect is not repaired and although the loading might be removed from the defect itself, it is probably redistributed to the surrounding cartilage. Still, the most commonly performed surgical procedure for FCDs is debridement.[138] Debridement is effective for smaller cartilage lesions within the knee as a first-line treatment.[139] Dozin et al. found that 30% of the patients in their study improved after initial debridement, and received no further treatment.[140] Further, Meissner et al. demonstrated good results after minimally treatment of knees in patients <40 years of age, diagnosed with Outerbridge grade 2 and 3 defects.[41]

The results indicate that these techniques result in symptomatic relief and that some patients experience little symptoms from the initial defect also for the long-term follow-up. The role in joint preservation is not clear and we do not know which patients who will benefit from palliating techniques only.

Reparative techniques

The subchondral bone plate between the defect and the bone marrow is penetrated allowing bone marrow and blood to enter the defect. This results in a fibrin clot. The clot initializes healing and the formation of articular cartilage, but the repair tissue is disorganized and resembles fibrocartilage more than hyaline cartilage.[93;106]

In MF the subchondral bone plate is penetrated with small awls making holes around 3 mm apart within the defect.[141] Patients experience improvement after 2-12 years whereas 20% report no benefit from the procedure.[136] The PROMs increase postoperatively in both general patients[106;107;142] and in athletes.[113] Thereafter comes a plateau after 12-24 months[80;143;144] or even a slight decline after 18-60 months.[107;145] Scores 11 years postoperatively, however, remain higher than prior to operation.[136] A BMI >30 is linked to inferior outcome.[80] There is better outcome in patients younger than 30-40 years.[40;106;107] A systematic review of MF demonstrated effective short-term results and insufficient data to conclude on the long-term outcome.[146] Reported survival

rates are around 75% but no studies have demonstrated a clear advantage of MF.[40]

Restorative techniques

Autologous transplantation - autologous chondrocyte implantation and matrix-associated autologous chondrocyte transplantation

In ACI, the chondrocytes are isolated from a less weight-bearing area of the knee and grown in cell cultures before they are implanted within the cartilage defect in a two-step procedure. In first generation ACI the cells are covered by a periosteal flap, whereas newer techniques include scaffolds where the chondrocytes are seeded and the scaffolds are implanted. Advances have led to different variations of solutions with scaffolds, matrices and 3D-systems for these procedures. The variety ranges from autologous periosteum to second generation xenograft tissue (porcine-derived type I/type III collagen cover) or third-generation biosynthetic scaffolds.[147] These are matrix-associated autologous chondrocyte transplantation (MACT), and the harvested chondrocyte are grown and cultivated on a 3D polymer scaffold. Recent advances have led to the possibility of performing ACI as a single-step procedure.[148] Histologic findings after transplantation techniques include partially hyaline-like repair tissue.[118;149] There are some disadvantages with these techniques as they require a long rehabilitation period. In the postoperative phase some complications, such as hypertrophy and arthrofibrosis, may occur. Hypertrophy, together with graft detachment have been related to the periosteal flap in first generation procedures[121] but seems to have been overcome with newer techniques.

ACI[118] is indicated for larger ($2cm^2$-$12cm^2$) full-thickness defects or for smaller defects where previous surgery with MF or MP has failed.[150] One study found better outcome with ACI over abrasion techniques in 50 patients.[151] Good to excellent results are demonstrated at both short-term and medium to long-term follow-up in 60-90% of patients in clinical observational studies,[40;96;139;150;152;153] and in one RCT including ACI.[110] A systematic review from 2011 with ACI as one of the interventions found good short-term outcomes.[126] One of the first long-term (10-20 years follow-up) case series found that 92% of patients were satisfied and would have done the ACI again.[130] These excellent long term results are still not reproduced to the same extent by other research groups, but one prospective cohort study found that less than 7% of all operated

patients had a complete failure 10 years after operation, although 45% had radiographic signs of OA.[134]

Studies on newer ACI-techniques demonstrate around 75% improvement in clinical scores after 5 and 10 years.[132;154] An RCT comparing first-generation ACI with MACT found no statistically significant differences.[155] However, the quality of research including MACT is considered to be low with mainly case series and studies with short to mid-term follow-up periods.[156] We are still lacking information to conclude precisely on results from the different techniques and to identify the patients who will benefit from ACI-techniques.

Mesenchymal cells and other cell-based techniques

Mesenchymal stem cells were used for cartilage defects in rabbits in 1994.[157] Mesenchymal stem cells have a potential for producing more hyaline cartilage compared to mature cartilage cells. Certain growth factors can be used to induce cell growth and chondrogenesis.[158] There are currently not enough evidence to conclude on the overall result of cartilage repair with mesenchymal stem cells.

There are also other less studied surgical treatment options. Autologous matrix-induced chondrogenesis (AMIC) combines MF with ChondroGide® (GeistlichPharma AG, Wolhusen, Switzerland). Interim analyses in an RCT comparing AMIC to MF for isolated cartilage defects demonstrated similar increases in defect filling 2 years after operation.[159] An FDA phase II RCT compared Neocart (an autologous cartilage tissue implant) with MF and found significantly better clinical scores in patients treated with Neocart after 2 year follow-up.[160]

Osteochondral transplants

Autologous osteochondral transplantation is a one-step procedure with the incorporation of an osteochondral plug into a defect with surrounding healthy cartilage. The plug is harvested from a non-weight bearing area within the knee, and donor-site morbidity in the long-term is a yet unresolved question. MP refers to the transplantation of one or several plugs into a large defect. The long-term outcome from a cohort study of MP showed improved subjective scores and good survival of the grafts on MRI.[161] The outcomes from clinical studies after 3 years follow-up are good and one randomized study found better results for OAT after 3 and 10 years when compared to MF.[39;106;162] A

study comparing MP with ACI in defects with mean size around 4 cm^2 found equal results after 2 years, but a higher failure rate for MP after 10 years (17% vs 55%).[110] Another study found clinical improvements in both groups after 2 years, whereas the histological findings demonstrated more fibrocartilage in the ACI-group.[96]

It is also possible to use osteochondral grafts from a donor, although it is not available everywhere. The technique is single-staged with a fresh allograft that contains hyaline articular cartilage and is shaped to match the defect identically. The technique is appropriate for treatment of very large chondral or osteochondral defects (4-20 cm^2) and after failure of previous treatment.[125] The survival rate is >80% after 10 years.[125;163]

Cartilage surgery for degenerative lesions

Degenerative cartilage is believed to have even less regenerative potential than healthy cartilage. The distinction between an acute focal lesion and a degenerative focal lesion is sometimes challenging as the development from acute defects to a degenerative lesion may be seen as a continuum. Cartilage defects should be surrounded by healthy cartilage in order to optimize the implantation process of the graft and prevent negative influence from cytokines in a surrounding degenerative milieu.[97] The surrounding cartilage depicts the quality of the remaining cartilage within the joint. There is a presence of inhibitory factors in the synovial fluid of chronic lesions as opposed to stimulating factors with acute lesions.[164] Still, promising results are demonstrated in mid-term (2-5 years) follow-up of isolated degenerative lesions treated with MF[165] and ACI,[135] and also for the treatment of early OA with ACI.[111] The latter study performed by Minas et al. followed 153 patients for 11 years after ACI for early stage OA. They concluded that they were able to delay the need for joint replacement as 92% of patients were functioning well after 5 years.

Rehabilitation and return to sports

An important factor for a good outcome after an FCD is the rehabilitation protocol. The role of rehabilitation alone is not fully understood.[42] The effect of exercise on articular cartilage is positive,[100] although high-intensity loading leads to injuries and degenerative changes.[25] The rehabilitation program depends on individual factors and reflects the 3 healing phases of cartilage. It begins with protection and activation allowing full active ROM and protected

weight-bearing for up to 6 weeks,[166] thereafter progressive joint loading and finally functional restoration of the joint, including a sports specific rehabilitation in athletes.[119] The length of each phase depends on the treatment choice as well as lesion and patient factors. Generally, there is a longer protection phase immediately after treatment compared to any other orthopedic surgery.

A study with early and accelerated weight bearing after cartilage repair showed good clinical outcomes without negative effects on the graft.[167] Also, the postoperative knee function score improved in patients who participated in sports after ACI compared to those that did not participate in sports after rehabilitation.[166] Rehabilitation after cartilage surgery is a research field of its own with increasing evidence concerning both rehabilitation alone, prehabilitation and post-surgical rehabilitation.

As these defects cause both pain and reduced function, the return to sport after treatment is an important outcome for athletes. Return to sports is normally not allowed until minimum a year after treatment. Some athletes are able to return to sports without surgery, but not all.[41] Only 7 of 28 patients still performed activity at their preinjury level at final follow-up although many returned to sports. For that study, the average follow-up was 14 years, and a decline in activity profile due to age must also be accounted for. There are mainly 3 different surgical options to consider when treating athletes, whereas a non-surgical approach is the fourth. MF is a technique with good short- to medium-term results but with a clinical deterioration seen after 2 years.[119] Still long-term outcomes are better than baseline.[107;113] Especially the rehabilitation after ACI is long and demanding.[168] OAT seems to lead to a higher rate of return to sports in young and active patients and has a shorter rehabilitation period.[39] Brophy et al. found that players in the National Football League (NFL) undergoing surgical treatment with MF instead of debridement for an FCD had slower return to sports, however biased with regards to lesion size.[169]

Table 4 demonstrates the return rates after different surgical techniques. Good and excellent rating was found in 67% after MF, 82% after ACI and 93% after OAT in a review.[126] The patients treated with OAT had the smallest defect sizes. The return rate to overall sports was 73%, whereas the return to preinjury sport level was 68%. The continuation of sports participation was further explored, and was found to be higher for the patients who underwent ACI.

Table 4. Summary of the return to sports from different surgical techniques.

Technique	*Return to sports*	*Time*	*Comment*
Chondroplasty	67%[170]	8.2 months	Average age 28 years and most lesions 1-2 cm^2. 35% of players had a concomitant MF performed and were less likely to return
MF	44%-77% [34;113;120;142;146;171]	8 +/- 1 months[34]	The study with the lowest return rate had on average larger lesions than the study with the best rate (4.9 cm^2 vs 3.8 cm^2)
ACI	33%-96% [34;128]	18 +/- 4 months[34]	Dependent on lesion size
OATS	91%-93% [106;142]	7 +/- 2 months[34]	Mean size 2 cm^2
MP	63% (90% <30 years and 23% >30 years)[172]	Not specified	26.5 months average follow up

Summarized outcome for surgery, current evidence

The concern that no clinical studies have included a control group of untreated patients was addressed already in 1996 in a critical review by Messner et al.[117] Studies both on the natural development of FCDs and the result from surgery exist. However, the risk of selection bias between these typically small studies is high. The patients in natural history studies are more likely to experience fewer symptoms and constitute smaller lesions. The results are therefore not comparable to clinical studies including surgery. The lack of a control group in an RCT means that we do not know how the outcomes after surgery differ from either natural history or rehabilitation alone. An ongoing multicenter RCT addresses this by comparing both MF and ACI with a non-operatively treated group.[173;174]

The overall results for reparative techniques demonstrate that around 70% of patients improve over a period of 10 years, although histological and radiological findings show varying results with evidence of degenerative changes. The majority of the patients undergoing cartilage repair regain good function and experience less symptoms after 2-5 years.[110;145;175;176] However, several studies find these initial good results to be followed by a clinical deterioration.[34;106;145] The patients reduce their activity level and some do not improve, or even experience worsening of symptoms and a decreased

function.[44;177-179] This deterioration in prognosis is observed also in patients treated non-surgically.

Table 5. Summary of RCTs in cartilage surgery. C-ACI is an ACI technique using a porcine-derived collagen membrane as a cover, whereas p-ACI uses periosteum as a cover.

Article	Size of lesion in mean cm^2 (range)	Interventions	Favorable result	Radiographic OA
Bentley, 2003 [109]	4.7 (1.0-12.0)	ACI (both p- and c-) vs MP	19 months: ACI 10 years: ACI [110]	Did not report radiographic OA
Horas, 2003 [96]	3.9 and 3.6 (3.2-5.6)	p-ACI vs OCT	24 months: OCT	Did not include radiographs at 2-year follow-up
Schneider, 2003 [182]	5.4	ACI vs CaReS	CaReS yields improvement after 30 months. Retrospective matched-pair: no stat sign difference between CaReS and MF	Included radiographs and MRI but did not report results
Knutsen, 2004 [143]	5.1 (ACI) and 4.5 (MF)	p-ACI vs MF	24 months, 5 years: no stat sign difference macroscopically or histologically [40] At 15 years they found a stat insignificant favor of MF[183]	1/3 at 5 years follow up 57% (ACI) and 48% (MF) after 15 years
Visna, 2004 [151]	-	ACI vs abrasive techniques	12 months: ACI	-
Bartlett, 2005 [175]	6.0 and 6.1 (1.0-22)	c-ACI vs MACI	12 months: no stat sign difference	Did not include radiographs
Dozin, 2005 [140]	2.0 and 1.9	p-ACI vs MP	6 months: 1/3 improved after debridement, of the remaining a non-sign favorable result for MP was demonstrated after a mean 10 months	Did not include radiographs
Gudas, 2005 [106]	2.8 (1.0-4.0)	MP vs MF	37.1 months: OAT 10 years: OAT [39]	Defined as K&L $\geq$ 1: 25% (OAT) and 48% (MF) after 10 years

Gooding, 2006 [184]	4.54 (1-12)	p-ACI vs c-ACI	24 months: no stat sign difference	Did not include radiographs
Park, 2008 [185]	5.0	c-ACI vs MACI	24 months: non-sign favorable result for c-ACI	Did not include radiographs
Saris, 2008 [186]	2.6 and 2.4	CCI vs MF	12 months: CCI 5 years: no stat sign difference [108]	Did not include radiographs
Saris, 2014	4.8 (3.0-20)	MACI vs. MF	24 months: MACI	Did not report OA on x-ray, but included MRI
Basad, 2010 [147]	(4-10)	MACI vs MF	24 months: MACI	Did not report OA on x-ray, but included MRI
Zeifang, 2010 [155]	4.1	p-ACI vs c-ACI	24 months: no stat sign difference	Did not report OA on x-ray, but included MRI
Crawford, 2012 [160]	2.9 and 2.5	ACI (Neocart) vs MF	24 months: no stat sign difference	Did not include radiographs
Ulstein, 2013 [187]	2.6 (2.0-5.2) and 3.0 (2.0-6.0)	MF vs OAT/MP	10 years: no stat sign difference	Defined as K&L $\geq$ 2: 17% (OAT) and 45% (MF) after 10 years

Radiographic deterioration after cartilage repair range from 17% to 57% (table 5). We can see these results in the light of the results from a cohort of patients undergoing non-operative treatment and one cohort of meniscectomized patients. In the natural history study by Messner et al., radiographic signs of OA were evident in nearly 60% of the injured knees, whereas radiographic OA in the uninjured knee was evident in 35% of the knees.[41] These numbers are comparable to the highest results reported after cartilage surgery. Nevertheless, some studies exclude "failures" from follow-up in surgical trials, which may lead to biased results. The meniscectomized patients in the study by Rockborn et al. were all <23 years of age at baseline.[180] Nearly 50% of the involved knees showed radiographic changes, whereas only 5 of 43 had similar changes in the opposite knee. The JSN seemed to be higher in patients with cartilage defects when compared to patients undergoing partial meniscectomy with intact cartilage. However, these studies obtained anteroposterior radiographs and did not seem to use the Synaflex frame,

which ensures standardized radiographs. Messner et al. used the Ahlbäck classification which includes standing extension views rather than light flexion.[181]

Several RCTs have been performed, but no gold standard treatment has been established. The included subjects have an average age of approximately 33 years, whereas the average follow-up ranges from 1-5 years.[146;188;189] So far, 3 studies on long-term outcomes >10 years postoperatively have been published. From table 5 we can see that the results from more advanced cartilage surgery varied with overall good results in around 75% of patients. ACI was better than MP in the Bentley-study, whereas MP was better than MF in the Gudas-study and MP and MF had similar outcomes in the Ulstein-study. Knutsen et al. demonstrated satisfactory results in 77% without differences between ACI and MF after 5 years,[40] and a statistically insignificant difference in favor of MF after 15 years.[183] In general, small lesions have best results with OAT or MF, whereas intermediate and larger lesions seem to have best results from ACI.

Several factors must however be accounted for and the treatment should consequently be individualized. Subgroups of patients with superior results are documented, and some advocates for a more precise patient selection in order to achieve better outcomes.[190] As FCDs represent a wide spectrum of both lesions and patients, we do not expect one single treatment approach to fit all, there is a need for an individualized treatment or a detailed algorithm based upon identified prognostic factors. The current assumption is that some patients should be treated non-surgically and some should be treated surgically. Differences may be due to different healing response in different locations of the knee, but it implies an issue that is important to explore: Whether non-operative treatment is better for some lesions. The key is to identify who belongs to which treatment arm.

Challenges with knee cartilage research

Improved research methodology within orthopedic surgery in general and cartilage studies specifically is requested.[191] RCTs are the research method of choice when determining efficacy of an intervention. The results from these studies are important clinical tools when deciding treatment for patients. In order to maintain high quality, and thereby minimize the risk of bias, the studies must be carefully designed and thoroughly planned. Over the past decades, the focus of methodological quality has increased and we now have guidelines for designing and running RCTs.

Table 5. Summarizes methodological issues.

Main problems with evidence	*How to address*
Low methodology level Low quality	Follow CONSORT, or the checklist to evaluate a report of non-pharmacological trial (CLEAR NPT)[200]
Heterogeneous population	Assess all relevant prognostic factors
Low external validity	Wider inclusion criteria
Different outcomes	Standardized outcomes
Presents biased results	Study external validity and heterogeneity of patient population
Lack of histology and second-look evaluations due to invasiveness Still questionable accuracy between arthroscopy and MRI Many different techniques with no planned research field	Develop reliable biomarkers
Lack of non-surgical control group	Is included in an ongoing clinical study (the Norwegian Cartilage Project study)
Short-term follow-up Large loss to follow-up	More long-term follow-up studies are coming
Retrospective chart reviews	Learn clinicians what tools to use and what information that should be filed

An editorial stated that only 20% of procedures in orthopedics are supported by a low-risk-of-bias RCT.[192] Lim et al. found that 37% of the total volume of procedures performed over a period of 3 years was supported by evidence from at least one RCT.[191] The result from too few RCTs is that many orthopedic procedures are never tested in a controlled study. The amount of procedures supported by RCTs is generally higher for treatment in pharmacology and internal medicine,[193] and reflects that most of the factors that are being evaluated when assessing the quality of an RCT are factors that are easier to maintain with a non-surgical intervention. This is demonstrated by the generally lower methodological quality of cartilage repair studies, as in 3

studies from 2005, 2011 and 2013.[142;194;195] They concluded that the quality is poor when measured with Coleman Methodology Score (CMS), although it was a bit higher in the later studies (58 and 50.4 versus 43.5). Benthien et al.[195] found that studies including MF had a higher CMS than studies including other techniques.

A study performed by Worthen et al. found 9 major limitations and 7 common biases when reviewing RCTs in cartilage repair.[196] They suggested more rigorous research for the future in order to minimize common biases. Their suggestions included strict study designs and patient selection criteria, larger patient enrollment, more extended follow-up and standardized clinical treatment pathways. The checklist for maintaining high internal validity in an RCT contains several factors that are to be addressed in all clinical intervention trials.[197;198] Previous methodological issues in clinical studies within the orthopedic field are addressed in table 6 and summarized according to a systematic review of outcome after surgery for chronic Achilles tendinopathy.[199] Suggestions on how to meet the challenges are listed in the same table. The review presented an inverse and linear relationship between CMS and reported success rate.[199] It is a particular problem that studies with poor methodology report higher success rates and vice versa.

Surgical RCTs are challenged with blinding of patients, whereas double-blinding is impossible when a surgical intervention is involved. The placebo effect of surgery challenges results and there is a lack of standardization among different surgeons. Treatment is difficult to standardize, as surgery is largely dependent on human factors, as is the rehabilitation that often differs with type of injury, activity level of patients and treatment modality.[128] There are some additional challenges with the particular patient population with FCDs of the knee that lead to limitations for RCTs in cartilage surgery.

- An FCD may be considered a softer parameter than other orthopedic conditions, such as fractures or total ligament ruptures. A specific defect may seem focal to one orthopedic surgeon while diffuse or just degenerative by others. Nevertheless, FCDs within the knee joint seem to play a large part of the clinical picture when evident, and we need to standardize the evaluation of FCDs.
- As there is no gold standard, there are likely to be geographic variations in treatment, rehabilitation and outcome measures.

- The population of patients is heterogeneous, with different number, size, localization and pathogenesis (acute, chronic or OCD) of the defects. This challenges the external validity.
- The heterogeneous population also influences the inclusion rate when strict inclusion criteria exist. There is a risk of selection bias by removal either of the healthiest, or in the worst case, the sickest patients. If the latter happens, the treatment might be over-rated and thereby applied to a patient population that the particular treatment method was never really tested on.
- Several RCTs exist, however none with a non-operatively treated control group. A non-surgical treatment or sham surgery is difficult to compare with actual surgery in an RCT due to patient preference.[201] Also, some studies compare ACI with MF, which complicates the results as these two methods have different indications concerning the size of the defect. MF is indicated for smaller lesions. MF for larger lesions is thereby bound to have a lower outcome than ACI for the same specter of lesions, and vice versa.
- Long-time follow-up is challenging and many patients undergo several surgical procedures, which further complicates the results. Most clinical studies have short to mid-term follow-up, whereas much longer follow-up, meaning 15-20 years, is required for this patient group. We need long-term follow-ups in order to find prognostic factors for OA. Reliable biomarkers for early OA will secure the identification of detecting patients at increased risk of OA.
- There are no existing systematic data collection because of multiple and fragmented research environments.

External validity

The strict inclusion criteria decrease the number of patients eligible for inclusion. The recruitment process is also restricted by that some patients decline inclusion in research projects. However, more patients decline participation due to unwillingness of undergoing surgery than due to unwillingness of undergoing non-operative treatment.[201] Frobell et al. found that the *a priori sample size calculation* must be multiplied by at least 5.5 in order to estimate the number needed to screen (NNS).[202] This means that the patient pool must be much larger than expected from the sample size calculation. Other examples of low patient inclusion are described. [196] With low

external validity the applicability of the results is reduced and the actual effectiveness of treatment methods in the general patient population remains unknown, no matter how many RCTs are performed.

RCTs and prospective cohort studies

Salomon and McLeod reviewed the literature and determined that 39% of clinical research questions could have been answered by an RCT under given perfect clinical research settings, and that only 3% of research questions regarding surgery against a nonsurgical intervention could have been answered by an RCT.[201] RCTs are considered the gold standard in finding the effect of an intervention, although prospective cohort studies are considered better with research questions about prognosis (table 7).

Table 6 is adapted from a hierarchy table published by the National Health and Medical Research Council in Australia. It displays level of evidence based upon type of research question, here represented by questions on intervention and prognosis.

Level	*Intervention*	*Prognosis*
I	A systematic review of level II studies	A systematic review of level II studies
II	An RCT	A prospective cohort study
III-1	A pseudorandomized controlled trial	
III-2	A comparative study with concurrent controls - non-randomized experimental study, cohort study, case control study	Analysis of prognostic factors amongst persons in a single arm of an RCT
III-3	A comparative study without concurrent controls - historic controls	A retrospective cohort study
IV	Case-series	Case-series

The efficacy of an intervention is studied in an RCT, but its effectiveness can never be assessed in a controlled clinical study.[203] A register makes it possible to find the effectiveness of treatments. Prospective cohort studies with high quality might complement and complete research gaps. It is not possible to conclude on the best treatment through a register, but the hypothesis might be more focused and the design of RCTs may then be better. We are lacking

real-life clinical data as the current RCTs are performed under controlled conditions. The limitations of both RCTs and the limitations of retrospective analyses make it important to initiate more clinical effectiveness research. A register may be a useful supplement in this.

Criteria for a successful register

Certain factors for success are identified in the literature and from the experience from other orthopedic registers. These should be considered prior to establishing a register. Completeness and validity of the data are crucial for a register. If not, reliable analyses cannot be performed. A successful register:

- provides information
- motivates for change
- initiates change

Resistance to change is a well-known obstacle in an already busy clinical day. The motivation for change must be high among the participants, meaning both the orthopedic surgeons and the patients. The change must not be too difficult or time-consuming, as this will outbalance the motivational strength. The registration process must be as easy as possible and all persons involved must be informed thoroughly. There are already other orthopedic registers, although none yielding information on isolated FCDs. The implementation process should proceed slowly, not overwhelming an already busy clinic. These aspects, together with the challenges with research within this field, make it necessary to perform a pilot register. A pilot will explore benefits and challenges with a cartilage surgery register, and also clarify whether it is room for another orthopedic register in the clinic and how such a register should be established and organized.

Research gap

The main gaps in research addressed in this thesis are the epidemiologic data on cartilage surgery in Norway and the expected geographic variations and low generalizability of current RCTs. All are important arguments for a register. We also investigate the long-term effect of an FCD and the role of an upcoming biomarker of early OA for a further study of the natural history and "risk" of a non-operative approach. The prognostic factors for individualized treatment are explored in relation to this biomarker. All these gaps can be

further evaluated in a cartilage surgery register, and we discuss the results from a pilot study of a cartilage surgery register.

Aims of the study

The main goal is to contribute to an improvement in, and a quality control of, the treatment of patients with FCDs of the knee. The aim of this PhD-project is to explore whether a quality register in cartilage surgery of the knee should be established. Specific aims are:

1. Establish epidemiological data on cartilage surgery in Norway.
    a. What is the incidence of cartilage surgery in Norway?
    b. Are there geographical differences in incidence and treatment trends?
2. Find the external validity of RCTs in cartilage surgery
3. Explore the effect of an FCD in developing secondary early OA of the knee within 12 years after diagnosis.
    a. Is dGEMRIC a useful biomarker?
4. Explore logistic challenges and whether it is possible to establish a cartilage surgery register in Norway

Methods

Paper I: Cartilage defects are commonly encountered during knee arthroscopy, and in Norway all surgeries are registered in the National Patient Register (NPR). In this project we wanted to find the burden of the disease. Within this field it is challenging to identify non-operated patients. We aimed to find the incidence of patients with FCDs undergoing various forms of surgery. We looked into a large national electronic database which constitutes all data on activity from the specialist health service in Norway. To be paid for surgeries, all hospitals, public and private, are obliged to report their activity to this database. We could therefore identify patients with FCDs undergoing knee surgery based on specific diagnostic and procedural codes to estimate the size of a potential future cartilage surgery register. We also explored geographical differences and trends of cartilage surgery.

Paper II: The generalizability of RCTs has been addressed in other fields of medicine and pharmacology. Performing RCTs in the surgical field is challenging. Particularly patient inclusion, placebo from surgery,

standardization of treatment, and blinding of patients are challenging. We wanted to examine to what degree the results from RCTs in cartilage repair are applicable to a clinical setting. If the external validity is low, results from RCTs have limited relevance for most of these patients, and we must consider alternative ways of obtaining knowledge. We assessed the inclusion criteria from existing RCTs and looked at the potential inclusion rate from a non-biased group of patients with FCDs considered for surgery.

Paper III: The outcome of non-surgical treatment is not well described in the literature and the natural history of FCDs remains unresolved. Some clinical studies have found similar results in untreated patients as in patients treated with cartilage surgery. An early biomarker is important for the identification of patients at increased risk of knee OA after an FCD. We identified a cohort of patients with previously diagnosed FCDs, treated both non-surgically and surgically. These subjects were evaluated with dGEMRIC as a biomarker for early OA. We also included T2 mapping, K&L knee radiographs and PROMs.

Paper IV - Pilot register: Prior to conclude on benefits and challenges of a register, we wanted to run a pilot register. Two hospitals included patients with an FCD of the knee detected during knee surgery. The lesions were isolated or in combination with other injuries or diseases. The pilot aimed to describe the patient population and identify logistic challenges and to assess the compliance of a cartilage surgery register. The compliance was tested to ensure complete data of a potential future register.

Summary of results

Paper I

Cartilage surgery is common in Norway as we identified around 2,500 yearly incidences of cartilage surgery. The national age-adjusted incidence rate is 56 per 100,000 inhabitants. The incidences vary between regions and a large part of the procedures are performed in private institutions. Advanced cartilage surgery is uncommon with 400 yearly procedures in Norway.

Paper II

Only 6 of the 137 eligible patients matched all the inclusion criteria in the RCTs on cartilage surgery. This represents 4% of the patient population, which means that results from RCTs are not easily generalized to patients seen in

the clinic. After excluding the most restricting article, 20% would have been eligible for inclusion in the remaining RCTs.[40;109;140;162;175;184;186]

Paper III

Surprisingly few subjects developed degenerative changes in their knees measured with dGEMRIC. We detected no difference in cartilage quality between injured and non-injured knee 12 years after diagnosis. There was no detectable difference between subgroups of patients concerning baseline size, degree or meniscal resection or between surgical and non-operative treatment. Still, radiographic degenerative changes were present.

Pilot register

We ran 2 pilot studies. The first was carried out in 2010 whereas the second is currently ongoing. The compliance varies from 18% to 73%. The inclusion mainly relies on a few orthopedic surgeons. We have encountered some logistical challenges, but believe that it is possible to increase the compliance.

Methodological considerations

Study cohort and inclusion process

Paper I

We collected the data through the NPR and the patient pool is thereby all citizens in Norway. Inclusion criteria were set to all patients undergoing cartilage surgery of the knee during 2008-11.

Paper II

The common inclusion criteria of the identified RCTs were matched to a population of patients with FCDs of the knee. All patients referred to an orthopedic clinic within a specific year with suspected symptomatic FCDs were examined and evaluated by an experienced cartilage orthopedic surgeon. If they were candidates for surgery, they were also eligible for enrolment. The patients were referred from either a primary health service or secondary health service, such as orthopedic departments in other hospitals.

Paper III

We identified a cohort of patients with previously diagnosed FCDs, treated both non-surgically and surgically from 2 previous clinical studies. The first paper contains data on 993 patients undergoing knee arthroscopy due to knee pain in 1999.[2] Patients with an ICRS score grade 3-4 FCD, classified as not having knee OA and with age <50 years at baseline were reexamined after 6 years.[204] In the present 12-year follow-up we invited patients with full-thickness FCDs and age <50 years at baseline, no total knee ligament injury and more than 50% of their lateral and/or medial meniscus intact. A cohort of patients previously included in an RCT on cartilage repair[143] was also invited to participate in the study. In total, 42 patients were eligible for inclusion and 21 signed a written consent. 10 patients were treated with either MF or ACI at baseline, 11 patients had not undergone cartilage repair, neither at baseline nor later, whereas 3 patients from the latter group had debridement performed at baseline.

Pilot register

We aimed to include all isolated FCDs. If additional FCDs or degenerative changes were present in other compartments, we still included these patients. If they had reached a state of OA they were excluded as they had reached the end-stage disease. 2 hospitals recruited patients over a 6-8 months period in 2010 for the first pilot. During the second, and still ongoing, pilot we expanded

Inclusion criteria

- Diagnosed focal cartilage defect (ICRS grade 1-4) during arthroscopy or open surgery
- Operations/ reoperations in patients with a known FCD
- Age 12-67 years

Exclusion criteria

- Generalized knee OA
- Other systemic diseases with a known increased risk of knee OA, such as rheumatoid arthritis

Figure 5. The inclusion and exclusion criteria in pilot 2.

to 5 including hospitals. The patient pool is thereby restricted to the geographic

areas that these hospitals serve, although a few patients are referred from other geographic areas. The inclusion and exclusion criteria of pilot 2 are outlined in figure 5.

Through a register where the inclusion criteria is an FCD, we are able to register patients with isolated FCDs and exclude patients with knee OA. As opposed to the existing electronic registers that rely on registration from the International Classification of Diseases 10th edition (ICD-10) codes, the registration is then more robust against over-registration. Duplicates are easily noticed based on personal data and operation date. The data from a register is easily and quickly accessible. The database contains a much bigger pool of patients with increasing opportunities of detecting poor outcomes, correlations and prognostic factors that are not possible to find in strictly controlled studies.

The entire patient cohort must be registered to avoid selection bias. When analyzing the patients that did not match the RCT inclusion criteria in paper 2, we found that a few did not match due to age, localization of lesions or the occurrence of several lesions. Most patients did not fit due to the size of the lesions. In addition, 42 patients were excluded due to 2 non-matching factors, 21 due to 3 non-matching factors and 4 due to no matching factors. The eligibility rate to the various RCTs ranged from 7%-80%, and this variance seemed to be mainly influenced by size of the lesions. Three articles had a much higher eligibility rate[109;175;184] and one had a much lower rate.[96] Due to this, we include all lesions that are encountered as an FCD in the pilot cartilage surgery register with no restriction or exclusion due to size of the defect. Inclusion is dependent on the clinical decision done by the orthopedic surgeon. We believe that this is the best way of including all clinically relevant FCDs. Variations may still occur but by removing size as a limiting factor, clinically relevant inclusion is much more attainable. A broad and standardized data collection on all possible relevant factors is necessary for answering questions regarding prognostic factors as is exact descriptions of localization, depth and size of the FCDs.

Wide inclusion leads to an unbiased and general population of patients with FCDs eligible for surgery. It is important to include all levels of care, not only University Hospitals. Roughly, 45% of the included patients had experienced either previous cartilage repair or ACL reconstruction. If we see more "worst cases", there might exist a bias between the patient population seen at University hospitals and the population seen at local hospitals. This may have happened in the inclusion to paper II and led to a lower eligibility rate. The German Registry does not register patients treated with simple debridement, other palliating techniques or where a non-surgical approach is applied.[124;205]

In that sense, our design is a more complete register for all patients with FCDs within the knee treated in the specialist health service.

Other registers

The easiest way of collecting the data would have been through one of the already existing registers. There are several national registers holding clinical data from the health system in Norway. Successful orthopedic registers are established in several countries for joint replacement surgery (Norway-1987, Sweden-1975, Finland-1980, Denmark-1995, Australia-1998) and knee ligament surgery (Norway-2004, Sweden-2005 and Denmark-2005). Success means high quality of the register and that useful information is achieved with high compliance of registration. All Norwegian citizens have a personal identification number which is registered when they are treated in both private and public health care. The patients can therefore be followed if they migrate or are treated later at another hospital. The NPR contains general information on treatment and admittances in the specialist health service.

The Norwegian Knee Ligament Register (NKLR) also registers cartilage defects, but only when the patient undergoes an ACL-reconstruction. The Norwegian Prosthesis Register collects data on patients undergoing prosthesis surgery, meaning that patients are already at the hard end point of a cartilage surgery register. There are certain individual cartilage surgery registers initiated by the industry and by individual orthopedic surgeons.[131] Industrial registers tend to include more advanced cartilage surgery than what is common trends in general.[206] Data from one of the recently established registers, the German Cartilage Registry, is available.[124;205] There are currently no existing register for a systematic data collection of patients with isolated FCDs diagnosed during knee surgery in Norway.

Validation of databases

We used data from the NPR in paper I and we performed a pilot of a paper-based cartilage surgery register. The NPR was established to contribute to epidemiological research. Data from electronic databases are both under- and overestimated when compared to a gold standard.[207;208] The results from a validation study of arthroscopic codes for cartilage injuries of the knee from public hospitals in Denmark was published in 2014.[209] The study assessed the validity using surgical descriptions in the medical records as gold standard and found the positive and negative predictive value to be 88% and 99%,

respectively.[209] The same validation study for cartilage injuries and cartilage surgery has not been performed with our national database. We could have included a validation of the NPR for these diagnoses in paper I. However, the aim of this study was an evaluation of the extent of the problem. The Danish NPR is based on the same coding systems for registration of activity and we thereby have a reasonable estimate on the validity of a national electronic database that uses these coding systems.

We also used data from the NKLR to avoid double-registration of patients with FCDs in addition to undergoing ACL-reconstruction. The completeness of the NKLR was 97% 21 months after establishment.[210] The 2 year results were decreasing, with lower rates for smaller hospitals.[211] They are now introducing electronic registration, and hopefully this will lead to a rise in compliance.

We collected data from the NPR on cartilage surgery using a combination of diagnostic and procedural codes derived from the NPR when performing paper I. Extracting data on this patient population is challenging as the registration to the NPR is based on ICD-10 and Nomesco Classification of Surgical Procedures (NCSP) codes that are too unspecific for identifying an FCD properly. The ICD-10 codes available for diagnosing FCDs do not reflect the complexity of these lesions. Although the ICD-10 contains both “acute FCD” (S83.3) and several codes for knee cartilage pathology, there are no codes for the common “non-acute FCD”, which might be subacute or chronic. The clinically important non-acute FCD is therefore difficult to identify. The ICD-10 system also does not allow for a proper identification of the specific factors of a defect, such as size, localization or depth. The different cartilage surgery techniques is neither clearly outlined nor organized within the NCSP coding system. The data on procedures is thereby also unspecific.

Many orthopedic surgeons tend to learn a few codes and then apply these when appropriate, leaving the activity somewhat unspecific at times. Our predefined codes matched with 92% of the reported diagnostic codes from members of the Norwegian Arthroscopic Association. However, the response rate was only 13%. The low response rate has limited effect on our final numbers since we have included most of the possible codes from the ICD-10 system. Many reported the use of M17 (knee OA) also for FCDs, and we included participants with M17-codes when these were coded together with procedures encountered as cartilage surgery. We excluded patients with knee OA by excluding participants without a concomitant procedural code. This may have led to both "false positive" included subjects and to an underestimation. We did not include the ICD-10 code M25.5 which codes for "pain in the knee joint", which may have led to an underestimation. These challenges co-exist

with the fact that some orthopedic surgeons might not code for FCDs at all if other intraarticular pathology is recognized. The existing data may be useful for the purpose of reports on knee cartilage injuries in total, but it is challenging to differentiate between injuries caused by trauma or degeneration.

We believe that *procedural* codes are reported in more detail than simply diagnostic codes as they are the basis for 60% of the government reimbursement to hospitals in Norway, and as such are reviewed several times by hospital controllers to ensure correct coding. However, all the uncertainties encountered about the diagnostic and procedural codes, make this an unreliable source for precise data on patients with FCDs. Additionally the NPR does not contain any form of outcomes or endpoints for this patient group. For paper I, we were mainly interested in the *burden* of cartilage surgery. We found that NPR was appropriate as a data source for estimating the burden of this particular disease on the specialist health service in Norway, using a combination of diagnostic and procedural codes. Overall, the Norwegian NPR is not suitable for obtaining precise data on patients with FCDs.

Pilot register

The patient records or surgical protocols are considered gold standard when it comes to valid data. However, large administrative databases allow for a more efficient data-collection, within its limitations, and may therefore be preferable when it comes to large amounts of data. It is still critical that the data are valid. High compliance is necessary to justify the establishment of a cartilage surgery register and is therefore main outcome of the pilot. Low compliance rate might lead to selection bias, and it is difficult to predict the direction of the bias. Maintaining high compliance and including all patients is therefore both a challenge and a necessity for any register.

As the compliance was low for the first pilot, the objective was to include even broader in the second pilot so that more patients were eligible and the inclusion of a patient occurred more frequently. We expected this to cause the registration process to be implemented in everyday clinical practice, leading to increased compliance. We calculated the compliance of the pilot register by going through the surgical protocols in each hospital. We identified all patients who matched the inclusion criteria based on the surgical descriptions from the operations during the inclusion period and matched those numbers with the records from the registration.

Outcomes

Several outcomes for the evaluation of patients FCDs may be considered whereas the most objective and standardized as of today is the development of knee OA, and TKR. Measures for current symptoms and function should be included, especially in short- and medium-term follow-up. Knee OA as an endpoint, both as a clinical and a radiological diagnosis, requires long-term follow-up and biomarkers for early OA may simplify the follow-up of patients where OA is a relevant outcome. These should be identified and developed. We included both objective and subjective outcomes (PROMs) in paper II, paper III and the pilot register (table 8).

Radiological outcomes

The assessment of the articular cartilage, both after non-surgically treated FCDs and after cartilage repair surgery, depends on high-resolution images. As changes in the cartilage structure occur without morphological changes, we also need techniques that assess the cartilage content. In the search of a biomarker of early OA, dGEMRIC seems promising. In paper III we performed a 12-year follow-up of patients with previously diagnosed FCDs on arthroscopy. We included dGEMRIC, T2 mapping of the injured knee and x-ray of both knees for the evaluation of knee OA according to K&L protocol. Protocols for dGEMRIC are established,[212;213] and the images were obtained correspondingly to standardized protocols. The dGEMRIC includes intravenous administration of gadolinium, which is bound to a chelate complex as gadopentetate dimeglumine (Gd-DTPA^{2-}), and a delayed image-acquisition. The delayed image-acquisition allows the contrast to penetrate the cartilage. Gd-DTPA^{2-} shortens T1 relaxation time in proportion to its concentration. T1 relaxation time measurements provides an inversely correlation to the contrast concentration whereas the contrast accumulates in an inverse relationship with [GAG].[84] The T1-values are transformed into the dGEMRIC index which again reflects the [GAG] throughout the cartilage.[212] A nearly linear relationship between dGEMRIC index and [GAG] in cartilage is seen.[86] A high dGEMRIC index means high [GAG] and good quality.

$$\text{dGEMRIC index} = [\text{Gd-DTPA}^{2-}] = (1/T1_{Gd} - 1/T1_{pre})/r1$$

$$r1 = 4.1\ s^{-1}\ mM^{-1}$$

Figure 6 outlines the calculation of the dGEMRIC index. Adapted from Hawezi et al[1]

The best distribution of the agent is achieved when the patient exercises prior to imaging.[212] The patients walked in stairs for 15 minutes immediately after contrast injection. Post-contrast images were taken 90 minutes after contrast

injection.[84;212;213] For the T1 imaging, a sagittal slice was oriented centrally on the MFC and the LFC. The T1 weighted images were transferred into color-coded T1 maps. The color blue represented areas absent of GAG, whereas red represents high levels of GAG. Originally, both pre- and post-contrast T1 were required to calculate delta R1 and depicting proteoglycan content. Previous studies looking at the difference between T1(Gd) and delta R1 found a high correlation between these in native cartilage.[214] The T1 of unenhanced native articular cartilage is also demonstrated to be constant, which implies that only post-contrast images are necessary.[212] However, the T1 after cartilage surgery changes[88] and only the delta R1 correlates with [GAG].[215] For imaging after cartilage repair, pre-contrast images is recommended in addition to post-contrast images, as the values for native cartilage are lower than values of repair cartilage.[215] The study cohort consists of both non-operated and operated patients, and we included both pre- and post-contrast images.

Outcome for paper II

We explored the generalizability of RCTs on the general population of patients with FCDs, meaning the external validity, in paper II. We measured the potential inclusion rate from an unselected cohort into RCTs on cartilage surgery. We performed a standardized literature search and identified 10 RCTs based on 8 different patient populations.[40;96;106;109;140;143;162;175;184;186] We failed to include Park 2008 (ACI vs MACI), Schneider 2003 (traditional ACI vs CaReS) and Visna 2004 (ACI vs abrasive techniques) in our article.[151;185;216] The article by Schneider et al. is however not available in the English language, but they have published an available case series on the same interventions in English.[182] A few more RCTs have since been published, two articles compare MACI with MF[147;217] and one article compares p-ACI vs c-ACI.[155] A systematic review with ACI as one of the interventions was published in 2011.[126]

All of the RCTs were evaluated according to the PRISMA-statement.[218] The common inclusion criteria from these studies served as a general description of the patient population that the results can be generalized to. These common inclusion criteria were matched to a population of patients with FCDs of the knee. The outcome was the eligibility rate for inclusion as a measure for external validity.

Patient reported outcomes

Validated outcome scores are essential for evaluating the progression of disease, after treatment and in long-term follow-up in clinical studies. The IKDC and KOOS are recommended for cartilage injuries as they have adequate reliability, validity and responsiveness in patients with pathology in the knee articular cartilage and after cartilage repair.[126;219] The subjective PROMs included in each study are outlined in table 8. The Lysholm Score[220] is commonly used to assess knee problems, it is validated,[221] it can be completed by the patients themselves,[222;223] and it quickly provides a good overview of knee symptoms presented in the outpatient clinic. The Lysholm Score, IKDC and KOOS maintain a close correlation in evaluating knees with cartilage defects.[224]

The KOOS score is validated for both cartilage injuries[225] and after cartilage repair,[226] and has acceptable test-retest reliability.[226;227] It consists of 42 items over 5 subscales; pain, symptoms, activity of daily living (ADL), sports and recreation and quality of Life (QoL). Each subscale is reported individually with a score ranging from 0–100, 100 being the best. Reference values for the general population exist.[228]

The Tegner activity score[229] is determined by the most demanding activity the patient is able to perform. The score ranges from 0–10, 0 being absent from work due to knee function and 10 being individuals competing on high-level in pivoting sports. The average Tegner score from normative data is 5.7.[230] Results from clinical trials are within the range of the normative data, however the patients included in clinical trials are often active at baseline.[145] There are other standardized outcome scores for assessing activity profile, for instance the Marx activity rating scale.[231] This scale emphasizes sports with increased knee joint impact, such as pivoting, and sports with frequent acceleration and deceleration. Patients with FCDs have a bimodal distribution of the activity level, and the Tegner thereby seemed more appropriate as it also includes subjects with very low activity.

Table 7. The included PROMs of paper II, paper II and the pilot register.

	Lysholm	Tegner	KOOS
Paper II	X		
Paper III	X	X	X
Pilot register		X	X

We included only the KOOS and Tegner in the pilot register in order to keep the data collection simple and short for patients. We chose KOOS over Lysholm because the NKLR include only KOOS, and we planned to include patients with combined injuries from the NKLR. Data can be pooled and all included patients are evaluated with the same subjective outcome measures.

Outcomes for the pilot register

Compliance of the database was discussed in the validation-section. The raw data must also be valid and reliable. Validity is defined as the ability to obtain all intended information that is clinically relevant for this group. The lesions are classified by location, size, depth and most likely pathogenesis. We also record any previous knee surgery and previous or additional injuries or surgery, if present. The validity of the cartilage form was assessed through an evaluation of all the different points of data collection throughout the form. This was done in collaboration with orthopedic surgeons from the participating hospitals. We developed the cartilage surgery form with the NKLR-form as a framework, but with focus on FCDs rather than ACL-injuries. We updated the form prior to the second pilot after a thorough discussion with the participating orthopedic surgeons. The goal was to obtain all relevant data, while maintaining a simple and minimally time-consuming form. The questions are arranged in a logic and chronological order to keep the scheme *flowing*, allowing for an easy and quick response.

The reliability of the cartilage form is an important issue, where a central aspect is the reliability of the specific data describing the lesions. The size is measured using a specific caliper and the localization is reported due to the anatomical location within the knee joint. An ongoing project is testing the reliability of the ICRS-grading (Kjennvold, unpublished). The PROMs and their reliability were discussed under the PROMs section. In addition to the soft end-points, end-stage OA (by arthroscopy, MRI or K&L-grading) will serve as a hard end-point. The hard endpoints for the NKLR and the National Prosthesis Registry are revision surgery and TKR. Many cartilage patients undergoes several surgical procedures, nearly 40% as detected in paper 2.[232] Revision surgery is therefore not a suitable hard endpoint for cartilage endpoint, and revision surgery will not lead to exclusion from the pilot register.

Design and methods – pilot register

The pilot register is designed as a prospective cohort. It is designed similar to the potential future cartilage surgery register. The patients will be followed at 5 and 10 years. We conducted two pilot studies throughout this project to make sure that the collection procedures are standardized and that the data is of high quality. The first pilot was carried out at two hospitals in the Southeast region of Norway. The logistics were kept simple and transparent so that one person could keep an overview of the paper-based data collection. Based on the results from pilot 1, we found it necessary to conduct another pilot to allow for adjustments of the form and the data collection. Pilot 2 is still running with planned inclusion until the end of 2017. Pilot 2 includes 3 hospitals in the western region and 2 hospitals in the Southeastern region. All 5 hospitals participate in a multicenter study, The Norwegian Cartilage Project. 2 hospitals started registration (OUS and Ahus) from 15 February 2015 whereas we expanded to 5 hospitals (Haukeland, Ålesund and Kristiansund) from March 2016. The registration period is elongated to minimum 2 years, and will provide more time for the cartilage surgery register to be established in each department.

By including a large amount of patients with wide, however still precise, inclusion criteria, and a standardized follow-up, the internal validity is prevailed. We then minimize systematic errors and selection biases and maintain a high quality trial design. We can account for the loss of randomization by controlling the prospective data collection, using objective outcome measures and stratified analyses. As long as there is a clinical equipoise regarding the treatment, this should be used as a tool for bringing the field forward.

Statistical considerations

Paper I

Numbers were extracted from a mandatory national electronic database where all activity in the specialist health service, including all public and most private hospitals, is reported. We defined cartilage surgery based on specific ICD-10 and NCSP codes. For the analyses, the patients were stratified based on year of surgery, geographical location, age and gender. Incidences are given per 100,000 person years. Age-adjusted incidences were also calculated based on population data from SSB. We used the chi square test to determine significance of distributions between the stratifications. The difference between years and geographical location was examined with RR and OR and 95%

confidence intervals (CI). Significance for all analyses was set to a p-value less than 0.05.

Paper II

We examined the proportion of patients seen in the clinic eligible for inclusion in RCTs. During the year of 2008, our clinic received 147 patients referred for cartilage surgery, whereas 10 were excluded. We thereby included more patients than each of the 8 RCTs, where Saris et al. included the most (n=118) and Horas et al. the least (n=40).[96;186] We therefore believe that we have included sufficient cartilage patients to answer our study hypothesis. A power analysis was performed to match the characteristics of included patients with the same characteristics from the RCTs. This resulted in a minimum of 101 included patients in this study. Continuously reported variables are presented as means with standard deviations and comparisons were tested by the Students unpaired t-test. Dichotomous variables are reported as frequency counts and percentages with comparisons performed by using the Fisher exact test. All tests were 2-sided with a significance level of $p < 0.05$.

Paper III

Both the single measurements from each regional of interest (ROI) and the average dGEMRIC index (values from several ROIs pooled together) from each condyle and for each knee were used for analyses. As the dGEMRIC measures had a normal distribution, we performed t-tests as initial analyses to explore any differences within, or between, the knees. Although the power was too low, we believed this was necessary to identify any potential large differences. We know from previous studies that these analyses have great variance, both between subjects and within the knee joint.[233;234] We considered a difference >100 ms to be clinically relevant.[235] As these measures are repeated, the variance is reduced. Using the contralateral knee as a control also decreases the number of patients needed. Significant age differences between subgroups for evaluation of potential bias were tested with the analysis of variance while sex differences were tested with Fisher exact test between the groups.

As we aimed at recruiting all eligible patients from a previous cohort, power analyses were not crucial for the inclusion process. Nevertheless, we examined the power with a one sided test with $1-\beta=0.80$, $\alpha=0.05$, mean value in population 410ms, and mean value in study group on 460ms and SD=80, the needed sample size was 20. The SD from the analyses in the paper varied from around 30 to over 200. The power calculations are based on an SD of 80.

The T2 mean values of each region were analyzed with the same tests as the dGEMRIC results. We used an independent t-test instead of a paired t-test when comparing injured condyle with corresponding condyle. Pearson correlation was used to test associations between injured and corresponding condyle. Possibly, a more adequate statistical method could have been to do repeated measures ANOVA of the means of median T2 values for each subregion. However, we demonstrated a near bell-shaped curve when all T2 values were pooled together indicating that a parametric test was appropriate. Although that shape disappeared for each of the 6 individual subregion. In the presence of statistically significant differences, these would have been further explored with non-parametric tests.

Paper IV

Power analysis were not applied as this is not an intervention study. Descriptive data are presented as means and standard deviations or as medians and interquartile ranges for continuous variables. Frequencies and percentages are used for summary of categorical variables. Linear or logistic regression analysis will be applied through univariable regression modelling for each outcome, to examine the time from symptoms to diagnosis and operation to identify to possible prognostic factors.

General discussion

Unstandardized treatment of FCDs in Norway

The Norwegian health care system is public and tax-funded which balances out possible geographic and socioeconomic differences. All patients should be provided the best level or care and it is therefore important to perform surgery on correct indications, with the appropriate techniques and with the correct rehabilitation programs. Until the best treatment for all patients is resolved there is a natural consequence that indications for surgery are made upon the preferences of the patient and the orthopedic surgeon, which may lead to unstandardized and variations in treatment.

Cartilage surgery is as common as ACL-reconstructions with 2,500 yearly procedures (paper I). Two studies on incidence rates were published prior to our study, both based on the same private-payer database in the United States.[138;206] They presented a large variation in their results with a yearly incidence ranging from 1.4 incidents per 100,000 inhabitants till 104

incidents/100,000. In 2014 Mor et al. found the incidence of arthroscopy-documented cartilage injuries within the knee in Denmark to be 40/100,000 person-years.[209] These numbers are in line with our findings. As suspected, we found varying incidence, both between different geographic areas and among the different age groups. We found a 30-fold difference in incidence between the counties with the lowest and highest incidence rate. There was also a high incidence for the oldest age group except from in the North region, which treated fewer older patients. This is in line with the clinical evidence that older patients benefit less from this type of surgery. For patients >65 years of age, the surgical technique was mainly debridement. Transplantation techniques seemed to be reserved for younger patients, which is in line with the literature were an upper age limit of 40 is suggested.[98]

There are private hospitals in Norway, in addition to the free public health care system mainly provided by public hospitals. Some private hospitals have reimbursement agreements for specific conditions, while some patients have private insurances or are paying out-of-pocket. There is a difference between private and public health care, as some ambulatory surgery centers in the USA have twice as high surgery rates as outpatient surgery in public hospitals. Public hospitals in Norway are paid per service, although the activity-related finances do not affect the individual surgeon`s income. The financial incentives for private and public hospitals might therefore differ. A Danish study[236] demonstrated an all over increase in meniscal procedures, although a larger increase in the private sector.

Several factors may explain these observed variations. The Danish study also found large regional differences in treatment of meniscal lesions.[236] These differences could not be explained by either different activity profile of the population or any regional differences in payment or financial incentives. It is unlikely that similar factors describe the variations seen in paper I. There is an increase in knee examinations with MRI in Norway. This may lead to more frequent surgical treatment due to increased diagnostic findings, also of asymptomatic conditions. We do not have numbers on MRI-documented cartilage injuries in Norway, but previous numbers from the Framingham study have demonstrated 60% cartilage injuries in the general population.[237]

Also, patient willingness for surgery is a factor for potential geographical differences and is previous shown to be higher in areas of high incidence for knee arthroplasty.[238] Some operations are performed without evidence from the literature. A survey among Canadian orthopedic surgeons illustrated that 41% reported no upper age limit for performing MF,[239] although studies have demonstrated a better outcome in patients younger than 30-40 years.[40;106;107]

The geographic variations cannot be explained by actual demographic differences among the population and are more likely to be described by local differences in guidelines, and even variations among orthopedic surgeons. The public health system allows patients to freely choose their treating hospital when elective surgery is performed. Also, local agreements where one hospital treats more of one particular disease or injury whereas another hospital handles other areas occur and may explain some of the differences. Due to anonymity of the patients, we were not able to obtain both home address and treating hospital, and were not able to see the patient flow between geographical locations from paper I. These differences can be further explored in a national register. If differences exist because there are large variations in indications for surgery, the variations should be monitored and studied.

RCTs in cartilage surgery

Paper II illustrates that only 4% of patients were eligible to inclusion in RCTs on cartilage repair. The results from RCTs are applicable to very few of the patients seen in the clinic, meaning that there is a bias between the population presented in the studies and the general patient population. The external validity of RCTs within cartilage surgery is low, although fluctuating. We identified strict inclusion criteria to be a great limitation for inclusion of patients and thereby the generalizability of the results.

McLeod et al. describe the problem with generalizing data and applying RCT results to all patients with a specific disease because of strict inclusion criteria and inherent differences in patients who volunteer for trials.[240] RCTs may help clarify whether there are differences among the various treatment modalities, given strict inclusion and exclusion criteria. The criteria are strict in order to reduce variability among treatment groups and to control for all factors beside the intervention methods. Different factors known to impact on the results must be equally distributed between treatment arms. This increases the internal validity and subsequently paradoxically leads to reduced external validity and generalizability of the results.[232] The applicability to the general patient population is thereby affected and the risk of selection bias occurs.

The insufficient methodological quality is an obstacle for the further evidence within this field, and perhaps with an emphasis on the low external validity. A study on the methodological quality, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[241] guidelines identified a statistically significant increase in quality, but the external validity remained low.[242] The most important goal of research is to develop and increase the

quality of diagnostics, treatment or follow-up of patients and external validation is the key for bringing information back to the patients. A low external validity is a major limitation in the application of results from RCTs to clinical practice.

To our knowledge, the eligibility rate has not been addressed in the orthopedic literature and the generalizability of orthopedic RCTs is therefore uncertain. Authors from other fields of medicine have identified eligibility rates of 33-75%.[244;245] Mitchell et al. examined patients prescribed with tyrosine kinase inhibitors for metastatic renal cell carcinoma in a real-life setting and compared them to patients included in RCTs.[246] They found that 39% of the patients who received the medication in the real-life setting would have been excluded from a clinical study. They concluded that inclusion criteria in clinical studies should be wider as the applicability rate was too low. Another solution may be to initiate larger phase IV-studies, meaning large prospective cohort studies in a real-life clinical setting, a cartilage surgery register. Both wider inclusions criteria in otherwise strict RCTs and more real-life settings or RCTs on clinical effectiveness, will lead to greater generalizability. However, such studies may lose control over the homogeneity across study groups resulting in lower internal validity, and still no more knowledge on prognostic factors or adverse events. Our findings support the addition of unbiased prospective cohort studies to address still unanswered clinical questions.

In some situations, the large challenges with RCTs may be of such a degree that they are unnecessary, or even inappropriate. Well-designed observational cohorts can then be a supplement or a substitute when the alternative is a low-quality RCT. The major drawback of an observational study is that the differences in treatment method depend on differences within the patient population. Grootendorst et al. describes some situations where RCTs are either unnecessary, inappropriate (hip fractures), not possible to perform (unethical) or inadequate.[243] RCTs are also inappropriate when the goal is the measurement of infrequent adverse outcomes and for adverse outcomes expected to occur long-term postoperatively, such as in cartilage surgery.

This does not mean that we do not need future RCTs. RCTs are still the most important method of depicting between different interventions, but there are definitely challenges in applying the results to “common” patients, since an RCT never will include exactly “common” patients. We must keep in mind also that more factors affect the outcome of treatment than the intervention itself and other research designs are therefore important supplements.

How does an FCD affect articular cartilage quality?

dGEMRIC

Paper III explored the long-term effect on knee articular cartilage quality after an FCD in both operated and non-operated patients, evaluated with dGEMRIC as the primary outcome. The dGEMRIC technique is a reliable variable for the content of GAG, and has good reproducibility for use in longitudinal studies including patients with early OA,[247] in healthy subjects,[66] in patients with superficial, deep and full-thickness defects[89] and also in patients with established OA.[248] The results varied from no visible cartilage degeneration to marked cartilage thinning. Although the number of patients was too small to conduct statistical analysis between subgroups, there was no indication of that the injured knee had lower dGEMRIC in comparison to the uninjured knee, nor was it any detectable difference between the injured and uninjured femoral condyle in the injured knee.

Table 8. The table demonstrates dGEMRIC values of different populations. The overall higher results laterally are believed to be due to cartilage thickness rather than GAG-content.

	dGEMRIC (ms)	
Cohort	*medially*	*laterally*
Early knee OA[254]	456-520	498-579
Healthy population and patients with knee OA[214]	455 (+/- 67) 683 (+/- 95) – 3T	
ACL-injured[233]	368 (+/- 48)	406 (+/- 44)
ACL-injury + partial meniscectomy[233]	296 (+/- 62)	380 (+/- 49)
Healthy population[233]	428 (+/-38)	445 (+/- 41)
Healthy volunteers[255]	418	488
After cartilage repair[251]	427 (+/- 159) – 3T	
Patients with painful knee[256]	479-541	
Reference population[251]	636 (+/- 181) – 3T	

There was a non-significant higher value of the injured condyle. These findings are in line with the results from Årøen et al. together with Souza et al., who did not find decreased quality of the cartilage immediately surrounding a focal defect. However, Tiderius et al. studied the contralateral *compartment* in the index knee, and not the corresponding compartment in the contralateral *knee*. The patients in the study by Årøen et al. had an average of 4 years duration of symptoms, whereas our study is a 12-year follow-up. The dGEMRIC for knees in different populations are displayed in table 9. Previous studies have found T1-values in healthy subject to be 426-570 ms, and these numbers are in line with the result from the current study.[212] There are few studies presenting dGEMRIC results in patients with FCDs,[249] and most studies are done in patients after cartilage repair,[251] meniscal resections,[82;233] ACL-injuries or in cohorts with known OA. Previous studies have demonstrated lower dGEMRIC index in patients with higher degrees of early OA (measured with Tönnis grading scale).[252] $T1_{Gd}$ values are lower with increasing age in lamb and sheep models, and may represent a reduction in GAG content with age.[253] T1 values are further higher with 3 T than with 1.5 T field strengths.[214] This must be taken into account when evaluating the results. We used 1.5 T field strength in the present study.

T2 mapping

The mean T2-values of each ROI in the injured knee varied from 48-54 ms. There were large intraarticular variation, as previously reported from another study on healthy knees.[257] Some T2 values for the healthy population have been calculated and the mean vary from 40-54 ms.[257;258] Another study found the range in subjects without diagnostic evidence of cartilage degeneration and normal BMI to be 29.3 – 37.5 ms.[259] Patients at risk of OA have higher mean T2 in the medial femur than healthy controls (37.7 ms vs 36.9 ms).[260] Jungmann et al. demonstrated findings evident of early OA, measured with T2 values, in all compartments except the LFC of the knee 9 years after mega-OATS.[261] They found mean transplant-value of 40 +/-3 ms, whereas the mean global value was 42 +/-3 ms. The results from our study are thereby higher than what is reported for some patient populations, but also still in line with values described for healthy populations.

A study evaluating the correlations between T2 and histological grades of human cartilage found that T2 mapping and histology correlated (weakly), and that T2 in cartilage with histological grade 0 was lower (51.9 ms) than for grade 2 (59.6 ms).[262] Higher T2 values are associated with progression of cartilage degeneration, defined as increased depth, width or number of a

lesion.[263] The relationship between T2 and development of OA does not appear to be linear, so the technique is useful for depicting between normal and mild degeneration of the cartilage, although a distinction based on severity is not possible.[264] The T2 values should however be interpreted with caution as the reproducibility of T2 value measurements from center to center and time point to time point is still not established. The median T2 values are probably better to report than mean values due to the large variability and potential outliers. This points out the need for standardized treatment methods and also standardized ROIs within the knee.

Whether there is a correlation between T2 mapping and GAG content is controversial.[265] We found a medium to large correlation between T2 and dGEMRIC values only in the posterior ROI of the LFC and the central ROI of the MFC. However, when evaluating the scatter plots (figure 7), it is evident that this relationship is the result from a single outlier and there is really no correlation. For the anterior and central ROIs at LFC and anterior and posterior ROIs on the MFC, there was no evident correlation between scores. The present study concludes with no correlation between dGEMRIC and T2 values. This inconsistency might be due to magic angle effect, as demonstrated previously by Mosher et al.[266] The magic angle effect occurs with curved articular surfaces and is reduced by lesser bending of the knee joint and by maintaining a parallel axis of the cartilage surface with the main magnetic field.

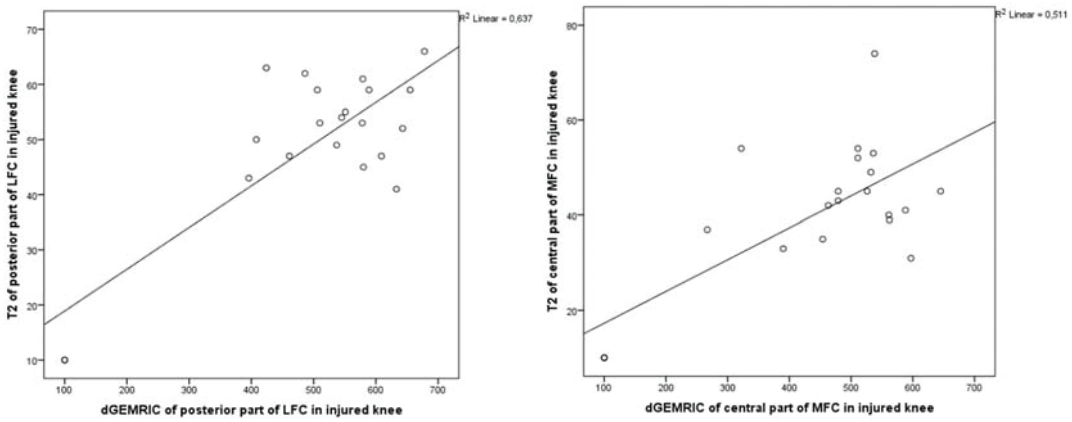

Figure 7. Scatter plots of T2 and dGEMRIC. There is no correlation as the relationship is a result from single outliers.

Is dGEMRIC reliable as a biomarker?

Although the dGEMRIC values were in line with previously described healthy subjects, both the T2 mapping and the plain radiographs demonstrated degenerative changes. For the radiographs there were degenerative changes in more than 80% of the injured knees. This is contradictory to other studies

that have found T1-weighted sequences to be more sensitive to the early degenerative changes within knee articular cartilage.[267] We did not find dGEMRIC to be a sensitive marker of early OA in this study as there was no difference between injured and non-injured knee 12 years after diagnosis. Altered gait mechanics following a traumatic FCD leading to a shift of the loading pattern within the joint may partially explain why the injured knees had similar results as the uninjured knees. Another possible explanation to the lacking difference between injured and non-injured knees is that similar degenerative changes are evident in the non-injured knees. A highly degenerated knee joint may yield unpredictable results. The wash-out kinetics of T1 vary between healthy and diseased cartilage.[85] This may have affected the knees differently in the present study, although the protocol was set up in accordance with previous recommendations.[212;213]

However, the overall results are not equivalent with degenerative changes when compared to previous values from healthy populations (table 9). Variations between equipment and centers occur. Still, some regions within the knees have unmeasurable values, which mean that the cartilage is too thin to be measured. It is possible that these areas represent the original defects and that the changes are strictly focal and thereby not assessed with our analyses, which are restricted to the predefined ROIs. The dGEMRIC is a sensitive tool for proteoglycan depletion, but it may depend on mechanically intact cartilage for precise measures.[268] Also, the radiographic diagnosis of OA is not associated with clinical symptoms,[269] and it is possible to have radiographic changes and still not qualify for the clinical diagnosis of knee OA.

The ROIs for evaluating the cartilage composition were placed in a standardized fashion. Previous studies on healthy subjects and patients with early OA have focused on the weight bearing areas (central ROI) of the cartilage which is most prone to early degenerative changes.[90;250] We found overall lower sores in the anterior ROIs. The central ROI on the MFC in the injured knee had the largest SD and the results are therefore uncertain. We concluded that little degeneration was detectable and that dGEMRIC did not act as a reliable measure for early OA in this population. We had no information on the localization of the defects in the sagittal plane in 13 patients, which challenges the interpretation of the results. Some areas had no detectable cartilage due to cartilage thinning. An exact knowledge on the baseline localization would have made it possible to see these areas in relation to the original defects.

A study evaluated cartilage quality with dGEMRIC quality 9-18 years after ACI.[270] Besides good cartilage quality, they also found evidence of

osteophytes and subchondral cysts. These findings are considered evidence of degenerative changes, and the occurrence of both good cartilage quality and degeneration may represent strictly local changes. Hingsammer et al. looked at dGEMRIC in hip dysplasia and found a globally decreased dGEMRIC index within the joint whereas tissue loss was a local finding.[252] Localized changes might explain why we did not demonstrate any difference in mean dGEMRIC, as the ROIs might have been placed outside the original defects. Still, we failed to identify any global decrease meaning that there was no decrease in overall knee joint health. Also, there is established a zonal variation, and a variation in contrast uptake, related to the depth of the articular cartilage.[255;256] The deeper layers tend to have a higher dGEMRIC index. This may relate to a higher content of GAG, but also to reduced uptake of contrast, since later studies have demonstrated this uptake to occur via the synovial joint fluid rather than the subchondral bone.[255]

The dGEMRIC as a biomarker must be further explored in both patients undergoing cartilage surgery and in patients treated non-operatively. There are no linear relationship between qMRI and arthroscopy when explored in 10 patients with suspected cartilage degeneration by Casula et al.[256] However, a mild correlation exists when ICRS grade 0 is removed. The focus should be to standardize the dGEMRIC protocols concerning characteristics of the baseline defect, as the study indicates that dGEMRIC can be reliable when applied to the exact location of the original defect. Furthermore, the dGEMRIC seems to vary both among individuals and within the knee joint. The intra- and interindividual variability makes it difficult to classify a specific value as normal or pathologic. The dGEMRIC might be a valuable tool for an indication of increased risk of OA and for longitudinal follow-up as decreased values mean loss of GAG. Longitudinal assessments should be performed to establish reference, or cut-off, values for early OA.

Prognostic factors

There are still many unclear aspects of prognostic factors. End-stage OA is a reliable outcome of knee joint health, but we also need biomarkers for early OA and a register may identify prognostic factors. We evaluated scatterplots on patient and defect characteristics against dGEMRIC results to find possible associations. The strongest association between baseline size and mean dGEMRIC based on injured or uninjured compartment was identified in defects on the LFC (figure 8).

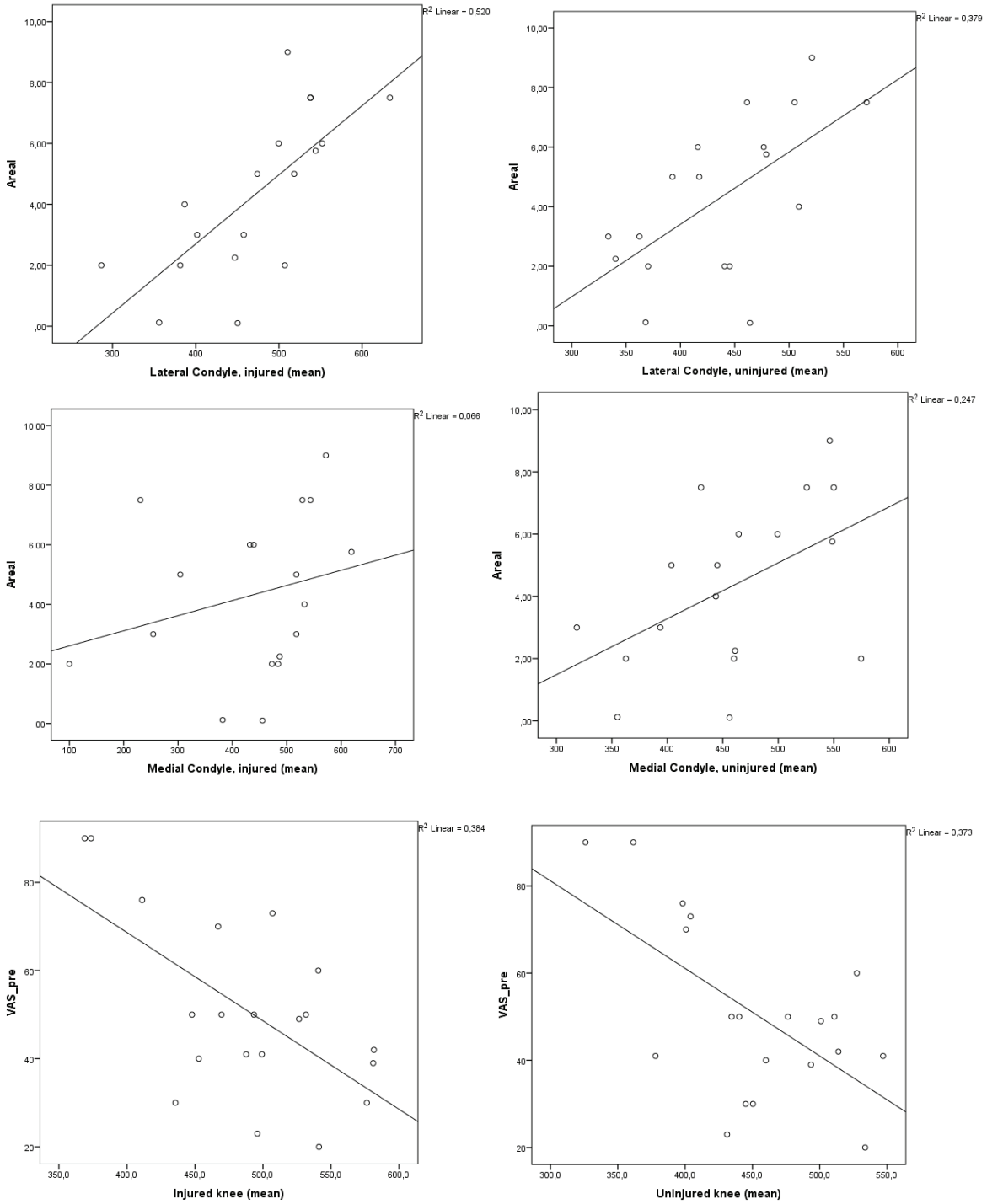

Figure 8. The figure illustrates scatter plots with regression lines regarding baseline size, and baseline VAS against mean dGEMRIC value of each injured and uninjured medial and lateral femoral condyle and injured and uninjured knee. The strongest association between baseline size and mean dGEMRIC based on injured or uninjured compartment was found in defects on the LFC, and only weak correlations for defects on the MFC. There was a weak correlation between VAS at baseline and the mean dGEMRIC value of both injured an uninjured knee.

We found a large and negative correlation (r=-0.673, p=0.033) between age at injury and dGEMRIC values for defects on the LFC. Low age at injury was associated with higher dGEMRIC at follow-up, and this is in line with previous

findings of better outcome for younger patients.[105] As the correlation exists in both knees, this may be considered a marker of the general joint health rather than symptoms from the focal defect. Another explanation is that high levels of pain leads to progressive degenerative changes bilaterally due to altered loading patterns.

A study looking at the relationship between the severity of hip dysplasia, found dGEMRIC index to correlate with the radiographic findings and pain.[271] The dGEMRIC index in symptomatic femoroacetabular impingement (FAI) is lower than in asymptomatic volunteers in a population of patients with grade 0 changes on conventional MRI.[272] We did not find any significant correlation between dGEMRIC and either K&L or PROMs in the present study.

10 patients underwent cartilage surgery at baseline. Cartilage surgery is demonstrated to affect the dGEMRIC index compared to native cartilage.[273] Pinker et al.[274] concluded that the [GAG] probably never reaches the level of normal healthy cartilage tissue after MACI. In the present study, there was a non-significant (p=0.152) difference between untreated/debrided defects and MF/ACI treated defects.

As dGEMRIC did not act as a reliable biomarker for early OA in the present study, further deductions on reliable prognostic factors are not possible and must be explored with other outcomes. It is therefore important to secure detailed descriptions of baseline factors in a cartilage surgery register as this is the best way of identifying clinically relevant prognostic factors.

Cartilage surgery register

Based on the current status on treatment of patients with FCDs of the knee and the challenges with high-quality research on this patient population, we wanted to explore a potential establishment of a cartilage surgery register. We explored the benefits of and challenges with a cartilage surgery register. Ultimately, we wanted to answer whether a cartilage surgery register should be established. The experiences from our pilot is that useful information is obtainable, although with challenges. Compliance and follow-up are the most obvious challenges. Care must be taken in the design and logistics of a register and a continuous effort to maintain high compliance is needed. This is not different from other registers. A cartilage surgery register seems important for the development of treatment indications, and how to identify patients who will benefit from surgical treatment.

Whether such a register is possible provide valuable data depends on 2 factors; that the data are valid and complete. The low compliance in pilot 1 seems to be a result from few participating hospitals and orthopedic surgeons and from a short registration period. We believe that this caused the registration to never truly be implemented into the daily clinical routine. We therefore decided to rerun the pilot before deciding the register's future, in order to identify challenges and assess whether complete data are attainable. The results from the second pilot is not included as it is still ongoing.

Paper I demonstrated large geographical variations in cartilage surgery. There are large variations in how these patients are treated, and there is a risk that individual surgeons opinions mean more than scientific evidence in some cases. For conditions where a surgical approach is necessary in order to regain function or prevent serious disease, it is easy to draw the conclusion that geographic variations follow variations in incidence of disease. For diseases or conditions where surgery has an unclear role, the variations may be caused by variations in diagnosis, or they can be attributed to physician and patient preferences.[275]

A challenge with patients undergoing cartilage surgery is that they often have had prior surgery.[34;109;137] Previous surgical procedures might impact on the current surgery and on prognosis.[135] This information is often difficult to attain as patients are admitted to different public hospitals and also visit private centers. The medical record system is separate for each hospital and the orthopedic surgeon must rely on the patient, who rarely has detailed information on the status and procedure. This probably also contributes to the large variations in treatment demonstrated in paper I.

Before these variations can be reduced, they must be identified, studied and acknowledged. We believe that both variations in diagnosis and preferences, the latter from both physician and patient, explain the reason for the observed variations. As there are no established gold standard treatment, such variations occur consequently.[276] The heterogeneous patient group might also contribute to the variations in treatment. These results are nevertheless important for planning and designing a national register. The numbers are appropriate for establishing a register, and the geographic variation reflects the need of more standardized conditions.

In paper II we found low external validity from RCTs on cartilage surgery. This means that many patients with FCDs are never studied in high-quality research. However, the most important reason for the lack of generalizability is the identified factors leading to ineligibility.[245] We identified *size* as the most

challenging factor, but also *age*, *localization* of defects and *number of* defects led to ineligibility. A cartilage surgery register will include and follow up all patients and will yield useful information on patients who are not included in RCTs. The heterogeneity seen in this patient group is a challenge for the generalizability of RCTs. Currently, care must be made when the orthopedic surgeon uses results from RCTs when deciding treatment for patients with FCDs as the results may not apply for the particular patient. This means that at least some trials should include a more unselected patient cohort. Observational studies with a prospective and standardized data collection and valid outcome measures may complement the results from RCTs.

Biomarkers of early OA are still lacking. Prognostic factors are also largely unresolved. A few factors for a good surgical result are identified. These factors are identified through RCTs, which is not designed for identifying prognostic factors as they are controlled for through the randomization of subjects. A cartilage surgery register, designed as a prospective cohort study, is therefore likely to contribute to new knowledge on prognostic factors.

The treatment of cartilage injuries is difficult, we have shown that large variations in treatment exists, and the generalizability is low. A cartilage surgery register has the potential to significantly impact clinical practice, such as the NKLR. Several clinical prognostic factors for outcome after ACL-reconstruction have been identified over the recent decades, where some have already led to alterations in treatment methods in Norway. Through the NKLR,[210] it was possible to discover an increased revision rate with hamstring tendon grafts compared to patellar tendon grafts (hazard ratio of 2.3).[277] Data from the NKLR have recently demonstrated a worsening in outcome if MF is performed in the same stage as the ACL-reconstruction.[278] The authors recommend avoiding doing both these surgical steps together, and rather reconstruct the ACL, rehabilitate and then evaluate cartilage surgery if sustained clinical symptoms. There is a large potential for increased quality in treating patients with FCDs of the knee with a specialized cartilage surgery register.

Compliance

In the first pilot, the compliance varied from 18% to 73% in pilot 1. Pilot 2 is ongoing in conjunction with a multicenter study in the same hospitals, which will cause more knowledge and activity around the pilot register. The inclusion criteria are less strict and the registration period is prolonged. This will hopefully results in that patients are included more frequently, and ensure

more complete data. High compliance is possible, but everyone involved must be motivated and the registration must be easy to conduct.

A paper published in 1992 looked at the completeness of an orthopedic database in England by comparing the database with Hospital Activity Data and found that overall completeness of the database increased after audit and feedback.[279] They suspected motivation to be the most effective factor in promoting correct use of the database. Frequent feedback to the participants is therefore an important factor for achieving high compliance as it acts as a motivational factor. Throughout pilot 2 we have given regular reminders to increase the compliance.

Strengths and weaknesses

Paper I

In paper I, data from the NPR was collected and incidences of cartilage surgery were calculated. The distinction between focal lesions, which are traumatic or degenerative, is difficult to make based on clinical examination. We encountered insufficient detail in the diagnostic and procedural codes used by the NPR. This is the largest study limitation and cannot be defeated by any methodological changes, but by information and education of orthopedic surgeons. This is a shortcoming of the ICD-10 system, which constitutes a challenge for cartilage pathology and affects the cartilage research field in general, including the current study. This can potentially be overcome by a revision of the current coding systems. The ICD-11 is already revised.

The strength of this study is that we have cross-sectional data from 4 years of a national cohort, as opposed to many similar studies where data are obtained from private insurance databases and involve only patients with a specific insurance plan. We based our data on specific surgical codes, which are more precise than the diagnostic codes. These codes are partly responsible for the yearly budget for each hospital and miscoding of surgical procedures leads to inconsistent funding.

Paper II

We searched for well designed RCTs and although we failed to include two studies, these would not have altered our result. There is a possibility that our included "general patient population" represent a biased population of the "worst cases" since some patients are referred from other hospitals to a

specialist hospital. The study revealed a substantial possibility of bias between the population presented in RCTs on cartilage surgery and those referred to a major orthopedic center.

Paper III

We found that dGEMRIC was not a reliable biomarker of early OA in paper III. The patients were diagnosed with an FCD 12 years prior and were expected to show early degenerative changes. The dGEMRIC technique is indicated for early OA, and our patient cohort may have had too advanced joint degeneration, which dGEMRIC was unable to identify.

The strength of this study is the inclusion of a group of patients with FCDs diagnosed with arthroscopy 12 years prior to dGEMRIC. A long-term follow up of non-operated patients has to our knowledge not been performed previously. We excluded patients with total ligament ruptures and unstable knees. However, the power of the study and potential false negative numbers may have influenced the results. We studied a small population where a few patients also had injuries in their uninjured knee. The ROIs in dGEMRIC and T2 mapping were drawn manually. The reader was an experienced radiologist with experience from reading MR images and also special training in drawing ROIs and analyzing dGEMRIC. The manual drawing is still a drawback as there is a large intraarticular variation. It is also previously demonstrated large variability in measures.[235] The intra- and interobserver variation is low[90] and previous studies have reported an intraclass correlation coefficient (ICC) for the measuring of dGEMRIC index to be 0.9.[252] The ICC of dGEMRIC readings was good in another study from this group.[249]

Pilot register

One of the strengths of a register is that it is an unbiased prospective cohort study. The patients are identifiable and may therefore be linked to other registers in the future. This means that the findings have a great potential external validity, as opposed to RCTs. However, as the inclusion relies on many different orthopedic surgeons and hospitals, the inclusion may vary. We have assessed operation descriptions in the medical records in order to check the compliance. A thorough analysis of inclusion bias was however not done. Certain challenges within surgical research are the difficulties of standardization and challenging patient enrolment, as described and demonstrated in paper II. Virtually all cartilage surgery occurs in an elective

setting, which allows thorough information and consideration on treatment options and prognosis. However, a register does not rely on strict randomization and patient, or surgeon, preferences do influence on the results.

A weakness of all registers is the internal validity, which will never be as high as a good quality RCT. But, it is possible to gain access to high quality data with a proper design, even in the absence of randomization and blinding. A register is the only method that measures the effectiveness of treatment in the general population. Internal validity is kept high with good control of all other variables.

As for all studies with inclusion based on surgical procedures, FCDs diagnosed with MRI and treated non-operatively are not included. As some patients and surgeons choose to “wait and see,” the time that elapses from when the symptoms actually appear until examination by an orthopedic surgeon will also vary greatly. This is a well-known diagnostic challenge for these defects as only around half of FCDs are encountered as acute.[2;8] ACL-ruptures based on MRI-findings are now included in the NKLR, and must also be considered for a potential future cartilage surgery register. A register contributes to a clinical validation of the defects as the surgeons are forced to consider the defect as a focal and localized defect or a change that is part of a degenerative status of the knee joint. The register thereby also contributes to education of younger surgeons as everyone involved in knee arthroscopy are involved in registration.

Conclusion

Cartilage surgery is common in Norway, on level with ACL-surgery. Surgical RCTs do not ensure high external validity. The dGEMRIC technique is not a good biomarker for long-term follow-up of patients with FCDs. Although the pilot register was unsuccessful, we nevertheless suggest that a nation-wide cartilage surgery register will benefit the quality of care and ultimately well-being of the patients.

The future

Objective of a future register

The aim of a future cartilage surgery register is to contribute to improved patient care, through continuous and systematic evaluation of the management of these patients in a real-life setting. Registers have the great opportunity of analyzing data on a significantly greater number of participants, when acceptable compliance is achieved.[280] Prognostic factors, failures and uncommon advents following any type of surgical technique or equipment can be identified. As for ACI it takes 2 years simply for the new tissue to mature.[282] And a cartilage surgery register will secure long-term follow-up data on this patient population. A register also addresses the factors identified by Worthen et al. to be important, specifically the larger patient enrolment and longer follow-up.[196]

A register will contribute to increased quality of the health care, as the adherence to clinical guidelines will be easier visible. The implementation of research results into the clinic will become easier to study. Potts et al. detected a decline in arthroscopic procedures for knee OA after publications had demonstrated their ineffectiveness.[281] The non-surgical treatment options are not fully explored, and never tested against a surgical intervention. With high methodological quality and standardized outcomes it is possible to compare different interventions in a cartilage surgery register.

A register will be helpful for planning health services and health economy. We will be able to see both where patients are treated and the results. A register will provide information on the costs of treatment. The outcomes of the pilot register may serve as both health outcomes and as an outcome for effectiveness of treatment. In that way, the register may serve both clinicians and health care leaders. It is also an increasing demand to report quality parameters for politicians and administrators to measure and compare results from different health services and regions. How quality is defined and measured is medically important, and the quality of treatment must be our priority. Data from a cartilage surgery register may be used directly when informing the patients in the outpatient clinic. The register will serve as an important supplement in the research field; to bridge the gap between basic research and RCTs in this field. By following large cohorts prospectively with standardized data collection and outcome measures in a uniform fashion, we will be able to rule out some of the methodological drawbacks in this field. Furthermore, it is ethically important that the accessibility to a register exists in order to tailor the best treatment available for each patient.

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Appendix

PILOTSTUDIE BRUSKREGISTER
Senter for Idrettsskadeforskning,
Norges Idrettshøgskole
Sognsveien 220
Postboks 4014 Ullevål
0806 OSLO

F.nr. (11 sifre) .....
Navn.....
Sykehus.....
(Skriv tydelig ev. pasient klistrelapp – **spesifiser sykehus.**)

FOKALE BRUSKSKADER I KNE

ALL KNEKIRURGI på pasienter med fokale bruskskader eller som tidligere har skadet/operert brusk i kneet.

(Bilateral operasjon = 2 skjema)
AKTUELL OPERASJONSDATO (dd.mm.åå) |__|__| |__|__| |__|__|

AKTUELT KNE (ett kryss) ☐ Høyre ☐ Venstre

AKTUELL OPERASJON (ev. flere kryss)
☐ Diagnostisk skopi ☐ Bruskkirurgi
☐ Meniskoperasjon ☐ Biopsi, øvrig
☐ Fjerning av implantat ☐ Synovektomi
☐ Osteosyntese ☐ Bentransplantasjon
☐ Osteotomi ☐ Protese
☐ Operasjon pga infeksjon ☐ Annet .....

DAGKIRURGISK OPERASJON ☐ Ja ☐ Nei

TIDLIGERE OPERASJON I AKTUELLE KNE (ev. flere kryss)
☐ ACL ☐ MCL ☐ PLC ☐ Medial menisk
☐ PCL ☐ LCL ☐ Brusk ☐ Lateral menisk
☐ Ingen ☐ Annet, spesifiser ....

ER DET VED TIDL. OPR. påvist fokal bruskskade i kne?:
☐ Ja ☐ Nei ☐ Vet ikke

HVIS TIDL PÅVIST: mnd/år påvist 1. gang (mm.åå): |__|__| |__|__|

HVIS TIDL PÅVIST: aktuell status for tidl påvist(e) bruskskade(r). (For koder – se i høyre kolonne. Bruk evt flere koder i hver rubrikk):

	Areal (cm^2)	ICRS gr* (1-4)	Tidligere beh*** (1-18)	Aktuell beh av tidl påviste skader*** (1-18)	Degenerative forandringer, ICRS*
Patella M					
Patella L					
Trochlea fem					
Med fem cond					
Med tib plat					
Lat fem cond					
Lat. tib plat					

ER DET NYOPPDAGEDE FOKALE BRUSKSKADER VED AKT. OPR:
☐ Ja ☐ Nei ☐ Vet ikke om ny el. tidl. påvist

HVIS JA; ER NYOPPDAGET SKADE TRAUMEUTLØST:
☐ Ja ☐ Nei ☐ Vet ikke

HVIS TRAUME; TRAUMEDATO: (mm.åå) |__|__| |__|__|

HVIS TRAUME: AKTIVITET VED TRAUMETIDSPKT.:
☐ Fotball ☐ Alpint
☐ Snowboard ☐ Håndball
☐ Arbeid ☐ Mosjon/friluftsliv
☐ Trafikk ☐ Ikke spurt
☐ Annet ..... ☐ Ukjent

HVIS IKKE TRAUME, symptomvarighet (i mnd) .....

ANDRE SKADER PÅVIST VED AKT. OPR. (inkl. de som ikke behandles)
☐ Menisk ☐ PLC ☐ Annet ....

HVILKE ICD-10 kode(r) ble brukt: ....

STATUS FOR NYOPPDAGET fokal bruskskade(r), og evt eksisterende degenerative forandringer (For koder – se under tabell og bruk evt flere koder):

	Areal (cm^2)	ICRS gr* (1-4)	Etiologi** (1-5)	Behandling *** (1-18)	Degenerative forandringer, ICRS*
Patella M					
Patella L					
Trochlea fem					
Med fem cond					
Med tib plat					
Lat fem cond					
Lat tib plat					

KODER:
***ICRS Grade:** 1 Nearly normal: Superficial lesions, soft indentation and/or superficial fissures and cracks; 2 Abnormal: Lesions extending down to <50% of cartilage depth; 3 Severely abnormal: Cartilage defects extending down >50% of cartilage depth as well as down to calcified layer; 4 Severely abnormal: Osteochondral injuries, lesions extending just through the subchondral boneplate or deeper defects down into trabecular bone.
****Sannsynlige årsaker:** 1 Traume; 2 CM: chondromalacia patellae; 3 OCD: osteochondritis dissecans; 4 Ukjent; 5 Annet: Spesifiser årsak i aktuelle rubrikk
*****Behandlingskoder**: 1 Ingen behandling; 2 Debridement; 3 Stabilisert bruskskaden; 4 Mikrofraktur; 5 Mosaikkplastikk; 6 Biopsi til dyrking; 7 Celletransplantasjon; 8 Celletransplantasjon med matrix; 9 Periosttransplantasjon; 10 Fiksering OCD; 11 Fjernet ost.mat OCD; 12 Annet: Spesifiser behandling i aktuelle rubrikk; **Ved bruk av BRUSKIMPLANTAT;** 13 MACI; 14 Chondrogide; 15 Cartipatch; 16 HYAF; 17 TrueFit; 18 Annet implantat: .....

AKTUELL BEHANDLING AV MENISK:

	Reseksjon	Sutur	Syntetisk fiksasjon*	Menisk-transpl.	Trepanering	Syling
Medial	☐	☐	☐	☐	☐	☐
Lateral	☐	☐	☐	☐	☐	☐

Hvis meniskreseksjon; angi andel gjenværende menisk i %
☐ Mediale: ..... ☐ Laterale: .....

PEROPERATIVE ORTOPEDISKE KOMPLIKASJONER
☐ Nei ☐ Ja, hvilke(n).....

OPERASJONSTID (hud til hud) .....min.

SYSTEMISK ANTIBIOTIKAPROFYLAKSE
☐ Nei ☐ Ja, hvilken.....

NSAIDs: ☐ Nei ☐ Ja, hvilken type .....

Kommentar.....
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.....
.....
.....

Lege: .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

Errata

Paper I-IV