

The Clinically Important Difference and Patient Acceptable Symptomatic State for Commonly Used Patient-Reported Outcomes After Knee Cartilage Repair

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Background: In patients undergoing cartilage restoration of the knee, limited information is available regarding clinically important difference (CID) and Patient Acceptable Symptomatic State (PASS) estimates for commonly used patient-reported outcome measures (PROMs).

Purpose: The objective of this study was to determine the CID and PASS in the population with knee cartilage restoration for the Knee injury and Osteoarthritis Outcome Score (KOOS), the International Knee Documentation Committee Subjective Knee Form (IKDC) score, and the Lysholm score.

Study Design: Cohort study (Diagnosis); Level of evidence, 2.

Methods: Between 2012 and 2017, patients who underwent a cartilage restoration procedure were prospectively enrolled. Patients completed the KOOS, IKDC, and Lysholm, all of which were scored from 0 to 100, and completed relevant anchor questions at baseline and 1 year postoperatively. Receiver operating characteristic curve analyses were conducted to determine CID and PASS cutoff points. Multivariable regression analyses were performed to determine the effect of age, sex, and baseline score on likelihood of achieving CID and PASS.

Results: Of the 113 patients enrolled, 53 (47%) were male, and the mean age was 36 years. The CID values for the PROMs were 10.7 for KOOS Symptoms, 8.3 for KOOS Pain, 8.8 for KOOS Activities of Daily Living (ADL), 30.0 for KOOS Sports and Recreation, 18.8 for KOOS Quality of Life (QOL), 9.2 for IKDC, and 13.0 for Lysholm. The PASS values were 71.5 for KOOS Symptoms, 72.2 for KOOS Pain, 86.8 for KOOS ADL, 43.8 for KOOS Sports and Recreation, 50.0 for KOOS QOL, 62.1 for IKDC, and 70.0 for Lysholm. Patients with higher baseline scores were more likely to achieve PASS for the IKDC (odds ratio, 2.28; $P = .03$). Baseline score did not have an effect on the likelihood of achieving CID. Younger age was an independent predictor of achieving PASS and CID across all outcomes ($P < .05$), but sex did not have such an effect.

Conclusion: This study determined CID and PASS values for the KOOS, IKDC, and Lysholm scores among patients treated with knee cartilage restoration. Younger age was a positive prognostic variable, and higher baseline scores implied achieving PASS for the IKDC. The information in this study can be used in designing randomized controlled trials, counseling individual patients as to anticipated outcomes, and conducting responder analyses when evaluating new cartilage technology from a regulatory perspective.

Keywords: clinically important difference; Patient Acceptable Symptomatic State; patient-reported outcome measures; cartilage restoration; cartilage repair; knee

In patients undergoing knee cartilage repair and/or joint preservation procedures, the ultimate goal is to generate or replace the defect with hyaline or hyaline-like cartilage; to normalize articular congruity; and to improve patient function, disability, and health.⁹ With respect to the last,

the International Cartilage Regeneration and Joint Preservation Society has endorsed the use of the International Knee Documentation Committee (IKDC) Subjective Knee Form and the Knee injury and Osteoarthritis Outcome Score (KOOS) because they represent 2 patient-reported outcome measures (PROMs) that fulfill the basic requirements for reliability, validity, and responsiveness in patients who undergo cartilage repair.¹³ Most commonly, such patient-reported outcomes (PROs) have been expressed as continuous data at the group level (ie, mean and SD), which can be difficult to interpret for many

readers and challenging to translate to the responses of individual patients.¹⁵ Additionally, the US Food and Drug Administration (FDA) has clearly indicated that individual-level response or “responder” analyses are required for the evaluation and approval of medical devices and technologies.¹⁵ Two concepts have been developed to aid in the understanding of outcome scores at the individual level: the clinically important difference (CID) and the Patient Acceptable Symptomatic State (PASS).

Jaeschke et al⁵ originally defined the term *minimal clinically important difference* (MCID) as “the smallest difference which patients perceived as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.”^{5,6} Norman et al¹⁰ defined CID as a difference that is clinically important (determined by the method of quantification) but not necessarily in any sense “minimal.”⁶ The PASS defines a level of symptoms below which patients consider themselves well and above which they consider themselves unwell.⁷ Unlike the CID, the PASS is an absolute value and not a change score.¹⁷ Another way to think of it is that the CID deals with the concept of improvement or “feeling better” whereas the PASS deals with well-being or “feeling good.”¹⁷ Both terms are clinically relevant for patients at the individual level and can be used to express results in clinical trials as the proportion of “improved” patients in the various treatment arms.¹⁷ As such, both the PASS and the CID are clinically relevant treatment targets and provide critical information to researchers for the design of studies that require sample size and power calculations.¹⁴

The 3 most common strategies used to determine the CID are the anchor-based, distribution-based, and opinion-based methods.^{6,14} The FDA’s final guidance to industry for demonstration of effectiveness using PROMs stated that the anchor-based approach should provide the primary evidence in determining *responder definition* (defined as the “individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit”).¹⁸ Anchor-based approaches rely on the relationship between the responses to the outcome instrument being evaluated and independent measures of improvement (ie, anchors). Examples of the latter include global transition questions or a “known-groups” approach with established clinical anchors.^{6,14}

The objective of this study was to determine the CID and PASS of commonly used PROMs in patients undergoing surgery for articular cartilage defects of the knee.

Determining the CID and PASS for these instruments would provide a useful clinical endpoint for decision making at the individual level and outcome assessment in large clinical trials. Furthermore, determining such clinical targets is a requirement by the FDA to demonstrate effectiveness of novel technologies in cartilage repair. We hypothesized that reliable estimates of CID and PASS values could be established using an anchor-based approach for the aforementioned treatment population.

METHODS

Design

This was a prospective longitudinal cohort study conducted at a high-volume tertiary care center that specializes in cartilage restoration of the knee. Institutional review board approval was obtained before the start of the study (No. 11102711-IRB01).

Participants

Inclusion criteria were as follows:

1. Individuals between the ages of 18 and 65 years with a symptomatic articular cartilage defect of the knee (Outerbridge grade 3 or 4) involving the femoral condyle, trochlea, or patella.
2. Possible surgical interventions included debridement, drilling, microfracture, augmented microfracture, osteochondral autograft or allograft transfer, autologous chondrocyte implantation, or DeNovo Natural Tissue (articulated articular cartilage; Zimmer). The aforementioned procedures could be performed in isolation or combined with a meniscal transplant, anterior cruciate ligament reconstruction, and/or periarticular knee osteotomy.

Exclusion criteria were as follows:

1. Bilateral knee or concomitant hip, foot, or ankle pathology contributing to overall impairment.
2. Associated ligamentous instability that was not corrected surgically.
3. Presence of widespread arthritis (ie, diffuse compartmental grade 3 or 4 Outerbridge changes) in the knee.
4. Lack of informed consent or inability to follow-up for a minimum of 1 year postoperatively.

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5. English language skills precluding completion of the questionnaires.

Procedures

Potential participants were identified preoperatively through history, physical examination, and magnetic resonance imaging findings. They were approached by a research assistant for participation and informed consent. Individuals who consented to participate completed baseline questionnaires including a demographic form, the KOOS, the IKDC Subjective Knee Form, and the Lysholm score. At surgery, all arthroscopic findings were documented and included findings from the examination under anesthesia, status of the cruciate ligaments, the Outerbridge grade of each articular surface, size of cartilage lesions, status of the menisci (previous resection, morphologic features of tear, treatment required), and details of the procedure itself. If the eligibility criteria were met, the patients continued in the study and completed the aforementioned outcome measures 1 year postoperatively as well as the anchor questions described below.

Standardized Measures

The KOOS includes 42 items in 5 separately scored subscales: Pain; Other Symptoms; Activities of Daily Living (ADL); Function in Sports and Recreation (Sports/Rec); and Knee-Related Quality of Life (QOL).¹ Each subscale is scored from 0 to 100 (worst to best). The IKDC Subjective Knee Form is a PROM that assesses symptoms, daily activity, and sports function due to a variety of knee conditions. It consists of 18 items that are summed and expressed as a percentage of the maximal total possible score. Scores range from 0 to 100 (worst to best).¹ The Lysholm score is an 8-item questionnaire that is scored from 0 to 100 (worst to best); it is filled out by a health care professional and focuses mainly on knee-specific symptoms including locking, instability, pain, swelling, stair climbing, and squatting.¹⁶

An anchor-based approach was used to determine the CID. For the KOOS, 5 global questions (related to each KOOS subscale) were used to determine whether patients were the same, had improved, or had deteriorated compared with the preoperative state: "Since your surgery, has there been any change in your *pain/symptoms/activities of daily living/sport and recreation/quality of life* as it is related to your knee?" For the IKDC and Lysholm, patients were asked, "Since your surgery, has there been any change in the overall function of your knee?" The response options for each of these questions were -7, a very great deal worse; -6, a great deal worse; -5, a good deal worse; -4, moderately worse; -3, somewhat worse; -2, a little worse; -1, almost the same, hardly any worse at all; 0, no change; 1, almost the same, hardly any better at all; 2, a little better; 3, somewhat better; 4, moderately better; 5, a good deal better; 6, a great deal better; 7, a very great deal better.

The anchor question designed by Tubach et al¹⁷ was used to determine the PASS for all the subscales of the KOOS and the overall IKDC score. At each follow-up,

patients were asked the following binomial (yes/no) question: "Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?"

Analysis Plan

As per the definition of Juniper,⁶ a score of 0, -1, or 1 on the global rating of change question was classified as "unchanged." We classified patients whose score was greater than or equal to +2 as having experienced a CID. A receiver operating characteristic (ROC) curve analysis was used to determine the cutoff point that optimally defined the CID based on sensitivity and specificity values for each observed change score.⁶ The PASS was also determined using a ROC curve analysis to define cutoff points for each PROM among patients who considered their state satisfactory. The area under the ROC curve (AUC) was calculated to assess reliability. An AUC value of 0.7 to 0.8 was regarded as acceptable, and an AUC value of 0.8 to 0.9 was regarded as excellent.² Multivariable regression analyses were performed to determine the effect of age, sex, and baseline score on CID and PASS estimates. *P* values <.05 were considered statistically significant. All statistical analyses were performed in SAS Version 9.2 (SAS Institute Inc).

RESULTS

The study included 113 patients with a mean \pm SD age of 36.2 ± 11.1 years, and 47% ($n = 53$) of participants were male. The mean body mass index was 27.4 ± 5.3 , and 15% ($n = 17$) of patients had workers' compensation claims. Whereas 58% ($n = 66$) of patients had previous knee surgery of some sort, 38% ($n = 43$) of the sample actually had a previous chondral procedure before enrollment.

The cartilage repair technique used for treatment at the time of study enrollment included 43% ($n = 49$) osteochondral allograft, 12% ($n = 13$) autologous chondrocyte implantation, 12% ($n = 13$) microfracture, 31% ($n = 35$) chondroplasty/debridement, and 3% ($n = 3$) particulated articular cartilage allograft. The mean size of the treated chondral lesion was 2.7 ± 1.6 cm². With respect to defect location, 23% ($n = 25$) of lesions were in the lateral femoral condyle; 36% ($n = 41$), medial femoral condyle; 30% ($n = 34$), patella; and 8% ($n = 9$), trochlea. We noted that 13% ($n = 15$) of the sample had a concomitant ipsilateral compartment meniscal allograft transplant, whereas 16% ($n = 18$) had an unloading osteotomy of the affected compartment. No patients had concomitant anterior cruciate ligament reconstruction.

Overall baseline and 1-year scores for the KOOS subscales, IKDC score, and Lysholm score are reported in Table 1. The CID and PASS values for the aforementioned PROMs at the 1-year follow-up are reported in Tables 2 and 3, respectively. Although we noted no floor effects for any of the outcomes at 1 year, ceiling effects were low and were observed as follows: KOOS Symptoms, 6%;

TABLE 1
Scores at Baseline and 1 Year^a

	Baseline			1 y		
	Mean ± SD	Median (IQR)	Range	Mean ± SD	Median (IQR)	Range
KOOS Symptoms	58.9 ± 16.6	60.7 (46.4-67.9)	14.3-96.4	75.5 ± 17.3	78.6 (64.3-89.3)	25.0-100
KOOS Pain	52.7 ± 14.8	52.8 (41.7-66.7)	16.7-86.1	70.2 ± 17.5	75.0 (59.7-83.3)	13.9-97.2
KOOS Activities of Daily Living	65.5 ± 17.3	66.2 (52.9-79.4)	22.1-100	82.7 ± 17.0	86.8 (73.5-97.1)	8.8-100
KOOS Sports and Recreation	28.7 ± 19.1	30.0 (15.0-40.0)	0-85.0	51.6 ± 28.8	55.0 (25.0-75.0)	0-100
KOOS Quality of Life	20.9 ± 15.5	18.8 (6.3-31.3)	0-68.8	46.1 ± 25.3	46.9 (31.3-62.5)	0-100
IKDC	38.8 ± 12.0	39.1 (31.5-46.0)	12.6-67.2	59.8 ± 20.3	62.6 (44.0-74.8)	14.4-100
Lysholm	46.8 ± 16.7	48.0 (35.0-57.0)	12.5-90	70.8 ± 19.5	73.0 (61.0-84.0)	11.0-100

^aIKDC, International Knee Documentation Committee Subjective Knee Form; IQR, interquartile range; KOOS, Knee injury and Osteoarthritis Outcome Score.

TABLE 2
Optimal Cutoff Points for the CID of the KOOS, IKDC Score, and Lysholm Score^a

	CID Grouping, +2 to +7		ROC Analysis	
	No.	Change Score, Mean ± SD	Optimal Change Score Cutoff	AUC
KOOS Symptoms	71	16.9 ± 17.8	10.7	0.71
KOOS Pain	69	17.8 ± 19.2	8.3	0.70
KOOS Activities of Daily Living	70	17.7 ± 17.7	8.8	0.70
KOOS Sports and Recreation	59	23.3 ± 24.9	30.0	0.72
KOOS Quality of Life	66	25.6 ± 24.3	18.8	0.85
IKDC	71	21.0 ± 18.9	9.2	0.85
Lysholm	71	23.6 ± 22.8	13.0	0.74

^aAUC, area under the curve; CID, clinically important difference; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee injury and Osteoarthritis Outcome Score; ROC, receiver operating characteristic curve.

KOOS Pain, 0%; KOOS ADL, 9%; KOOS Sports/Rec, 3.5%; KOOS QOL, 1.8%; IKDC, 1.8%; Lysholm, 3.5%.

Our multivariable analyses demonstrated that baseline score (upper vs lower 50th percentile) did not have an effect on the likelihood of achieving CID for the IKDC score, KOOS subscales, or Lysholm score. In contrast, patients who had a higher baseline score (upper 50th percentile) were statistically more likely to achieve PASS for the IKDC (odds ratio, 2.28; $P = .03$). Among patients with higher baseline scores, a trend was observed toward being more likely to achieve the PASS for the KOOS Sports/Rec subscale alone (odds ratio, 1.99; $P = .07$). Younger age, but not sex, was an independent predictor of achieving PASS and CID across all the outcome measures in this study ($P < .05$).

Table 4 reports the proportion of patients who achieved the MCID, PASS, or both across all outcome measures of interest. We found that 71%, 65%, and 69% of patients achieved the CID for KOOS Pain, KOOS Symptoms, and IKDC, respectively. Further, 58%, 61%, and 50% of the sample achieved PASS for KOOS Pain, KOOS Symptoms, and IKDC, respectively. We noted that 52% of treated patients achieved both CID and PASS values for the KOOS Pain subscale. For all remaining outcome measures, less than half of the patients achieved both CID and PASS values. A general conclusion from these findings is that

two-thirds of patients can be expected to achieve the CID for KOOS Pain, KOOS Symptoms, and IKDC.

Table 4 also illustrates that the percentage of patients with a baseline score at or above the PASS threshold was lowest for the IKDC (4%) and highest for the KOOS Sports/Rec subscale (22%). We also observed that baseline scores had a minimal effect on ability to achieve CID. The proportion of patients who could not achieve CID across PROMs due to a high baseline score ranged from 0% to 5%.

DISCUSSION

In a diverse population of patients undergoing cartilage restoration procedures of the knee, we have reported estimates of the CID and PASS for the KOOS, IKDC score, and Lysholm score at 1 year after surgical intervention. Our findings are significant because they can inform the design of future clinical trials related to cartilage restoration and provide benchmarks for the clinical improvement expected from individuals when undergoing treatment using novel cartilage repair technologies. From a regulatory perspective, such responder analyses will allow for the selection of appropriate technologies for patients. Rather than just analyze a given treatment in terms of means and SDs at the group level, we can assess patients

TABLE 3
Optimal Cutoff Points for the PASS of the KOOS, IKDC Score, and Lysholm Score^a

	Score, Mean ± SD		ROC Analysis	
	Did Not Achieve PASS (n = 56)	Achieved PASS (n = 57)	Optimal Final Score Cutoff	AUC
KOOS Symptoms	67.6 ± 18.3	83.2 ± 12.2	71.5	0.75
KOOS Pain	60.2 ± 17.8	80.0 ± 10.4	72.2	0.84
KOOS Activities of Daily Living	73.6 ± 18.6	91.6 ± 8.9	86.8	0.83
KOOS Sports and Recreation	34.6 ± 25.9	67.9 ± 21.0	43.8	0.83
KOOS Quality of Life	29.3 ± 19.9	62.4 ± 18.4	50.0	0.89
IKDC	45.8 ± 15.1	73.4 ± 14.6	62.1	0.90
Lysholm	58.1 ± 17.8	81.4 ± 13.8	70.0	0.87

^aAUC, area under the curve; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee injury and Osteoarthritis Outcome Score; PASS, Patient Acceptable Symptomatic State; ROC, receiver operating characteristic curve.

TABLE 4
Patients Achieving CID and/or PASS and an Analysis According to Baseline Scores^a

	Above Optimal Scores on CID, n (%)	Above Optimal Scores on PASS, n (%)	Above Optimal Scores on CID and PASS, n (%)	Baseline Score at or Above PASS, %	Baseline Score Preventing Patients From Achieving CID, %
KOOS Symptoms	73 (65)	69 (61)	54 (48)	17	3
KOOS Pain	80 (71)	65 (58)	59 (52)	11	0
KOOS Activities of Daily Living	72 (64)	52 (46)	42 (37)	10	5
KOOS Sport and Recreation	46 (41)	70 (62)	45 (40)	22	2
KOOS Quality of Life	57 (50)	56 (50)	44 (39)	5	0
IKDC	78 (69)	56 (50)	53 (47)	4	0
Lysholm	46 (41)	44 (39)	34 (30)	8	1

^aCID, clinically important difference; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee injury and Osteoarthritis Outcome Score; PASS, Patient Acceptable Symptomatic State.

at the individual level and analyze outcomes according to the proportion of patients who achieve CID and/or PASS estimates across treatment arms.

Over the past several years, efforts have been made to determine clinically relevant changes across multiple PROMs after cartilage surgery of the knee. In 2010, Greco et al⁴ studied 50 patients undergoing a variety of cartilage procedures (debridement, shaving, drilling, autologous chondrocyte implantation, abrasion arthroplasty, microfracture) and used an anchor-based approach to determine the MCID for the IKDC, Western Ontario and McMaster Universities Osteoarthritis Index, Cincinnati Knee Rating System, and various domains of the 36-Item Short Form Health Survey. The observed MCID for the IKDC was 6.3 in the Greco et al study compared with a CID of 9.2 in our study. Greco et al did not provide any estimates for the KOOS or Lysholm scores or for the PASS after cartilage repair. Liu et al⁸ established MCID and PASS thresholds for the IKDC, Lysholm, and KOOS at 12 months after patients were treated using meniscal allograft transplant. Limitations of that study were that a distribution-based approach was used to calculate the MCID and the sample size for the PASS data was only 34 patients. Wang et al¹⁹ conducted a 2-year prospective follow-up study to determine MCID and substantial clinical benefit

(SCB) estimates for the IKDC and Knee Outcome Score Activities of Daily Living scale among patients treated using either osteochondral autograft or allograft transplant. The strengths of this study were the large sample size (n = 173), the use of an anchor-based approach, and optimized internal validity because of the focus on a particular surgical technique. Finally, Ogura et al^{11,12} used anchor- and distribution-based approaches to calculate MCID and SCB estimates for the KOOS, IKDC, Lysholm, and 12-Item Short Form Health Survey 1 year after osteochondral allograft transplant¹² or autologous chondrocyte implantation.¹¹ Details of the methods and estimates of clinically relevant improvements for the aforementioned studies are summarized in Table 5.

One of the strengths of our study is its statistical power to confidently achieve our result. A post hoc power analysis of our AUC calculations for the PASS scores revealed study power of 0.986, well above the standard for beta error of 0.8.³ In order for our study to become underpowered (beta <0.8) for an AUC of 0.7 with 113 participants, an allocation ratio of greater than 7:1 between those who answered yes to the PASS anchor (or scored +2 to +7 for CID anchors) and those who did not would have to have been observed rather than our roughly 1:1 ratio (57:56 patients) for the PASS analysis. This post hoc

TABLE 5
Estimates of Clinically Significant Change Published in the Literature
for Patients Undergoing Cartilage Restoration of the Knee^a

Study	Surgical Technique	Follow-up	Patients, n	Method	Measure of Change	KOOS	IKDC	WOMAC	Other PROM
Liu et al ⁸	Meniscal allograft transplant	1 y	98	Distribution based	MCID	Pain, 9.9 Symptoms, 9.7 ADL, 9.5 S/R, 13.3 QOL, 14.6	9.9	NR	Lysholm, 12.3
Wang et al ¹⁹	Osteochondral autograft or allograft	2 y	173	Anchor based	MCID/SCB	NR	17/30	NR	KOS ADL, 10/17
Greco et al ⁴	Heterogeneous	1 y	50	Anchor based	MCID	NR	6.3	Pain, 17.5 Stiffness, 6.3 Physical function, 8.1 Total, 11.5	CKRS, 14.0 SF-36 PCS, 4.8 SF-36 MCS, 2.7
Ogura et al ¹¹	Autologous chondrocyte implantation	1 y	92	Distribution and/or anchor based	MCID/SCB	Pain, 18.8/27.7 Symptoms, 8.4/14.3 ADL, 17.3/29.4 S/R, 16.9/30 QOL, 19.6/37.5	16.4/34.4	NR	Lysholm, 10.5/29 SF-12 PCS, 8.2/14.7 SF-12 MCS, 4.6/4.4
Ogura et al ¹²	Osteochondral allograft	1 y	86	Distribution and/or anchor based	MCID/SCB	Pain, 16.7/27.7 Symptoms, 6.3/10.7 ADL, 9.2/25 S/R, 25/30 QOL, 9.3/31.3	9.8/26.9	NR	Lysholm, 9.2/25 SF-12 PCS, 4.2/12.1 SF-12 MCS, 4.6/NA

^aADL, Activities of Daily Living; CKRS, Cincinnati Knee Rating Scale; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee injury and Osteoarthritis Outcome Score; KOS, Knee Outcome Score; MCS, mental component summary; MCID, minimal clinically important difference; NA, not applicable; NR, not reported; PCS, physical component summary; PROM, patient-reported outcome measure; QOL, Quality of Life; SCB, substantial clinical benefit; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey; S/R, Sports and Recreation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

analysis demonstrates the statistical robustness of our findings. An additional post hoc analysis of our findings revealed that a significant proportion of patients did achieve CID and PASS estimates 1 year after surgery. Using the IKDC as an example, 69% and 50% of patients achieved the CID and PASS, respectively, whereas 47% achieved both. Ogura et al^{11,12} reported that 50% and 47% of patients achieved the SCB for the IKDC 1 year after treatment using osteochondral allograft and autologous chondrocyte implantation, respectively. Wang et al¹⁹ reported that 53% and 31% of patients achieved MCID and SCB thresholds, respectively, for the IKDC after treatment using osteochondral autograft or allograft 2 years postoperatively. Although differences in these numbers are difficult to explain across studies and methodological techniques, they do provide useful information that can be shared with patients at the time of informed consent, for sample size determinations in prospective studies, and for regulatory purposes.

The current study is an important contribution to the literature for many reasons. The diverse nature of the surgical procedures increases the generalizability of the findings and may be more applicable to assessing outcomes for a new cartilage technology as opposed to estimates of clinical improvement for a particular surgical technique. Our findings also confirmed that patient factors, in particular younger age, are important predictors of achieving established CID and PASS thresholds after treatment. Moreover, the reliability of the cutoff points identified in this study for CID and PASS across all included outcome measures was acceptable to excellent. In particular, the AUC for CID estimates ranged from 0.70 to 0.85. For the PASS, the

reliability of the identified cutoff points was excellent (AUC > 0.80) with the exception of the KOOS Symptoms subscale (AUC, 0.75). The reliability of the PASS and CID cutoff points for the IKDC was excellent, with AUC values of 0.90 and 0.85, respectively. Along with the findings published by Liu et al,⁸ this is the only study reporting estimates of PASS for commonly used PROMs after cartilage repair. However, in the study by Liu et al, several of the PASS cutoff points had AUC values <0.70.

From the perspective of patient status at baseline, our data demonstrated that patients with higher baseline IKDC scores were more likely to achieve PASS. These latter findings, however, could not be generalized to other PROMs or used to predict who would surpass CID thresholds determined for the population undergoing cartilage repair. For a proportion (4%-22%) of patients, the baseline score was at or above the PASS for a given PROM. In these patients, it was still possible to achieve the CID, as indicated by the low number of patients who could not achieve CID due to a high baseline score. For example, 4% of patients had a baseline IKDC score above the PASS. Nonetheless, all patients were able to achieve CID. These findings reflect that the importance of CID and PASS is relative and that the outcome measure applied in a clinical setting depends on context and purpose. Furthermore, the low ceiling effects observed in this sample across PROMs meant that, in general, CID can still be achieved for those with a high baseline score.

The limitations of the current work include the limited internal validity of the estimates. The enrolled sample was treated using a wide variety of surgical techniques,

and such clinical heterogeneity may confine the usefulness of our PASS and CID estimates in the context of cartilage repair in general (ie, when considering new technologies vs such a benchmark) as opposed to any single surgical technique. This, along with the small number of patients receiving each treatment method, does not allow interpretation of the findings for a particular procedure. Another limitation is that a small subset of patients may have had further improvement if follow-up had been extended to 2 years. This could have affected CID and PASS estimates. Differing time lines to return to sports depending on the type of surgery may have affected KOOS Sports/Rec and KOOS QOL subscale scores that were not fully delineated in this study. Furthermore, the current study population had a significant proportion of people who underwent revision cartilage surgery and/or concomitant procedures. Once again, although this limits the applicability of our findings to a particular procedure, it reflects the complex and heterogeneous nature of the population with cartilage injury and optimizes external validity. Finally, selection bias exists because the number of people who declined participation in the study was not recorded.

This was the first study to determine CID and PASS values for the KOOS, IKDC score, and Lysholm score among patients treated using knee cartilage restoration. Younger age was a positive prognostic variable, and higher baseline scores implied achieving PASS for the IKDC. The information in this study can be used for designing randomized controlled trials, counseling individual patients as to anticipated outcomes, and conducting responder analyses when evaluating new cartilage technology from a regulatory perspective.

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