

Appraisals in Meta-journal Hour 12

By Salwana Ahmad and BH Chew

The paper:

Effect of Physical Therapy vs Arthroscopic Partial Meniscectomy in People with Degenerative Meniscal Tears: Five-Year Follow-up of the ESCAPE Randomized Clinical Trial.

[doi:10.1001/jamanetworkopen.2022.20394](https://doi.org/10.1001/jamanetworkopen.2022.20394)

Why was this study conducted?

1. Previous studies from RCTs and Systematic Reviews between arthroscopic partial meniscectomy versus exercise therapy in patients with a degenerative meniscal tear showed that:
 - Has no clinically meaningful patient benefit in the first 2 years of follow-up.
 - Lack of clinically relevant differences in important patient-reported outcomes, such as knee function in 3- 5-year follow-ups.
 - Conflict of outcomes:
 - Associated with a slightly increased risk of radiographic knee OA.
 - 5 times higher risk for total knee replacement (ie, the treatment for end-stage knee OA) after surgery.
 - Found no clinically relevant difference between the 2 treatments for OA progression.
2. A need for a substantial reduction of meniscal surgeries for this population although the current evidence suggests nonoperative management is best in patients with degenerative meniscal tears.
3. However, there is insufficient evidence for high-quality evidence about the long-term effects (ie, 3- 5 years and beyond) of the studied condition.

Aim:

Primary objective: To compare patient-reported knee function at the 5-year follow-up after arthroscopic partial meniscectomy and exercise-based physical therapy in patients with a degenerative meniscal tear.

Secondary objective: To assess the progression of radiographic and symptomatic evidence of knee osteoarthritis.

Hypothesis: Exercise-based physical therapy is non-inferior to arthroscopic partial meniscectomy over 5 years.

How was it done?

Study Design and participants

1. A noninferiority, multicenter randomized clinical trial by the Orthopedic Research Consortium Mid-West Netherlands
2. 5 years follow-up assessment.
3. Conducted in the Orthopedic Departments (secondary and primary) of 9 hospitals in the Netherlands.



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4. 321 patients aged 45 to 70 years with a degenerative meniscal tear with symptomatic, non-obstructive MRI confirmed.
5. Male and female, multi-ethnic.
6. Data collection took place between July 12, 2013, and December 4, 2020 (~7 years)

Adverse events (AEs) and Additional Knee Surgery up for a 2-year follow-up were reported previously (van de Graaf et al., 2018). Based on the question asked in the 5 years follow-up questionnaire, patients were asked? "Did you have additional knee surgery performed on your affected knee in the last 3 years?" If yes, patients were asked to specify the type of surgery (arthroscopic partial meniscectomy, total knee replacement, partial knee replacement, cartilage surgery, or other). Descriptive information was reported following additional knee surgeries.

Randomization and Blinding

- The number of patients screened for eligibility was not available.
- Randomization 1:1 ratio and varying block size up to a maximum of 6, stratified by hospital and age (45-57 and 58-70 years).
- Patients, clinicians, and research staff were not blinded except the radiologist in charge of examining the radiographic images.
- Analyses and interpretations of the results were done based on data that were blinded for treatment allocation. Treatment allocation was unblinded after the researchers reached a consensus on the interpretation of the results.
- Figure 1 below showed the presents the patient flow through the trial and patients' completion, withdrawal, not complete and loss to follow-up status reported.

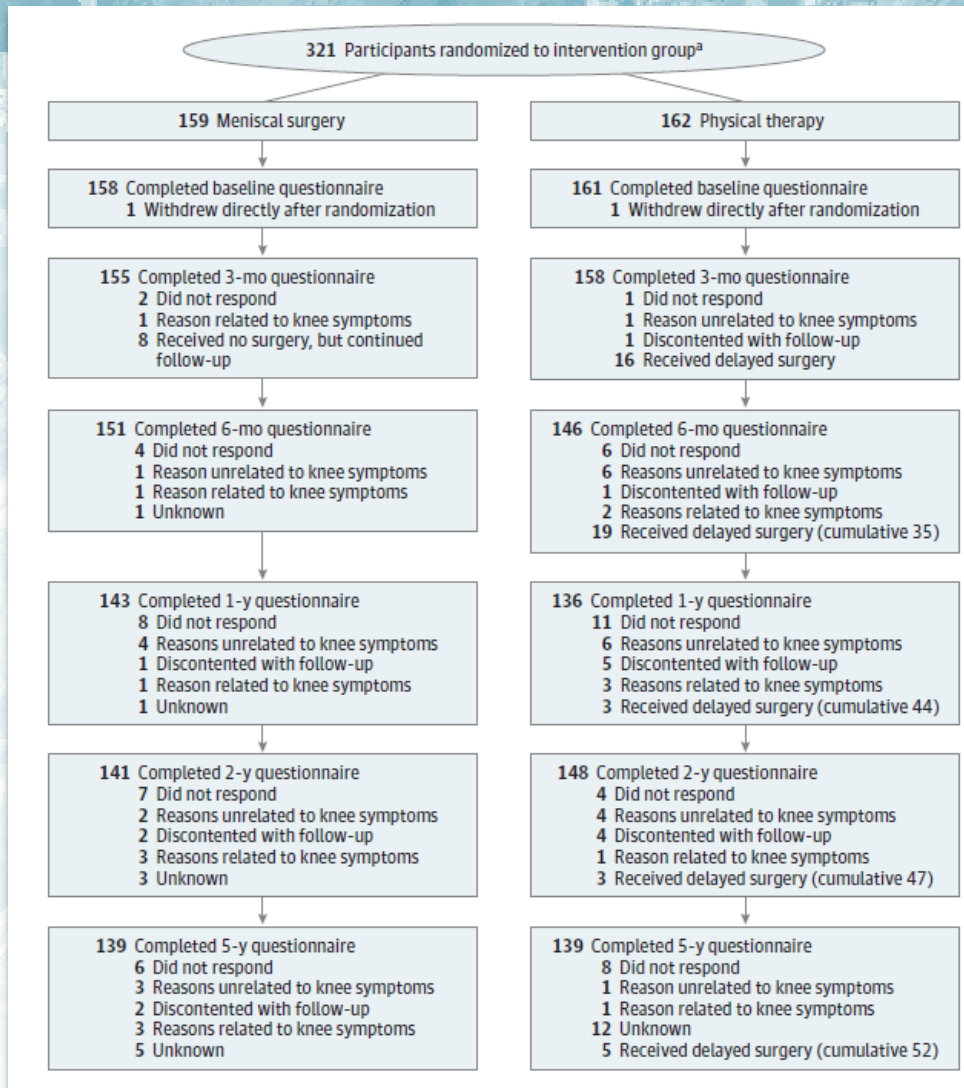


Figure 1. presents the patient flow through the trial.

From the results:

- After the randomization process, 1 patient in each group withdrew from participation.
- At the end of the follow-up, 278 participants (87.1%) completed the follow-up: 139 in each group, with a mean follow-up time of 61.8 months (range, 58.8-69.5 months).
- In the surgery arm, a total of 19 patients (12.0%) did not complete the follow-up at 5 years while in the physical therapy arm, a total of 22 patients (13.6%) did not complete the follow-up at 5 years.
- In 4 patients (1 physical therapy vs 3 surgery), the loss to follow-up was related to the lack of knee symptoms.
- Other reasons for loss to follow-up were patients did not respond to the questionnaires and reminders (8 physical therapy vs 6 surgery), patients did not wish to complete the follow-up (0 physical therapy vs 2 surgery), the reason was unrelated to knee symptoms (1 physical therapy vs 3 surgery), or the reason was unknown (12 physical therapy vs 5 surgery).
- During the follow-up period, 52 of 162 participants (32.1%) in the physical therapy group underwent delayed arthroscopic partial meniscectomy due to the persistence of knee symptoms in which 44 patients within the first 2 years of follow-up and 5 patients within the last 3 years of the trial

Eligibility

Inclusion criteria:

- Patients between 45 and 70 years of age at presentation.
- A meniscal tear was visualized on MRI.
The meniscal tear can either be isolated or combined with a partial asymptomatic Anterior Cruciate Ligament (ACL) injury or an asymptomatic degenerative ACL shown on MRI with no abnormal clinical findings (a negative Lachman test and Pivot Shift).
- Mental competence.
- Willingness to comply with follow-up schedule.
- Written informed consent.

Exclusion Criteria:

- Knee locking or trauma leading to acute surgery.
- One of the following associated injuries on the index knee:
 - a. Asymptomatic partial ACL rupture or any total ACL rupture determined by clinical examination (positive Lachman test and/or positive Pivot Shift) and shown on MRI.
 - b. A complete PCL injury.
 - c. Cartilage changes down to the bone; grade 4 of the Kellgren Lawrence Grading Scale for Osteoarthritis visualized on X-ray.
 - d. An injury to the lateral/posterolateral ligament complex with significantly increased laxity.
- A history of knee surgery other than diagnostic arthroscopy on the index knee.
- Tumors on MRI suspected malignancy.
- Obese patients with BMI > 35.
- ASA 4-5 (appendix D) patients which can interfere with revalidation.
- The general disease that affects the physical function or systemic medication/abuse of steroids (e.g., rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, gout, pseudogout)
- Any other medical condition or treatment interfering with the completion or assessment of the trial, e.g. contraindications to MRI or surgery.
- Drugs or alcohol abuse.
- Patients were unable to speak or read Dutch.

Intervention and Control Arm

**Arthroscopic Partial Meniscectomy –
within 4 weeks after randomization**

- A standardized intra-articular inspection:
 - the knee joint, including assessment of the lateral and medial meniscus, the anterior cruciate ligament, the level of chondropathy, and a general classification of the level of cartilage degeneration.
- Removal of the affected part of the meniscus by surgery
- After surgery, all patients received written postoperative instructions, including a home exercise program.
- Eight weeks after surgery, patients visited the outpatient orthopedic clinic for a clinical consultation.
- Only refer patients for physical therapy only in the case of delayed recovery following the guidelines of the Dutch Orthopedic Association.

***Costs for surgery were covered by the patient's health insurance.**

**Exercise-Based Physical Therapy -
within 2 weeks of randomization**

- The treatment protocol - a physical therapist-led incremental exercise program over a period of 8 weeks, consisting of 16 sessions of 30 minutes each.
- If knee symptoms persisted following the physical therapy program (e.g., knee pain, limitations in daily activities, or mechanical dysfunction), the patient could attend additional physical therapy sessions or opt for arthroscopic partial meniscectomy based on a shared decision after consultation with the orthopedic surgeon.
- ***Optional delayed APM (cross-over) when PT treatment has failed.**
- ***Costs for 16 physical therapy sessions were compensated for patients because this therapy is not reimbursed by the basic Dutch health insurance**

VS

***Patients did not receive financial compensation for participating in the study.**

ESCAPE Trial

Baseline	3, 6, 12 months	2 years	5 years
<ul style="list-style-type: none"> • Patient characteristics. • The level of OA assessed on radiographic images. • Several patient-reported outcome measures (Self-administered questionnaires) 	<ul style="list-style-type: none"> • Self-administered questionnaires 	<ul style="list-style-type: none"> • Primary endpoint Protocol and 2-years results were published 	<ul style="list-style-type: none"> • The level of OA assessed on radiographic images. Several patient-reported outcome measures (Self-administered questionnaires)

Change in Primary and Secondary Outcomes Measures (the details of the measure can be found in [Supplemental 1: Study Protocol](#)):

Primary Outcome Measure:

- i. Patient-reported outcome on knee-specific symptoms, function, and sport activity.
 - International Knee Documentation Committee Subjective Knee Form based on the intention-to-treat principle.

Secondary Outcome Measure:

- i. Progression in knee osteoarthritis based on radiographic images.
 - Kellgren Lawrence Grading Scale for Osteoarthritis radiographic evidence to assess the presence and grade of knee OA.
 - The severity of joint space narrowing and osteophytes in knee OA's Score based on The Osteoarthritis Research Society International (OARSI) Atlas Sum Score.
 - Progression on OARSI based on OARSI sum score.
 - Patients who underwent partial or total knee replacement surgery received the score of end-stage knee OA.
- ii. Symptomatic Knee Osteoarthritis
 - Patient Acceptable Symptom State of the Knee Osteoarthritis Outcome Score-Physical Functioning Short-Form (KOOS-PS) score.
- iii. Additional Patient-Reported Outcomes.
 - Pain during activities.
 - KOOS-PS Score - 5 years.
 - Quality of Life score of EuroQol 5 Dimension 5 Level (EQ-5D-5L).

Physical Therapy Protocol

Exercise/Repetitions	Repetition or Time	Week	Week	Week	Week	Week	Week	Week	Week	
		0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	
1. Calf raises on a leg press	3 x 12									
2. Balance on wobble board on both feet.	-	←————→								
3. Stationary bicycling for warming up and cooling down or cardiovascular training.	Gradual increase 7-15 min or longer									
4. Pully, strap around the healthy ankle, stay and keep balance on injured side, move healthy leg forward, backward and sideward by standing in all 4 directions.	3 x 12									
5. Standing hip extension in a "multi-hip" trainings device.	3 x 12	←————→								
6. Stair walking, walking, running, jumping according the patients ICF challenging with throwing a ball	10 Min									
7. Leg press, place the shinbone horizontal and the knee starting at 110°, unilateral.	3 x 12									
8. Calf raises standing on one leg.	3 x 12									
9. Lunges (according the needs of the patient) with < 90° knee flexion.	3 x 12									
10. Balance on wobble board on one foot challenging with throwing a ball.	3 min									
11. Crosstrainer as cardiovascular and cooling down training	10 min or more									

Table 1 the exercise program for comprised 16 supervised sessions during 8 weeks

Sample Size Calculation

Continuous outcome non-inferiority trial for the IKDC Subjective Knee Form.

Significance level (alpha)	5%
Power (1-beta)	90%
Standard deviation of outcome	18
Non-inferiority limit, d	8
Calculate sample size	
Sample size required per group	87
Total sample size required	174

Level of significance = 5%
Power = 90%
Standard deviation = 18
Non-inferiority threshold = 8

Adjusted sample size (Sakpal, 2010) is with 20% loss to follow-up and 25% of delayed APM in PT Group:

$$\begin{aligned}
 N1 &= n/(1-d) \\
 &= 87/(1-0.45) \\
 &= \mathbf{158 \text{ per group}}
 \end{aligned}$$

Total sample size for two arms required a minimum of **316 individuals**.

Data Analysis

Analysis 2 years and 5 years follow up

- ❑ Descriptive statistics: Baseline characteristics, frequencies of further surgeries, partial or total knee arthroplasties, patients who received delayed surgery following physical therapy, and secondary outcomes for knee OA.
- ❑ Continuous outcome measure using Linear Mixed-Model analyses with a random intercept:
 - Level : 3 Clustered level (Repeated measure-participant-hospital)
 - Independent variables : Treatment group, baseline values of the outcome.
 - Confounders : Level of OA at baseline using the KL classification, baseline pain during weight bearing, body mass index at baseline (<25, 25-30, or >30-35), and sex.
 - Random effect : Intervention effect
- ❑ Noninferiority threshold of 11 points, 1-sided α level of 0.025. Statistical significance was assessed at the 0.05 level for secondary outcome measure.
- ❑ Intention-to-treat Analysis – 2 allocated groups for 5 years follow-up study
- ❑ As-treated analysis – 3 allocated groups of APM, PT, PT delayed APM

What was the finding?

Patients:

[Table 1](#) reports the baseline characteristics for the surgery and physical therapy groups:

- 321 patients reported having a mean (SD) age of 58 (6.6) years inclusive of 161 women (50.2%) and 160 men (49.8%) who were grouped to either surgery (n = 159) or physical therapy (n = 162).
- During the follow-up period, 52 of 162 participants (32.1%) in the physical therapy group underwent delayed arthroscopic partial meniscectomy due to the persistence of knee symptoms: 44 patients within the first 2 years of follow-up and 5 patients within the last 3 years of the trial
- The other details about completion, withdrawal, did not complete and loss to follow up were shown in [Figure 1](#). as mentioned above)

Primary Outcome Measure

Patient Reported Knee Function

Intention-to-treat-Analysis

From baseline to the 5-year follow-up:

- The overall crude between-group difference was 3.5 points (95% CI, 0.7-6.3 points; $P < .001$ for noninferiority) and was 3.8 points (95% CI, 0.8-6.8; $P < .001$ for noninferiority) after adjusting for confounding factors.
- Based on the IKDC questionnaire score for knee function results as shown in [Table 2](#):
 - The surgery group had a mean (SD) improvement of 29.6 (18.7) points (from 44.8 [16.6] to 74.7 [18.4] points).
 - The exercise-based physical therapy group had a mean improvement of 25.1 (17.8) points (from 46.5 [14.6] to 73.1 [17.7] points)
 - Based on the crude mixed-model analysis, a mean between-group difference in patient-reported knee function on the IKDC at the 5-year follow-up of 2.8 points (95% CI, -0.9 to 6.5 points; $P < .001$ for noninferiority).
 - After adjusting for confounders, there was a mean between-group difference of 3.4 points (95% CI, -0.7 to 7.4 points; $P < .001$ for noninferiority).
 - A positive between-group value was observed in showing that greater mean improvement on the IKDC questionnaire in the surgery group compared with the physical therapy group. The between-group differences are significantly smaller than the noninferiority threshold of 11 points, indicating that physical therapy is not inferior to arthroscopic partial meniscectomy.
 - No clinically meaningful difference between physical therapy and surgery was observed based on Between-Group Intervention Effects Indicated By International Knee Documentation Committee (IKDC) Subjective Knee Form Questionnaire for Physical Therapy (PT) vs Surgery as shown in [Figures 3A and 3B](#).

As-Treated Analysis

- Based on the IKDC questionnaire score for knee function results as shown in Table 2:
 - The overall crude difference between physical therapy and arthroscopic partial meniscectomy was 2.4 points (95% CI, -0.8 to 5.5 points; $P < .001$ for noninferiority).
 - The difference between physical therapy and delayed surgery was -3.8 points (95% CI, -8.2 to 0.6 points; $P < .001$ for noninferiority).
 - Between-group differences were significantly different from the noninferiority threshold, indicating that physical therapy was not inferior to arthroscopic partial meniscectomy.

Secondary Outcome Measure as shown in details in [Supplement 2](#)

Radiographic Knee OA

From baseline to 5 years-follow up from 222 radiographic images were analyzed, (surgery, $n = 112$; physical therapy, $n = 110$).

- A progression of at least 1 point on the OARSI sum score in 52% ($n = 42$) of the physical therapy group, 54% ($n = 61$) of the surgery group, and 70% ($n = 21$) of the delayed-surgery group.
- A mean (SD) progression of 1.1 (2.2) points in the surgery group (from 1.9 [1.5] to 3.0 [2.6]) and 1.1 (2.1) points in the physical therapy group (from 2.1 [1.6] to 3.4 [2.7]) from baseline to 5 years.
- We found no significant difference ($P = .16$) between the 3 groups in the progression of the OARSI sum score from baseline to 5 years.
- The mean (SD) progression was 1.1 (2.2) points in the surgery group, 0.8 (2.1) points in the physical therapy group, and 1.7 (2.2) points in the delayed surgery group from a maximum of 18 points.

Symptomatic Knee OA

- It was symptomatic knee OA in 6 patients: 4 in the surgery group and 2 in the physical therapy group.

Additional Patient-Reported Outcomes and Surgeries

From baseline to 5 years-follow up:

- No statistically significant differences between the 2 treatment groups in pain, general physical health, and quality of life.
- In the physical therapy group ($n = 52$) that underwent delayed meniscal surgeries, further knee surgeries were performed in 17 patients ($n = 5$ surgery; $n = 12$ physical therapy).

How much can we take out from this research/paper?

This research is ground-breaking, practice-changing if not life-changing to patients with degenerative knee diseases but not too serious (check out the eligibility criteria). With the availability of physical therapy sessions, patients with mild to moderate symptomatic, degenerative, magnetic resonance imaging–confirmed meniscal tear could be treated fairly well after 5 years of follow-up when compared to arthroscopic partial meniscectomy.

The research was well conducted from the scientific robustness and in an efficient manner (sample size was adjusted to be just adequate) and analyzed using the appropriate strategies although some areas such as a change from GEE in the protocol to LMM could be explained. However, this is believed to be a better statistical choice. As the treated analysis was conducted beside ITT and results were presented and showed the between-group differences were all lesser than the pre-specified minimally important different scores on IKDC.

Application of evidence from this study to our setting does require proper selection of patients who are similar in characteristics to this study samples, similar if not the same arthroscopic partial meniscectomy procedures or exercise-based physical therapy regimen, availability of locally validated outcome measurement tools, and an agreed between-group different of the outcome score. Absent in any of these will require caution of evidence application to local clinical practices, or require replications of studies leading to a similar trial to inform a truly non-inferiority of exercise-based physical therapy to arthroscopic partial meniscectomy.

References

- van de Graaf, V. A., Noorduyn, J. C. A., Willigenburg, N. W., Butter, I. K., de Gast, A., Mol, B. W., Saris, D. B. F., Twisk, J. W. R., & Poolman, R. W. (2018). Effect of Early Surgery vs Physical Therapy on Knee Function Among Patients With Nonobstructive Meniscal Tears: The ESCAPE Randomized Clinical Trial. *JAMA*, *320*(13), 1328–1337. <https://doi.org/10.1001/JAMA.2018.13308>