SUPPLEMENTARY APPENDIX A: DEVELOPMENT OF INDICATOR RANKING AND EXPLANATION OF UNDERLYING ASSUMPTIONS AND ANALYSES

Indicator ranking

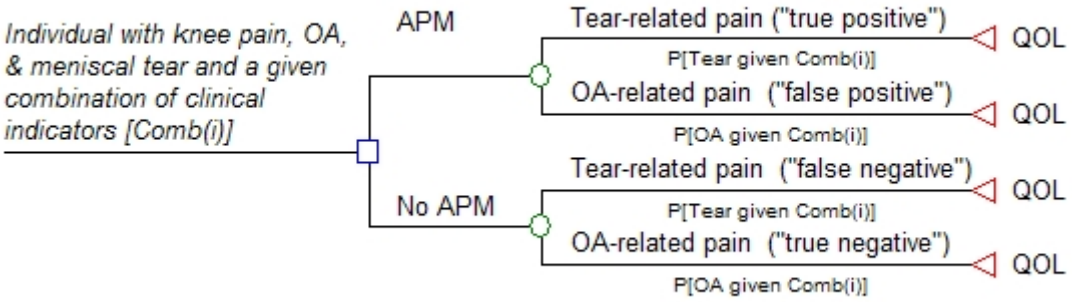
The use of Bayesian probability revision theory requires that we make assumptions regarding the probability that an individual manifests a particular clinical indicator under the circumstance that that individual's pain is primarily due to their meniscal tear or, alternatively, due to their underlying osteoarthritis (OA). Below are descriptions of the assumptions underlying the 4 clinical indicators and the base estimates listed in Table 1:

- The dichotomization of Tear Type into Low likelihood of causing pain or symptoms (radial, horizontal, or oblique partial-thickness tears) versus High likelihood (displaced, vertical, complex full-thickness tears) is based on data by Zanetti et al (1), who found a statistically significant, 3-fold difference in the prevalence of displaced, vertical, or complex full-thickness tears in symptomatic versus asymptomatic, contralateral knees (33.3% versus 11.1%). We assumed a conservative 2.3-fold increase in the probability of finding High versus Low likelihood meniscal tears among individuals with tear-related pain. While some data dispute the association of tear type and pain (2), additional data by the same authors support a lower probability of High versus Low likelihood tears among individuals with OA (3).
- We categorized the presence of mechanical symptoms as None, Possible (buckling or giving way), and Probable mechanical symptoms (intermittent locking or catching), based on data noting that buckling is common among patients with OA (4) and that locking is specific for meniscal pathology (5). Although McMurray's test may be more specific for meniscal tear (5), it is poorly reproducible (kappa value 0.16, 95% CI: -0.01-0.33) (6). We chose mechanical symptoms because of its specificity (91%, 95% CI: 80-98%) (5) and reproducibility (kappa 0.44, 95% CI: 0.26-0.62) (6). As the specificity of Probable mechanical symptoms is >90% in patients with OA (5), we assumed that 5% of individuals with OA-related pain would have such symptoms, that 60% would have no mechanical symptoms, and the remainder (35%) would have Possible mechanical symptoms. This is consistent with data (4) noting 27% prevalence of buckling in adults with severe knee pain and increased buckling in individuals with underlying OA (versus without OA). Our population has both OA and pain sufficient to warrant surgery. While the sensitivity of Probable mechanical symptoms for detecting the *presence* of a meniscal tear is only 11% (5), we assumed the likelihood of finding either Possible or Probable mechanical symptoms would be much greater among individuals with tear-related pain (i.e., symptomatic tears). We also assumed Probable mechanical symptoms would be less likely than Possible mechanical symptoms among individuals with tear-related pain, reflecting the relative prevalence of these symptoms in practice.
- We dichotomized Pain Pattern as Increased (in last 3 months) versus Static pain based on published recommendations that pain pattern be used to identify arthroscopic partial meniscectomy (APM) candidates (7) and data showing the predictive capability of clinical indicators varies according to pain acuity (5), No further data exist, so we assumed 70% of individuals with tear-related pain have Increased Pain Pattern while 70% of those with OA-related pain have Static Pain Pattern.
- We categorized Magnetic resonance imaging (MRI) bone marrow lesions (BMLs) as None, Mild, or Severe, based on the Whole-Organ MRI Score (WORMS) (8,9). Although

not commonly used in clinical decision making for APM, BMLs were included in the ranking based on data demonstrating a more than 2-fold prevalence of severe BMLs in symptomatic versus asymptomatic OA (10,11). These data are reflected in our 2-fold increase in the likelihood of Severe versus Mild BMLs in individuals with OA-related pain. A prospective case-control study that found incident knee pain was associated with ≥2 unit increase in BML score (adjusted OR 3.2, 95% CI 1.5-6.8) (9). As data document marrow edema at the site of meniscal tears (12), the above refer to BMLs *not* localized to the site of the tear. We also assumed BMLs would be less common and less severe in individuals with tear- versus OA-related pain.

Outcome assumptions

Figure 1. Hypothetical decision tree underlying the outcome assumptions, where QOL indicates quality of life outcome (i.e., 2-year increases in International Knee Documentation Committee or Subjective Knee Form or IKDC scores).



Below is a description of the evidence supporting the outcome assumptions listed in Table 1: 6-month data from the only randomized clinical trial comparing APM with nonoperative management in this population found no difference in clinical outcomes (13). Published responsiveness data in a population with isolated meniscal disorders define a minimally detectable change in IKDC score as 8.8 to 20.5 points (0-100 scale, with 100 being no disability or pain) (14,15). Mean IKDC scores for middle-aged individuals with knee complaints are <30, as compared with >60 in those without knee complaints (16). Data from various arthroscopic interventions describe 40-50 point increases in post-operative IKDC scores (17,18). Therefore, we assumed a 50-point increase in IKDC score for performing APM in individuals with tear-related pain. Based on data defining the relative standardized response mean of nonsteroidal antiinflammatory therapy for OA as approximately half that of APM for meniscal tear (19-22), the benefit of conservative therapy among individuals with OA-related pain likely does not exceed 50% of the benefit individuals with tear-related pain receive from APM. Therefore, we assumed only a 25-point IKDC increase for nonoperative treatment in individuals with OA-related pain.

Analyses

Table A. All possible combinations of indicators, ranked by likelihood ratio of tear-related pain

Rank	Tear Type	Mechanical Symptoms	Pain Pattern	BMLs	Probability in tear-related pain (a)	Probability in OA-related pain (b)	Likelihood Ratio (=a/b)
1	High	Probable	Increased	None	0.0662	0.0005	147.00
2	High	Possible	Increased	None	0.1323	0.0032	42.00
3	High	Probable	Increased	Mild	0.0515	0.0014	38.11
4	High	Probable	Static	None	0.0284	0.0011	27.00
5	Low	Probable	Increased	None	0.0284	0.0011	27.00
6	High	Possible	Increased	Mild	0.1029	0.0095	10.89
7	High	Probable	Increased	Severe	0.0294	0.0027	10.89
8	Low	Possible	Increased	None	0.0567	0.0074	7.71
9	High	Possible	Static	None	0.0567	0.0074	7.71
10	High	Probable	Static	Mild	0.0221	0.0032	7.00
11	Low	Probable	Increased	Mild	0.0221	0.0032	7.00
12	Low	Probable	Static	None	0.0122	0.0025	4.96
13	High	None	Increased	None	0.0221	0.0054	4.08
14	High	Possible	Increased	Severe	0.0588	0.0189	3.11
15	Low	Possible	Increased	Mild	0.0441	0.0221	2.00
16	High	Possible	Static	Mild	0.0441	0.0221	2.00
17	High	Probable	Static	Severe	0.0126	0.0063	2.00
18	Low	Probable	Increased	Severe	0.0126	0.0063	2.00
19	Low	Possible	Static	None	0.0243	0.0172	1.42
20	Low	Probable	Static	Mild	0.0095	0.0074	1.29
21	High	None	Increased	Mild	0.0172	0.0162	1.06
22	High	None	Static	None	0.0095	0.0126	0.75
23	Low	None	Increased	None	0.0095	0.0126	0.75
24	Low	Possible	Increased	Severe	0.0252	0.0441	0.57
25	High	Possible	Static	Severe	0.0252	0.0441	0.57
26	Low	Possible	Static	Mild	0.0189	0.0515	0.37
27	Low	Probable	Static	Severe	0.0054	0.0147	0.37
28	High	None	Increased	Severe	0.0098	0.0324	0.30
29	High	None	Static	Mild	0.0074	0.0378	0.19
30	Low	None	Increased	Mild	0.0074	0.0378	0.19
31	Low	None	Static	None	0.0041	0.0294	0.14
32	Low	Possible	Static	Severe	0.0108	0.1029	0.10
33	High	None	Static	Severe	0.0042	0.0756	0.06
34	Low	None	Increased	Severe	0.0042	0.0756	0.06
35	Low	None	Static	Mild	0.0032	0.0882	0.04
36	Low	None	Static	Severe	0.0018	0.1764	0.01

High = High likelihood of tear-related pain; Low = Low likelihood of tear-related pain; Possible = Possible presence of mechanical symptoms (e.g., giving way); Probable = Probable presence of mechanical symptoms (e.g., locking); Static = Static pattern of pain; Increased = Increased pain within the last three months; Mild = Mild BMLs; Severe = Severe BMLs.

Below are the calculations used to estimate the likelihood of tear-related pain: using Bayes' Theorem (23), we used the above probabilities in Table A to refine the original estimate of the prevalence of tear- and OA-related pain:

$$\mathrm{P}(Tear|Comb_i) \equiv \frac{\mathrm{P}(Comb_i|Tear)\times \mathrm{P}(Tear)}{\mathrm{P}(Comb_i|Tear)\times \mathrm{P}(Tear)+\mathrm{P}(Comb_i|OA)\times \mathrm{P}(OA)}$$

and

$$\mathrm{P}(OA|Comb_i) \equiv \frac{\mathrm{P}(Comb_i|OA)\times \mathrm{P}(OA)}{\mathrm{P}(Comb_i|Tear)\times \mathrm{P}(Tear)+\mathrm{P}(Comb_i|OA)\times \mathrm{P}(OA)}$$

Where Tear = Tear-related pain; OA = OA-related pain; *i* ranges from 1 to 36 and $Comb_i$ = the *i* the possible combination of Tear Type, Mechanical Symptoms, Pain Pattern, and BMLs. As the likelihood ratios are calculated by dividing the probability of finding a given indicator combination among individuals with pain primarily due to meniscal tear by the probability of finding a given indicator combination among individuals with pain primarily due to OA, they are also dependent on the underlying assumptions for the base estimates described above. By conducting sensitivity analyses on the probability of each of the given indicators, we are also conducting sensitivity analyses on each of the underlying components of the LR. As many different combinations of probabilities can yield the same LR, we chose to perform sensitivity analyses on the indicator probabilities (i.e., LR components), rather than on the LRs themselves.

Table 1 also lists the ranges of plausible values that were used in sensitivity analyses to test the base estimate assumptions. For each variable, the categories are mutually exclusive and collectively exhaustive and will depend on whether that individual's knee pain is primarily due to their meniscal tear or primarily due to their OA. Therefore, the probabilities of each category for a given clinical indicator must sum to 1. For example, a given individual whose knee pain is due to their meniscal tear must have exactly one of either: No mechanical symptoms, Possible mechanical symptoms (such as buckling or giving way), or Probable mechanical symptoms (such as locking). If we assume that, among individuals with pain due to their meniscal tear, the probability of having No mechanical symptoms is 0.10 and that of having Possible mechanical symptoms is 0.60, then the probability of having Probable mechanical symptoms must be 0.30. Therefore, while there are wide ranges of values given in Table 1, each particular model "run" must use those values for any given clinical finding that sum to 1. In order to test an appropriately wide spectrum of underlying assumptions in one-way sensitivity analyses, we ran the model assuming that a given clinical indicator was 1) more predictive of whether an individual's pain was primarily due to their meniscal tear than the base estimate, 2) less predictive than the base estimate, and 3) no better than chance. We chose to test only assumptions with clinical face validity. For example, we did not test the assumption that No mechanical symptoms was more predictive of pain due to meniscal tear than Probable mechanical symptoms, but we did test a very broad range of probabilities (0.10-0.80) for Probable mechanical symptoms, as this is less common in clinical practice than Possible

mechanical symptoms, but is presumed to be a highly specific clinical finding (5). As noted in the Results section of the manuscript, although the rank order of the indicator combinations might change between analyses, varying the input assumptions for the predictive ability of the clinical indicators had little impact on clinical outcomes.

SUPPLEMENTARY APPENDIX B: RESULTS OF PRIMARY AND ALL SENSITIVITY ANALYSES USING A 50% BASE PREVALENCE OF TEAR-RELATED PAIN ASSUMPTION

Base-case analysis assuming 50% base prevalence of tear-related pain

Increases in IKDC scores

Figure A, corresponding to Figure 2 in the main manuscript, displays the expected 2-year increases in population IKDC scores at each possible APM cutoff. The horizontal axis lists the 36 possible indicator combinations and the vertical axis represents the average incremental improvement in the population's IKDC score. Each data point represents the average increase in the IKDC score for the population if one were to use that combination as the APM cutoff. Moving from left to right, one performs APM on more of the population, most of whom have tear-related pain, and outcomes increase; as one continues rightward, fewer individuals have tear-related pain and outcomes diminish.

Maximizing IKDC scores

Using indicator combination 27 (Low-Probable-Static-Severe) as the cutoff – operating on all subjects in symptom combination ranks 1-27 and not operating on ranks 28-36 – maximizes 2-year increases in population IKDC scores, producing an average benefit of 31.2 points. Using this cutoff, 80.6% of the population would receive optimal treatment. Selecting a less aggressive cutoff from ranks 17-23 yields a lower total average incremental benefit (28-30 IKDC score points) but ensures that a greater proportion (>83%) of the population receives optimal treatment.

Sensitivity analyses assuming 50% base prevalence of tear-related pain

Increases in IKDC scores

Varying assumptions (across ranges in Table 1) had little impact on clinical outcomes. Increases in population IKDC scores were less than minimally detectable cutoffs for all variables except base prevalence. Those results are discussed in the main manuscript.

Maximizing IKDC scores

Varying assumptions also had little impact on the APM cutoff rank that yielded the greatest increases in IKDC score. Figure B, which corresponds to Figure 3 in the main manuscript, is a tornado diagram demonstrating the impact of one-way sensitivity analyses on the operable cutoff rank that produces maximal 2-year increase in IKDC scores. For 10 of 13 variables, one-way sensitivity analyses reversed the treatment (from APM to nonoperative treatment or vice versa) for <12% of the population. Varying base prevalence changed treatment for 92% of the population (see main manuscript). When the increases in 2-year IKDC scores for individuals with OA-related pain receiving either conservative therapy or APM were varied, 47% would experience a change in treatment.

Omitting each indicator from the analysis in sequence produced a change in treatment for ≤6% of the population compared with the base-case analysis. Figure C, corresponding to Figure 3 in the main manuscript, illustrates how eliminating each indicator had little impact on the overall ability to discriminate between individuals with tear- versus OA-related pain. The total AUC for the base-case ROC curve was 92.02; AUC values for the sensitivity analyses ranged from 86.13 to 89.86.

Multi-way sensitivity analyses, simultaneously varying base prevalence assumption with APM efficacy

Figure C shows the maximal improvement in average population IKDC score across the full range of possible base prevalences for tear-related pain. Colored curves reflect analyses where the response to surgical and nonoperative treatment for tear- and OA-related pain were varied, while the black curve represents base-case assumptions. Overall, decreasing the prevalence of tear-related pain decreased maximal improvements in IKDC scores, although outcomes did increase slightly as the prevalence of tear-related pain approached zero due to floor effect. Both removing the "penalty" of a 25-point decrease in IKDC score for not performing APM in individuals with tear-related pain and/or adding a "penalty" for performing APM in those with OA-related pain had little impact on improvements in IKDC scores (pink, green, and orange curves) or ranks producing optimal and worst outcomes (not shown). In contrast, decreasing APM efficacy for tear-related pain decreased maximal improvements in population IKDC scores, regardless of the underlying base prevalence of tear-related pain (light blue and red curves). These decreases were accentuated by holding to the assumption that nonoperative treatment in OA-related pain produced only 50% of the benefit of APM in tear-related pain (dark green and brown curves).

Two-way sensitivity analyses, simultaneously varying both tear-related pain and OA-related pain indicator assumptions

To address concerns that one-way sensitivity analyses of the indicator assumptions might be inadequate to detect variability in the model, we also performed two-way sensitivity analyses by varying the predictive probabilities of the indicators among those with tear-related pain and OA-related pain simultaneously. For example, we performed analyses using the following probabilities of finding a High likelihood Tear Type among individuals with tear- and OA-related pain, respectively:

a) 0.95 among tear-related/0.05 among OA-related pain
b) 0.50 among tear-related/0.05 among OA-related pain
c) 0.95 among tear-related/0.50 among OA-related pain
d) 0.50 among tear-related/0.50 among OA-related pain

The impact of these analyses is summarized in Figure D below. The row titled "Tear type in tear-related and OA-related pain simultaneously varied" (horizontal bar in red) in Figure D summarizes the impact of these additional analyses on the on the operable cutoff rank resulting in maximal improvement in 2-year overall population IKDC scores. The optimal rank ranged from rank 15 to 23 and the maximum improvement in population IKDC score ranged from 23.7 to 28.5.

Multi-way sensitivity analyses, simultaneously varying the predictive value of all 4 predictive indicators

We also examined the impact of varying the predictive value of all 4 predictive indicators simultaneously among individuals with tear-related or OA-related pain. As improving the predictive value of any indicator would improve the overall predictive value of the model, we focused our analyses on changes in input assumptions that reduced the predictive ability of the indicators. Given the complexity of varying these probabilities noted above, we chose the following representative combinations to test several "worse" case scenarios. (In the example

provided, each probability refers to the probability of a given indicator among individuals with tear-related pain):

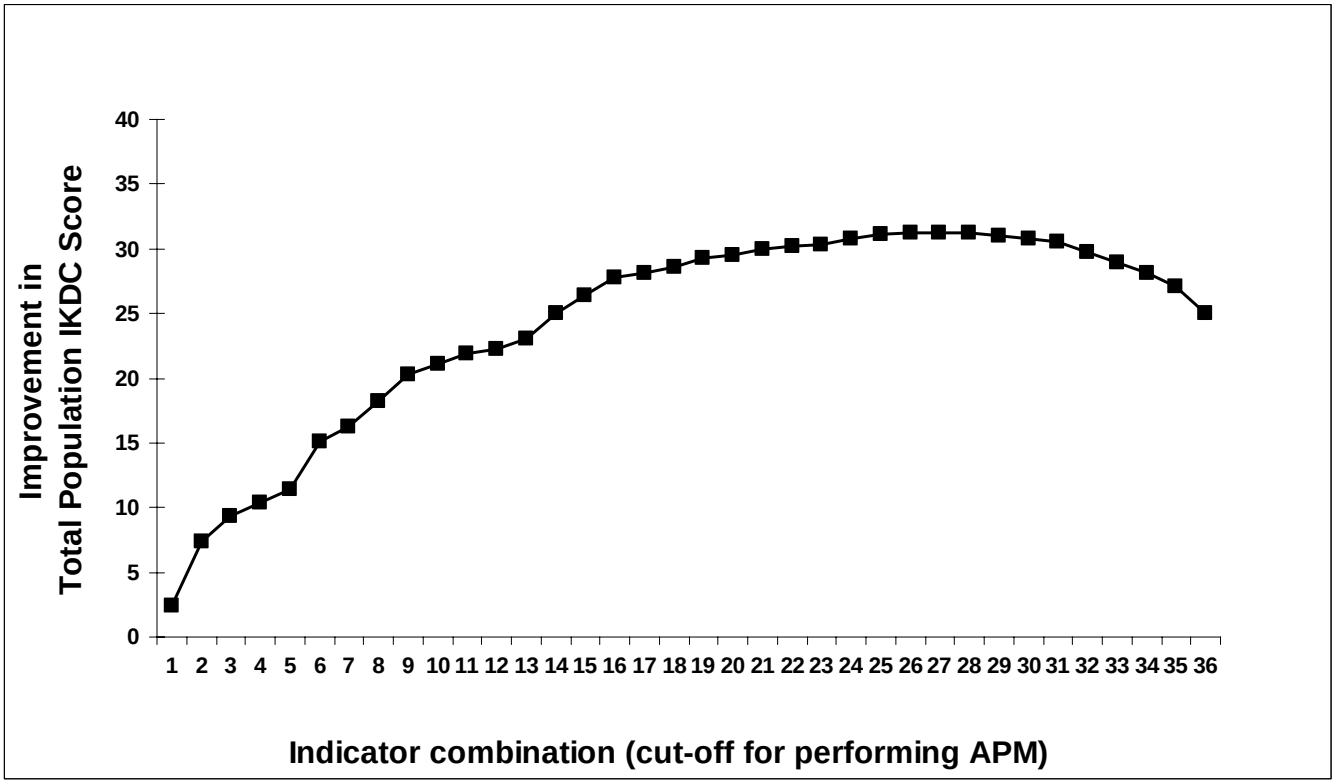
a) Reduce 2 indicators to lowest predictive probabilities and leave 2 at base-case values:
   i. Low likelihood Tear Type 0.3, High likelihood Tear Type 0.7
   ii. No Mechanical Symptoms 0.1, Possible Symptoms 0.6, Probable Symptoms 0.3
   iii. Increased Pain Pattern 0.5, Static Pain Pattern 0.5
   iv. Mild BMLs 0.33, Moderate BMLs 0.4, Severe BMLs 0.27

b) Reduce all indicators to lowest predictive probabilities:
   i. Low likelihood Tear Type 0.5, High likelihood Tear Type 0.5
   ii. No Mechanical Symptoms 0.33, Possible Symptoms 0.33, Probable Symptoms 0.34
   iii. Increased Pain Pattern 0.5, Static Pain Pattern 0.5
   iv. Mild BMLs 0.33, Moderate BMLs 0.40, Severe BMLs 0.27

c) Reduce all indicators to an intermediate predictive level (i.e., less predictive than base-case values, but greater than chance):
   i. Low likelihood Tear Type 0.4, High likelihood Tear Type 0.6
   ii. No Mechanical Symptoms 0.2, Possible Symptoms 0.5, Probable Symptoms 0.3
   iii. Increased Pain Pattern 0.6, Static Pain Pattern 0.4
   iv. Mild BMLs 0.3, Moderate BMLs 0.5, Severe BMLs 0.2

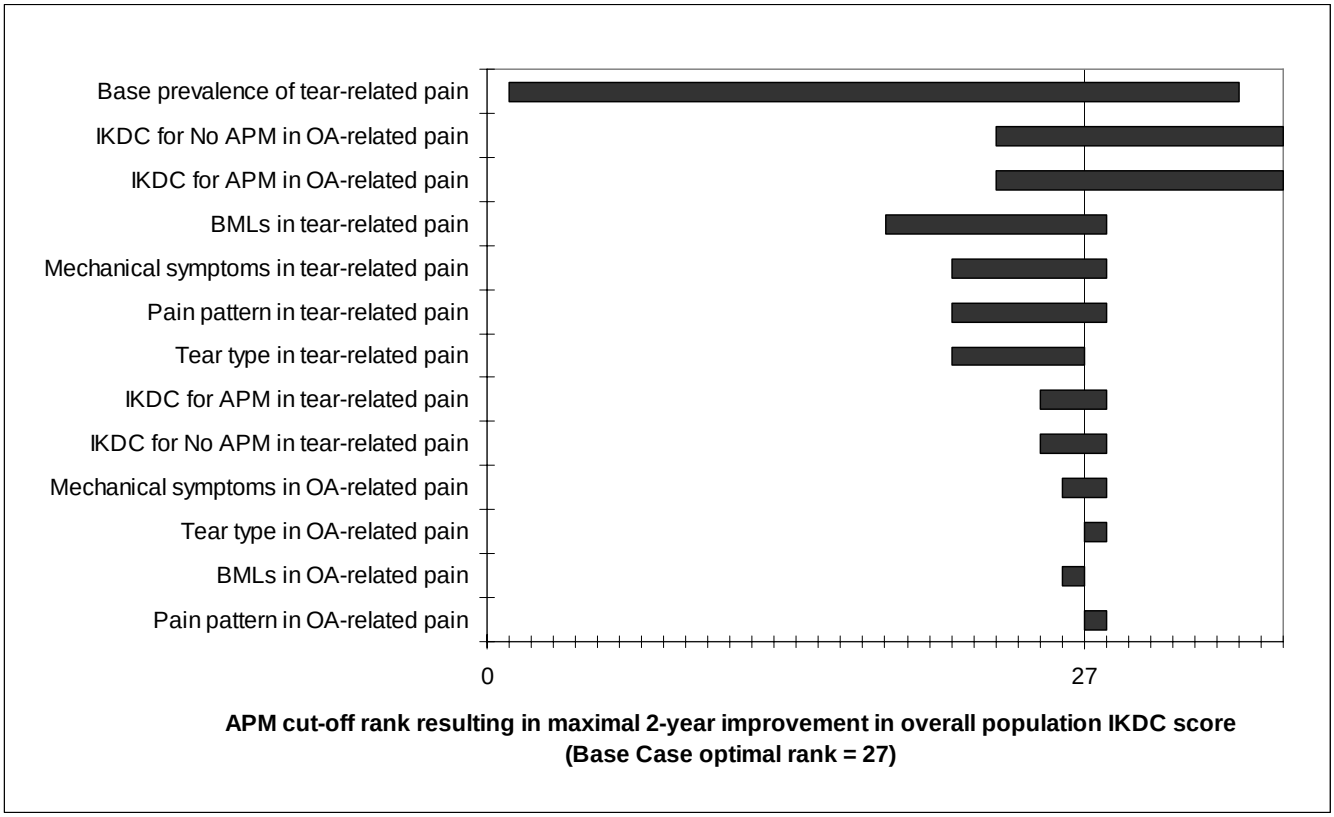
The results of these analyses are also summarized in Figure D below. The row titled “Vary all tear-related pain indicator probabilities simultaneously” (horizontal bar in red) in Figure D summarizes the impact of these additional analyses on the on the operable cutoff rank resulting in maximal improvement in 2-year overall population IKDC scores. The optimal rank ranged from rank 20 to 21 and the maximum improvement in population IKDC score ranged from 21.2 to 23.4.

Figure A. Total 2-year population outcomes according to the indicator combination rank used as the cutoff for performing APM, assuming 50% base prevalence of tear-related pain.



Rank 1 refers to the indicator combination of High likelihood tear type, Probable mechanical symptoms, Increased pain pattern and None BMLs (highest LR of tear-related pain) and rank 36 refers to the indicator combination of Low likelihood tear type, No mechanical symptoms, Static pain pattern and Severe BMLs (lowest LR of tear-related pain). Refer to Table A for an explanation of ranks.

Figure B. Tornado diagram demonstrating the impact of one-way sensitivity analyses of all model assumptions on the operable cutoff rank resulting in maximal increases in 2-year overall population IKDC scores, assuming 50% base prevalence of tear-related pain.



The horizontal bars represent the variation from the optimal cutoff (identified in the base-case analysis and at which maximal outcomes are achieved for the population) that is produced by varying each model assumption, listed along the vertical axis, through the full range of its plausible values.

Figure C. Maximal improvements in average population IKDC score achieved under varying assumptions of the base prevalence of tear-related pain and the efficacy of APM.

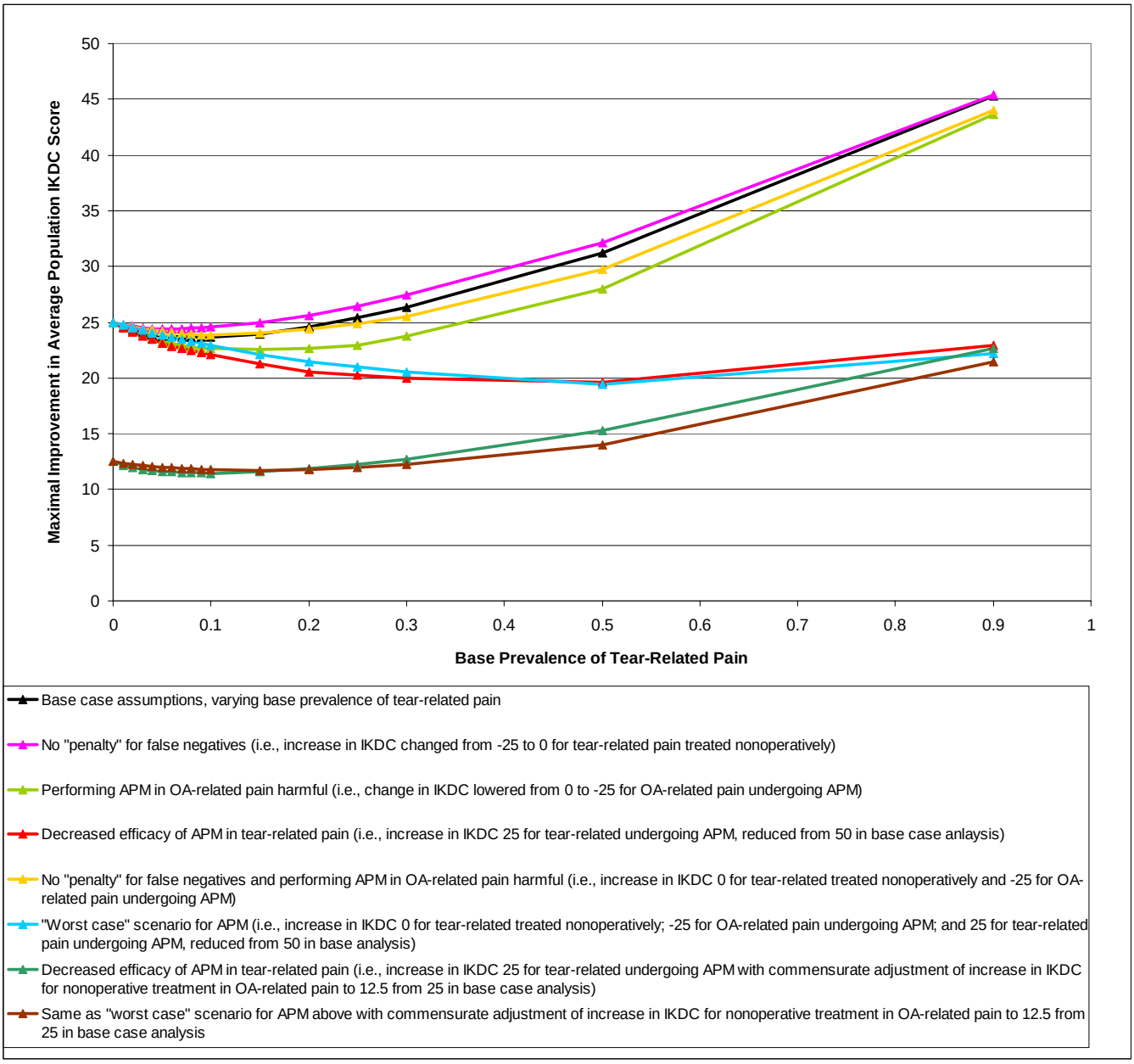
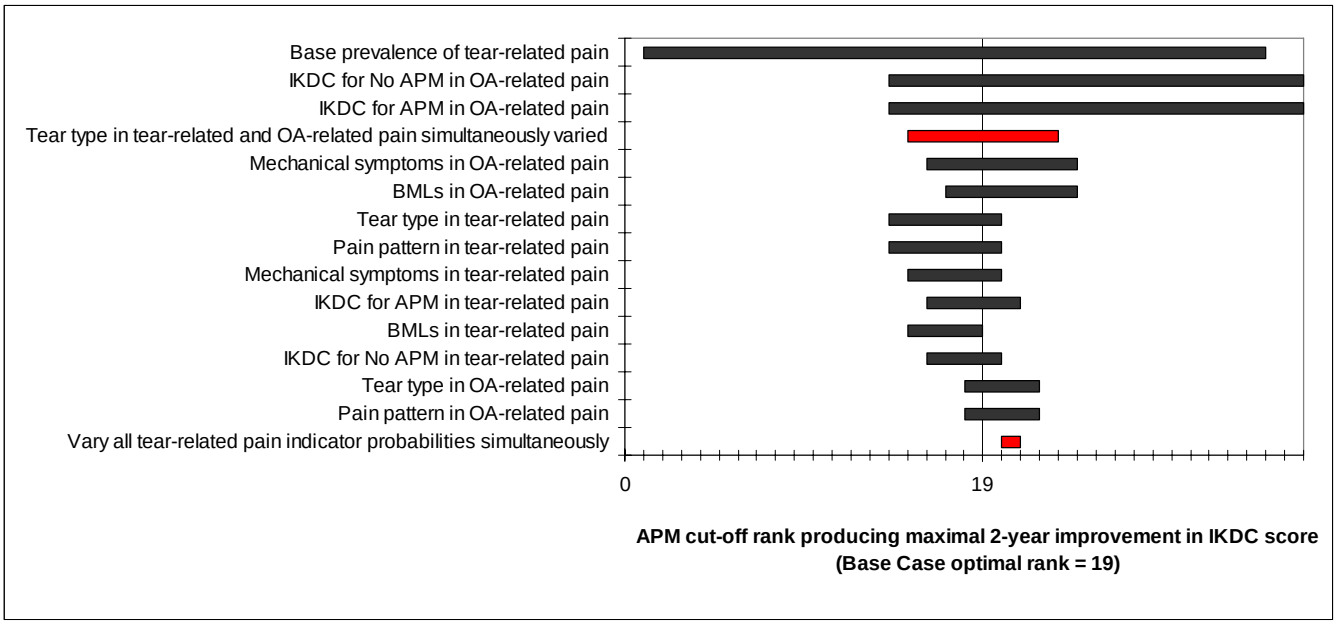
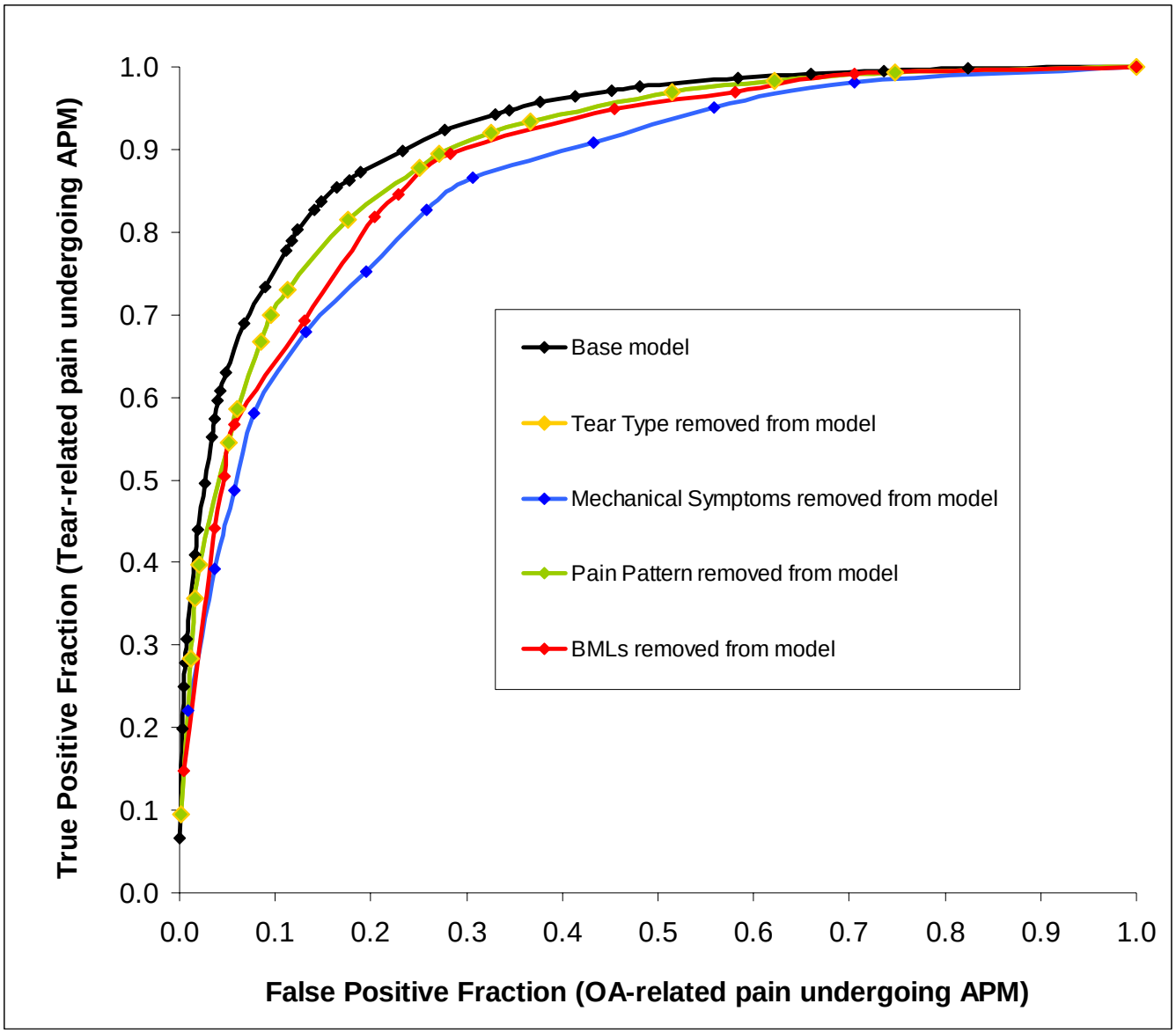


Figure D. Tornado diagram demonstrating the impact of multi-way (versus one-way) sensitivity analyses of model assumptions on the operable cutoff rank resulting in maximal improvement in 2-year overall population IKDC scores.



SUPPLEMENTARY APPENDIX C: RECEIVER OPERATING CHARACTERISTIC CURVE ANALYSIS

Figure 1. ROC curves for base-case and sensitivity analysis of independence assumption.



The proportion of the population with tear-related pain undergoing APM (i.e., the "true-positive fraction") is plotted on the vertical axis and the proportion with OA-related pain undergoing APM (i.e., the "false-positive fraction") is plotted on the horizontal axis for each of the 36 indicator cutoff ranks. Each colored curve represents the ROC curve achieved when that indicator is excluded from the model.

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