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Early Magnetic Resonance Imaging–Based Changes in Patients With Meniscal Tear and Osteoarthritis: Eighteen-Month Data From a Randomized Controlled Trial of Arthroscopic Partial Meniscectomy Versus Physical Therapy

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Objective. The present study was undertaken to evaluate changes in knee magnetic resonance imaging (MRI) findings over the course of 18 months in subjects with osteoarthritic change and meniscal tear treated with arthroscopic partial meniscectomy (APM) or nonoperatively with physical therapy (PT).

Methods. We used 18-month follow-up data from the Meniscal Tear in Osteoarthritis Research Trial. MRI results were read with reference to the MRI Osteoarthritis Knee Score. We focused on 18-month change in bone marrow lesions (BMLs), cartilage thickness, cartilage surface area, osteophyte size, effusion-synovitis, and Hoffa-synovitis. We used multinomial logistic regression to assess associations between MRI-based changes in each feature and treatment type.

Results. A total of 351 subjects were randomized, and 225 had both baseline and 18-month MRI results. In both treatment groups, patients experienced substantial changes in several MRI-based markers. In 60% of the APM group, versus 33% of the PT group, cartilage surface area damage advanced in ≥2 subregions (adjusted odds ratio 4.2 [95% confidence interval 2.0–9.0). Patients who underwent APM also had greater advancement in scores for osteophytes and effusion-synovitis. We did not find significant associations between treatment type and change in cartilage thickness, BMLs, or Hoffa-synovitis.

Conclusion. This cohort of patients with meniscal tear and osteoarthritis showed marked advancement in MRI-based features over 18 months. Patients treated with APM showed more advancement in some features compared to those treated nonoperatively. The clinical relevance of these early findings is unknown and requires further study.

INTRODUCTION

Recent estimates suggest that 14 million adults in the US have knee osteoarthritis (OA), including 8 million individuals under 65 years of age (1). Of these, ~80% have a concomitant meniscal tear (2). Nonoperative treatment of symptomatic meniscal tear typically includes a physical therapy (PT) regimen (muscle strengthening, endurance, flexibility, and balance training). Surgical treatment

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SIGNIFICANCE & INNOVATIONS

- To our knowledge, this is the first study to use data from a randomized controlled trial investigating surgical versus nonoperative treatment for patients with knee osteoarthritis and meniscal tear to evaluate the early magnetic resonance imaging (MRI)–based changes over an 18-month period for patients undergoing arthroscopic partial meniscectomy (APM) or physical therapy.
- We found marked MRI-based advancement in both groups. In addition, we found that patients who were treated with APM had higher odds of advancement in cartilage surface area, osteophytes, and effusion-synovitis, although the data did not provide sufficient evidence to establish an association between treatment type and change in cartilage thickness, bone marrow lesions, or Hoffa-synovitis.
- The clinical relevance of these findings requires further study and should be considered a research priority.

typically consists of arthroscopic partial meniscectomy (APM). Data from several large clinical trials have suggested that patients with meniscal tear and osteoarthritic changes treated with APM plus PT experience similar pain relief compared to patients treated with PT alone, although crossover from PT to APM makes interpretation challenging in several of these trials (3–7).

In patients with OA, meniscal tear has been shown to be an independent risk factor for progression of cartilage damage (8). Observational studies have suggested that a history of APM may be associated with a higher risk of incident OA (9,10). It is unclear in these studies whether the risk of progression is attributable to the initial meniscal damage or to the surgical treatment. This question can best be addressed in a clinical trial setting, in which all subjects have knee pain and meniscal tear and are deemed surgical candidates by their orthopedic surgeons. The aim of our study was to evaluate early magnetic resonance imaging (MRI)–based changes in patients with meniscal tear and OA treated with APM and those treated nonoperatively.

PATIENTS AND METHODS

Study sample. We used data from the Meniscal Tear in Osteoarthritis Research (MeTeOR) Trial, a multicenter randomized controlled trial (RCT) investigating APM plus PT versus PT alone to treat symptomatic meniscal tear in OA (4). Subjects were recruited from orthopedic surgery clinics in 7 US referral centers. Eligible subjects were ages ≥45 years old, had evidence of meniscal tear on MRI, evidence of OA changes on MRI or radiography, and knee symptoms. The full inclusion and exclusion criteria have been published elsewhere (11).

Subjects were randomized to APM with PT or PT alone. For subjects undergoing APM, the surgeon used standard arthroscopic portals and trimmed the damaged meniscus back to a stable rim (11). Surgeons also trimmed loose fragments of cartilage and bone but did not penetrate the subchondral bone. Subjects randomized to the PT arm followed a standardized, strengthening-based PT protocol, including weekly sessions with a therapist and home-based exercises; generally the program lasted 6 weeks (4,11). Subjects were permitted to see their orthopedic surgeons throughout the study and could discuss with the surgeon the option of crossing over to receive APM if symptoms persisted despite PT.

Outcome. Subjects underwent MRI at baseline as part of routine clinical care. Each of the centers performed cartilage-sensitive sequences, permitting us to assess the MRI results with semiquantitative methods. At 18 months, subjects underwent MRI using the same sequences as performed at baseline. Baseline and 18-month MRI results were read using the MRI OA Knee Score (MOAKS) in pairs, unblinded to time by an experienced musculoskeletal radiologist (AG) who is an expert in semiquantitative MRI analysis of knee OA (12). In a sample of 10 subjects, the MOAKS total OA scores for this reader were closely associated to the total OA scores of another highly experienced reader, with an interclass correlation of 0.98 (13). The reader was blinded to the subject treatment and all other demographic information. We focused on 18-month change in several joint features: bone marrow lesions (BMLs), cartilage surface area, cartilage thickness, osteophyte size, effusion-synovitis, and Hoffa-synovitis. Given the biomechanical models demonstrating greater contact pressures associated with APM, we envisioned that the most striking effects would be observed in cartilage damage (with contact pressures transmitted directly to cartilage) and osteophytes (bony enlargement in response to greater contact pressure) (14,15). In the MOAKS system, each joint feature is divided into subregions, and each subregion is scored on an ordinal scale from 0–3. We assessed change in each feature as described below.

BMLs. BML size is assessed in 14 subregions, and thus the change in number of subregions affected has a theoretical range of –14 to 14 because BMLs can both develop and resolve. We assessed the change in the number of subregions affected by any BML (i.e., with a score >0). We assessed the maximum advancement in BML size score across all subregions, which was grouped into "no change," "advancement by 1 grade," and "advancement by 2+ grades." We also assessed whether there were any subregions with improvement in score and whether there were any subregions with advancement in score.

Cartilage. Cartilage surface area and thickness were analyzed separately. We assessed the number of subregions with advancement, the number of subregions with new cartilage damage (i.e., a score of 0 at baseline and >0 at follow-up), and the maximum advancement across all subregions. The number of subregions with advancement and the number of subregions with new damage have a possible range of 0–14; based on distribution these were grouped into 0, 1, 2+ subregions. Maximum

advancement was grouped into "no change," "advancement by 1 grade," and "advancement by 2+ grades."

Osteophytes. We assessed the number of locations with advancement, the number of locations with new osteophytes, and the maximum advancement across all locations. Osteophytes are scored in 12 locations, and thus the number of locations with advancement and the number of locations with new osteophyte has a possible range of 0–12. Based on distribution, the number of locations with advancement was grouped into 0, 1, 2+ subregions, and the number of locations with new osteophytes and the maximum advancement across all subregions were grouped into "no advancement" versus "any advancement."

Synovitis. Effusion-synovitis represents a combination of effusion and synovial thickening, and Hoffa-synovitis is seen as hyperintensity on fat-suppressed water sensitive sequences and is a sensitive but not specific surrogate marker for the true synovitis. They are each rated on an ordinal scale from 0–3. Changes were classified as "improvement," "no change," and "advancement."

Statistical analyses. We first evaluated the association between baseline characteristics and treatment group to ensure that the groups were balanced after excluding crossovers. Baseline Kellgren/Lawrence (K/L) grade was imbalanced between the treatment groups and was thus adjusted in multivariable models. For each joint feature considered, we used multinomial logistic regression with structural advancement of that feature as the dependent variable and treatment group as the independent variable. We calculated odds ratios (ORs) with associated 95% confidence intervals (95% CIs), where the OR represents the increased odds of experiencing structural advancement for subjects receiving APM versus PT. To adjust for multiple testing, we used the Holm step-down procedure (16,17).

The primary analysis compared subjects randomized to and receiving APM with subjects randomized to and receiving PT without crossover to APM. The analysis is mechanistic in focus; consequently, it examines how the treatment received (surgical versus nonoperative) affects progression. Subjects who crossed over from PT to APM had higher baseline pain and slower initial clinical improvement. Since these factors may be associated with more rapid structural progression, we did not include the crossovers in the primary analysis (18). We performed a secondary as-treated analysis, also mechanistic in focus, in which subjects crossing over from PT to APM within 6 months of randomization were analyzed in the surgical group. Finally, we performed an intent-to-treat (ITT) analysis, in which subjects were analyzed according to randomization group irrespective of treatment received. This analysis was considered important because baseline factors, known and unknown, could be more important and have a bigger impact than the intervention. Subjects crossing over from PT to APM between 6 and 18 months were excluded from all analyses to ensure that subjects analyzed in the surgical arm in as-treated analyses were exposed to surgery for at least 12 months. Subjects randomized to the APM arm who did not receive surgery were also excluded. This group was very small, and unlike the PT-to-APM crossovers, where we have information on treatment received (number of PT visits, date of surgery), we do not know what other treatment

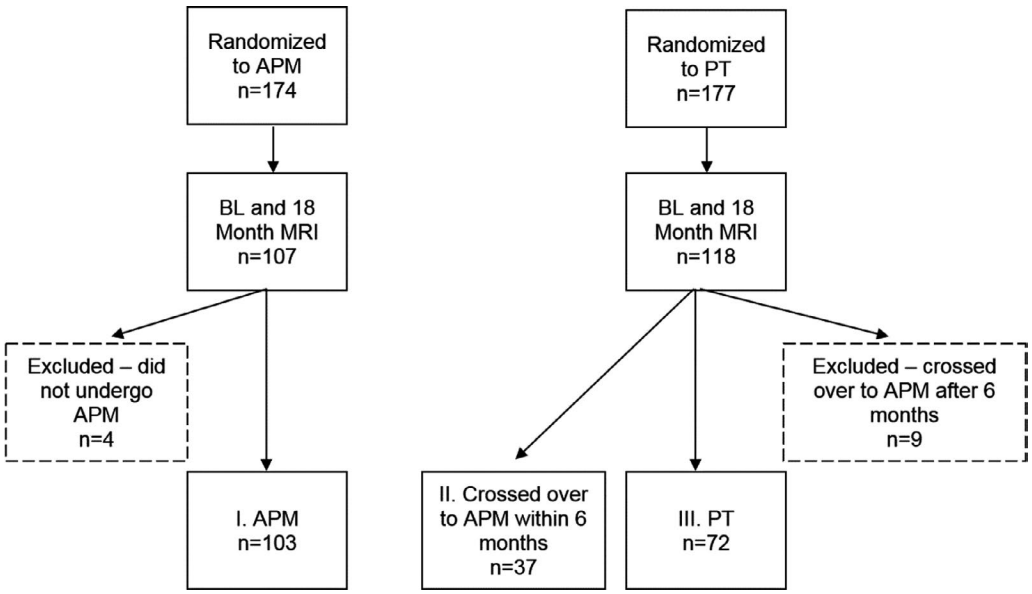

Figure 1. Sample details and analytic cohorts. A total of 351 subjects were enrolled and randomized in the Meniscal Tear in Osteoarthritis Research Trial, and 225 had both baseline and 18-month results from magnetic resonance imaging (MRI). A total of 13 were excluded from all analyses, leaving 103 in the arthroscopic partial meniscectomy (APM) group, 37 in the APM to physical therapy (PT) crossover group, and 72 in the PT group. The primary analysis is APM (bottom left) versus PT (bottom right). The first secondary analysis is as-treated: APM plus APM to PT crossover (bottom left plus bottom middle) versus PT (bottom right). The second secondary analysis is intent-to-treat: APM (bottom left) versus APM to PT crossover plus PT (bottom middle plus bottom right). BL = baseline.

courses, if any, this group pursued. When these subjects were included in the analyses, the results did not differ meaningfully.

Sensitivity analyses to examine the impact of missing data were conducted. For each outcome, we used multiple imputation (MI) to impute an outcome for those subjects missing baseline and/or 18-month MRI data (19,20). We did this under 2 different assumptions: first, we assumed that the missing data were associated with observed covariates (treatment group, K/L grade, sex, race, and baseline MOAKS if available [missing at random (MAR)]). Then, we assumed that the missing data were associated both with observed covariates and with unobserved outcomes; that is, that structural progression may be better or worse than expected based on observed covariates alone (missing not at random [MNAR]). We took a so-called tipping-point approach, asking how severe the missing data mechanism must be in order to change the study's conclusions (21). To do this, we imputed data under various not-at-random mechanisms ranging from more (MNAR1) to less (MNAR5) plausible. Details of each mechanism are described in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract. All analyses were conducted using SAS, version 9.4.

RESULTS

Cohort characteristics. A total of 351 subjects were randomized, and 225 subjects had both baseline and 18-month MRI results. Of the 225 with paired MRI data, 9 subjects crossed over from PT to APM between 6 and 18 months, and 4 subjects were randomized to APM but did not undergo surgery (Figure 1). These 13 subjects (5.8%) were excluded from all analyses. A total of 175 subjects were included in the primary analysis: 103 were randomized to and underwent APM, and 72 were randomized to PT and did not cross over. An additional 37 patients were randomized to PT and crossed over to APM in the first 6 months. Thus, the secondary as-treated analysis consisted of 212 subjects (140 subjects in the APM group and 72 in the PT group), and the ITT analysis consisted of 212 subjects (103 in the APM group and 109 in the PT group). The included subjects did not differ on baseline characteristics compared to the subjects excluded (see Supplementary Tables 1 and 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract).

The primary analytic sample was 56% female sex and 89% white race. The mean ± SD age was 59 ± 7 years, and the mean ± SD baseline score for the Knee Injury and Osteoarthritis Outcome Score pain subscale (0–100 scale; 100 indicates worst pain) was 45 ± 16. The treatment groups were balanced on baseline demographics and clinical characteristics, with the exception of K/L grade. The APM group had a higher percentage of patients with K/L grade 3 and a lower percentage of patients with K/L grade 2 compared to the PT group (Table 1). The treatment groups were balanced on baseline MOAKS (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract).

Table 1. Cohort characteristics*

	Treatment	
	APM plus PT (n = 103)	PT alone (n = 72)
Sex		
Male	44 (43)	33 (46)
Female	59 (57)	39 (54)
Race		
Nonwhite	12 (12)	8 (11)
White	91 (88)	64 (89)
Age, mean ± SD years	58.9 ± 7.9	58.4 ± 6.1
BMI, mean ± SD, kg/m^2	29.8 ± 6.1	30.0 ± 5.3
Baseline KOOS pain score, mean ± SD†	44.7 ± 15.4	46.1 ± 17.2
Baseline WOMAC pain score, mean ± SD†	37.8 ± 17.2	40.7 ± 17.8
Baseline WOMAC function score, mean ± SD†	35.7 ± 17.5	38.0 ± 19.5
Baseline K/L grade		
0	23 (22)	14 (19)
1	26 (25)	19 (26)
2	23 (22)	22 (31)
3	31 (30)	17 (24)
Meniscal tear category‡		
None or signal abnormality on meniscus	0 (0)	2 (3)
Nondegenerative simple tear	13 (13)	9 (13)
Short degenerative complex tear	42 (41)	24 (33)
Long degenerative complex tear	33 (32)	19 (26)
Meniscal root tear	15 (15)	18 (25)

* Values are the frequency (%) unless indicated otherwise. APM = arthroscopic partial meniscectomy; PT = physical therapy; BMI = body mass index; KOOS = Knee Injury and Osteoarthritis Outcome Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; K/L = Kellgren/Lawrence.
† Range 0–100; 100 indicates worst pain.
‡ Based on central readings; patients were enrolled on the basis of readings at local centers.

The median number of days between randomization and intervention start (surgery or first PT visit) was 21 for the APM group and 9 for the PT group.The median time between baseline MRI and 18-month MRI was 579 days (19.1 months); the median time between randomization and 18-month MRI was 542 days (17.9 months).

Change in joint features. *Cartilage*. The number of subregions with advancement in cartilage surface area score ranged 0–7 with a mean ± SD score of 1.9 ± 1.9. The mean ± SD number of subregions with advancement in cartilage surface area score was 2.3 ± 1.9 in the APM group compared to 1.3 ± 1.6 in the PT group (Figure 2A). Among subjects undergoing APM, 19% had 0 subregions with advancement in cartilage surface area score, 21% had 1 subregion with advancement, and 60%

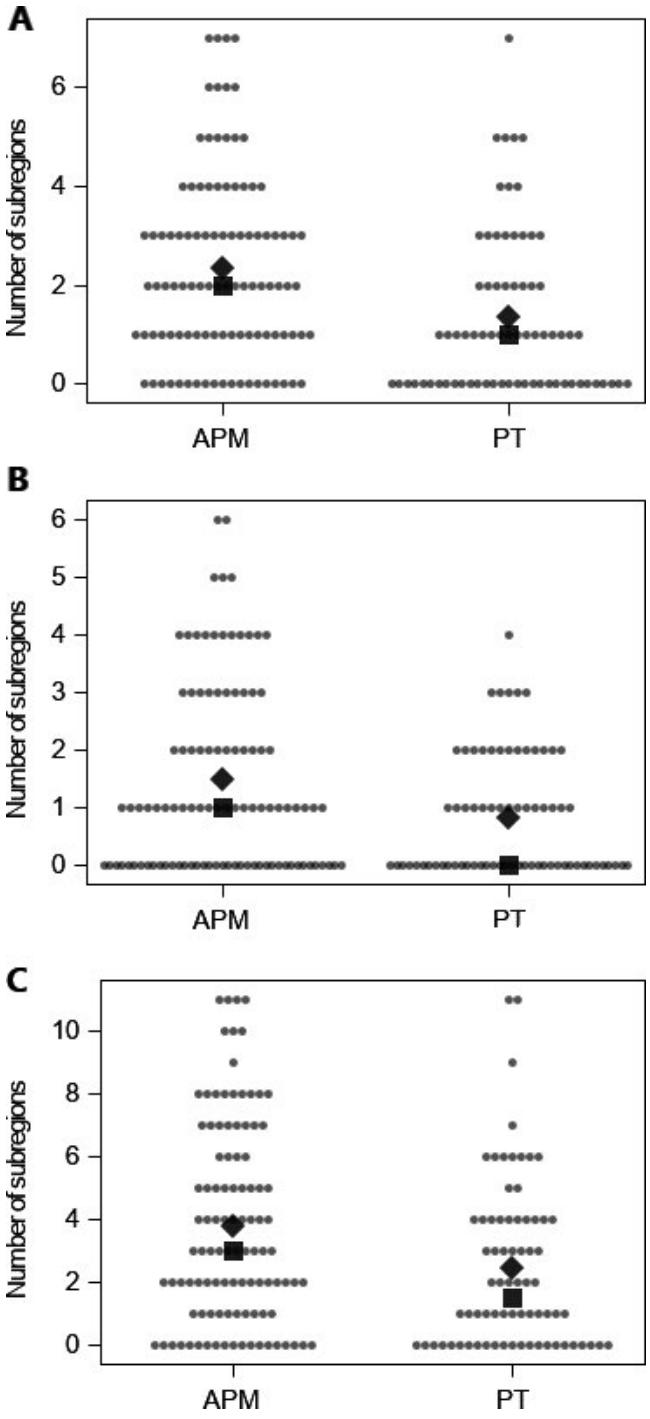

Figure 2. Early magnetic resonance imaging (MRI)–based advancement in cartilage and osteophytes by treatment group (primary analysis). Each panel shows the distribution of MRI-based advancement by treatment group for **A**, cartilage surface area, **B**, cartilage thickness, and **C**, osteophytes. Number of subregions with advancement is along the y-axis, and treatment group (arthroscopic partial meniscectomy [APM] versus physical therapy [PT]) is along the x-axis. Circles represent individual participants, diamonds the mean, and squares the median.

had 2+ subregions with advancement. Among subjects in the PT arm, 43% had 0 subregions with advancement in cartilage surface area score, 24% had 1 subregion with advancement, and 33% had 2+ subregions with advancement. This translates to a 2-fold increased odds of 1 subregion with advancement (OR 2.0 [95% CI 0.9–4.8]) and a 4.2-fold increased odds of 2+ subregions with advancement for APM versus PT (OR 4.2 [95% CI 2.0–9.0]) (Table 2). We also found significantly increased odds of advancement for APM versus PT when evaluating the number of subregions affected by cartilage surface area damage and maximum advancement in damage score (Table 2).

The number of subregions with advancement in cartilage thickness score ranged 0–6 with a mean ± SD of 1.2 ± 1.4. The mean ± SD number of subregions with advancement in cartilage thickness score was 1.5 ± 1.6 in the APM group and 0.8 ± 1.0 in the PT group (Figure 2B). Of subjects undergoing APM, 38% had 2+ subregions with advancement compared to 26% of those receiving PT. Compared to subjects receiving PT, subjects receiving APM had approximately 2-fold elevated odds of having 2+ subregions with advancement, but these associations did not reach statistical significance (OR 1.98 [95% CI 0.96–4.10]) (Table 2). Similarly, patients who had APM had 2-fold greater odds of advancement in the number of subregions affected by reduced cartilage thickness scores and maximum advancement in cartilage thickness score; these associations did not reach statistical significance (Table 2).

Osteophytes. The number of locations with advancement in osteophyte score ranged 0–11 with a mean ± SD of 3.2 ± 3.0. The mean ± SD number of locations with advancement in osteophyte score was 3.8 ± 3.2 in the APM group compared to 2.4 ± 2.7 in the PT group (Figure 2C). Osteophyte advancement was frequent: 82% of subjects in the APM group and 68% of subjects in the PT group experienced advancement in MRI-based osteophyte score in at least 1 subregion. Subjects undergoing APM had a 2.6-fold increased odds of having 2+ subregions with advancement in osteophyte score compared to 0 subregions (OR 2.6 [95% CI 1.3–5.6]) (Table 2).

BMLs. The change in the number of subregions affected by BMLs ranged from –4 to 7 with a mean ± SD of 0.4 ± 1.4. The mean ± SD change in the number of subregions with any BML was 0.6 ± 1.6 subregions in the APM group and 0.2 ± 1.1 in the PT group (Figure 3A). Treatment was not significantly associated with change in BMLs (Table 2).

Synovitis. Of subjects undergoing APM, 14% experienced advancement in Hoffa-synovitis compared to 10% of subjects receiving PT (Figure 3B). This difference was not statistically significant. Of subjects undergoing APM, 24% experienced advancement in effusion-synovitis, 45% had no change, and 31% improved (Figure 3C). Of subjects receiving PT, 8% experienced advancement, 40% no change, and 51% improvement. The adjusted odds of advancement versus improvement associated with APM was 5.0 (95% CI 1.8–13.8).

Secondary analysis. The subjects included in the secondary analysis did not differ on baseline characteristics compared to the subjects who were excluded (see Supplementary Tables 4 and 5,

Table 2. Association between treatment group and advancement, primary analysis*

	APM (n = 103)	PT (n = 72)	*P*	APM vs. PT, OR (95% CI)
Cartilage surface area				
Number of SRs with advancement in cartilage surface area score			0.0008†	
0 SRs with advancement	19 (19)	31 (43)		
1 SR with advancement	21 (21)	17 (24)		2.03 (0.85–4.82)
2+ SRs with advancement	61 (60)	24 (33)		4.22 (1.99–8.96)
Number of additional SRs affected by any cartilage surface area damage			0.0075†	
0 additional SRs affected	35 (35)	42 (58)		
1 additional SR affected	35 (35)	16 (22)		2.82 (1.32–6.01)
2+ additional SRs affected	31 (31)	14 (19)		2.67 (1.21–5.87)
Maximum advancement in cartilage surface area score across all SRs			0.0015†	
No change	19 (19)	31 (43)		
Advance by 1 grade	33 (33)	22 (31)		2.50 (1.13–5.53)
Advance by 2+ grades	49 (49)	19 (26)		4.19 (1.91–9.20)
Cartilage thickness				
Number of SRs with advancement in cartilage thickness score			0.1666	
0 SRs with advancement	39 (39)	38 (53)		
1 SR with advancement	24 (24)	15 (21)		1.55 (0.70–3.45)
2+ SRs with advancement	38 (38)	19 (26)		1.98 (0.96–4.10)
Number of additional SRs affected by any cartilage thickness damage			0.1896	
0 additional SRs affected	52 (51)	43 (60)		
1 additional SR affected	21 (21)	18 (25)		1.01 (0.48–2.16)
2+ additional SRs affected	28 (28)	11 (15)		2.09 (0.92–4.75)
Maximum advancement in cartilage thickness score across all SRs			0.1787	
No change	39 (39)	38 (53)		
Advance by 1 grade	32 (32)	19 (26)		1.66 (0.80–3.45)
Advance by 2+ grades	30 (30)	15 (21)		1.97 (0.90–4.32)
Osteophytes				
Number of locations with advancement in osteophyte score			0.0097†	
0 locations with advancement	19 (18)	23 (32)		
1 location with advancement	10 (10)	13 (18)		0.89 (0.31–2.51)
2+ locations with advancement	74 (72)	36 (50)		2.64 (1.25–5.58)
Any additional locations affected by any osteophyte			0.0230	
No	30 (29)	33 (46)		
Yes	73 (71)	39 (54)		2.10 (1.11–3.99)
Any advancement in osteophytes score across all locations			0.0388	
No	19 (18)	23 (32)		
Yes	84 (82)	49 (68)		2.13 (1.04–4.35)
BMLs				
Change in number of SRs affected by any BML			0.3595	
Improvement	19 (19)	14 (20)		
No change	38 (37)	33 (46)		0.90 (0.38–2.09)
1 additional SR affected	23 (23)	16 (23)		1.10 (0.42–2.87)
2+ additional SRs affected	22 (22)	8 (11)		2.10 (0.71–6.23)
Maximum advancement in BML size score across all SRs			0.2543	
No change	39 (38)	36 (51)		
Advance by 1 grade	31 (30)	19 (27)		1.53 (0.73–3.22)
Advance by 2+ grades	32 (31)	16 (23)		1.85 (0.85–4.02)
Any SRs with improvement in BML size score			0.9042	
No	53 (52)	38 (54)		
Yes	49 (48)	33 (46)		1.04 (0.56–1.92)
Any of SRs with advancement in BML size score			0.1102	
No	39 (38)	36 (51)		
Yes	63 (62)	35 (49)		1.68 (0.89–3.16)
Hoffa-synovitis and effusion-synovitis				
Change in Hoffa-synovitis			0.6610	
Improvement	27 (26)	17 (24)		
No change	62 (60)	47 (66)		0.80 (0.39–1.64)
Advance	14 (14)	7 (10)		1.19 (0.39–3.62)
Change in effusion-synovitis			0.0063†	
Improvement	32 (31)	37 (51)		
No change	46 (45)	29 (40)		1.84 (0.94–3.59)
Advance	25 (24)	6 (8)		4.99 (1.80–13.85)

* Values are the number (%) unless indicated otherwise. Analysis adjusted for baseline Kellgren/Lawrence grade. APM = arthroscopic partial meniscectomy; PT = physical therapy; SR = subregion; BML = bone marrow lesion.
† Statistically significant after Holm correction.

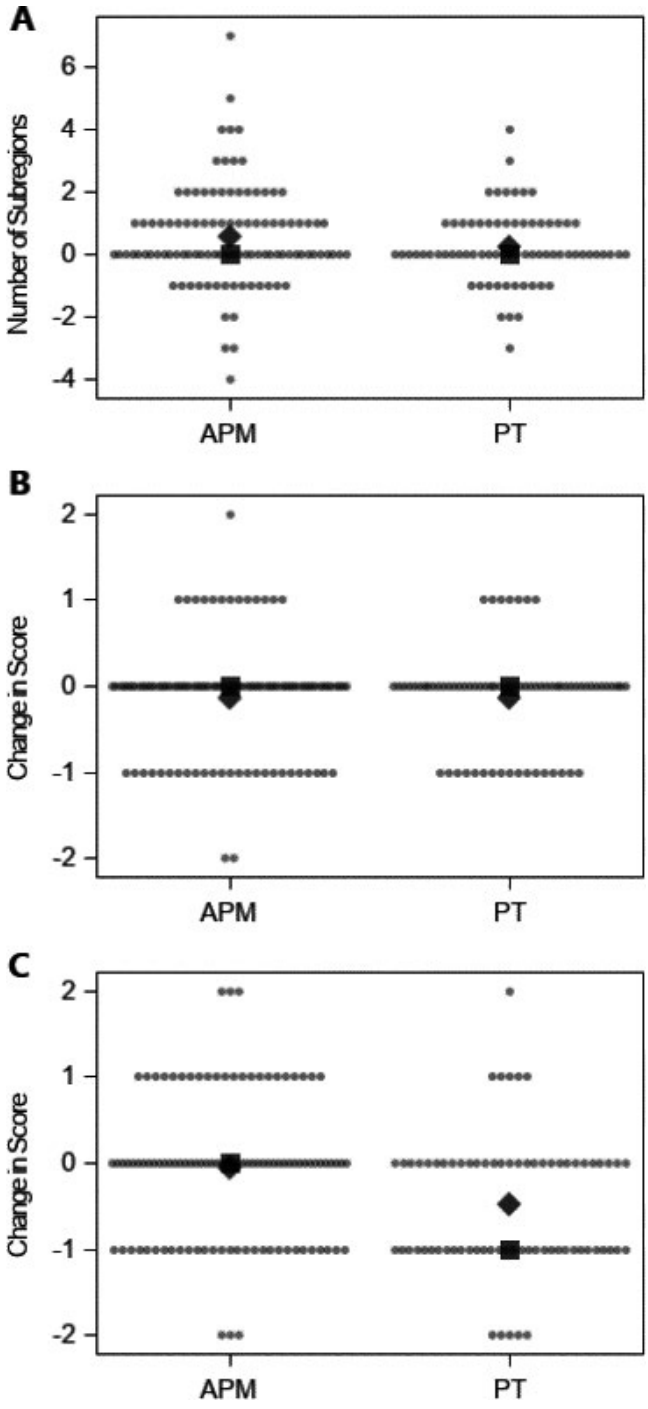

Figure 3. Early magnetic resonance imaging (MRI)–based advancement in bone marrow lesion (BML), Hoffa-synovitis, and effusion-synovitis by treatment group (primary analysis). Each panel shows the distribution of MRI-based advancement by treatment group for **A**, BML, **B**, Hoffa-synovitis, and **C**, effusion-synovitis. Advancement is along the y-axis, and treatment group (arthroscopic partial meniscectomy [APM] versus physical therapy [PT]) is along the x-axis. Advancement is measured in number of subregions for BML and in change in score for Hoffa-synovitis and effusion-synovitis. Circles represent individual participants, diamonds the mean, and squares the median.

available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract).

As treated. Secondary analysis was performed for the as-treated sample, which included the 37 subjects who crossed over from PT to APM in the APM group. Results were similar to the main analysis, with statistically significant differences between treatment arms in cartilage surface area, osteophytes, and effusion-synovitis (see Supplementary Table 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract). As in the primary analysis, we did not find significant associations between treatment group and changes in BML, cartilage thickness, or Hoffa-synovitis.

ITT. The ITT analysis included the 37 subjects who crossed over from PT to APM in the PT group. Results were similar to the main analysis, with increased odds of advancement of cartilage surface area and advancement in effusion-synovitis in the APM versus PT groups. The odds of advancement in osteophytes were in the same direction but attenuated in this analysis compared to the primary and as-treated analyses and did not reach statistical significance (see Supplementary Table 7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23891/abstract). As in the primary and secondary analyses, we did not find significant associations between treatment group and changes in BML, cartilage thickness, or Hoffa-synovitis.

Sensitivity analysis for missing data. Sensitivity analysis with MI for missing data demonstrated similar associations as the main analysis under a MAR mechanism. That is, if we assume that patients missing 18-month cartilage-change data are similar to those with data or that we can reasonably impute change from subject characteristics (age, sex, K/L grade, baseline MOAKS if available), then our conclusions do not change (Table 3). As we change the missing data mechanism and assume that subjects in the APM group with missing data are progressing less than observed APM subjects, and/or PT subjects with missing data are progressing more than observed PT subjects, the associations are attenuated. Generally, in order to change the conclusion about the association between treatment group and progression, we would have to assume an extreme missing data mechanism: namely, that PT subjects with missing data progress in the same fashion as observed APM subjects and APM subjects with missing data progress in the same fashion as observed PT subjects.

DISCUSSION

We evaluated data from an RCT of APM with PT versus PT alone and found that both treatment groups had substantial early

Table 3. Association between treatment group and progression, sensitivity analysis with multiple imputation for missing data*

	Primary analysis	Secondary as-treated analysis	MAR	MNAR1	MNAR2	MNAR3	MNAR4	MNAR5
Cartilage surface area								
Number of SRs with advancement in cartilage surface area score								
0 SRs with advancement (Ref.)								
1 SR with advancement	2.0 (0.9–4.8)	1.7 (0.8–3.8)	1.7 (0.7–4.0)	1.2 (0.5–2.7)	1.4 (0.6–3.0)	1.3 (0.5–3.2)	1.4 (0.7–2.9)	1.0 (0.4–2.2)
2+ SRs with advancement	4.2 (2.0–9.0)	3.3 (1.7–6.5)	3.3 (1.6–6.5)	2.5 (1.2–5.2)	2.0 (1.01–3.9)	2.0 (0.97–4.2)	2.2 (1.2–4.0)	1.4 (0.7–2.8)
Number of additional SRs affected by any cartilage surface area damage								
0 additional SRs affected (Ref.)								
1 additional SR affected	2.8 (1.3–6.0)	2.4 (1.2–4.8)	2.6 (1.3–5.2)	2.0 (0.98–4.1)	1.9 (0.9–4.0)	1.8 (0.9–3.5)	1.7 (0.9–3.4)	1.4 (0.7–2.6)
2+ additional SRs affected	2.7 (1.2–5.9)	2.1 (1.0–4.5)	2.3 (1.1–5.0)	1.8 (0.8–3.7)	1.8 (0.8–4.0)	1.5 (0.7–3.3)	1.7 (0.8–3.6)	1.3 (0.6–2.6)
Maximum advancement in cartilage surface area score across all SRs								
No change (Ref.)								
Advance by 1 grade	2.5 (1.1–5.5)	2.0 (1.0–4.2)	1.9 (1.0–3.9)	1.3 (0.6–2.6)	1.6 (0.8–3.2)	1.5 (0.7–3.4)	1.6 (0.8–3.1)	1.1 (0.5–2.1)
Advance by 2+ grades	4.2 (1.9–9.2)	3.3 (1.6–6.7)	3.2 (1.6–6.5)	2.4 (1.2–4.9)	2.1 (1.1–4.2)	2.1 (1.0–4.5)	2.1 (1.1–4.0)	1.4 (0.7–2.8)
Cartilage thickness								
Number of SRs with advancement in cartilage thickness score								
0 SRs with advancement (Ref.)								
1 SR with advancement	1.6 (0.7–3.4)	1.4 (0.7–3.1)	1.4 (0.7–2.9)	1.0 (0.4–2.2)	1.2 (0.6–2.6)	1.4 (0.6–3.1)	1.3 (0.6–2.8)	1.1 (0.5–2.4)
2+ SRs with advancement	2.0 (1.0–4.1)	1.9 (1.0–3.8)	1.9 (1.0–3.6)	1.5 (0.7–3.0)	1.4 (0.7–2.9)	1.4 (0.7–3.0)	1.5 (0.8–3.0)	1.1 (0.6–2.3)
Number of additional SRs affected by any cartilage thickness damage								
0 additional SRs affected (Ref.)								
1 additional SR affected	1.0 (0.5–2.2)	0.9 (0.5–1.9)	0.8 (0.4–1.6)	0.7 (0.3–1.6)	0.7 (0.3–1.6)	0.9 (0.4–1.7)	0.9 (0.4–2.0)	0.9 (0.4–1.7)
2+ additional SRs affected	2.1 (0.9–4.8)	1.9 (0.9–4.1)	1.9 (0.9–4.1)	1.7 (0.8–3.5)	1.7 (0.8–3.7)	1.5 (0.7–3.4)	1.5 (0.7–3.1)	1.2 (0.6–2.6)
Maximum advancement in cartilage thickness score across all SRs								
No change (Ref.)								
Advance by 1 grade	1.7 (0.8–3.4)	1.7 (0.8–3.3)	1.6 (0.8–3.3)	1.2 (0.6–2.5)	1.5 (0.7–3.2)	1.5 (0.7–3.0)	1.3 (0.7–2.7)	1.2 (0.6–2.3)
Advance by 2+ grades	2.0 (0.9–4.3)	1.8 (0.8–3.7)	1.8 (0.9–3.7)	1.4 (0.7–2.8)	1.4 (0.7–2.9)	1.5 (0.7–3.2)	1.4 (0.7–2.7)	1.3 (0.6–2.6)
Osteophytes								
Number of locations with advancement in osteophyte score								
0 locations with advancement (Ref.)								
1 location with advancement	0.9 (0.3–2.5)	0.8 (0.3–2.0)	0.7 (0.3–1.8)	0.7 (0.3–1.6)	0.6 (0.2–1.7)	0.7 (0.3–1.9)	0.8 (0.3–2.1)	0.7 (0.3–1.9)
2+ locations with advancement	2.6 (1.3–5.6)	2.5 (1.2–5.0)	2.4 (1.1–5.0)	1.9 (1.0–3.7)	1.7 (0.9–3.4)	1.7 (0.9–3.3)	1.9 (1.0–3.6)	1.2 (0.6–2.3)
Any additional locations affected by any osteophyte								
No (Ref.)								
Yes	2.1 (1.1–4.0)	2.0 (1.1–3.6)	1.9 (1.1–3.4)	1.6 (0.8–3.0)	1.3 (0.7–2.4)	1.5 (0.8–2.8)	1.5 (0.8–2.6)	1.2 (0.7–2.1)
Any advancement in osteophytes score across all locations								
No (Ref.)								
Yes	2.1 (1.0–4.4)	2.0 (1.0–3.9)	2.0 (1.0–3.9)	1.8 (0.8–3.7)	1.6 (0.8–3.1)	1.5 (0.8–2.9)	1.5 (0.8–3.0)	1.3 (0.7–2.5)

(Continued)

Table 3. *(Cont'd)*

	Primary analysis	Secondary as-treated analysis	MAR	MNAR1	MNAR2	MNAR3	MNAR4	MNAR5
Bone marrow lesions								
Change in number of subregions affected by any BML								
Improvement (Ref.)								
No change	0.9 (0.4–2.1)	1.2 (0.6–2.8)	1.2 (0.6–2.6)	0.9 (0.4–1.9)	0.9 (0.4–2.1)	1.0 (0.4–2.3)	0.9 (0.4–1.9)	0.8 (0.4–1.8)
1 additional SR affected	1.1 (0.4–2.9)	1.3 (0.5–3.3)	1.1 (0.4–2.9)	0.9 (0.3–2.2)	1.0 (0.4–2.2)	1.0 (0.5–2.4)	0.9 (0.4–2.2)	0.9 (0.4–2.1)
2+ additional SR affected	2.1 (0.7–6.2)	2.1 (0.7–6.0)	2.0 (0.7–5.6)	1.4 (0.5–4.4)	1.6 (0.5–5.0)	1.6 (0.5–5.2)	1.5 (0.5–4.3)	1.3 (0.5–3.5)
Maximum advancement in BML size score across all SRs								
No change (Ref.)								
Advance by 1 grade	1.5 (0.7–3.2)	1.5 (0.7–2.9)	1.4 (0.7–2.9)	1.1 (0.6–2.2)	1.3 (0.6–2.8)	1.3 (0.6–2.7)	1.3 (0.6–2.6)	1.1 (0.5–2.2)
Advance by 2+ grades	1.9 (0.9–4.0)	1.3 (0.6–2.8)	1.3 (0.6–2.9)	1.0 (0.5–1.9)	1.1 (0.6–2.3)	1.1 (0.5–2.4)	1.1 (0.6–2.1)	1.1 (0.5–2.2)
Any SRs with improvement in BML size score								
No (Ref.)								
Yes	1.0 (0.6–1.9)	0.8 (0.4–1.4)	0.8 (0.5–1.5)	0.7 (0.4–1.3)	1.0 (0.5–1.8)	0.9 (0.5–1.7)	0.9 (0.5–1.6)	1.0 (0.5–1.9)
Any of SRs with advancement in BML size score								
No (Ref.)								
Yes	1.7 (0.9–3.2)	1.4 (0.8–2.5)	1.5 (0.8–2.6)	1.1 (0.6–2.0)	1.3 (0.7–2.3)	1.3 (0.7–2.3)	1.2 (0.7–2.3)	1.2 (0.6–2.2)
Hoffa-synovitis and effusion-synovitis								
Change in Hoffa-synovitis								
Improvement (Ref.)								
No change	0.8 (0.4–1.6)	0.8 (0.4–1.6)	0.8 (0.4–1.7)	0.7 (0.3–1.5)	0.7 (0.4–1.4)	0.8 (0.4–1.6)	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Advance	1.2 (0.4–3.6)	1.7 (0.6–4.7)	1.8 (0.6–5.5)	1.3 (0.5–3.5)	1.5 (0.5–4.4)	1.5 (0.5–4.2)	1.2 (0.4–3.6)	1.1 (0.4–3.1)
Change in effusion-synovitis								
Improvement (Ref.)								
No change	1.8 (0.9–3.6)	1.9 (1.0–3.6)	1.9 (1.02–3.4)	1.6 (0.9–3.0)	1.6 (0.9–2.9)	1.4 (0.8–2.5)	1.6 (0.8–3.0)	1.2 (0.6–2.1)
Advance	5.0 (1.8–13.8)	4.1 (1.5–10.9)	4.1 (1.5–11.4)	3.7 (1.3–10.6)	2.6 (1.0–6.5)	2.7 (1.0–7.4	2.5 (1.0–6.2)	1.7 (0.7–4.2)

* Values are the odds ratio (95% confidence interval) for progression for arthroscopic partial meniscectomy vs. physical therapy presented in cells. MAR = missing at random; MNAR = missing not at random; SR = subregion; Ref. = reference; BML = bone marrow lesion.

advancement of MRI-based biomarkers of each of the structural joint features examined. Patients undergoing APM had greater early advancement in MRI-based markers over 18 months than those treated nonoperatively for cartilage surface area, osteophytes, and effusion-synovitis.

Two RCTs found no differences in radiographic advancement between subjects treated with APM and those treated nonoperatively for degenerative meniscal tear (5,6). However, radiographic OA grade is an insensitive marker of structural change (22,23); both studies found radiographic advancement rates of <5%. Roemer et al found that both meniscal damage and partial meniscectomy were associated with incident OA (K/L grade 2) over 4 years in a nested case-control sample from the Osteoarthritis Initiative (10). In addition, the authors used MOAKS to evaluate MRI-based cartilage progression, defining progression as any increase in either size or thickness of cartilage damage. In the incident OA cases, partial meniscectomy was associated with worsening cartilage damage compared to knees with meniscal damage and without meniscectomy, and to knees without meniscal damage. However, only 26 knees underwent meniscal surgery and had MRI results. Our analysis builds on the work of Roemer et al (10) by taking advantage of the large MeTeOR Trial cohort. In MeTeOR, all subjects had documented meniscal tear, and all had substantial enough pain and functional limitation that subjects and their enrolling surgeons were prepared to proceed to APM. This balancing of structural and symptom severity between treatment groups is difficult to achieve in observational studies. The surgeries in MeTeOR were done in a uniform manner, and follow-ups were at regular intervals post randomization. Like Roemer et al (10), we found associations between APM and subsequent cartilage advancement.

To our knowledge, this is the first study to evaluate early MRI-based changes in a follow-up evaluation of data from an RCT of APM versus nonoperative therapy. We found that MeTeOR participants who had APM had higher likelihood of MRI-based advancement in cartilage surface area, osteophytes, and effusion-synovitis. We did not find significant associations between treatment type and advancement in BMLs or Hoffa-synovitis. The lack of association between treatment and BMLs and Hoffa synovitis may reflect the transient nature of BMLs and synovitis; these features do not reflect cumulative damage as do cartilage damage and osteophytosis. The results were similar in the main per-protocol analysis and in the secondary as-treated and ITT analyses.

The clinical relevance of these early MRI findings remains uncertain. It will be important to determine whether subjects who demonstrate these changes in imaging findings over 18 months are at higher risk of worsening in symptom severity, functional limitation, and total joint replacement over subsequent follow-up. The findings underscore the importance of clinical follow-up of this cohort and, more generally, of individuals with meniscal tear treated either operatively or nonoperatively.

Only 225 of 351 randomized patients (64%) had MRI data available both at baseline and 18 months. Although our analyses found associations between some aspects of structural disease progression and treatment group, we were concerned about the amount of missing data. Our tipping-point sensitivity analysis with MI suggested that it would take an extreme missing data mechanism to change the conclusions. We would have to assume that PT patients with missing data are actually advancing at rates similar to the APM patients, and that APM subjects with missing data actually progress at rates similar to PT subjects. Although this extreme scenario does not seem plausible, we can never rule out a missing data mechanism with 100% certainty.

These results should be interpreted within the context of the study limitations. The primary analytic sample was limited to those subjects undergoing MRI at 18 months. Of patients randomized to PT, 31% crossed over to APM within 6 months of randomization. Subjects crossing over to APM had shorter symptom duration and greater baseline pain; thus, the balancing of confounders inherent to randomization may have been disrupted. We evaluated differences in known potential confounders between the groups and adjusted where necessary. However, we cannot be certain that the groups were balanced on unknown confounders. To further minimize risk of bias, we conducted 3 sets of analyses, all adjusted for K/L grade and factors imbalanced at baseline: the primary analysis that excluded crossovers, a sensitivity as-treated analysis that included crossovers in the APM group, and an ITT analysis that included crossovers in the PT group. All 3 of these analyses yielded similar conclusions. Due to the multinomial nature of many of the outcomes variables, we used logistic regression and present ORs. ORs overstate relative risks, especially when the prevalence of the outcome is high, as in this analysis (24). Thus, these ORs should not be interpreted as relative risks. Caution should be taken in generalizing these results to a more general knee OA cohort. First, inclusion criteria for the MeTeOR Trial included evidence of meniscal tear on MRI results and symptoms consistent with torn meniscus (i.e., clicking, catching, popping). Each patient had to be willing to undergo APM if randomized to the APM group (11). Thus, the MeTeOR Trial may be more generalizable to patients with knee OA and meniscal tear with symptoms. Patients were recruited from academic medical centers, and only 26% of eligible subjects agreed to participate in the MeTeOR RCT (4). Finally, this analysis is a secondary analysis of an RCT, and as such, we did not conduct a formal power analysis (25). To address the uncertainty in our parameter estimates, we included 95% CIs (26).

In discussing treatment options for symptomatic meniscal tear, patients and providers must weigh the potential benefits and risks of treatment options, including these findings on structural advancement. Future work will assess the association between early structural advancement and subsequent pain, function, and risk of total knee replacement. Clinicians should be aware that regardless of treatment, there was MRI evidence of progression. At this point, the clinical meaning of the MRI-based changes doc-

umented in this study is unknown. Assessing the relevance of these MRI-based changes is an important research priority.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Collins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Collins, Losina, Marx, Guermazi, Jarraya, Jones, Levy, Mandl, Martin, Wright, Spindler, Katz.

Acquisition of data. Losina, Guermazi, Jarraya, Katz.

Analysis and interpretation of data. Collins, Losina, Katz.

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APPENDIX A

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