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Diagnostic Performance of Histopathology, Microbiological Methods, and Biomarkers in Periprosthetic Joint Infection: A Systematic Review With Contextual Surgical and Therapeutic Implications

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Abstract

Periprosthetic joint infection (PJI) is among the most serious complications following total joint arthroplasty and remains diagnostically challenging because no single investigation reliably confirms or excludes infection across all clinical phenotypes. This systematic review evaluated the diagnostic performance of histopathology, microbiological methods, and serum and synovial biomarkers in PJI, with surgical and therapeutic implications considered contextually. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework. PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched from inception to August 1, 2026, with backward citation searching. The formal evidence set was restricted to primary clinical diagnostic, cohort, and comparative studies; systematic reviews, meta-analyses, and narrative reviews were excluded from the primary evidence synthesis and used only for contextual interpretation and citation searching. Primary diagnostic studies were appraised using QUADAS-2, while non-diagnostic cohort and comparative evidence was appraised using ROBINS-I. Because of substantial clinical and methodological heterogeneity, a structured narrative synthesis was performed without a de novo meta-analysis. A total of 1,504 records were identified, 421 duplicates were removed, 1,083 records were screened, and 236 full-text reports were assessed. After excluding 223 full-text reports, 13 primary studies were included in the qualitative synthesis. Included studies supported the high confirmatory value of histopathology, improved microbiological yield with optimized culture and sonication, and clinically useful performance of synovial biomarkers and molecular tests in selected settings. For example, frozen section histology demonstrated 73.7% sensitivity and 98.8% specificity in one included cohort, sonicate fluid culture achieved 78.5% sensitivity compared with 60.8% for tissue culture in a landmark prospective study, and synovial C-reactive protein showed an area under the curve of 0.951 with 74.2% sensitivity and 98.0% specificity. Overall, PJI diagnosis is most reliable when histopathology, microbiology, biomarkers, clinical presentation, infection chronicity, implant stability, and operative findings are integrated; no single test should independently dictate implant retention, explantation, or reimplantation.

Categories: Pathology, Orthopedics, Infectious Disease
Keywords: alpha-defensin, biomarkers, calprotectin, dair, histopathology, microbial culture, periprosthetic joint infection, prosthetic joint infection, revision arthroplasty, sonication

Introduction And Background

Total hip and knee arthroplasty are highly successful reconstructive procedures, but periprosthetic joint infection (PJI) remains one of their most consequential complications. PJI is associated with repeat surgery, prolonged antimicrobial exposure, functional decline, substantial healthcare expenditure, and increased morbidity. Biofilm formation on prosthetic surfaces contributes to diagnostic difficulty because organisms may be metabolically quiescent, spatially heterogeneous, and difficult to recover using conventional culture [1].

PJI may present with overt sinus formation or acute systemic features, but chronic and low-grade infections can resemble aseptic loosening. Diagnosis therefore relies on the integration of clinical findings, synovial fluid analysis, microbiological cultures, histopathology, and selected biomarkers. The 2018 evidence-based definition, the European Bone and Joint Infection Society (EBJIS) definition, and the Infectious Diseases Society of America (IDSA) guidance all emphasize multimodal interpretation, although they differ in their thresholds and in how they classify uncertain cases [2-4].

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Diagnostic evidence in PJI spans histopathology, microbiology, serum markers, synovial tests, and molecular methods, while clinical decisions depend on integrating these findings with the clinical presentation and operative context [1-4]. This review therefore evaluates these diagnostic domains together with their surgical and therapeutic implications.

Despite advances in diagnostic methods, PJI remains challenging to diagnose across different clinical presentations. Existing reviews have commonly evaluated individual diagnostic modalities, whereas comparatively less attention has been given to how histopathology, microbiological methods, serum and synovial biomarkers, and molecular diagnostics perform alongside one another within different diagnostic frameworks. A clearer distinction is also needed between evidence demonstrating diagnostic accuracy and evidence demonstrating effects on subsequent surgical or antimicrobial outcomes.

Accordingly, this review evaluates the complementary diagnostic contributions of these modalities while considering surgical and therapeutic implications separately as contextual clinical interpretations unless directly supported by included outcome studies.

Review objectives

The primary objective of this systematic review was to evaluate the diagnostic performance and clinical utility of histopathology, conventional and optimized microbiological methods, serum and synovial biomarkers, and molecular diagnostic techniques in adults undergoing evaluation for suspected PJI.

A secondary objective was to examine how diagnostic findings may inform surgical and antimicrobial management, including debridement, antibiotics, and implant retention (DAIR), one-stage revision, two-stage revision, reimplantation, and organism-directed antimicrobial therapy. Surgical and therapeutic implications were interpreted separately from diagnostic accuracy and were considered contextual unless directly evaluated by an included outcome study. The review question and its Population, Intervention/index tests, Comparator/reference standard, and Outcomes (PICO) framework are summarized in Table *1* [5].

PICO component	Definition
P (Population)	Adults undergoing evaluation or revision surgery for suspected PJI after hip or knee arthroplasty
I (Intervention/index tests)	Histopathology; conventional and optimized microbial culture, including sonication; serum and synovial biomarkers; and molecular microbiology
C (Comparator/reference standard)	Accepted PJI reference standards and/or comparator diagnostic methods, including MSIS/ICM, EBJIS, IDSA, or clinically interpretable composite definitions [2-4]
O (Outcomes)	Sensitivity, specificity, predictive values, likelihood ratios, AUC, microbiological yield, surgical strategy, antimicrobial implications, reinfection, and treatment success

TABLE 1: PICO framework for the review question

These frameworks are not interchangeable. MSIS/ICM and EBJIS provide diagnostic classification frameworks with different criteria, thresholds, and weighting of individual tests, whereas IDSA guidance is primarily intended to support clinical diagnosis and management. Consequently, the same patient may not necessarily be classified identically under every framework. These differences were considered when interpreting diagnostic accuracy across studies [2-4].

PJI, periprosthetic joint infection; MSIS, Musculoskeletal Infection Society; ICM, International Consensus Meeting; EBJIS, European Bone and Joint Infection Society; IDSA, Infectious Diseases Society of America; AUC, area under the curve

Review

Methodology

Reporting Standard, Registration, and Protocol

The review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and expanded checklist [6]. The review was not prospectively registered in PROSPERO. No separate review protocol was published; therefore, no amendments to a prospectively registered protocol were applicable.

Eligibility Criteria

Eligible studies were primary clinical investigations of adults with a hip or knee arthroplasty undergoing evaluation or treatment for confirmed or suspected PJI. Studies were required to evaluate histopathology, frozen or permanent sections, synovial or tissue culture, sonication, serum biomarkers, synovial biomarkers, or clinically relevant molecular diagnostics; use an accepted PJI reference standard, including MSIS/ICM, EBJIS, IDSA, or another clinically interpretable composite definition [2-4]; and report diagnostic accuracy, organism-detection yield, surgical decision-making, antimicrobial outcomes, reinfection, or treatment success. Eligible designs comprised prospective or retrospective diagnostic accuracy studies, cohort studies, and comparative clinical studies.

Studies were excluded if they involved superficial surgical-site infection without prosthetic involvement, nonhuman or purely laboratory models without clinical outcomes, isolated case reports or uncontrolled series without extractable diagnostic or treatment outcomes, duplicate or overlapping cohorts without additional relevant data, reports lacking clinically interpretable diagnostic or treatment outcomes, or secondary literature such as systematic reviews, meta-analyses, and narrative reviews. Relevant secondary publications were retained separately only for contextual interpretation, comparison with prior evidence, and backward citation searching.

The primary evidence was grouped for narrative synthesis into histopathology; conventional and optimized microbiology; molecular diagnosis; serum biomarkers; synovial cellular and soluble biomarkers; and surgical or therapeutic implications.

Information Sources

The literature search covered PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library from database inception to August 1, 2026. Reference lists of included studies and relevant systematic reviews were examined for additional eligible reports. All database searches were last conducted on August 1, 2026.

Search Strategy

The search strategy combined free-text terms relating to PJI, arthroplasty, histopathology, microbiological culture, sonication, serum and synovial biomarkers, and molecular diagnostic methods. Relevant spelling variants and free-text synonyms were included where applicable. Molecular terms included polymerase chain reaction (PCR), next-generation sequencing, metagenomic sequencing, and related molecular diagnostic terminology. Complete, reproducible, database-specific search strategies, including field restrictions, Boolean operators, limits, and search yields, are provided in Appendix A.

The electronic search strategies were not independently peer-reviewed by an information specialist, which is acknowledged as a limitation of the review.

Selection Process

Two reviewers independently screened the titles and abstracts of all records remaining after duplicate removal against the prespecified eligibility criteria. Reports considered potentially eligible by either reviewer underwent full-text assessment, and the same two reviewers independently assessed full-text eligibility. Disagreements were resolved through discussion and consensus; when agreement could not be reached, a third reviewer was consulted. Reasons for full-text exclusion were recorded and categorized as wrong population or condition, wrong diagnostic modality, absence of an extractable diagnostic or clinical outcome, inadequate or undefined reference standard, ineligible report type, duplicate or overlapping cohort, insufficient full-text information, preclinical or laboratory-only investigation, or another prespecified eligibility reason. No automation or machine-learning tool was used to make final inclusion or exclusion decisions.

Data Collection Process and Data Items

Two reviewers independently extracted data from each eligible report using a standardized data extraction form developed before formal extraction. Extracted variables included first author, publication year, country, study design, sample size, anatomical joint, PJI reference definition, acute or chronic infection phenotype, index diagnostic test, prespecified diagnostic threshold, specimen type, microbiological processing method, prior antimicrobial exposure, sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, area under the receiver operating characteristic curve, microbiological yield, causative organisms, surgical strategy, antimicrobial approach, follow-up duration, reinfection or treatment success outcomes, funding source, and disclosed conflicts of interest. Extraction discrepancies were resolved by direct comparison with the source report and consensus between reviewers. Where multiple publications described an overlapping population, the report containing the most complete and clinically relevant dataset was prioritized. No missing diagnostic result was imputed; data not reported by the original investigators were recorded as not reported. No automated extraction tool was used. Diagnostic accuracy estimates and 95% confidence intervals were extracted directly from the original publications

where reported; no confidence intervals were independently recalculated. AUC values were treated separately from threshold-specific sensitivity and specificity.

Outcomes and Effect Measures

Primary diagnostic outcomes were sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios, diagnostic odds ratio, AUC/SROC, and microbiological pathogen detection yield. Secondary outcomes were the influence of diagnostic information on DAIR, one-stage revision, two-stage revision, reimplantation, organism-directed antimicrobial therapy, and infection-free or reoperation outcomes. Estimates are presented with 95% confidence intervals when reported in the source literature.

Risk of Bias Assessment

Two reviewers independently assessed eligible primary diagnostic accuracy studies using QUADAS-2, evaluating patient selection, index test, reference standard, and flow/timing, with applicability concerns considered for patient selection, index test, and reference standard [7]. QUADAS-2 domain and overall judgments were expressed as low, high, or unclear risk of bias. Non-diagnostic cohort and comparative studies were assessed using ROBINS-I across the domains of confounding, selection of participants, classification of interventions/exposures, deviations from intended interventions/exposures, missing data, outcome measurement, and selection of the reported result [8]. ROBINS-I overall judgments were expressed as low, moderate, serious, critical, or no information. Disagreements were resolved through discussion and consensus.

No patient-reported questionnaire or proprietary clinical scale was administered. QUADAS-2, ROBINS-I, and GRADE were applied as published methodological appraisal frameworks [7-9]; the original tool forms were not reproduced in this manuscript.

Synthesis Methods

Because of substantial clinical and methodological heterogeneity in PJI definitions, anatomical sites, acute versus chronic infection, diagnostic thresholds, specimen number, culture media and incubation, prior antimicrobial exposure, and study design, a de novo meta-analysis was not undertaken. The 13 included primary studies were synthesized narratively by diagnostic and clinical domain. Study-level estimates were reported where available.

Potential sources of heterogeneity were examined qualitatively by joint, infection chronicity, reference standard, assay threshold, organism virulence, antibiotic exposure, and laboratory method. Formal subgroup meta-regression and sensitivity analyses were not performed because no new quantitative pooling was conducted.

Reference standard definitions were retained as reported by the original investigators; participants were not retrospectively reclassified using a single PJI definition. Because MSIS/ICM, EBJIS, IDSA, and study-specific composite definitions differ in diagnostic criteria, thresholds, and intended use, variation in reference standards was considered an important source of clinical and methodological heterogeneity. Results were therefore interpreted within the reference standard used by each study rather than assumed to be directly interchangeable across definitions.

Potential incorporation bias was specifically considered when an index test, or a component closely related to the index test, contributed to the composite reference standard used to define PJI. This issue was incorporated into the QUADAS-2 reference standard judgment.

The feasibility of quantitative pooling was assessed separately for each diagnostic domain. Diagnostic accuracy pooling using bivariate or hierarchical models was considered appropriate only when multiple studies evaluated sufficiently comparable index tests in similar clinical populations, applied compatible diagnostic thresholds and reference standards, and reported data permitting construction of diagnostic two-by-two tables. These conditions were not met. Histopathology studies differed in specimen number, frozen versus permanent section assessment, thresholds, reference standards, and clinical purpose, including initial diagnosis and reimplantation assessment. Microbiological studies evaluated different techniques, including conventional tissue culture, blood culture bottle inoculation, extended culture, and implant sonication. Synovial biomarker studies evaluated different analytes rather than repeated estimates of the same index test, and molecular diagnosis and several clinical outcomes were represented by individual studies. Consequently, clinically meaningful bivariate or hierarchical pooling was not considered appropriate, and a structured narrative synthesis was retained.

Reporting Bias and Certainty Assessment

Formal funnel plot asymmetry testing was not performed because no new meta-analysis with a sufficiently

homogeneous set of studies was conducted. Selective reporting and small-study effects were considered qualitatively during evidence appraisal. Certainty was summarized using GRADE principles for diagnostic tests and strategies, considering risk of bias, inconsistency, indirectness, imprecision, and potential publication bias [9]. Diagnostic conclusions were categorized as high, moderate, low, or very low certainty.

Results

Study Selection

The searches identified 1,504 records: 612 from PubMed/MEDLINE, 488 from Embase, 211 from Scopus, 90 from Web of Science, 74 from the Cochrane Library, and 29 through citation and reference searching. After removal of 421 duplicates, 1,083 records underwent title and abstract screening; 842 were excluded. Of 241 reports sought for retrieval, five were not retrieved. A total of 236 full-text reports were assessed for eligibility, of which 223 were excluded. Thirteen primary diagnostic, cohort, or comparative studies were included in the qualitative evidence synthesis. No de novo meta-analysis was performed. The study-selection process is shown in Figure *1*; reasons for full-text exclusion are provided in Appendix B.

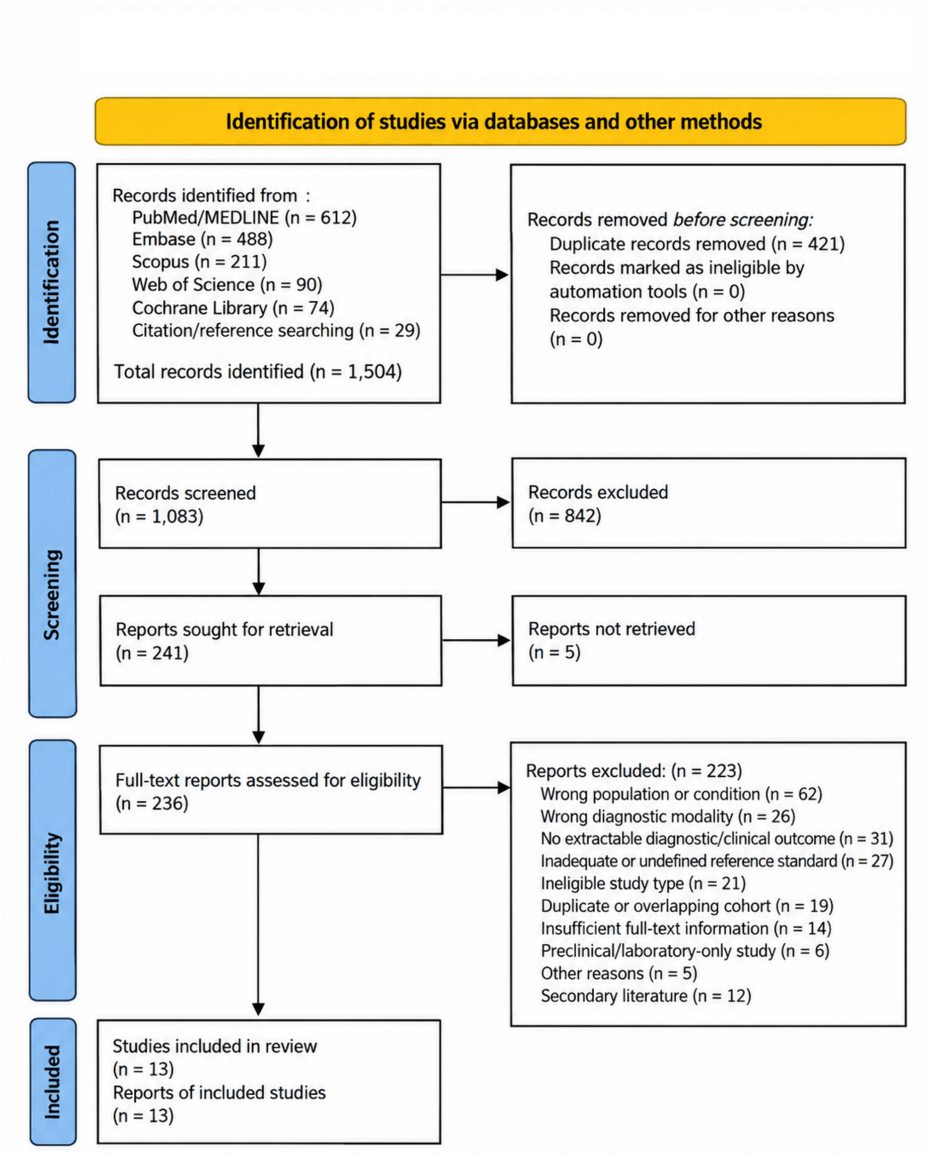


FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The formal evidence set comprised 13 primary clinical studies. The flow diagram was prepared according to PRISMA 2020 [6].

Although 236 full-text reports were assessed, the final primary evidence set was restricted to studies

satisfying all prespecified eligibility criteria simultaneously: an eligible adult hip or knee arthroplasty population, evaluation of a prespecified diagnostic or clinical domain, use of an accepted or clinically interpretable PJI reference standard, an eligible primary clinical study design, and extractable diagnostic or clinical outcomes. A substantial proportion of otherwise relevant literature consisted of systematic reviews or narrative reviews, studies without an appropriate reference standard, overlapping cohorts, studies evaluating tests outside the prespecified scope, or publications without extractable outcomes. Consequently, only 13 primary studies fulfilled all eligibility requirements for the formal synthesis. Reasons for exclusion were recorded prospectively by predefined category and are summarized quantitatively in Appendix B. A publication-by-publication exclusion appendix was not prospectively maintained; therefore, individual exclusion reasons were not retrospectively reconstructed to avoid post hoc misclassification.

Characteristics of Included Primary Studies

Thirteen primary studies met the prespecified eligibility criteria and were included in the formal qualitative evidence synthesis. These comprised diagnostic accuracy studies, prospective or retrospective cohorts, and comparative clinical studies addressing histopathology, microbiology, synovial biomarkers, molecular diagnosis, and surgical management. Their characteristics and key findings are summarized in Table 2.

Study	Design/population	N; PJI cases, n (%)	Reference standard/outcome definition	Index test and threshold	Sensitivity (95% CI)	Specificity (95% CI)	Principal finding/additional outcome
Sigmund et al., 2023 [10]	Retrospective diagnostic study; revision THA/TKA	119; EBJIS: 46 (39%); ICM: 40 (34%); IDSA: 32 (27%)	EBJIS 2021, ICM 2018, and IDSA 2013 criteria, evaluated with histology excluded from the reference definition	Histopathological assessment of multiple periprosthetic membrane/pseudocapsule specimens; diagnostic performance assessed according to specimen number	Five specimens: 76.5% (67.6-81.4) using EBJIS	Five specimens: 86.8% (81.3-93.5) using EBJIS	Three to six specimens produced the highest diagnostic performance; five-specimen AUC approximately 0.81.
Straub et al., 2024 [11]	Retrospective cohort; hip/knee two-stage revision	226; all had previously diagnosed PJI (100%)	Subsequent reinfection after second-stage reimplantation; minimum one-year follow-up	Permanent and frozen-section histology at reimplantation; histology classified using the SLIM system	35% for prediction of reinfection	63%	Reinfection occurred in 40/226 (18%). Positive permanent histology did not predict reinfection; PPV 17%, NPV 81%, accuracy 58%; frozen/permanent agreement 91%.
Trampuz et al., 2007 [12]	Prospective diagnostic study; revision/resection THA/TKA	331; 79 (23.9%)	Standardized non-microbiological PJI criteria	Sonicate fluid culture; clinically significant cutoff ≥5 CFU of the same organism per plate	Sonicate culture: 78.5%; tissue culture: 60.8%	Sonicate culture: 98.8%; tissue culture: 99.2%	Sonication was more sensitive than tissue culture, particularly after antimicrobial exposure; tissue vs. sonicate sensitivity after recent antibiotics was 45.0% vs. 75.0%.
Peel et al., 2016 [13]	Prospective cohort; consecutive revision arthroplasties	369; 117 (31.7%) by IDSA criteria	IDSA PJI criteria; Bayesian latent-class model also examined	Periprosthetic tissue inoculated into paired aerobic/anaerobic blood culture bottles versus conventional agar/broth	Paired BCBs: 60.7% (51.2-69.6) by IDSA; conventional media: 44.4% (35.3-53.9)	Paired BCBs: 98.8% (96.6-99.8); conventional media: 98.8% (96.6-99.8)	Under Bayesian modeling, paired BCB sensitivity was 92.1% vs. 62.6% for conventional media; BCBs also shortened time to positivity.
Fernández-Sampedro et al., 2017 [14]	Prospective diagnostic study; hip/knee revision arthroplasty	498; 130 (26.1%)	Berbari/Osmon-type clinical composite: purulence, permanent-section acute inflammation, communicating sinus tract, or qualifying concordant cultures	Sonicate fluid culture ≥20 CFU/plate; tissue/synovial culture, CRP, and histopathology also assessed	Sonication: early 83.3%, delayed 94.3%, late 80.5%	Varied by infection timing; study reported timing-specific estimates	Sonication performed particularly well in delayed and late PJI; combining histology with sonicate fluid culture reached 100% sensitivity across timing categories.
Liukkonen et al., 2024 [15]	Retrospective comparative cohort; revision hip arthroplasty for PJI	369 revisions; all PJI (100%)	2013 International Consensus diagnostic criteria; clinical outcome = reoperation/death after PJI revision	DAIR (n=134), one-stage revision (n=114), two-stage revision (n=121); not a diagnostic accuracy study	NA	NA	One-year reoperation: 36.6% after DAIR, 20.2% after one-stage revision, and 21.5% after two-stage revision. Non-randomized treatment allocation limits causal interpretation.
Kwiecien et al., 2017 [16]	Retrospective diagnostic study; revision THA/TKA	200 procedures; 38 (19.0%) met modified MSIS criteria	Modified MSIS criteria	Intraoperative frozen section histology; approximately ≥5 PMNs/HPF evaluated in multiple sites	73.7% (59.7-87.7)	98.8% (97.1-100.0)	PPV 94.1%, NPV approximately 93.4%, accuracy 94.0%; frozen and permanent sections showed 97.6% concordance.
Larsen et al., 2018 [17]	Prospective multidisciplinary diagnostic study; hip/knee prosthetic failure	114 revisions; initially 43 PJI and 71 aseptic-failure cases; final diagnostic comparison 42 PJI	Multidisciplinary clinical classification incorporating conventional diagnostic work-up; diagnosis was subsequently refined using	Joint fluid, soft-tissue biopsy and prosthetic-component cultures at 6 and 14 days; 16S rRNA sequencing	14-day culture: 39/42 (93%) PJI confirmed; 16S sequencing: 33/42 (79-83%, depending specimen	Test-specific; e.g., false-positive frequencies varied by specimen	Extended 14-day culture of joint fluid, soft tissue and prosthetic components improved confirmation; sequencing supplied additional information in selected cases.

			study findings		set)		
Mozella et al., 2023 [18]	Prospective diagnostic study; failed/revision total knee arthroplasty	84; 62 (73.8%) PJI and 22 non-PJI	2018 ICM criteria	Serum markers, synovial WBC/PMN%, histopathology and microbiological culture; ≥2 concordant cultures considered microbiologically diagnostic within ICM framework	Tissue/microbiological culture: 77.4%; histopathology: 43.7%; synovial WBC: 75.6%	Culture: 100%; histopathology: 100%; synovial WBC: 100%	Multimodal assessment demonstrated differing performance across serum, synovial, microbiological, and histopathological tests.
Baker et al., 2022 [19]	Retrospective diagnostic cohort; patients evaluated before revision arthroplasty	621; 194 PJI (31.2%), 394 aseptic, 33 inconclusive	2018 ICM criteria	Synovial CRP; study-derived cutoff approximately 6.9 mg/L	74.2%	98.0%	AUC 0.951 (95% CI 0.932-0.970). Serum CRP AUC was 0.926; combined serum + synovial CRP AUC was 0.964.
Lazic et al., 2022 [20]	Prospective cohort; revision THA/TKA with concomitant local inflammation	33; 17 (51.5%) confirmed PJI	Modified EBJIS 2021 definition	Synovial calprotectin lateral-flow assay; ROC-derived optimal threshold 70.5 mg/dL	0.88 (95% CI 0.64-0.99)	0.81 (95% CI 0.54-0.96) using the prespecified classification; ROC-derived threshold analysis reported specificity approximately 0.88	AUC 0.89. Study specifically evaluated difficult settings such as recent surgery, dislocation, and implant breakage.
Cazanave et al., 2013 [21]	Diagnostic cohort; revision/resection hip and knee arthroplasty	434; 144 (33.2%) PJI	Standardized PJI definition	Genus-/group-specific PCR panel applied to sonicate fluid; positive organism-target detection	PCR: 77.1%; sonicate culture: 72.9%; tissue culture: 70.1%	PCR: 97.9%; sonicate culture: 98.3%; tissue culture: 97.9%	Sonicate fluid PCR provided same-day microbiological information and was more sensitive than tissue culture.
Deirmengian et al., 2015 [22]	Retrospective diagnostic laboratory study; synovial samples submitted during PJI work-up	1,937 paired alpha-defensin/culture samples; independent PJI status was not established for the whole cohort	No independent reference standard classification suitable for standalone diagnostic accuracy analysis in this study	Synovial alpha-defensin immunoassay; S/CO >1 considered positive	NA - not designed as a standalone diagnostic accuracy study	NA - not designed as a standalone diagnostic accuracy study	498/1,937 samples were alpha-defensin positive; 244 of these were also culture-positive. Alpha-defensin responses occurred across a broad range of organisms, Gram types, and virulence categories.

TABLE 2: Characteristics, reference standards, diagnostic thresholds, and principal outcomes of included primary studies

Diagnostic accuracy estimates are presented as reported by the original investigators. Where a study evaluated prognostic or treatment outcomes rather than diagnostic accuracy, sensitivity and specificity are shown as not applicable. Alpha-defensin organism-responsiveness data from Deirmengian et al. were not interpreted as standalone diagnostic accuracy evidence. Differences in reference standards, thresholds, infection timing, specimen processing, and clinical setting limit direct comparison of estimates across studies.

AUC, area under the curve; BCB, blood culture bottle; CFU, colony-forming unit; CI, confidence interval; CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; EBJIS, European Bone and Joint Infection Society; HPF, high-power field; ICM, International Consensus Meeting; IDSA, Infectious Diseases Society of America; MSIS, Musculoskeletal Infection Society; NA, not applicable; NPV, negative predictive value; PCR, polymerase chain reaction; PJI, periprosthetic joint infection; PMN, polymorphonuclear neutrophil; PPV, positive predictive value; rRNA, ribosomal ribonucleic acid; ROC, receiver operating characteristic; S/CO, signal-to-cutoff ratio; SLIM, synovial-like interface membrane; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell

Risk of Bias in Included Primary Studies

Risk-of-bias judgments for the 13 included primary studies are presented in Table *3*. Among the 11 diagnostic studies assessed using QUADAS-2, seven were judged to have an unclear risk of bias, and four were judged to have a high risk of bias overall; none met the criteria for an overall low risk of bias judgment after signaling-question-level assessment. The two non-diagnostic cohort or comparative studies assessed using ROBINS-I were judged to have moderate and serious risks of bias, respectively. The principal methodological concerns were incompletely reported patient-selection and blinding procedures, incorporation of index test components into composite PJI reference standards, data-derived diagnostic thresholds, incomplete independence between microbiological index tests and final diagnostic classification, and confounding by indication in nonrandomized treatment comparisons.

Study	Framework/domain judgments	Overall judgment	Principal concern
			Retrospective diagnostic sampling; consecutive/random

Sigmund et al., 2023 [10]	QUADAS-2: Patient selection unclear; index test unclear; reference standard low; flow/timing low	Unclear	enrolment and blinding of histological interpretation were not clearly reported. Histology was excluded from the respective reference definitions, reducing incorporation bias.
Straub et al., 2024 [11]	ROBINS-I: Confounding moderate; participant selection moderate; classification of exposure low; deviations low; missing data low; outcome measurement low; selection of reported result low	Moderate	Retrospective reimplantation cohort with potential residual confounding affecting the association between histological findings and subsequent reinfection.
Trampuz et al., 2007 [12]	QUADAS-2: Patient selection unclear; index test unclear; reference standard low; flow/timing low	Unclear	Prospective diagnostic study with standardized sonication and tissue culture, but consecutive/random enrolment and explicit blinding of index test interpretation were not sufficiently reported.
Peel et al., 2016 [13]	QUADAS-2: Patient selection low; index test unclear; reference standard unclear; flow/timing low	Unclear	Consecutive prospective revision cohort, but blinding and complete independence of the reference standard interpretation from microbiological findings were not fully demonstrable.
Fernández-Sampedro et al., 2017 [14]	QUADAS-2: Patient selection low; index test unclear; reference standard low*; flow/timing low	Unclear	Sonicate fluid culture was not incorporated into the reference definition, but blinding of index test interpretation was not clearly reported. Incorporation concerns were greater for conventional culture and histopathology.
Liukkonen et al., 2024 [15]	ROBINS-I: Confounding serious; participant selection moderate; classification of intervention low; deviations moderate; missing data low; outcome measurement low; selection of reported result low	Serious	Non-randomized allocation to DAIR, one-stage revision, or two-stage revision resulted in substantial confounding by indication.
Kwiecien et al., 2017 [16]	QUADAS-2: Patient selection unclear; index test unclear; reference standard unclear; flow/timing low	Unclear	Retrospective selected revision population; consecutive enrolment and independence/blinding of index and reference standard interpretation were not clearly documented.
Larsen et al., 2018 [17]	QUADAS-2: Patient selection unclear; index test unclear; reference standard unclear; flow/timing low	Unclear	Final diagnostic classification incorporated conventional diagnostic and microbiological information; threshold pre-specification and blinding were incompletely reported.
Mozella et al., 2023 [18]	QUADAS-2: Patient selection unclear; index test unclear; reference standard high; flow/timing low	High	Several evaluated tests, including synovial cellular parameters, microbiological culture, and histopathology, also contributed to the 2018 ICM diagnostic framework, creating incorporation bias.
Baker et al., 2022 [19]	QUADAS-2: Patient selection unclear; index test high; reference standard high; flow/timing unclear	High	Retrospective cohort; the approximately 6.9 mg/L synovial CRP cutoff was study-derived, and synovial CRP contributes to the ICM reference framework, creating threshold and incorporation-bias concerns.
Lazic et al., 2022 [20]	QUADAS-2: Patient selection low; index test high†; reference standard low; flow/timing low	High†	Prospective design with an independent reference definition; however, the approximately 70.5 mg/dL optimal cutoff was ROC-derived rather than prespecified.
Cazanave et al., 2013 [21]	QUADAS-2: Patient selection unclear; index test unclear; reference standard low; flow/timing low	Unclear	PCR was independent of the reference standard, but consecutive enrolment and blinding procedures were not sufficiently explicit.
Deirmengian et al., 2015 [22]	QUADAS-2: Patient selection unclear; index test unclear; reference standard high; flow/timing unclear	High	Paired-sample study designed primarily to assess alpha-defensin organism responsiveness rather than standalone diagnostic accuracy against a fully independent clinical reference standard.

TABLE 3: Study-level risk of bias assessment of the primary diagnostic and cohort evidence

*Fernández-Sampedro et al. [14]: The reference standard judgment is index test-dependent. Sonicate fluid culture was not incorporated into the reference definition and therefore has a low risk of incorporation bias, whereas conventional culture and histopathology contributed to the composite definition and require more cautious interpretation.

†Lazic et al. [20]: The high index test judgment applies to the ROC-derived optimal cutoff. If the prespecified assay classification is regarded as the principal index test interpretation, the index test domain would be low/unclear rather than high.

DAIR, debridement, antibiotics, and implant retention; CRP, C-reactive protein; ICM, International Consensus Meeting; PCR, polymerase chain reaction; PJI, periprosthetic joint infection; ROC, receiver operating characteristic

Study-level risk-of-bias judgments are summarized in Table 3. Detailed QUADAS-2 signalling-question responses, applicability assessments, and supporting rationales are presented in Table 4, while detailed ROBINS-I domain-level assessments for the non-diagnostic cohort and comparative studies are presented in Table 5.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Domain judgments: patient selection/index test/reference standard/flow & timing	Applicability: patient/index/reference	Overall judgment	Supporting evidence/rationale from source
Sigmund et al., 2023 [10]	U	Y	U	U	Y	Y	Y	Y	Y	Y	Unclear/Unclear/Low/Low	Low/Low/Low	Unclear	Retrospective diagnostic evaluation of revision THA/TKA specimens. Histological performance was examined against EBJIS, ICM, and IDSA definitions with histology excluded from the respective reference definition, reducing incorporation bias. The publication does not clearly establish consecutive/random enrolment or blinding of histological interpretation; these items were therefore judged unclear.
Trampuz et al., 2007 [12]	U	Y	Y	U	Y	Y	Y	Y	Y	Y	Unclear/Unclear/Low/Low	Low/Low/Low	Unclear	Prospective trial comparing sonicate fluid culture with conventional periprosthetic tissue culture in patients undergoing hip or knee revision/resection arthroplasty. The reference definition was based on standardized clinical/non-microbiological criteria. Explicit blinding and consecutive/random enrolment were not clearly reported in the accessible methods and were therefore judged unclear.
Peel et al., 2016 [13]	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Low/Unclear/Unclear/Low	Low/Low/Low	Unclear	Prospective investigation of consecutive revision arthroplasty patients comparing tissue inoculation into aerobic/anaerobic blood culture bottles with conventional culture. IDSA criteria were used as the principal clinical reference standard, with latent-class modeling also performed. Independence of all reference standard interpretation from microbiological findings was not completely demonstrable, so this item was judged Unclear.
Fernández-Sampedro et al., 2017 [14]	Y	Y	Y	U	Y	Y	Y*	Y	Y	Y	Low/Unclear/Low/Low*	Low/Low/Low	Unclear	Prospective study including 130 consecutive patients and evaluating diagnostic tests across early, delayed, and late PJI. For sonicate fluid culture, incorporation bias was minimized because sonication was not part of the diagnostic reference definition. Histopathology and conventional cultures contributed to the composite definition and therefore have greater incorporation concerns when considered as separate index tests.
Kwiecien et al., 2017 [16]	U	Y	U	U	Y	Y	U	Y	Y	Y	Unclear/Unclear/Unclear/Low	Low/Low/Low	Unclear	Retrospective evaluation of 200 revision procedures comparing intraoperative frozen-section histology with modified MSIS criteria. Frozen-section sensitivity and specificity were 73.7% and 98.8%, respectively. Consecutive enrolment and blinding of index/reference interpretation were not clearly reported, resulting in unclear judgments for those signaling questions.
Larsen et al., 2018 [17]	U	Y	U	U	U	U	U	Y	Y	Y	Unclear/Unclear/Unclear/Low	Low/Low/Unclear	Unclear	Prospective multidisciplinary investigation assessing joint fluid, tissue, prosthetic-component cultures, and 16S rRNA sequencing. Of 156 enrolled patients, 111 underwent 114 revisions. Final clinical classification incorporated conventional diagnostic information, including microbiological findings, creating uncertainty regarding complete independence of the reference standard for some index tests. Threshold prespecification and blinding were not fully reported.
Mozella et al., 2023 [18]	U	Y	Y	U	Y	Y	N	Y	Y	Y	Unclear/Unclear/High/Low	Low/Low/Unclear	High	Prospective revision-TKA study evaluating serum markers, synovial WBC/PMN%, culture and histopathology using the 2018 ICM framework. The reference score itself includes several of the evaluated parameters; the published methods describe ESR, CRP, synovial leukocyte count, PMN%, culture, and histology as components of diagnosis. This creates incorporation bias for those index tests.

Baker et al., 2022 [19]	U	Y	U	U	N	Y	N	Y	Y	U	Unclear/High/High/Unclear	Low/Low/Unclear	High	Retrospective diagnostic cohort of 621 patients evaluating synovial CRP using the 2018 ICM definition. The reported 6.9 mg/L threshold was study-derived rather than strictly prespecified. Synovial CRP also contributes to the ICM diagnostic scoring framework, creating incorporation-bias concerns. Completeness of the analytic cohort and blinding were not fully reported in the accessible description.
Lazic et al., 2022 [20]	Y	Y	Y	U	N	Y	Y	Y	Y	Y	Low/High/Low/Low	Low/Low/Low	High†	Prospective cohort assessing synovial calprotectin in difficult inflammatory settings. The study used a defined PJI reference framework, and calprotectin was not part of that reference definition, minimizing incorporation bias. However, the reported optimal cutoff of approximately 70.5 mg/dL was ROC-derived, so threshold prespecification was judged no. Blinding was not clearly stated.
Cazanave et al., 2013 [21]	U	Y	U	U	Y	Y	Y	Y	Y	Y	Unclear/Unclear/Low/Low	Low/Low/Low	Unclear	Diagnostic cohort of 434 subjects comparing sonicate fluid PCR with sonicate and tissue culture using a standardized PJI definition. PCR was not part of the clinical reference standard, reducing incorporation bias. The assay panel and positivity criteria were specified, but consecutive enrolment and blinding were not sufficiently explicit and were therefore judged Unclear.
Deirmengian et al., 2015 [22]	U	Y	U	U	Y	N	U	U	NA	Y	Unclear/Unclear/High/Unclear	High/Low/High	High	Retrospective analysis of 1,937 paired alpha-defensin and culture samples. The primary purpose was to examine alpha-defensin responsiveness across different organisms rather than standalone diagnostic accuracy against an independent clinical reference standard. Consequently, reference standard validity and applicability were considered a great concern.

TABLE 4: Detailed QUADAS-2 signaling question and applicability assessment

Signaling questions were judged unclear whenever the publication did not provide sufficient methodological information for a defensible yes or no judgment. Potential incorporation bias was considered when an index test, or a closely related component, contributed to the composite reference definition. Applicability concerns were assessed separately for patient selection, index test, and reference standard. Overall risk of bias was categorized as high when at least one domain was high, unclear when no domain was high but at least one domain was unclear, and low only when all domains were low.

*For Fernández-Sampedro et al., the reference standard judgment differs according to the index test. Sonicate fluid culture was not incorporated into the reference definition and therefore has a lower risk of incorporation bias; conventional culture and histopathology contributed to the composite definition and require more cautious interpretation.

†For Lazic et al., the high index test judgment applies to the interpretation of the ROC-derived optimal threshold. If the prespecified manufacturer or assay classification, rather than the post hoc ROC-derived cutoff, is treated as the principal index test, the index test judgment may be considered low/unclear rather than high.

CRP, C-reactive protein; EBJIS, European Bone and Joint Infection Society; ESR, erythrocyte sedimentation rate; ICM, International Consensus Meeting; IDSA, Infectious Diseases Society of America; MSIS, Musculoskeletal Infection Society; PJI, periprosthetic joint infection; PMN, polymorphonuclear neutrophil; PMN%, percentage of polymorphonuclear neutrophils; PCR, polymerase chain reaction; rRNA, ribosomal ribonucleic acid; ROC, receiver operating characteristic; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell

Study	Confounding	Selection of participants	Classification of intervention/exposure	Deviations from intended intervention/exposure	Missing data	Outcome measurement	Selection of reported result	Overall judgment	Supporting rationale
Straub et al., 2024 [11]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate	Retrospective reimplantation cohort with potential residual confounding. Clinical characteristics influencing reimplantation and reinfection risk could not be fully controlled.
Liukkonen et al., 2024 [15]	Serious	Moderate	Low	Moderate	Low	Low	Low	Serious	Allocation to DAIR, one-stage revision, or two-stage revision was non-randomized. Patient characteristics, infection chronicity, implant condition, organism factors, and surgical selection may have influenced both treatment allocation and outcome, producing substantial confounding by indication.

TABLE 5: Detailed ROBINS-I domain assessment

ROBINS-I assessment rule

ROBINS-I assessments considered bias due to confounding, participant selection, classification of interventions or exposures, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result. The overall judgment reflected the highest level of concern across the domains. Accordingly, the serious confounding judgment for the Liukkonen study resulted in an overall serious risk-of-bias classification.

DAIR, debridement, antibiotics, and implant retention

Histopathology

Among the included primary studies, Kwiecien et al. reported frozen-section sensitivity of 73.7% and specificity of 98.8% in 200 revision procedures [16], while Mozella et al. found histopathology to be highly specific in a prospective multi-test comparison [18]. Sigmund et al. showed that three to six representative periprosthetic tissue specimens provided the strongest diagnostic performance across major reference standards [10]. At reimplantation, Straub et al. found that permanent and frozen histology did not reliably predict subsequent reinfection [11].

Histopathological performance varied according to the neutrophil threshold applied, the number and location of specimens obtained, the reference standard used to define PJI, and the clinical setting in which histology was performed. Therefore, estimates from initial revision surgery, reimplantation assessment, and prediction of subsequent reinfection should not be treated as interchangeable.

Microbial Culture and Optimized Microbiology

Among the included primary studies, culture performance depended strongly on specimen type and laboratory technique. Trampuz et al. reported sensitivity and specificity of 78.5% and 98.8%, respectively, for sonicate fluid culture, compared with 60.8% sensitivity and 99.2% specificity for conventional tissue culture [12]. Peel et al. showed improved recovery and shorter time to positivity when periprosthetic tissue was inoculated into blood culture bottles [13]. Fernández-Sampedro et al. found sonication particularly useful in delayed and late PJI and demonstrated improved accuracy when microbiological and histological evidence were combined [14]. Larsen et al. reported that extended culture across joint fluid, tissue, and components improved microbiological confirmation [17], while Mozella et al. reported tissue-culture sensitivity of 77.4% and specificity of 100% in a prospective knee cohort [18].

Culture-Negative PJI and Molecular Diagnosis

Within the included primary evidence addressing molecular diagnosis, Cazanave et al. demonstrated that sonicate fluid PCR provided 77.1% sensitivity and 97.9% specificity and could provide microbiological information on the day of surgery [21].

Serum Biomarkers

Serum inflammatory markers were represented within multimodal diagnostic studies rather than by a dedicated serum-marker cohort in the included primary evidence. Mozella et al. assessed serological markers alongside synovial fluid, culture, and histopathology in patients undergoing evaluation for knee PJI [18]. Because the primary evidence set did not contain a dedicated serum-marker accuracy study, no standalone pooled or domain-level serum-marker estimate was derived from the included primary studies.

Synovial Cellular and Soluble Biomarkers

Synovial fluid testing contributed important local diagnostic information in the included primary studies. Baker et al. reported an area under the curve of 0.951 for synovial C-reactive protein, with 74.2% sensitivity and 98.0% specificity [19]. Lazic et al. reported calprotectin sensitivity of 0.88 and specificity of 0.81 despite concomitant local inflammation [20]. Deirmengian et al. demonstrated that the alpha-defensin response occurred across a broad range of organisms associated with PJI [22]. Because this study primarily evaluated organism responsiveness, it was not interpreted as providing standalone sensitivity or specificity estimates for alpha-defensin.

Comparative Diagnostic Performance of Included Primary Studies

Diagnostic performance estimates from the included primary studies reporting quantitative accuracy data are summarized in Table *6*.

Test/study	Population/PJI cases	Reference standard	Diagnostic threshold/cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI), if reported	Interpretation
Histopathology specimen number - Sigmund et al. [10]	119 revision THA/TKA; 46 PJI (39%) by EBJIS, 40 (34%) by ICM, 32 (27%) by IDSA	EBJIS 2021, ICM 2018, and IDSA 2013, with histology excluded from the respective reference definition	Five tissue specimens shown here for the EBJIS analysis; three to six specimens generally produced the best performance depending on reference standard	76.5% (67.6-81.4)	86.8% (81.3-93.5)	0.81 for the specimen-number model	Diagnostic performance varied with specimen number and reference standard; three to six specimens provided the strongest performance.
Sonicate fluid culture - Trampuz et al. [12]	331 revision/resection arthroplasties; 79 PJI (23.9%)	Standardized non-microbiological PJI criteria	≥5 CFU of the same organism per plate	78.5%; 95% CI NR	98.8%; 95% CI NR	0.89 (0.85-0.93)	Sonicate fluid culture was more sensitive than conventional periprosthetic tissue culture, which had sensitivity 60.8% and specificity 99.2%.
Periprosthetic tissue culture in paired aerobic/anaerobic blood culture bottles - Peel et al. [13]	369 revision arthroplasties; 117 PJI (31.7%) by IDSA criteria	IDSA PJI criteria	Positive paired aerobic/anaerobic blood culture bottle tissue culture	60.7% (51.2-69.6)	98.8% (96.6-99.8)	NR	Blood culture bottle inoculation was more sensitive than conventional agar/thioglycolate culture under the IDSA reference standard (44.4% sensitivity).
Sonicate fluid culture - Fernández-Sampedro et al. [14]	130 patients with PJI categorized as early (n=18), delayed (n=35), or late (n=77)	Clinical composite PJI definition used by the investigators	Sonicate fluid culture; clinically relevant sonication threshold used by study	Timing-specific estimates; sonication was most sensitive in delayed/late PJI	Timing-specific; combined histology + sonication specificity ranged approximately 95.8-100%	Early 0.917; delayed 0.951; late 0.901 for sonicate fluid culture	Accuracy differed substantially according to infection timing. Combining histopathology with sonicate fluid culture yielded 100% sensitivity across early, delayed, and late categories.
Frozen-section histopathology - Kwiecien et al. [16]	200 revision procedures; 38 PJI (19%)	Modified MSIS criteria	Histological neutrophil threshold used for intraoperative frozen section diagnosis	73.7% (59.7-87.7)	98.8% (97.1-100.0)	NR	Frozen section histology showed high specificity but only moderate sensitivity; performance should therefore be interpreted mainly as confirmatory rather than exclusionary.
Periprosthetic tissue culture - Mozella et al. [18]	84 revision TKA patients; 62 PJI (73.8%) and 22 non-PJI	2018 ICM criteria	≥2 concordant positive cultures within the diagnostic framework	77.4%; 95% CI NR	100%; 95% CI NR	NR	Tissue culture showed the strongest microbiological performance in this multimodal study.
Histopathology - Mozella et al. [18]	84 revision TKA patients; 62 PJI	2018 ICM criteria	Histopathological positivity according to the study/ICM diagnostic framework	43.7%; 95% CI NR	100%; 95% CI NR	NR	Histopathology was highly specific but had relatively low sensitivity in this cohort.
Synovial WBC count - Mozella et	84 revision TKA patients; 62 PJI	2018 ICM criteria	Study/ICM synovial leukocyte threshold	75.6%; 95% CI NR	100%; 95% CI NR	NR	Synovial leukocyte count demonstrated high specificity and greater sensitivity than

al. [18]							histopathology in the same cohort.
Synovial CRP - Baker et al. [19]	621 patients evaluated before revision arthroplasty; 194 PJI, 394 aseptic, 33 inconclusive	2018 ICM criteria	6.9 mg/L	74.2%; 95% CI NR	98.0%; 95% CI NR	0.951 (0.932-0.970)	Synovial CRP showed high discrimination and specificity. The AUC should be reported separately from threshold-specific sensitivity and specificity.
Synovial calprotectin - Lazic et al. [20]	33 patients; 17 confirmed PJI (51.5%)	Modified EBJIS 2021 definition	Prespecified assay classification	88% (64-99)	81% (54-96)	0.89	Calprotectin retained useful diagnostic performance despite concomitant local inflammatory conditions.
Synovial calprotectin - Lazic et al. [20], ROC-derived threshold	Same cohort	Modified EBJIS 2021 definition	70.5 mg/dL	88%	88%	0.89	The ROC-derived optimal threshold produced higher specificity than the prespecified binary assay classification; these analyses should not be conflated.
Sonicate fluid PCR - Cazanave et al. [21]	434 revision/resection arthroplasties; 144 PJI (33.2%) and 290 aseptic failures	Standardized PJI definition	Any positive result from a 10 assay genus/group-specific PCR panel	77.1% (69.3-83.7)	97.9% (95.6-99.2)	NR	Sonicate fluid PCR was more sensitive than tissue culture defined as ≥2 concordant positive tissues and provided same-day microbiological information.
Sonicate fluid culture - Cazanave et al. [21]	Same 434 patient cohort	Same standardized PJI definition	Positive sonicate fluid culture according to study criteria	72.9% (64.9-80.0)	98.3% (96.0-99.4)	NR	Sonicate fluid culture had slightly lower sensitivity than PCR but similarly high specificity.
Conventional tissue culture - Cazanave et al. [21]	Same 434 patient cohort	Same standardized PJI definition	≥2 tissue specimens growing the same organism	70.1% (62.0-77.5)	97.9% (95.6-99.2)	NR	Requiring concordant tissue cultures preserved high specificity but reduced sensitivity compared with sonicate fluid PCR.

TABLE 6: Diagnostic accuracy estimates reported by included primary studies

Diagnostic estimates were extracted as reported by the original investigators. AUC values are presented separately from threshold-specific sensitivity and specificity and should not be interpreted as equivalent measures. Confidence intervals are shown where reported and readily extractable from the original publication; values not reported are designated NR. Estimates should not be used to rank tests directly because the studies differed in patient populations, reference standards, diagnostic thresholds, specimen processing, infection timing, and clinical setting.

AUC, area under the curve; CFU, colony-forming unit; CI, confidence interval; CRP, C-reactive protein; EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; IDSA, Infectious Diseases Society of America; MSIS, Musculoskeletal Infection Society; NR, not reported; PJI, periprosthetic joint infection; PCR, polymerase chain reaction; ROC, receiver operating characteristic; THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell

Results of Syntheses and Heterogeneity

Across the 13 included primary studies, no single test demonstrated consistently high sensitivity and specificity across the included clinical contexts. Apparent differences in diagnostic performance should not be interpreted as direct evidence that one test is superior to another because studies differed in patient populations, thresholds, reference standards, clinical settings, and study designs. High-specificity findings were reported for frozen-section histology, tissue culture in selected cohorts, synovial C-reactive protein, and sonicate fluid PCR, while optimized microbiological methods improved organism recovery [12, 18, 19, 21]. Heterogeneity remained substantial because the studies differed in reference standards, infection timing, anatomical joint, thresholds, prior antimicrobial exposure, laboratory protocols, and clinical purpose [10-22]. These differences limited direct quantitative ranking of tests.

No de novo statistical synthesis, meta-regression, or formal sensitivity analysis was undertaken because the primary studies were clinically and methodologically heterogeneous.

Reporting Bias and Certainty of Evidence

Formal funnel plots and asymmetry tests were not generated because no de novo meta-analysis was

undertaken. Certainty of evidence was assessed using GRADE principles at the level of specific diagnostic or clinical outcomes rather than broad diagnostic domains [9]. Judgments considered risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. When only one eligible study contributed to an outcome, inconsistency and publication bias could not be formally assessed. The principal certainty-of-evidence judgments are summarized in Table *7*. A detailed outcome-specific GRADE evidence profile, including judgments for risk of bias, inconsistency, indirectness, imprecision, publication bias, and the rationale for each overall certainty rating, is presented in Table *8*.

Specific outcome/body of evidence	Included study/studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Rationale for certainty judgment
Frozen section histopathology for initial diagnosis of PJI	Kwiecien et al. [16]; supported by diagnostic histology findings from Sigmund et al. [10] and Mozella et al. [18]	Some concerns	Serious	Not serious	Serious	Undetected/not formally assessable	Low	Frozen section histology showed high specificity in the available diagnostic evidence, but sensitivity was lower and varied with sampling strategy, histological threshold, reference standard, and clinical setting. Limited numbers of directly comparable studies and heterogeneous methods reduced certainty.
Number of histological specimens required for PJI diagnosis	Sigmund et al. [10]	Some concerns	Not assessable	Not serious	Serious	Not assessable	Low	The study suggested that approximately three to six representative specimens provided the strongest diagnostic performance. Certainty was limited because this conclusion was derived primarily from a single retrospective diagnostic study and could not be independently replicated within the included evidence set.
Histopathology at second-stage reimplantation for prediction of subsequent reinfection	Straub et al. [11]	Serious	Not assessable	Not serious	Serious	Not assessable	Very low	Histology at reimplantation showed limited ability to predict subsequent reinfection. Evidence came from one retrospective cohort and concerned prognostic performance at reimplantation rather than initial PJI diagnosis. Residual confounding and limited precision substantially reduced certainty.
Conventional tissue culture for microbiological diagnosis of PJI	Trampuz et al. [12], Peel et al. [13], Fernández-Sampedro et al. [14], Larsen et al.[17], Mozella et al. [18]	Some concerns	Serious	Not serious	Not serious	Undetected/not formally assessable	Moderate	Culture consistently provided organism-level information, but sensitivity varied according to specimen type, number of samples, incubation method, prior antimicrobial exposure, and reference standard. Specificity was generally high, but methodological heterogeneity limited direct comparison.
Sonicate fluid culture compared with conventional tissue culture	Trampuz et al. [12], Fernández-Sampedro et al. [14]	Low to some concerns	Some concerns	Not serious	Some concerns	Not assessable	Moderate	Prospective evidence indicated improved organism recovery with sonication, particularly in biofilm-associated infection and after antimicrobial exposure. However, differences in patient populations, infection timing, thresholds, and comparator culture techniques prevented quantitative pooling.
Blood culture bottle inoculation of periprosthetic tissue for organism recovery	Peel et al. [13]	Low	Not assessable	Not serious	Serious	Not assessable	Low	Blood culture bottle inoculation increased diagnostic yield and shortened time to positivity compared with conventional media in one prospective study. Certainty was limited because this technique was represented by a single directly eligible study.
Synovial C-reactive protein for diagnosis of PJI	Baker et al. [19]	Some concerns	Not assessable	Not serious	Some concerns	Not assessable	Low	Synovial CRP showed strong discrimination (AUC 0.951) and high specificity in a large cohort. Certainty was downgraded because evidence came primarily from one retrospective study, with potential incorporation/reference standard concerns and no independent replication within the formal evidence set.
Synovial calprotectin for diagnosis of PJI	Lazic et al. [20]	Low	Not assessable	Some concerns	Serious	Not assessable	Low	Calprotectin demonstrated sensitivity of 0.88 and specificity of 0.81 in the included prospective study. The small sample size and specific clinical setting, including concomitant local inflammatory conditions,

								limited precision and generalizability.
Sonicate fluid PCR for diagnosis of PJI	Cazanave et al. [21]	Low	Not assessable	Some concerns	Some concerns	Not assessable	Moderate	Sonicate fluid PCR demonstrated sensitivity of 77.1% and specificity of 97.9% and provided rapid microbiological information. Certainty was limited by reliance on a single major diagnostic cohort and potential variation in molecular platforms, organism targets, and laboratory implementation.
Alpha-defensin organism responsiveness across PJI pathogens	Deirmengian et al. [22]	Serious	Not assessable	Serious	Some concerns	Not assessable	Very low for diagnostic accuracy	The study demonstrated alpha-defensin responses across a broad range of PJI organisms but was not designed to provide standalone diagnostic sensitivity and specificity against an independent reference standard. It therefore supports biological/organism responsiveness rather than definitive diagnostic accuracy conclusions.
Comparative effectiveness of DAIR, one-stage revision, and two-stage revision	Liukkonen et al. [15]	Serious	Not assessable	Some concerns	Some concerns	Not assessable	Very low	Evidence was derived from one non-randomized comparative cohort. Treatment allocation was subject to substantial confounding by indication and patient selection, preventing causal conclusions regarding superiority of one surgical strategy.
Use of diagnostic findings to guide antimicrobial or surgical management	Diagnostic evidence [12-14, 17-22] plus Liukkonen et al. [15]	Serious	Serious	Serious	Serious	Not assessable	Very low	Most included studies evaluated diagnostic performance rather than whether testing improved treatment outcomes. Associations between improved diagnostic yield and subsequent surgical or antimicrobial benefit were therefore indirect. Management implications should be interpreted as contextual rather than as demonstrated treatment effects.

TABLE 7: Certainty of evidence for specific diagnostic and clinical outcomes

Certainty was assessed using a GRADE-informed approach at the level of specific outcomes or bodies of evidence rather than broad diagnostic domains. Judgments considered risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. Because no de novo meta-analysis was performed and several outcomes were represented by a single study, publication bias could generally not be formally assessed. “Not assessable” therefore does not indicate absence of publication bias.

AUC, area under the curve; DAIR, debridement, antibiotics, and implant retention; PCR, polymerase chain reaction; PJI, periprosthetic joint infection

Specific outcome/body of evidence	Contributing study/studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Rationale
Frozen section histopathology for initial diagnosis of PJI	Kwiecien [16]; supporting histological evidence from Sigmund [10] and Mozella [18]	Serious/some concerns	Serious	Not serious	Serious	Not assessable	Low	Histopathology generally demonstrated high specificity, but sensitivity varied. Differences in thresholds, specimen sampling, reference standards, and clinical setting reduced certainty.
Number of histological specimens required for PJI diagnosis	Sigmund [10]	Some concerns	Not assessable	Not serious	Serious	Not assessable	Low	Three to six representative specimens produced the strongest performance, but the conclusion was derived primarily from one retrospective diagnostic study.
Histopathology at second-stage reimplantation for prediction of subsequent reinfection	Straub [11]	Serious	Not assessable	Not serious	Serious	Not assessable	Very low	Evidence came from one retrospective cohort and concerned prediction of reinfection at reimplantation rather than initial PJI diagnosis.
								Culture consistently provided

Conventional periprosthetic tissue culture for diagnosis of PJI	Trampuz [12], Peel [13], Fernández-Sampedro [14], Larsen [17], Mozella [18]	Some concerns	Serious	Not serious	Not serious	Not assessable	Moderate	organism-level information, but sensitivity varied with specimen type, sampling, processing, incubation, previous antimicrobial exposure, and reference standard.
Sonicate fluid culture compared with conventional tissue culture	Trampuz [12], Fernández-Sampedro [14]	Low/some concerns	Some concerns	Not serious	Some concerns	Not assessable	Moderate	Sonication improved organism recovery in prospective studies, but populations, infection timing, thresholds, and comparator culture methods differed.
Blood culture bottle inoculation of periprosthetic tissue	Peel [13]	Low	Not assessable	Not serious	Serious	Not assessable	Low	Improved recovery and shorter time to positivity were demonstrated, but evidence was principally derived from one directly eligible prospective study.
Synovial CRP for PJI diagnosis	Baker [19]	Some concerns	Not assessable	Not serious	Some concerns	Not assessable	Low	A large cohort showed high discrimination and specificity, but retrospective design and potential reference standard incorporation concerns reduced certainty.
Synovial calprotectin for PJI diagnosis	Lazic [20]	Low	Not assessable	Some concerns	Serious	Not assessable	Low	Diagnostic performance was promising, but the small sample size and specific inflammatory clinical setting limited precision and generalizability.
Sonicate fluid PCR for PJI diagnosis	Cazanave [21]	Low	Not assessable	Some concerns	Some concerns	Not assessable	Moderate	High specificity and useful sensitivity were demonstrated in a sizeable diagnostic cohort, but evidence was dominated by one molecular approach and implementation may differ among laboratories.
Alpha-defensin organism responsiveness across PJI pathogens	Deirmengian [22]	Serious	Not assessable	Serious	Some concerns	Not assessable	Very low for diagnostic accuracy	The study demonstrated alpha-defensin responses across diverse organisms but did not establish standalone diagnostic sensitivity and specificity against a fully independent reference standard.
Comparative outcomes of DAIR, one-stage revision, and two-stage revision	Liukkonen [15]	Serious	Not assessable	Some concerns	Some concerns	Not assessable	Very low	Evidence was derived from one non-randomized comparative cohort with substantial confounding by indication; superiority of one strategy cannot be inferred.
Use of diagnostic findings to improve surgical or antimicrobial outcomes	Diagnostic studies [12-14, 17-22] and Liukkonen [15]	Serious	Serious	Serious	Serious	Not assessable	Very low	Most included studies assessed diagnostic performance rather than whether the test itself improved reinfection, reoperation, functional outcomes, or survival. Improved diagnostic yield should therefore not be equated with demonstrated treatment benefit.

TABLE 8: Outcome-specific GRADE evidence profile

Certainty was assessed using GRADE principles at the level of specific diagnostic or clinical outcomes rather than broad diagnostic domains. Judgments considered risk of bias, inconsistency, indirectness, imprecision, and potential publication bias. Where only one eligible study contributed to an outcome, inconsistency and publication bias could not be formally assessed. “Not assessable” therefore does not indicate absence of inconsistency or publication bias.

AUC, area under the curve; CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; PCR, polymerase chain reaction; PJI, periprosthetic joint infection

Surgical Outcome Evidence From Included Studies

Debridement, antibiotics, and implant retention (DAIR): Only one included comparative primary study directly evaluated different surgical strategies. Liukkonen et al. compared outcomes after DAIR, one-stage revision, and two-stage revision in 369 revision hips [15]. Because treatment allocation was nonrandomized and the study was judged to have a serious risk of bias due to confounding by indication, the findings were interpreted as observational comparative evidence rather than evidence of the superiority of one surgical strategy. No pooled estimate of treatment effectiveness was generated.

The included microbiological studies showed that culture, optimized specimen processing, and sonication can improve organism recovery and provide microbiological information relevant to targeted treatment [12-14, 17, 18].

One-stage revision: In the Liukkonen cohort, one-stage revision was evaluated alongside DAIR and two-stage revision; because treatment allocation was nonrandomized, the findings were interpreted as comparative observational evidence rather than proof of the superiority of one surgical strategy [15].

The comparative findings from the 369-hip cohort support cautious interpretation of treatment differences because patient selection and confounding by indication may influence observed outcomes [15].

Two-stage revision and reimplantation: Among the included primary studies, Straub et al. evaluated 226 two-stage revisions and assessed histopathology at reimplantation [11].

Straub et al. found that permanent and frozen histology at reimplantation did not reliably predict subsequent reinfection, indicating that histology alone was insufficient as a marker of eradication in that cohort [11].

Therapeutic Implications

Across the included primary microbiological studies, culture and sonication provided organism-level information, whereas histology and biomarker studies primarily informed diagnostic classification [12-14, 17-22].

In diagnostically difficult cases, Cazanave et al. showed that sonicate fluid PCR could provide same-day microbiological information with 77.1% sensitivity and 97.9% specificity [21].

Contextual Diagnostic and Management Framework

A practical integration of the diagnostic findings with management decisions is summarized in Table *9*.

Clinical situation	Priority investigations	Interpretation	Management implication
Painful arthroplasty, low/moderate suspicion	Clinical assessment + serum CRP/ESR; aspirate if suspicion persists [2-4]	Normal serum markers lower but do not eliminate probability	Escalate to aspiration according to the overall clinical probability of PJI [2-4]
Chronic painful/loose arthroplasty	Synovial WBC/PMN%, culture, and selected synovial biomarkers [2-4, 19, 20, 22]	Concordant synovial abnormalities strongly increase probability	Concordant abnormalities should increase suspicion for PJI and inform septic revision planning [2-4, 19, 20, 22]
Equivocal preoperative work-up	Multiple intraoperative cultures + histology [2-4, 10, 12-14, 16-18]	High-specificity positive findings can establish infection	High-specificity positive findings can establish or strongly support infection and alter the surgical/antimicrobial pathway [2-4, 10, 12-14, 16-18]
Acute PJI with stable components	Prompt cultures + operative assessment [4, 15]	Early confirmed infection may remain DAIR-eligible	Early infection with stable components may remain eligible for an implant-retention strategy in appropriately selected patients [4, 15]
Chronic biofilm disease	Tissue culture, histology, and sonication after component removal [1, 12-14, 17, 18]	Implant-associated biofilm favors exchange strategy	Established biofilm disease generally favors an exchange strategy tailored to host, organism, and reconstruction factors [1, 12-14, 17, 18]
Culture-negative suspected PJI	Repeat optimized culture, sonication, and selective molecular diagnostics [2-4, 21]	Negative routine culture does not prove aseptic failure	Negative routine culture alone should not be equated with aseptic failure when other evidence supports infection [2-4, 21]
Second-stage reimplantation	Integrated clinical, serological, microbiological, histological, and operative assessment [4, 11]	No single eradication test is definitive	No single eradication test is definitive; reimplantation should follow integrated multidisciplinary assessment [4, 11]

TABLE 9: Contextual diagnostic and management framework

Management implications in this table integrate the findings of the formal diagnostic evidence synthesis with contextual guideline and secondary review evidence. They should not be interpreted as treatment effect estimates derived solely from the 13 included primary studies.

CRP, C-reactive protein; DAIR, debridement, antibiotics, and implant retention; ESR, erythrocyte sedimentation rate; PMN%, percentage of polymorphonuclear neutrophils; PJI, periprosthetic joint infection; WBC, white blood cell

Discussion

Principal Findings and Interpretation

This review demonstrates that histopathology, microbial culture, and biomarkers are complementary rather than interchangeable. Histopathology provided high-specificity confirmatory information in the included studies [10, 11, 16, 18]. Culture and optimized microbiological methods contributed organism-level information and improved recovery in selected settings [12-14, 17, 18]. Synovial C-reactive protein and calprotectin provided diagnostic accuracy information in the included primary evidence [19, 20], while Deirmengian et al. demonstrated alpha-defensin responsiveness across a broad spectrum of PJI organisms without establishing standalone diagnostic accuracy [22].

The distinction between confirmation and exclusion is clinically important. Positive high-specificity findings can materially increase diagnostic confidence, whereas negative histology or routine culture may not exclude every chronic or low-grade infection, particularly when biofilm-associated organisms or prior antimicrobial exposure are present [1, 10-14, 16-18].

Culture performance depends on specimen number, sampling site, transport, aerobic and anaerobic conditions, incubation duration, blood culture bottle use, prior antimicrobial exposure, and biofilm-disrupting methods such as sonication [12-14, 17, 18]. Diagnostic pathways should therefore consider the quality of microbiological sampling and processing in addition to the final culture result [12-14, 17, 18].

Contextual Surgical and Antimicrobial Implications

The formal evidence synthesis primarily addressed diagnostic performance. Consequently, the following surgical and antimicrobial considerations should be interpreted as contextual clinical implications rather

than direct treatment-effect estimates from the included diagnostic studies. Except for the Liukkonen comparative cohort, the included evidence did not directly establish whether a particular diagnostic strategy improved surgical success, reinfection, or antimicrobial outcomes.

Improved diagnostic yield should not automatically be interpreted as improved treatment effectiveness. Although identification of an organism may facilitate susceptibility-directed antimicrobial therapy, the included diagnostic studies were generally not designed to determine whether the diagnostic intervention itself improved reinfection, reoperation, functional, or survival outcomes.

Contextual Comparison With Supporting Secondary Evidence

Supporting systematic reviews, considered separately from the formal primary evidence set, are broadly consistent with the primary histopathology findings. Meta-analytic evidence characterizes histopathology as a high-specificity confirmatory modality and shows that frozen-section sensitivity is lower than its specificity [23, 24]. A contemporary comprehensive review of culture methods likewise emphasizes the importance of specimen number, processing, incubation, and interpretation when optimizing microbiological diagnosis [25].

For culture-negative infections, supporting review evidence describes clinically important residual diagnostic uncertainty after routine culture [26]. A recent meta-analysis of molecular methods suggests an adjunctive role for 16S rDNA PCR, multiplex PCR, and metagenomic next-generation sequencing in selected difficult or culture-negative cases [27].

Supporting meta-analytic evidence indicates only moderate diagnostic performance for serum C-reactive protein and supports its use mainly as a screening component rather than a stand-alone confirmatory test [28]. Secondary evidence also supports clinically useful performance of synovial biomarkers and cellular parameters, including alpha-defensin, leukocyte esterase, synovial C-reactive protein, calprotectin, synovial white blood cell count, and polymorphonuclear neutrophil percentage, although thresholds and reference definitions remain heterogeneous [29-32].

For surgical management, prior systematic and clinical reviews report variable DAIR success and emphasize timing, debridement quality, pathogen characteristics, implant stability, and antimicrobial selection when considering implant retention or exchange [33-36]. Recent international consensus work has continued to refine diagnostic definitions, antimicrobial duration, and repeat-DAIR recommendations, underscoring that treatment algorithms continue to evolve [37, 38].

Reference standard heterogeneity remains an important limitation because MSIS/ICM, EBJIS, and IDSA frameworks can classify some cases differently, which affects measured diagnostic performance [2-4]. Recent international consensus work has continued efforts toward harmonized definitions and updated management recommendations [37, 38].

Limitations of the Included Evidence

The included primary evidence has several limitations. Many studies were retrospective or single-center, and incorporation bias can occur when an index test forms part of the reference definition. Diagnostic thresholds, specimen number, microbiological methods, prior antibiotic exposure, and contamination rules varied across studies. Acute and chronic infections were sometimes evaluated using different biological and diagnostic frameworks, and hip and knee evidence predominated. Several clinical domains were represented by only one or a small number of primary studies, limiting precision and generalizability. Supporting systematic reviews may contain some of the same primary cohorts, but they were not included in the formal evidence set or quantitatively combined with the primary studies [10-22].

Supporting systematic reviews were used only for contextual comparison and were not incorporated into the formal primary evidence synthesis. Because several reviews address overlapping diagnostic topics, some underlying primary cohorts may be represented in more than one secondary publication. No quantitative synthesis was performed across these reviews, thereby avoiding double counting of overlapping primary data.

Limitations of the Review Process

The review addressed a broad multimodal diagnostic and management question, and the included primary studies were heterogeneous in design, reference standard, clinical phenotype, and outcome reporting. No de novo meta-analysis was performed, so direct head-to-head statistical comparisons between all tests were not possible. Grey literature was not a major component of the synthesis, and selective publication of favorable diagnostic thresholds cannot be excluded. The review was not prospectively registered, and no separate protocol was published, which reduces protection against post hoc methodological changes.

The database search strategies were not independently peer-reviewed by an information specialist, which may have limited search sensitivity despite the use of multiple databases, free-text synonyms, and backward citation searching.

Implications for Practice

A practical diagnostic sequence begins with clinical assessment and serum screening, followed by aspiration with synovial cytology, biomarkers, and culture when suspicion persists [2-4, 35, 36]. When revision surgery is undertaken, multiple intraoperative tissue cultures and histopathology should be obtained, with sonication considered when components are removed and selective molecular testing considered when culture-negative infection remains probable [25-27, 35, 36]. Surgical strategy should integrate infection chronicity, implant fixation, soft-tissue quality, organism and susceptibility profile, biofilm maturity, host status, and reconstructive feasibility [33-36].

Implications for Future Research

Future research should prioritize prospective multicenter studies using standardized PJI reference definitions; separate validation of diagnostic thresholds for acute postoperative, acute hematogenous, and chronic PJI; standardization of tissue sampling, sonication, incubation, and contamination criteria; and head-to-head comparison of synovial biomarkers using the same reference standard. Additional studies should evaluate incremental diagnostic value, cost-effectiveness, molecular diagnostics with standardized contamination controls, and the relationship between diagnostic strategy and patient-centered outcomes.

Conclusions

PJI requires integration of clinical assessment with histopathological, microbiological, synovial, and selected molecular findings. Across the included studies, no individual diagnostic test demonstrated consistently high sensitivity and specificity across all clinical contexts. Histopathology generally provided high-specificity confirmatory information, while optimized microbiological methods, including blood culture bottle inoculation and sonication, increased organism recovery in selected settings. Synovial C-reactive protein, calprotectin, and molecular testing demonstrated potentially useful diagnostic performance in individual studies; however, differences in thresholds, populations, reference standards, and study methods limit direct comparisons among tests. Evidence concerning alpha-defensin organism responsiveness should not be interpreted as standalone diagnostic accuracy evidence. Evidence directly comparing surgical strategies was limited to one nonrandomized cohort with substantial risk of confounding. Accordingly, surgical and antimicrobial implications should primarily be regarded as contextual interpretation rather than direct evidence of improved treatment outcomes. Further prospective studies using standardized PJI definitions, prespecified diagnostic thresholds, and comparable outcome measures are needed.

Appendices

Appendix A

Database/platform	Complete search strategy	Limits/last searched	Records identified
PubMed/MEDLINE	("periprosthetic joint infection"[Title/Abstract] OR "prosthetic joint infection"[Title/Abstract] OR PJI[Title/Abstract]) AND (histopathology[Title/Abstract] OR histology[Title/Abstract] OR "frozen section"[Title/Abstract] OR culture[Title/Abstract] OR microbiology[Title/Abstract] OR sonication[Title/Abstract] OR biomarker*[Title/Abstract] OR "alpha-defensin"[Title/Abstract] OR "alpha defensin"[Title/Abstract] OR "leukocyte esterase"[Title/Abstract] OR calprotectin[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR CRP[Title/Abstract] OR "erythrocyte sedimentation rate"[Title/Abstract] OR ESR[Title/Abstract] OR "synovial white blood cell"[Title/Abstract] OR "white blood cell count"[Title/Abstract] OR "polymorphonuclear neutrophil"[Title/Abstract] OR "interleukin-6"[Title/Abstract] OR "D-dimer"[Title/Abstract] OR PCR[Title/Abstract] OR "next-generation sequencing"[Title/Abstract] OR "metagenomic sequencing"[Title/Abstract]) AND (arthroplasty[Title/Abstract] OR hip[Title/Abstract] OR knee[Title/Abstract] OR revision[Title/Abstract])	Database inception to August 1, 2026; no date restriction; no language restriction; clinically relevant human literature	612
Embase	('periprosthetic joint infection':ti,ab,kw OR 'prosthetic joint infection':ti,ab,kw OR pji:ti,ab,kw) AND (histopathology:ti,ab,kw OR histology:ti,ab,kw OR 'frozen section':ti,ab,kw OR culture:ti,ab,kw OR microbiology:ti,ab,kw OR sonication:ti,ab,kw OR biomarker*:ti,ab,kw OR 'alpha defensin':ti,ab,kw OR 'leukocyte esterase':ti,ab,kw OR calprotectin:ti,ab,kw OR 'c reactive protein':ti,ab,kw OR crp:ti,ab,kw OR 'erythrocyte sedimentation rate':ti,ab,kw OR esr:ti,ab,kw OR 'synovial white blood cell':ti,ab,kw OR 'polymorphonuclear neutrophil':ti,ab,kw OR 'interleukin 6':ti,ab,kw OR 'd dimer':ti,ab,kw OR pcr:ti,ab,kw OR 'next generation sequencing':ti,ab,kw OR 'metagenomic sequencing':ti,ab,kw) AND (arthroplasty:ti,ab,kw OR hip:ti,ab,kw OR knee:ti,ab,kw OR revision:ti,ab,kw)	Database inception to August 1, 2026; no date or language restriction	488
Scopus	TITLE-ABS-KEY("periprosthetic joint infection" OR "prosthetic joint infection" OR PJI) AND TITLE-ABS-KEY(histopathology OR histology OR "frozen section" OR culture OR microbiology OR sonication OR biomarker* OR "alpha defensin" OR "alpha-defensin" OR "leukocyte esterase" OR calprotectin OR "C-reactive protein" OR CRP OR "erythrocyte sedimentation rate" OR ESR OR "synovial white blood cell" OR "polymorphonuclear neutrophil" OR "interleukin-6" OR "D-dimer" OR PCR OR "next-generation sequencing" OR "metagenomic sequencing") AND TITLE-ABS-KEY(arthroplasty OR hip OR knee OR revision)	Database inception to August 1, 2026; no date or language restriction	211
Web of Science Core Collection	TS=("periprosthetic joint infection" OR "prosthetic joint infection" OR PJI) AND TS=(histopathology OR histology OR "frozen section" OR culture OR microbiology OR sonication OR biomarker* OR "alpha defensin" OR "alpha-defensin" OR "leukocyte esterase" OR calprotectin OR "C-reactive protein" OR CRP OR "erythrocyte sedimentation rate" OR ESR OR "synovial white blood cell" OR "polymorphonuclear neutrophil" OR "interleukin-6" OR "D-dimer" OR PCR OR "next-generation sequencing" OR "metagenomic sequencing") AND TS=(arthroplasty OR hip OR knee OR revision)	Database inception to August 1, 2026; no date or language restriction	90
Cochrane Library/CENTRAL	#1 ("periprosthetic joint infection" OR "prosthetic joint infection" OR PJI):ti,ab,kw #2 (histopathology OR histology OR "frozen section" OR culture OR microbiology OR sonication OR biomarker* OR "alpha defensin" OR "alpha-defensin" OR "leukocyte esterase" OR calprotectin OR "C-reactive protein" OR CRP OR "erythrocyte sedimentation rate" OR ESR OR "synovial white blood cell" OR "polymorphonuclear neutrophil" OR "interleukin-6" OR "D-dimer" OR PCR OR "next-generation sequencing" OR "metagenomic sequencing"):ti,ab,kw #3 (arthroplasty OR hip OR knee OR revision):ti,ab,kw #4 #1 AND #2 AND #3	Database inception to August 1, 2026; no date or language restriction	74
Backward citation/reference searching	Reference lists of included primary studies and relevant systematic reviews were examined for additional eligible reports	Completed August 1, 2026	29
Total			1,504

TABLE 10: Complete reproducible database-specific search strategies

Appendix B

Reason for full-text exclusion	n
Wrong population or condition	62
Wrong diagnostic modality	26
No extractable diagnostic or clinical outcome	31
Inadequate or undefined reference standard	27
Ineligible study type	21
Duplicate or overlapping cohort	19
Insufficient full-text information	14
Preclinical or laboratory-only study	6
Other reasons	5
Secondary literature	12
Total	223

TABLE 11: Full-text exclusions and reasons

Of 236 full-text reports assessed for eligibility, 223 were excluded, and 13 primary studies were included in the formal qualitative evidence synthesis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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