ACL UPDATE: OBJECTIVE MEASURES ON KNEE INSTABILITY (V MUSAHL, SECTION EDITOR)

Objective measurements of static anterior and rotational knee laxity

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Abstract Several devices allow to measure anterior and rotational static knee laxity. To date, the use of rotational laxity measurements in the daily clinical practice however remains to be improved. These measurements may be systematically integrated to the follow-up of knee injuries. Physiologic laxity measurements may particularly be of interest for the identification of risk factors in athletes. Furthermore, knee laxity measurements help to improve the diagnosis of knee soft tissue injuries and to follow up reconstructions. Further prospective follow-ups of knee laxity in the injured/reconstructed knees are however required to conclude on the best treatment strategy for knee soft tissue injuries.

Keywords Anterior cruciate ligament · Knee · Laxity · Diagnosis . Reconstruction

Introduction

Clinical assessment of knee laxity is useful to diagnose knee injuries and to evaluate the success of reconstruction procedures. Anterior and rotational knee laxity is usually evaluated manually with the Lachman, the anterior drawer,

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 \boxtimes Romain Seil rseil@yahoo.com the dial, or the pivot shift tests. The latter is recognized to be more closely correlated with "giving-way" episodes described by patients with anterior cruciate ligament (ACL) injuries as it tests the knee in more than one direction. Static tests, which evaluate the knee in one or several specific directions, are of higher interest to quantify laxity characteristics of the knee envelope as well as to diagnose and follow-up knee soft tissue injuries [[1\]](#page-5-0).

Devices to measure anterior and rotational knee laxity have been designed to reproduce manual tests and to allow for an objective and standardized evaluation of knee laxity. Static laxity measurements must be interpreted with caution as more than one structure contributes to restrain the knee in one direction. The primary restraint for anterior laxity between 0 and 30° of knee flexion is the ACL [\[2](#page-6-0)•]. Secondary restraints include the iliotibial band, the collateral ligaments, the menisci, and the popliteal tendon [\[2](#page-6-0)•]. Between 0 and 30° of knee flexion, internal rotation is primarily restrained by the posterior oblique ligament and the iliotibial band. Secondary restraints include the ACL, the medial collateral ligament (MCL), the menisci, the popliteal tendon, and the anterolateral ligament (ALL) [[2](#page-6-0)•]. It must be highlighted that contributing structures vary with the degree of knee flexion so that patient position and/or arthrometer must be chosen in relation to the structure(s) to be analyzed. The purpose of this article is thus to provide an overview of current devices and knowledge on static knee laxity measurements.

Arthrometers

Static anterior knee laxity

Devices measuring anterior knee laxity reproduce the Lachman test: the patient is lying supine and the knee tested

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at 20° of flexion. The patient must be relaxed as a muscle contraction may limit the anterior displacement [[3\]](#page-6-0). Furthermore, the leg must be tested in neutral rotation [[4\]](#page-6-0).

- KT-1000 and KT-2000 [\[5](#page-6-0)]: The KT-1000 is one of the most commonly used devices to measure anterior knee laxity. Its reproducibility was however questioned as examiner experience [\[6](#page-6-0)] and hand dominance [[7](#page-6-0)] have been reported to influence its measurements. The interrater error was estimated at 2.9 mm for experienced examiners [\[8](#page-6-0)].
- Stryker Knee Laxity Tester (Stryker, Kalamazoo, MI) [\[9](#page-6-0)]: The reliability of the Stryker Knee Laxity Tester is similar than for the KT-1000® with an Intraclass Correlation Coefficient (ICC) superior to 0.9 [[10\]](#page-6-0). More than 50 % of the displacement measured with the Stryker Knee Laxity Tester is due to soft tissues deformation at a load of 180 N [\[11\]](#page-6-0).
- Rolimeter (Aircast Europa, Neubeuern, Germany) [[12](#page-6-0)]: This arthrometer is as reliable as the KT-1000® [\[12,](#page-6-0) [13\]](#page-6-0) even when used by novice examiners [\[14\]](#page-6-0).
- GNRB (Genourob, Laval, France) [[15\]](#page-6-0): The GNRB® proposes a motorized application of the force. It is more reliable than the KT-1000® regardless of the examiner's experience [\[16](#page-6-0)]. Vauhnik et al. reported a low precision of the device with measurement errors up to 3.8 mm [[17\]](#page-6-0). However, much lower measurements errors of 1.2 mm have recently been reported [[18\]](#page-6-0) in a study that insisted strongly on the standardization of patient positioning and testing protocol.
- RadioStereometry Analysis (RSA) [[19\]](#page-6-0): This method requires the surgical implantation of intra osseous tantalum beads of a diameter of 0.8 to 1.6 mm [\[19](#page-6-0)]. To determine the anatomical positions of the markers, two orthogonal radiographs are obtained simultaneously. This tridimensional technique has a precision of 0.1 mm [\[20\]](#page-6-0) and is not influenced by skin movement artifacts [\[21](#page-6-0)]. It is however invasive.
- Telos Stress Device (Telos GmbH, Hungen-Obbornhofen, Germany): This method requires a lateral radiograph realized in a constraint position. The anterior displacement is represented between (1) a line perpendicular to both tibial plateau and tangent to the posterior corner of the medial condyle (2) perpendicular to both tibial plateau and tangent to the posterior border of the medial tibial plateau. Reliability of posterior displacement between testers is estimated to reach an ICC of 0.91 and the measurement errors reached 2.77 mm [\[22\]](#page-6-0).
- Lerat's method [[23](#page-6-0)]: In this invasive method, a mass of 9 kg is attached to the patient's thigh above his patella to induce a posterior translation of the femur compared to the tibia. This technique seems to be reliable with an intra-tester ICC superior to 0.9 [[24](#page-6-0)].

Static rotational knee laxity

Rotational knee laxity measurements of the tibia with respect to the femur are not yet used in the daily clinical practice. The amount of torque applied usually varies between 5 and 15 Nm depending on lower limb fixation and patient comfort. Most researchers apply this torque from internal to external rotation or from external to internal rotation to obtain a complete cycle of rotation. A solution to avoid the hysteresis phenomenon, which comes along with this technique and influences the reproducibility of the measurements [[25,](#page-6-0) [26\]](#page-6-0), is to perform separate measurements of internal and external rotation and to include "preconditioning trials."

Rotational knee laxity is influenced by the patient's position and by the location of rotation measurement. Knee rotation is higher if the knee is flexed at 90° compared to 20° and if the hip is extended compared to the flexed position at 90° [\[27](#page-6-0)]. To avoid overestimation of the measurements when rotation is measured at the foot, a solution is to measure tibial rotation directly at the proximal tibia via electromagnetic sensors [\[28](#page-6-0)].

- Rottometer [\[26\]](#page-6-0): The patient sits on a modified chair with knees and hips flexed to 90°. The inter-rater ICC varied between 0.49 and 0.85 depending on the amount of torque and degree of knee flexion. The highest ICC was obtained for the highest torque (9 Nm) and the higher degree of knee flexion (90°) [[29](#page-6-0)]. The measurements between examiners varied between −7.9° and 3.8° [\[29\]](#page-6-0).
- Device by Musahl et al. [\[30](#page-6-0)]: To measure the relative rotation of the tibia with regards to the femur, magnetic sensors are placed on the Aircast Foam Walker boot, on the medial surface of the proximal tibia and on the anterior surface of the thigh. The examiner holds the leg while applying the torque, which may influence muscle relaxation and flexion angles. An initial cadaver study reported a high intra- and inter-rater ICC (>0.94) [[30](#page-6-0)]. In 11 healthy subjects, the inter-rater ICC was the greatest at 90° of knee flexion (0.88). Measurement errors reached 3.2° for the total range of rotation at 90° of knee flexion and 5.1° at 30° [[31\]](#page-6-0). The average side-to-side difference (SSD) between normal knees was 3.5° [[31\]](#page-6-0).
- Device by Park et al. [\[32](#page-6-0)]: Park et al. [[32](#page-6-0)] presented the first motorized device to measure knee rotational laxity. The patient sits in a modified chair with the hips flexed at 85° and knees at 60°. No data is available on its reproducibility.
- Rotameter [[33](#page-6-0)]: Two prototypes of the Rotameter exist. In both versions, the subject is lying prone to reproduce the dial test position. Hips are extended and knees flexed at 30°. The Rotameter overestimates the total range of rotation at 5, 10, and 15 Nm by an average of 5, 10, and 25°, respectively [[33](#page-6-0)]. ICCs for these different torques were

superior to 0.67 [[34\]](#page-6-0). Regarding the second version of the Rotameter, it yields lower values for rotational laxity than the first device due to improvements in the standardization of the patient installation and joint fixation. The Minimum Detectable Change (MDC) has been determined to reach 4.2° for internal rotation and 5.9° for external rotation [[18](#page-6-0)]. Individualized normative references have been established taking into account gender and body mass [[18,](#page-6-0) [35](#page-6-0)].

- Robotic Knee Testing system [[36\]](#page-6-0): The patient lies supine with knees flexed at 25°. Electromagnetic sensors placed on the proximal tibia showed that tibial rotation represented in average 48.7 % of the total rotation measured at the foot [\[36\]](#page-6-0). Inter-rater ICC for total range of rotation reached 0.97 at a torque of 5.65 Nm [[36\]](#page-6-0). The average expected difference between two measurements as measured with the repeatability coefficient reached 6.9° for internal rotation and 3.5° for external rotation [\[37](#page-6-0)].
- Rotational Measurement Device [[38\]](#page-6-0): Subjects are positioned at 90° of knee flexion. Measurement at the foot overestimated rotation on average by 136 % compared to the Rotational Measurement Device. The latter only slightly overestimated rotation (2°) compared to electromagnetic sensors placed on the tibia [\[38\]](#page-6-0). Intra-rater ICC of the device reached 0.9 [\[38\]](#page-6-0).

Static multiplanar laxity

- Genucom Knee Analysis System (FARO Medical Technologies, Montreal, Ontario, Canada): This arthrometer allows to measure antero-posterior laxity and rotational and varus-valgus laxity [\[39](#page-6-0)]. At 20° of knee flexion, the least significant difference reached 17.5°. In other words, a difference of 17.5° is required to indicate a real change in rotational laxity of a tested person between 2 measurements [\[40\]](#page-6-0).
- Vermont Knee Laxity Device [\[41\]](#page-7-0): The Vermont Knee Laxity Device measures anterior, rotational, and varusvalgus laxity. The subject lies supine with knees flexed at 20° and hips at 10°. The intraclass correlation coefficient (ICC) is above 0.86 for internal, external, and total range of rotation [[42](#page-7-0)]. Measurement errors were evaluated at 5 to 7°, respectively, for internal (IR) and external rotation (ER) [[42](#page-7-0)].

Knee laxity in the non-injured knee

Physiological laxity represents the amount of laxity which is considered to lie within the "normal" range and is specific to every individual.

Physiological laxity, knee function, and injuries

The contralateral knees of ACL-injured patients display greater anterior and rotational knee laxity than knees of healthy individuals [\[36](#page-6-0), [43](#page-7-0), [44,](#page-7-0) [45](#page-7-0)•]. As such, increased physiological laxity could be a risk factor for ACL injuries. Indeed, subjects with excessive physiological knee laxity have been reported to have movement patterns associated with non-contact ACL injury mechanisms. They display greater hip and knee movements in the transverse, sagittal, and frontal planes during drop landings [[46\]](#page-7-0). Furthermore, they have greater increase in anterior and rotational knee laxity with exercise and fatigue [\[47](#page-7-0)•, [48\]](#page-7-0).

Even though the influence of physiological knee laxity on knee function has not been clearly established, several studies suggest it could influence the outcome of ACL reconstructions [[49](#page-7-0)–[51](#page-7-0)]. After ACL reconstruction with a bonepatellar-tendon-bone graft (BPTB), patients with an increased physiological laxity have lower Lysholm [\[50](#page-7-0), [51](#page-7-0)] and IKDC subjective [\[49](#page-7-0)–[51](#page-7-0)] scores. As preoperative scores were not reported, it remains unclear whether lower outcomes are the consequence of the ACL reconstruction or of the injury itself.

Influencing factors

Although gender has been previously reported to significantly influence anterior knee laxity, several studies reported a minor difference of less than 1.5 mm [[43,](#page-7-0) [52](#page-7-0)–[54](#page-7-0)]. As for rotational knee laxity, it has been shown that women have up to 40 % higher knee rotation compared to men [[32\]](#page-6-0). This difference has been confirmed by several investigations [\[18,](#page-6-0) [32](#page-6-0), [36](#page-6-0), [55\]](#page-7-0). It may represent one of the factors explaining the higher risk for ACL injuries in females. Body mass also influences rotational laxity with increased body mass being related to lower knee rotation [[18,](#page-6-0) [56](#page-7-0)].

Age does not influence anterior or rotational knee laxity measurements in adults [[18,](#page-6-0) [53,](#page-7-0) [55\]](#page-7-0). However, increased anterior and rotational knee laxity in the pediatric population has been observed [\[57](#page-7-0)–[59\]](#page-7-0). Knee laxity is indeed reported to develop during knee growth and maturation. It stabilizes at approximately 14 years for girls and 16 years for boys [\[57](#page-7-0)–[59\]](#page-7-0). Unlike in adults, no difference has been observed in the pediatric population between boys and girls both in anterior and rotational knee laxity [\[57,](#page-7-0) [58\]](#page-7-0).

The influence of the menstrual cycle on knee laxity has also been debated [\[60\]](#page-7-0), and a recent systematic review revealed that six out of nine studies found no significant variation of anterior knee laxity throughout the menstrual cycle. Two other studies reported a significant variation of knee laxity during the menstrual cycle of about 0.5 mm and the last study of 1.5 mm [\[61](#page-7-0)]. These observed variations are minor and the ability of existing devices to detect such little differences can

be questioned. As for rotational knee laxity, no variation during the menstrual cycle could be observed [\[62\]](#page-7-0).

An association may also exist between lower extremity alignment and knee laxity. Shultz et al. [\[63](#page-7-0)] demonstrated that a greater genu recurvatum and a greater navicular drop were predictors of a greater anterior knee laxity. In another study, the authors determined the different knee laxity profiles existing in healthy subjects when considering anterior, rotational, and varus-valgus knee laxity as well as genu recurvatum [[56](#page-7-0)]. The subjects with increased laxities were characterized by greater navicular drop, lower BMI, lower Q-angle, lower tibial torsion, lower quadriceps peak torque and shorter femur length compared to subjects with decreased laxities. Some differences were however minor and their clinical meaning is not yet established.

Normative references

Although laxity measurements overestimate knee laxity, normative references must be established to define "normal" laxity for each device. Mouton et al. proposed a methodological approach to calculate standardized laxity scores for anterior and rotational knee laxity taking into account influencing individual characteristics [[18\]](#page-6-0). For rotational knee laxity, sex and body mass were found to significantly influence its measure and to explain a non-negligible amount of the variability in internal and external rotation (46 to 60 %). As a consequence, the latter parameters were taken into account to calculate an individualized score which has the advantage to allow for the direct comparison of individuals, regardless of differences in sex or body mass.

The different laxity types (sagittal and rotational) have recently been shown to be only weakly correlated [[18](#page-6-0), [54\]](#page-7-0). The consideration of both laxities may thus provide complementary information and should allow to establish more detailed individual knee laxity profiles. The existence of knee laxity profiles have been suggested [[56\]](#page-7-0). By combining measurements of anterior displacement and internal and external rotation, Mouton et al. showed that only 32 % of the participants displayed a laxity profile with all three scores within the average plus or minus one standard deviation [[18](#page-6-0)]. The diversity of the identified profiles highlights both the complexity of multidirectional knee laxity and the necessity for individualized care of knee injuries and diseases.

Knee laxity in the injured knee

Diagnosis of ACL injuries

The diagnosis of ACL injuries with arthrometers is currently based on the SSD observed in anterior laxity measurements between the injured and the healthy knee. The "gold standard" to describe the objective function of the knee is currently the IKDC objective score. It allows to classify laxity in four grades. A SSD in anterior laxity inferior to 3 mm is classified as normal (grade A), between 3 and 5 mm as nearly normal (grade B), between 6 and 10 mm as abnormal (grade C), and superior to 10 mm as severely abnormal (grade D). This classification has never been questioned and it is generally accepted that a SSD greater than 3 mm relates to an ACL injury regardless of the device used to measure anterior knee laxity.

At this threshold, the KT-1000® performed at a maximal manual force seem to display the highest sensitivity and specificity for the diagnosis of complete ACL injuries compared to other devices (Table [1\)](#page-4-0). It is important to highlight that most studies reported the sensitivity and the specificity of arthrometers to diagnose ACL injuries by only considering complete ACL tears, which are the easiest to detect. With the GNRB®, for all types of ACL tears (including total tears, partial tears, and ligament remnants) and regardless of associated meniscocapsular injuries, the sensitivity and specificity of the GNRB® reached, respectively, 75 and 95 % for the ATD at 200 N and an optimal threshold of 1.2 mm [\[67](#page-7-0)•].

To improve the diagnosis of ACL injuries, additional analysis of rotational knee laxity has been proposed [[68](#page-7-0)]. Cadaveric studies revealed that the section of the ACL led to 2.4 to 4° increase in rotation in knee flexion angles below 30° [\[69](#page-7-0), [70\]](#page-7-0). Above this degree of flexion, the increase in rotation induced by the lesion was not detectable anymore [\[25,](#page-6-0) [71\]](#page-7-0). Early in vivo studies demonstrated a similar increase of rotation in the injured knee by 10 % (3°) compared to the healthy knee [\[72](#page-7-0)]. More specifically, the posterolateral bundle may play a specific role in restraining rotation as its section induced the major increase (3° at 5 Nm) in internal rotation [\[73](#page-7-0)]. To date, only the sensitivity and specificity of the Rotameter to detect an ACL injury has been reported in the literature [[67](#page-7-0)•]. A threshold of 3.2° for the SSD in internal rotation at 5 Nm allowed to correctly identify 38 % of patients (sensitivity) and reject 95 % of healthy subjects (specificity). Although the sensitivity appears to be low, it remains superior to the sensitivity of 24 % reported for the pivot shift test in a previous meta-analysis [[74\]](#page-7-0).

The different characteristics of the force-displacement curve (i.e., slope, representative of knee stiffness) have not been deeply explored yet in the context of ACL injuries. In the 1980s, this characteristic was shown to be modified in the ACL-injured knee [\[72](#page-7-0), [75](#page-7-0)], but its use in the diagnosis of ACL injuries has only been recently proposed [\[15](#page-6-0), [76](#page-7-0)]. To further improve the diagnosis of ACL injuries, consideration of the slope is advised as it has been shown to increase the specificity of anterior and rotational knee laxity tests to 100 %. As a result, simultaneous consideration of displacement and knee stiffness provide a test without a false positive [[67](#page-7-0)•].

The concomitant analysis of anterior and rotational knee laxity measurements as well as the concomitant analysis of

the SSD in final displacement and of the slope of the load– displacement curve further improves the diagnosis of ACL rupture. With this combination, a positive result was correct in 100 % of patients (sensitivity: 81 %) regardless of the subtype of the ACL tear and the associated injuries [[67](#page-7-0)•]. This performance is similar to the one reported for MRI (sensitivity 81 %, specificity 96 %) [[77\]](#page-7-0).

Further considerations for diagnosis

The studies which investigated the diagnostic performance of arthrometers were often limited to patients with complete ACL lesions. Based on arthroscopy, it is however possible to differentiate partial tears (the antero-medial bundle being more often concerned than the posterolateral one) from complete ACL lesions presenting either as a totally resorbed ligament or as a healed remnant on the intercondylar notch or the PCL [\[78\]](#page-7-0). These different lesions influence the SSD observed in anterior and rotational knee laxity measurements [\[76](#page-7-0), [79](#page-8-0)–[82](#page-8-0)]. As such, only considering complete tears to evaluate the diagnostic performance of an arthrometer cannot reflect its true diagnostic capacity. It is thus preferable to consider all kinds of ACL lesions and to determine if different types can be identified prior to surgery [[67](#page-7-0)•].

It is recommended to take into account associated lesions when interpreting the laxity measurements in the context of diagnosis to avoid false positives. Indeed, only 40 % [[83\]](#page-8-0) of all ACL lesions can be considered as isolated. A lesion of the collateral ligaments may influence tibial rotation [[84\]](#page-8-0) while a medial meniscus lesion can modify anterior displacement due to its stabilizing role in ACL ruptures [[84\]](#page-8-0).

Fig. 1 Follow-up of anterior knee laxity (GNRB) in a female patient who sustained a knee injury during alpine skiing at the age of 18. The ACL was not reconstructed and she was addressed to our hospital at the age of 21. A nonoperative treatment was initiated and regular laxity measurements were performed. During this year of follow-up, her laxity

increased (in red: injured knee −1/2/3/4). A decision for ACL reconstruction was finally taken. The healthy knee (green) was stable and reproducible over time (less than 0.8 mm difference between the four tests)

While rotational knee laxity is mainly investigated in ACL injuries, it may also be of interest in other lesions such as posterolateral corner injuries. These injuries indeed induce an increase in tibial external rotation of 6 to 14° [\[85](#page-8-0), [86](#page-8-0)], resulting in a posterolateral rotational instability. Clinically, these injuries are best assessed with the dial test [[87\]](#page-8-0). The latter does not allow for an objective assessment but, to the authors' knowledge, results of instrumented measurements have never been reported in such injuries. Finally, as knee osteoarthritis affects rotational knee laxity [\[88](#page-8-0)], rotational knee laxity measurements may also have the potential to be an indicator of the type and severity of osteoarthritis.

Knee laxity after anterior cruciate ligament reconstruction

Ligament reconstruction surgery aims to restore knee laxity in all directions. Knee laxity measurements are therefore of interest as a postoperative control to follow the graft evolution (Fig. [1](#page-4-0)) and detect potential anomalies like elongation, recurrent tears, increased postoperative laxities. These may occur in graft malpositioning [\[89](#page-8-0), [90\]](#page-8-0) or graft failures [[91](#page-8-0)]. Numerous studies reported knee laxity measurements at a specific time point after ACL reconstruction. Their conclusions are difficult to generalize, due to the diversity of graft types, surgical techniques, fixations, associated injuries, rehabilitation approaches, but also the measurement techniques. Prospective follow-up studies with systematic measurements of knee laxity are missing, so that the current knowledge on postoperative changes of knee laxity and on the graft ligamentisation process is poor.

This lack of methodological scientific evidence may explain why many studies have shown no difference in anterior laxity after different types of surgical reconstruction between a bone-patellar tendon-bone (BPTB) and a semitendinosus (ST) autograft [\[92](#page-8-0)–[94](#page-8-0)]. However, two meta-analyses comparing the two main graft types (BPTB vs. ST) have demonstrated that a SSD superior to 3 mm was less frequent in BTPB compared to ST grafts [[95](#page-8-0), [96](#page-8-0)]. Regarding the use of allografts, some authors reported similar outcomes compared to autografts [[97](#page-8-0), [98](#page-8-0)], while others suggested that they may be inferior [\[99](#page-8-0)]. As for the double-bundle HS autograft technique, there are indications suggesting that it may be superior in terms of sagittal and rotational laxity [[100](#page-8-0)–[102](#page-8-0)].

The current knowledge on knee laxity after ACL reconstructions as well as after many other surgical interventions thus needs to be improved. For example, medial meniscectomy may influence postoperative knee laxity [[84\]](#page-8-0). The same conclusion holds true for the anterolateral capsular structures of the knee [[103](#page-8-0)]. As for posterolateral corner injuries, Tardy et al. reported that external rotation was in average similar to a healthy control group after reconstruction [[104\]](#page-8-0).

The authors also found a remaining increase in internal rotation of the tibia in 40 % of patients. They assumed that this finding was either due to the surgical technique or to associated lesions and/or unrecognized soft tissue damage at the time of injury.

Conclusions

Static knee laxity measurements offer the possibility to improve the understanding of the capsuloligamentous knee envelope, both in healthy and injured knees as well as after different types of reconstruction procedures. The recent development of rotational laxity measurement devices has added significant knowledge to the field. The combination of knee laxities is now possible and has led to the concept of knee laxity profiles in healthy knees. The high variability between individuals as well as the ability to identify knees with increased physiological knee laxity may be of interest in the screening and prevention programs for athletes. Indeed, subjects with excessive physiological knee laxity may have a greater risk to sustain an ACL injury as well as to display inferior outcomes after an ACL reconstruction.

The combination of laxity assessments in ACL-injured knees has shown to improve the diagnostic capacity of arthrometers. Although the knowledge of preoperative knee laxity measurements is evolving, some factors are still insufficiently understood. The same holds true for postoperative laxity measurements after ligament reconstructions. As such, future studies may help not only to individualize the care of knee injuries but also to improve the understanding of degenerative diseases.

Compliance with ethical standards

Conflict of interest Caroline Mouton, Daniel Theisen, and Romain Seil declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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