Sport has become an integral part of society with ritual, religious, recreational and economic significance. Modern society derives a great deal of benefit from sports participation, as it allows a shift of focus from (hard) work to fun and leisure, physical and mental fitness and, albeit currently with insufficient uptake, counteracts the ongoing epidemic of obesity. In the United States, a continuous increase in both frequent and occasional runners, as well as a steady increase in sport-related injuries underline the progressing interest in physical exercise and its consequences. Unfortunately, musculoskeletal injuries are common in sports and correspond to 80% of all sport-related injuries. Joint injuries, especially in the knee, have become more common due to the increase in physical activity of both young and old participants in sport at all levels. Activities that involve running, jumping, physical contact and fast changes in direction impose an additional burden on the knee, with forces that can reach up to 10 times body weight. The intensity and level at which sports are played have dramatically increased in the last century resulting in even more strain on the musculoskeletal system. Not surprisingly, a European emergency department found 8% of all injuries to be knee injuries related to sports and recreation.

The exact incidence and prevalence of cartilage defects remains unknown. In the Netherlands, it is estimated that 3000 to 5000 patients are affected annually. For focal defects, young and middle-aged patients (aged 18 to 45) have the highest recorded prevalence with up to 50% of patients...
having a sports-related injury. One study found 44% of random subjects (n=372) with or without a family history of osteoarthritis (OA) to have a cartilage defect, of which 35% reported pain. In 1000 symptomatic patients undergoing arthroscopy, 61% of patients had a chondral or osteochondral cartilage defect, of which 28% had an isolated defect. As with the epidemiology, the aetiology of cartilage defects is not exactly clear, although there is a relation to trauma and osteochondritis dissecans. Several reports found untreated cartilage defects to progress to deeper lesions over a period of 2 years. Cartilage defects are also more common in radiographic OA and have been shown to predict cartilage loss over a period of 2 years with an increased risk of total knee replacement after 4 years.

In 1743 William Hunter published the first paper on cartilage and its diseases: ‘On the structure and diseases of articulating cartilages’ in which he stated: “If we consult the standard chirurgical writers from Hippocrates down to the present age, we shall find, that an ulcerated cartilage is universally allowed to a very troublesome disease; that it admits a cure with more difficulty than carious bone; and that, when destroyed, it is not recovered”. For his time, he had great insight; as although we have come to understand cartilage defects do not heal spontaneously, we are still trying to understand the mechanisms of cartilage damage and OA.

In orthopaedic practice, cartilage defects are considered troublesome injuries, which can cause symptoms such as pain, swelling and locking, as well as limit function and impede quality of life, similar to patients with OA. Currently, young and middle-aged patients represent the majority of those seeking treatment. These patients will often visit multiple centres and receive multiple treatments prior to receiving definitive care. In turn, the related absenteeism from work and high healthcare costs associated with these injuries create a large socioeconomic burden. Thus, the prospect of early and adequate treatment with a cost-effective intervention may greatly benefit society.

**ARTICULAR CARTILAGE REPAIR OF THE KNEE**

In the early 1970s, arthroscopy became increasingly common and together with the development of the MRI scan in 1977, gave light to a new era in which adequate diagnosis of knee injuries and minimal invasive knee surgery became possible. Early treatment of focal cartilage defects included removal of loose bodies and debridement. In the 1980s, originally applied to horses and in 1981 to humans, Richard Steadman introduced the microfracture treatment. In this arthroscopic procedure, multiple small penetrations in the subchondral bone allow for an influx of bone marrow causing local fibrous-like tissue repair. Mid- to long-term reports have been encouraging, with good clinical outcomes reported up to 11 years following surgery, although larger defects (>2 cm²) have been found to show an inferior response compared to smaller defects (<2 cm²) and deterioration of clinical outcome has been reported after 2 to 5 years in athletes.

In October of 1987, Mats Brittberg and Lars Peterson were the first to perform an autologous chondrocyte implantation (ACI) in a human knee. Since then, a rapid development in regenerative medicine has given rise to a variety of cell implantation techniques resulting in different generations of ACI. In the first generation ACI, a biopsy was taken from a non-weight-bearing location and isolated chondrocytes
were cultured before re-implantation after 2 to 3 weeks under an autologous periosteal cover. In the second generation, introduced in 2002, a collagen cover or bioresorbable film replaced the periosteal cover, aiming to prevent periosteal hypertrophy and improve ease of use. The third generation, in which cells are implanted on an open-structured collagen matrix after 6 to 9 weeks, is used today. This technique allows for non-sutured implantation that has considerably improved ease of use. The introduction of molecular screening, in which a panel of genes are used to characterise the chondrogenic capacity of cells, has established new cell-based release criteria and production guidelines for clinical care. While the majority of ACIs are performed using a mini-arthrotomy, there are specialised centres that use an arthroscopic approach for defects on the femoral chondyle, depending on the product used and the experience of the surgeon. Various randomised controlled trials and good clinical outcomes of up to 20 years has supported the introduction of this advanced therapeutic medicinal product as standard care in specialised clinics. However, high treatment costs along with the burden on patients that have to undergo two surgeries with an interval of up to 2 months, is driving the transition to a fourth generation of ACI. Here, the focus lies on a single-stage procedure with considerably lower costs. Techniques include microfracture augmentation, in which a cell-stimulating cover is placed above microfracture penetrations to keep the blood clot in place and aid in local regeneration. For cell-based procedures, both autologous and allogeneic multipotent mesenchymal stromal (stem) cells are being explored as these cells have the capability to differentiate into a cartilaginous lineage and circumvent the need for cellular expansion. However, safety and efficacy as well as non-inferiority to ACI have yet to be shown.

**Evolving treatment algorithms**

In the last 2 decades, the field of regenerative medicine has been characterised by a rapid development in tissue engineering techniques. The downside of this phenomenon is that there has been less room for (long-term) evaluation of clinical outcome and focus on prognostic factors that determine this outcome. Ideally, a patient with a cartilage defect is profiled using evidence-based tools such as prognostic factors, biomarkers and imaging techniques that aid in determining the best suitable treatment strategy for that individual patient and predicting its success rate. Clinical trials have provided some indications as to which factors influence treatment outcome including age, defect size and activity level.

**Defect size as primary treatment indicator**

Defect size is currently used as one of the primary indicators for treatment selection. Two randomised controlled trials comparing ACI with microfracture found inferior clinical outcome after microfracture for defects larger than 4 and 2 cm. This was seen in prospective studies which found similar size thresholds that reduced clinical outcome of microfracture after a mean of 2 to 11 years. The clinical outcome after ACI or osteochondral autologous transplantation (OAT) has not been found to correspond to defect size. However, defects greater than 4 cm seem to respond better to ACI than OAT, possibly due to difficulty in acquiring enough fibrous tissue to cover the entire defect and/or the greater pressure exposed to the tissue. In a more recent randomised controlled trial, the histological and functional outcomes of ACI were also significantly better than.

**The intensity and level at which sports are played have dramatically increased in the last century, resulting in even more strain on the musculoskeletal system. Not surprisingly, a European emergency department found 7% of all injuries to be knee injuries related to sports and recreation.**
those for microfracture in defects averaging 2.5 cm². Thus although no single size threshold can be identified, defects greater than 2 to 3 cm² can be considered more suited for transplantation procedures, while microfracture would be more suitable for smaller defects. Indeed, one systematic review concluded that defects larger than 2.5 cm² should be treated with ACI or OAT. Individual decision-making is considered to be important as relative defect size and depth (i.e. in comparison to the femoral condyle) and the extent to which joint homeostasis has been disturbed varies between patients. As defect size is currently a primary treatment selection indicator, it is difficult to compare between treatments for similar defect sizes.

**Treatment selection for smaller (<2 cm²) defects**

Debridement can be considered as an initial treatment for defects <2 cm² in less demanding patients, for those defects that are found incidentally during arthroscopy and in mild to moderate OA. However, randomised controlled trials in patients with OA have shown that arthroscopic debridement has no advantage over optimal physical and medical care. Although debridement of small defects can provide symptomatic relief in terms of pain, catching and locking, the response to treatment of these defects as well as their natural history remains unpredictable.

Both microfracture and OAT are generally considered good options for smaller (<2 to 3 cm²) defects. OAT may be indicated in defects where the subchondral layer is damaged. For chondral defects of 2 to 3 cm², microfracture or ACI is usually preferred over OAT, based on the possible risk of donor-site morbidity. However, the bone portion also influences treatment choice. Although strong supporting evidence is lacking, donor-site morbidity may lead to pain, tissue deterioration and a decline in knee function. In contrast, in a case series following 112 patients, Paul et al found neither size nor number of donor grafts influenced clinical outcome. Concerning smaller defects, more complex procedures such as ACI are generally reserved for those with high activity requirements and revision cases, as marrow stimulation techniques seem less reliable in these instances.

**Treatment selection for larger (>2 cm²) defects**

For larger (>2 cm²) defects, both ACI and allograft transplantation have shown good to excellent results. Local availability as well as surgeon and patient preference will still largely determine the treatment of choice as a randomised controlled comparison between these interventions is lacking. For ACI, good to excellent clinical outcome has been reported up to 20 years after surgery in 70 to 90% of patients with defects >3 cm².

An advantage of allograft transplantation might be that it permits treatment of relatively large defects, particularly when there is accompanying bone loss. Shasha and colleagues found an 85% femoral condylar graft survival rate at 10 years and a 65% graft survival rate after failed tibial plateau fracture. Bugbee et al demonstrated an 86% success rate after allograft transplantation for unipolar defects averaging 8.2 cm² while 54% of bipolar defects were rated good to excellent. Malalignment (and early) OA may also reduce clinical outcome after allograft transplantation. Interestingly, Ossendorf et al recently demonstrated good mid-term results after ACI in 51 patients with large and complex articular defects.

For larger defects deeper than 8 to 10 mm allograft transplantation is not feasible, in such cases the ACI-sandwich technique can be a viable option. Here, a bone graft such as obtained from the iliac crest or a non-weight-bearing portion of the knee is implanted first, after which a cellular implant is used. For example, Barlett et al used a sandwich technique with two matrix-induced ACI (MACI) membranes and a bone graft in deep osteochondral defects (mean 5.2 cm², range 2.2 to 8.0) and found good to excellent results after 1 year in all eight patients treated.

**Single-stage cartilage repair**

Recently, single-stage procedures have become increasingly popular as they allow faster rehabilitation and reduce the burden of having to undergo two separate
surgeries. Different types of augmented microfracture techniques are being investigated, with the basic principle of using a scaffold to keep the bone marrow-derived clot in place. For cell-based cartilage repair, a single-stage procedure would require omitting the expansion of autologous cells. A possible solution would be to replace the use of autologous chondrocytes with stem cells due to the low cell density in native cartilage and the large surface area to volume ratio of the defect, or combine them with another cell type. Autologous mesenchymal stem cells (MSCs) have proven capable of providing cartilage regeneration in both animal models and humans (small cohorts). However, the number of MSCs in adult tissues is low and obtaining sufficient autologous MSCs would require an expansion phase, bringing this procedure back to two separate interventions. Expanded allogeneic MSCs could be an attainable cell option as they have low immunogenicity based on their low expression levels of human leukocyte antigen and major histocompatibility complex class I and II. Several studies have also shown that a combination of MSCs and chondrocytes can lead to cartilage formation, a combination of allogeneic MSCs and autologous chondrocytes could be applied for single-stage cartilage repair. Earlier in-vitro and in-vivo experiments showed that when chondrocytes with their pericellular matrix (chondrons) are mixed with MSCs, reproducible cartilage regeneration can be achieved. This mixture seems to be more beneficial than using MSCs alone, which may have a tendency to enter the bone differentiation pathway. Current studies are not conclusive on the exact cellular mechanisms behind these co-cultures; some suggest MSCs differentiate and survive in-vivo up to 6 months, while others suggest MSCs have a chondroinductive role i.e. stimulate cartilage regeneration through trophic factors while slowly disappearing from the culture. The promising results of this cell mixture applied to a goat model, as shown by superior histological tissue regeneration compared to microfracture, has stimulated a Good Manufacturing Practice (GMP) for advanced therapy medicinal products (ATMP) to be tested in a first-in-man trial for safety and efficacy.

The Instant MSC Product Accompanying Autologous Chondron Transplantation (IMPACT) trial included 35 patients who received treatment for a focal cartilage defect with a single surgical procedure. Here, the primary research questions were focused on the safety and feasibility of using a mixture of recycled autologous chondrons and allogeneic MSCs for single-stage cartilage repair. Initial findings at 1 year are promising, with safety and clinical improvement shown (unpublished data). While single-stage procedures are promising, future clinical data will provide more answers on the applicability of stem cell and combined stem cell procedures.

**SHOULD PATIENT AGE BE USED AS A PRIMARY INDICATOR?**

Patient age is considered to influence clinical outcome after cartilage repair as a variety of studies reported that patients under 30 years of age benefit more from cartilage repair in terms of clinical outcome when compared to older patients. Conversely, a recent randomised controlled trial in patients aged 18 to 50 years did not find a correlation between age and clinical outcome. In fact, several other studies did not find a correlation between age and treatment success. One study demonstrated low failure rates in patients of 45 years and older while another study showed no difference in clinical outcome after ACI in patients of 40 years and older compared to younger patients. Thus overall, there is insufficient and inconclusive data to support age as a primary indicator for treatment selection. What’s more, a variety of studies show early evidence up to 9 years of successful clinical outcome in patients with a mean age between 34 and 57 with degenerative cartilage defects and early OA. The use of a standardised criteria for early OA and larger (randomised) trials may allow treatment algorithms to be further expanded to this challenging patient population.

**Table 1**

<table>
<thead>
<tr>
<th>Defect size</th>
<th>Femoral condyle</th>
<th>Patellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5 cm²</td>
<td>Microfracture</td>
<td>ACI</td>
</tr>
<tr>
<td>2.5 - 4 cm²</td>
<td>ACI</td>
<td>ACI</td>
</tr>
<tr>
<td>&gt; 4 cm²</td>
<td>ACI</td>
<td>ACI</td>
</tr>
</tbody>
</table>

Table 1: Treatment algorithm for chondral defects. ACI=autologous chondrocyte implantation.

**Table 2**

<table>
<thead>
<tr>
<th>Defect size</th>
<th>Femoral condyle</th>
<th>Patellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.5 cm²</td>
<td>OAT</td>
<td>OAT/ACI</td>
</tr>
<tr>
<td>2.5 - 4 cm²</td>
<td>ACI sandwich/allograft</td>
<td>OAT/ACI</td>
</tr>
<tr>
<td>&gt; 4 cm²</td>
<td>ACI sandwich/allograft</td>
<td>OAT/ACI</td>
</tr>
</tbody>
</table>

Table 2: Treatment algorithm for osteochondral defects. ACI=autologous chondrocyte implantation. OAT=osteochondral autologous transplantation.
Surgical debridement with an additional cartilage biopsy may allow fast return to play, delaying the need for re-implantation and subsequent rehabilitation to the off-season\(^\text{20}\)

TREATMENT DELAY
Currently, patients with cartilage defects and long-standing complaints despite treatment(s) are frequently referred to specialised knee centres. In fact, the average patient suitable for cartilage repair has received 2.1 prior treatments, which are potential impediments to clinical outcome\(^{\text{65,66}}\). The time from the onset of symptoms to intervention (treatment delay) is an important factor in determining clinical outcome. This has been corroborated in a randomised controlled trial comparing microfracture to ACI\(^\text{\text{67}}\). It could well be that a disturbed joint homeostasis that comes with a cartilage defect as well as inactivity are important factors in causing this deterioration. Moreover, previous procedures, especially anterior cruciate ligament reconstruction are important factors to take into account when consulting a patient, as they can negatively affect treatment outcome. A recent larger study confirmed these findings\(^{\text{68}}\). In 142 patients treated with ACI, defects on the femoral condyles and trochlea, male gender, short duration of symptoms, small lesion size, younger age and lack of a previous intervention had a positive influence on clinical outcome, although others have found that gender does not influence clinical outcome.

TREATMENT ALGORITHM FOR (PROFESSIONAL) ATHLETES
A randomised controlled trial demonstrated that more active patients (as indicated by the Tegner score) achieved superior clinical results, regardless of treatment type\(^{\text{19}}\). In a 5-year follow-up study, ACI was found to be more durable in terms of (sport-related) activity compared to microfracture\(^{\text{69}}\). Interestingly, deterioration in sports activity has been observed after microfracture, possibly due to poor morphology of the repair tissue, defect fill and peripheral integration\(^{\text{15}}\). Nevertheless, microfracture has been found to be an effective short-term (up to 5 years) solution in different high-impact (professional) sports such as American football and soccer\(^{\text{31,36}}\). Thus, for fast return to play, especially from a (professional) athlete’s point of view, microfracture can be considered a reasonable choice. Given the shorter rehabilitation time, OAT may be considered a good alternative to microfracture and ACI. If a larger defect is found and a more durable repair is desirable, ACI may be the first treatment of choice. If it concerns a professional athlete and depending on the seasonal programme, a surgical debridement with an additional cartilage biopsy may allow fast return to play, delaying the need for re-implantation and subsequent rehabilitation to the off-season\(^{\text{70}}\).

SUMMARY
An increasingly active (athletic) population with high sport demands has triggered a rapid development of treatment modalities aimed at cartilage repair and restoring joint function. The current extensive literature includes a variety of treatment algorithms, which are needed, as there is a considerable variation in the availability of treatment options in the different healthcare systems around the world. Considering the literature, early diagnostics for cartilage defects and concomitant injuries are required, as a disturbed joint homeostasis and treatment delay reduce clinical outcome.

Debridement can be considered as initial treatment for defects <2 cm\(^2\) in less demanding patients, especially for defects found incidentally during arthroscopy and in mild to moderate OA\(^{\text{65,66}}\).

Full-thickness defects smaller than 2.5 cm\(^2\) respond well to microfracture and OAT, the latter being indicated in osteochondral defects.

For larger defects (>2.5 cm\(^2\)), cell therapy such as ACI is generally the treatment of choice. Depending on availability and experience, (fresh) osteochondral allograft transplantation or the ACI-sandwich technique (cells on top of an autologous bone graft) can be used in large osteochondral defects.

Cartilage repair for treatment of (early) OA is still in its infancy and an evidence-based algorithm is difficult to construct. As such, careful treatment selection is warranted, specifically in more advanced OA and younger patients. Tables 1 and 2 provide a summary of the constructed evidence-based treatment algorithm.

References
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CARTILAGE – SURGICAL OPTIONS TARGETED TOPIC