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CONSENSUS

The 2025 International Consensus Meeting on Musculoskeletal Infection: Research Priorities and Future Directions

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ABSTRACT

Musculoskeletal infection (MSKI) is a leading cause of implant failure following orthopedic surgery for trauma or elective procedures and it is associated with catastrophic outcomes for patients and healthcare systems worldwide. International Consensus Meetings (ICM) aim to define state-of-the-art, influencing clinical standards of care and accelerating discoveries by setting research priorities. The 3rd ICM was held on May 8–10, 2025 in Istanbul (Turkey) and included a 2-year-long Delphi process that culminated with in-person voting by 1205 delegates on 102 General and 30 Biofilm-specific MSKI questions. Consistent with prior ICMs, a Research Priorities Workgroup was established after the voting to interpret the results and summarize the most important future directions. Here, the group reports on several critical research priorities that emerged, which should be addressed to advance the field. These include: (1) improving diagnostics through standardized patient sampling, advanced non-invasive imaging technologies, and biofilm-specific biomarkers; (2) developing clinically relevant in-vitro and in-vivo models to rigorously and reproducibly test antibiofilm strategies; (3) identifying high priority immunological research areas, including deciphering the role of T-cell immunity in biofilm persistence, and if T cell targeting therapies can be harnessed to disrupt chronic biofilm-associated infection; (4) clinically evaluating novel anti-biofilm technologies on larger cohorts of patients; and (5) addressing translational barriers through the use of multi-center data collection and large-scale data

ICM 2025 Biofilm Research Priorities Workgroup

tools to accelerate clinical application. These research priorities aim to enhance the prevention, diagnosis, and treatment of biofilm-associated MSKI.

1 | Introduction and Background

Musculoskeletal infection (MSKI) remains a major source of morbidity after trauma care and arthroplasty, contributing to nonunion, implant failure, reoperation, and increased mortality. Procedure volumes continue to expand in aging populations; in the United States, revision hip and knee arthroplasty are projected to rise by ~280% and ~400% from 2014 to 2040, respectively, with substantial growth in estimated costs and revision burden [1]. Registry data reveal that aseptic loosening is no longer the major cause of failure, while septic loosening is increasing as a complication [2]. Concurrently, fracture-related infection (FRI) imposes a sustained global burden [3]. Across implant-associated infections, biofilm is the dominant barrier to eradication, driving antimicrobial tolerance and immune evasion. These clinical and mechanistic challenges keep translational thresholds high and create the demand for better models and outcomes that predict clinical performance [4, 5].

Previous clinical International Consensus Meetings (ICM) on orthopaedic infection have standardized key definitions, diagnostic criteria, and management pathways, and they employed predefined Delphi thresholds for grading agreement (No Consensus 50.1%–59%, Weak 60%–65%, Strong 66%–99%, Unanimous 100%) [6, 7]. This framework improves cross-study comparability and clinical decision-making while delineating domains where evidence remains insufficient and where preclinical work must better align with clinical questions.

Specifically regarding biofilm, a workgroup consisting of 28 experts convened at the 2018 clinical consensus meeting in Philadelphia discussed 13 questions regarding the following topics: (1) surface modifications to prevent/inhibit biofilm formation; (2) therapies to prevent and treat biofilm infections; (3) polymicrobial biofilms; (4) diagnostics to detect active and dormant biofilm in patients; (5) methods to establish minimal biofilm eradication concentration for biofilm bacteria; and (6) novel anti-infectives that are effective against biofilm bacteria. The summary stated that despite the intention to discuss these questions from the perspective of clinical intervention, the data were largely based on preclinical studies and there were minimal to low levels of clinical data on these topics [8], which resulted in narrative expert opinions. A major topic of interest was the characterization of the timeline of biofilm infections (acute vs. chronic) to potentially enable better diagnostics and treatment. It was not clear to what extent such a definition could influence clinical management of infections. There was consensus that all involved implant surfaces were susceptible to biofilm formation despite evidence that physicochemical properties, such as surface charge and topography, interfered with the timeline and extent of biofilm formation in vitro. The limitations of using the minimum inhibitory concentration (MIC) of antibiotics for guiding treatments were defined with the recommendation of focusing on the minimum biofilm eradication concentration (MBEC) for biofilm relevance. Moreover, obtaining more clinical information on bacteriophage therapy was considered a priority.

Encouraged by the progress made in guiding clinical consensus by previous efforts, a research consensus effort was organized by the Musculoskeletal Infection Research Interest Group (RIG) of the Orthopaedic Research Society (ORS) [9] and considered 65 questions regarding in-vitro testing [10], host immunity [11], treatments, and animal models [12]. The main motivation was to outline a path for increasing the standardization and rigor of musculoskeletal infection-related research.

The Istanbul ICM2025 and the ORS research track delineated a research agenda with five pillars: (1) Extending pathogen scope and ecology beyond staphylococci to Gram-negative rods, Cutibacterium/anaerobes, fungi, and defined polymicrobial consortia studied in host-relevant microenvironments; (2) Understanding synovial-fluid aggregates by resolving formation kinetics, phenotype, antimicrobial tolerance, and dispersal, and standardization of models that recapitulate joint fluid; (3) Understanding persistence biology including bacterial populations in intracellular reservoirs, small-colony variants, extracellular DNA (eDNA) regulation, and host immune signatures linked to treatment failure; (4) Investigating methods of improving study quality including defining minimum datasets, appropriate controls, and harmonized reporting to permit cross-study comparison; and (5) Demonstrating the breadth of therapeutic innovation by optimizing systemic and local antibiotic exposures and carriers with pharmacokinetic/pharmacodynamic (PK/PD) principles, and evaluate non-antibiotic strategies using prespecified, clinically anchored endpoints. Collectively, these priorities specify focus areas and the methodological stringency required for results to be robust, reproducible, and clinically meaningful.

The goal of this document is to present a prioritized research agenda in the pursuit of understanding, preventing, and treating MSKI.

2 | Methodology

At the conclusion of the voting at ICM2025 in Istanbul, a quorum of the biofilm section was assigned this consensus article. The work commenced with the review of all the questions (https://www.icmortho.org/documents) and identifying those that were deemed the most important research priorities going forward.

Based on this review, the questions whose scope was considered in this article were B1-B32 (except B1, B6, and B31), which pertained to the in-vitro and preclinical evaluation of biofilm and G5, G7-8, G11-12, G25, G36, G37, G50-56, G69-73, G85-87, G92, G94-95 from the general session, which were deemed relevant. Here, we provide research priorities and describe the consensus discussion on these questions with expert opinions on future directions.

This document outlines key themes for prioritization of research efforts and funding. The identified themes from the consensus questions were diagnostics and infection characterization, testing

strategies against biofilm-associated infections, advances in the understanding of immunity against infections and clinical treatment strategies. Additionally, it was also deemed important to include potentially significant areas that should include questions for consensus building in the next ICM; namely, those that can aid in overcoming translational barriers: the enhancement of reproducibility and rigor, the integration of artificial intelligence and machine learning, and the improvement of in-vitro organoid/organ-on-chip models.

3 | Results and Discussion

3.1 | Improving Diagnostics and Infection Characterization (Figure 1)

Biofilms are now recognized as the most important etiologic agent in implant-associated infections and the primary driver of chronicity, antimicrobial tolerance, and immune evasion (B15). Clinical data show that biofilm-forming organisms (B8)—particularly *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*—are responsible for persistent infections that resist conventional treatment. Despite the centrality of biofilm-associated challenges in PJI, the detection workflows often ignore the presence of these biofilms. Thus, robust biofilm detection and the incorporation of an efficient "biofilm-aware" diagnostic framework in the clinical setting is a priority.

Bacterial biofilms exist in distinct reservoirs: on the implant surface, in local soft and osseous tissue, and in the osteo-lacuno canalicular network of cortical and trabecular bone within the joint environment (B9, B10 [13]). There is also strong evidence suggesting the existence of biofilm-like aggregates in the synovial fluid (B17). Sampling methodologies are crucial for precise downstream diagnosis. Current protocols include pre- and post-operative swabs of the surgical site and implant materials, as well as testing of debrided tissue and synovial fluid. There is a significant gap in our characterization of biofilm as these methodologies selectively detect viable and culturable bacteria in suspension and often fail to capture microbial communities embedded in a matrix with various physiological traits unique to the biofilm life cycle. The biofilm retrieval and recovery methodologies must be optimized and standardized to reduce pre- and post-operative diagnostic variability. There is currently no validated method for detecting biofilms in vivo in routine clinical practice (B23). The detection of dormant bacterial phenotypes, including viable but non-culturable (VBNC) cells (B18), small-colony variants (SCVs), and intracellular pathogens, represents another challenge in biofilm diagnostics. These phenotypes often evade conventional detection methods, contributing to treatment failure. Furthermore, in polymicrobial infections, antagonistic interactions among the organisms could interfere with accurate pathogen detection and treatment [14].

Identifying biomarkers that reflect biofilm burden and activity is a crucial and necessary area in facilitating the shift towards biofilm diagnostics from the current diagnostic methods for bacteria in suspension. Extracellular DNA, neutrophil extracellular traps (NETs), and nuclease activity (B21) are emerging as potential indicators of biofilm presence and characteristics. These markers could enable earlier detection and stratification of infection severity. To support these efforts, physiologically relevant in-vitro models must be developed and standardized. Models incorporating human, animal, or synthetic synovial fluid and host factors, such as fibrinogen and hyaluronic acid, can better simulate the in-vivo biofilm environment, allowing for more accurate testing of diagnostic and therapeutic interventions. Emerging technologies, including fluorescence imaging, optical coherence tomography (OCT), confocal laser-scanning microscopy (CLSM), and peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) probes, have shown promise in preclinical models (B23). Biofilm-specific detection technologies, next-generation "omics"-based approaches, sensitive viability dyes, and advanced imaging techniques are needed to clarify microbial physiological status and capture elusive phenotypes within biofilms. Robust preclinical testing is necessary to adapt standardized sampling and biofilm detection tools for human use and integrate these technologies into surgical and diagnostic workflows.

Antibiotics remain our most potent tool against MSKI despite their reduced activity against biofilms without prior debridement. Future research should also focus on improving antibiotic

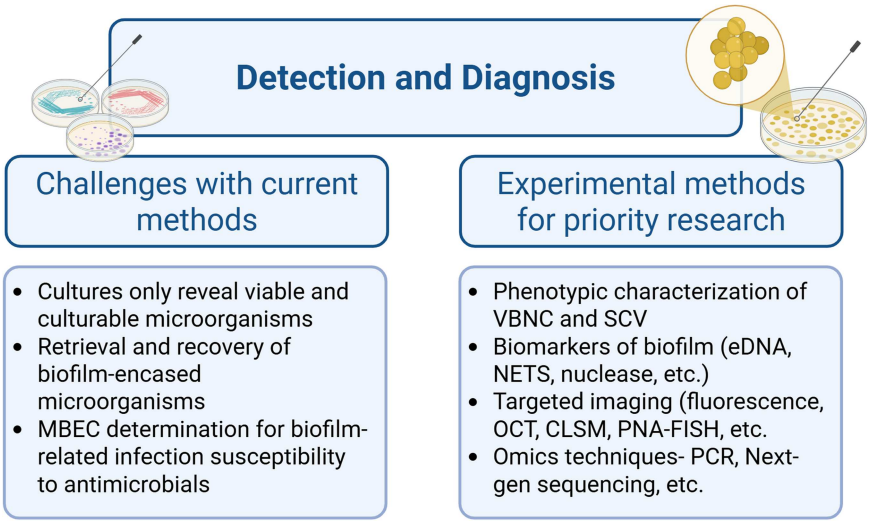

FIGURE 1 | Detection and diagnosis. Overview of challenges in current diagnostic approaches and emerging experimental methods for detecting biofilm-related infections.

selection and regimens for biofilm infections. While MIC testing is standardized and clinically validated, it assesses the susceptibility of planktonic cells and is a poor predictor of biofilm susceptibility (B18, B23 [15]). The minimum biofilm eradication concentration (MBEC) offers more realistic insights, but testing remains experimental, without standardized parameters or proven clinical value (G86). Evidence shows that although antibiotics may achieve MIC levels in bone and joint tissues, they often fall short of MBEC thresholds, exposing a major gap in our understanding of how to optimize current treatment strategies. The understanding of factors that contribute to the differences between the MBEC values of experimental biofilms in vitro and clinical biofilms is also an important issue (G86) [16]. Research priorities include developing standardized MBEC protocols, incorporating the relevant pharmacokinetics of active agents in the study of biofilm, and evaluating whether MBEC-guided clinical therapy improves outcomes compared with MIC-based approaches. Tolerability at MBEC-level dosing must also be assessed (G87), as effective concentrations in vitro often exceed safe levels in vivo. Integration of MBEC testing into diagnostic workflows, correlation with outcomes, and investigation of synergistic antibiotic combinations are priorities to refine treatment of implant-associated biofilm infections. Recommended follow-on questions are listed in Table 1.

TABLE 1 | Improving diagnostics and infection characterization: Recommended follow-on questions.

- Can standardized sampling methodologies to retrieve bacteria/biofilm from all relevant locations be developed?
- Are there methods to identify SCVs and VBNCs that can be integrated into the clinical PJI diagnosis framework?
- Is there a set of methods to decisively determine biofilm presence in vivo with an integrated imaging and biomarker detection workflow?
- Should antibiotic PK/PD be determined in biofilm environments for antibiotic dosing guidance?
- Is there a minimum set of data to determine whether biofilm-based susceptibility (e.g., determination of the MBEC) has an added clinical value?
- Can biofilm-based susceptibility testing identify synergistic antibiotic combinations effective against biofilm-associated infections?

3.2 | How to Test Strategies Against Biofilm-Associated Infections (Figure 2)

The preclinical testing strategies for anti-infective and antibacterial prevention and treatment remain extremely varied in study design as well as reported outcomes, both in vitro and in animal models of MSKI. There was strong consensus on the need to have a minimum set of reported outcomes (B4, B5, B11, B12), especially to improve the level of scientific evidence and the reproducibility across different studies. The need for improved rigor and reproducibility was a recurring theme of discussion and agreement, and is undoubtedly a priority in MSKI research. This goal can be achieved by higher scrutiny of the power of statistical study design, as well as randomization and blinding. Ethical considerations, especially under the framework of the 3Rs (Replacement, Reduction, Refinement), must also guide model design and reporting, with ongoing debate about whether ethical concerns themselves should constitute a special level of evidence.

In-vitro/ex-vivo testing conditions are currently not sufficiently representative of clinical conditions and therefore, study outcomes cannot be applied to the clinical management of infections. Thus, developing more clinically relevant testing methods in vitro and in preclinical environments is a priority. The current consensus effort identified clear and complementary outcome measures in preclinical models (B11) towards this priority. In addition, current research confirms that biofilm formation in synovial fluid is not only possible but also highly relevant to prosthetic joint infections (B17). In-vitro studies consistently demonstrate that suspended biofilm aggregates of *S. aureus* (including both methicillin-sensitive and resistant strains) and coagulase-negative staphylococci (CoNS) readily

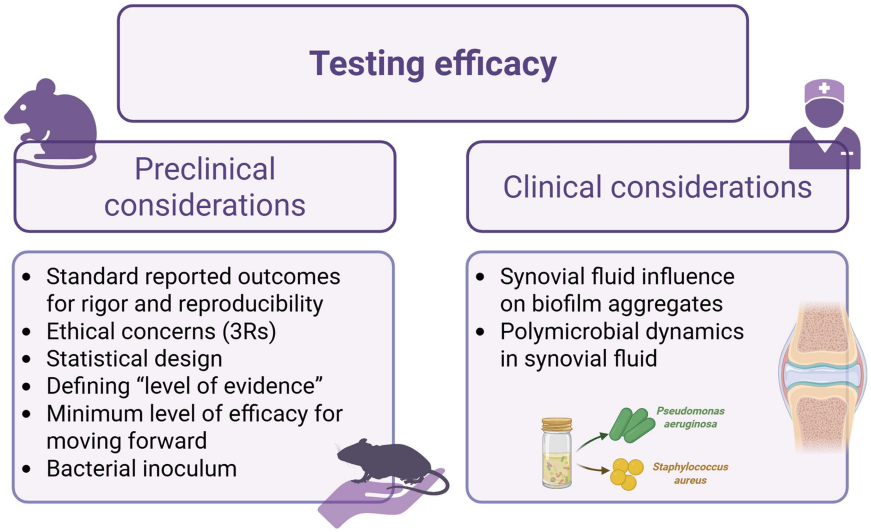

FIGURE 2 | Testing efficacy. Comparison of preclinical and clinical considerations in testing antimicrobial efficacy against biofilm infections.

form in human, bovine, porcine, and equine synovial fluid as well as in various synthetic synovial formulations. More recently, a broader range of pathogens, including Gram-negative bacteria (such as *Pseudomonas aeruginosa, E. coli, Klebsiella pneumoniae*, and *Proteus mirabilis*), Gram-positive bacteria (*including Streptococcus agalactiae*, *Enterococcus faecalis*, and *Cutibacterium acnes*), as well as *Candida* species, have also been shown to aggregate in synovial fluid, further demonstrating its importance in testing environments [17].

A limitation of the current evidence is its reliance on a limited range of microorganisms. However, systematic reviews indicate that this narrow focus overlooks the broader microbial diversity present in both clinical and animal infections (B8, G80-G85). To address this knowledge gap between in-vitro and in-vivo conditions, there was strong consensus that preclinical testing needs to include more clinically relevant microorganisms and especially polymicrobial communities, which constitute a large fraction of infections. Concurrently, better profiling of the clinical infection environment is desirable with the pathogen characteristics, the composition of the synovial fluid (e.g., fibrinogen, fibronectin, hyaluronic acid) and antibiotic tolerance. Additionally, clarification is needed on how polymicrobial communities interact with one another, and whether these interactions substantially impact clinical outcomes. In-vitro/ex-vivo testing with higher clinical relevance can only be designed with this knowledge. The recommended follow-on questions are listed in Table 2.

TABLE 2 | How to test strategies against biofilm-associated infections: Recommended follow-on questions.

- Is there a minimum level of efficacy that justifies moving forward to clinical testing?
- Can combination therapies be tested preclinically in a clinically relevant manner?
- Are in-vitro testing conditions for antibacterial efficacy comparable to *in vivo* conditions?
- Does synovial fluid influence biofilm formation in vivo and how?
- Should the antibiotic susceptibility and physiological status of biofilms be tested in the presence of synovial fluid?
- Are polymicrobial biofilm dynamics known in the presence of synovial fluid?
- Is there a preferred statistical design for "conclusively" predicting clinical efficacy based on in-vitro or preclinical results?
- Is there a definition of the level of evidence in preclinical studies (low, moderate, strong), and should ethical concerns be indicated as a special "level"?
- Is there a minimum level of bacterial inoculum to establish a periprosthetic infection in each animal model?

3.3 | What is the Role of Host Immunity in the Fight Against Biofilm? (Figure 3)

Recently, there have been developments in further understanding host-pathogen interactions in MSKI. Neutrophils and macrophages, which are the primary defensive cells against bacteria, remain ineffective against bacterial cells encased within biofilm. In addition to the physical barrier of the biofilm extracellular matrix, biofilms create local microenvironmental conditions that can impair leukocyte activity [18]. Recent work visualizing real-time interactions of these immune cells with implant surfaces revealed that immune cells reached and colonized these avascular surfaces effectively; however, they were unable to prevent biofilm maturation [19]. This work may redefine our understanding of the "race to the surface" [20], which has been the foundation for the development of surfaces that delay bacterial attachment and biofilm formation with the hypothesis that this delay could prevent infections. This new finding suggests the limited utility of this strategy alone, also supporting the earlier consensus discussion on the lack of impact on clinical management.

Beyond innate immunity, the role of adaptive and humoral responses in biofilm infections is still poorly understood. Biofilm protects bacteria from host defenses, making immune clearance difficult even when neutrophils and macrophages reach the surface. Preclinical studies have provided evidence that vaccines may protect against biofilm-related infections [21]. However, no effective vaccine has been developed so far,

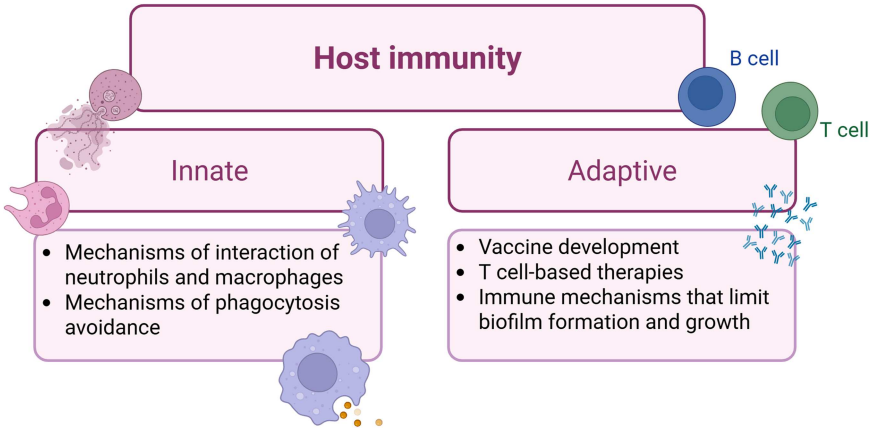

FIGURE 3 | Host immunity. Summary of innate and adaptive immune mechanisms relevant to biofilm infections.

underscoring a significant gap in our understanding of protective adaptive immunity. Clarifying how host immunity interacts with biofilm, and identifying which immune mechanisms can limit biofilm growth, will be essential to guide rational vaccine development. A better understanding of these processes could also support broader immunological approaches to prevent or control biofilms and is an important priority for MSKI research (G94). The recommended follow-on questions are listed in Table 3.

3.4 | Clarification of Efficacious Clinical Strategies and Evaluation of the Feasibility of Novel Treatments (Figure 4)

Among the discussed questions and answers, there was a clear distinction between the optimization of conventional treatments, such as irrigation solutions, and demonstrating the feasibility of novel treatments. Thus, we present the research priorities in two subsections.

TABLE 3 | Host immunity: recommended follow-on questions.

- Are the mechanisms by which neutrophils and macrophages interact with biofilm structures on implant or tissue surfaces known?
- Are the molecular mechanisms that prevent phagocytosing immune cells from effectively clearing biofilm bacteria known?
- Are the specific in-vivo adaptive and humoral immune mechanisms that contribute to either limiting or failing to limit biofilm growth known?
- Can T cell–based therapies or vaccines enhance protective immunity against biofilm-associated infections?
- Are there specific immune pathways or targets for immunomodulation in preventing or disrupting biofilm formation and maturation? (High-level evidence)

3.5 | Approaches Aiming to Optimize the Delivery of Antibacterials (Figure 4)

Application of antibiotics in free forms topically or in delivery vehicles as well as antimicrobial coatings for implanted devices was considered to optimize existing antimicrobial strategies (G34, G36, G37, G52, G56). Although there is some evidence that different antimicrobials and other therapies exhibit antibiofilm activity preclinically (B7, B27), mechanical debridement of established biofilms is currently the clinical method with the most consistent results. Antibiotics then support the prevention of re-infection and there is a plethora of new technologies designed to enable or enhance antibiotic action at the site of an orthopaedic infection. The consensus for most of these technologies representing some antibacterial efficacy was positive (B19), however delegates' detailed responses showed that there is a lack of robust, standardized preclinical (as mentioned in 3.2) and clinical data to support their use. Currently there isn't sufficient evidence to change established biofilm management without mechanical debridement and antibiotic treatment. Randomized clinical studies with clearly stated hypotheses that can serve specific indications and capture the diversity of the patient population and treatment types are a priority for conclusively evaluating new strategies [22].

The technologies that have progressed furthest along the pipeline are antibiotic and silver-coated implants (B22, B27, G53, G56). These implants are not approved for use in the US but have been on the European market for over a decade; despite this, there are no large-scale prospective clinical studies that aim to evaluate their efficacy. Silver-coated megaprostheses are indicated for limb-salvage surgeries; thus, their outcomes are limited to a small number of patients and are generally heterogeneous. Similarly, antibiotic and silver-coated fracture fixation devices have been applied in trauma care, with generally positive results, but a relatively limited number of patients were included in these studies. Nevertheless, these technologies may result in cost-effectiveness in patients at high risk of infection [23]. Another technology for providing sustained release of antibiotic agents is a degradable hydrogel based on hyaluronic acid. These technologies have shown promise in small studies and may be more widely applicable as the carrier can be used with any medical device similar to antibiotic-loaded cement

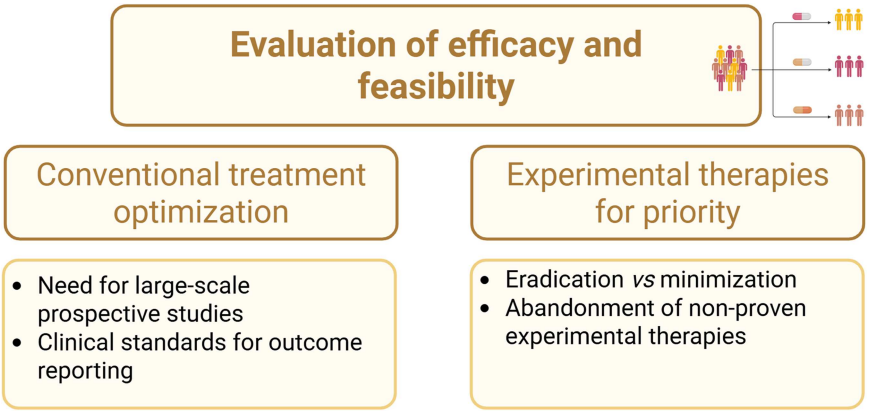

FIGURE 4 | Evaluation of efficacy and feasibility. Framework for optimizing conventional treatments and prioritizing experimental therapies. Emphasis is placed on the need for large-scale, standardized clinical studies and the differentiation between eradication vs. minimization strategies. Non-evidence-based experimental approaches should be discontinued.

coatings. The planned randomized controlled trial using this antibiotic-loaded hydrogel coating (SINBIOSE-H [24]), if successful, may set a new standard for evaluating these technologies. The ongoing lack of randomized controlled trials for conclusively evaluating the efficacy of these technologies with the potential to decrease the infection burden on a larger group of patients is creating a bottleneck for their widespread use.

Likewise, capturing the outcomes of diverse groups of patients retrospectively in a coherent and rigorous manner, for example by detailed reporting of MSKI cases available in registries (G101), can also be valuable in guiding future RCTs. However, there is an urgent need to set a clinical standard for what constitutes effective local antibacterial technology. Studies should include careful definition of the patient population, randomization, inclusion of appropriate controls, robust outcome measures, such as implant survival and reoperation rate over a sufficiently long follow-up period, in addition to outcomes such as wound healing complications, wound drainage/leakage, surgical site infection and PJI (G97, G100). Standardizing clinical study protocols to evaluate not only direct outcomes but also to generate feedback for future clinical studies and enhance preclinical study design with greater predictive power is essential.

3.6 | Novel Technologies Designed to Combat Biofilm (Figure 5)

As biofilms are the main challenge of treating implant-associated infection (B15), the development of a treatment that can "eradicate" established biofilm on an implant in a patient (e.g., PJI) would be transformative for MSKI. Many new technologies aimed at detaching or destroying biofilm in situ are in development. The ICM considered questions on potential treatments using physical technologies such as ultrasound (B16), electric fields (B26) and photodynamic therapy (B32), active agents targeting bacteria and biofilm such as monoclonal antibodies (B13), proteolytic enzymes (B14), antimicrobial peptides (G58, G59, G95), and bacteriophage therapy (G57, G95). The consensus was that while these technologies demonstrate promising antibiofilm effects in vitro, the current level of evidence for their use in clinical infections is low and there is a need to increase rigor, reproducibility and standardization of preclinical evaluation methods. Based on the information available, ICM2025 concluded that there is no direct evidence for these discussed technologies that they: (1) are feasible as defined by a rational dosing regimen that can be given to a broad patient population based on biofilm characteristics and location; and/or (2) can "eradicate" biofilm in vivo defined as disintegration of the extracellular polymeric substance and killing all associated microbes. The strategies with the highest potential antimicrobial effect remain those that provide an active agent as their main mechanism of action and several are worth mentioning due to ongoing clinical efforts to demonstrate their impact.

Anti-DNABII antibodies (B13) target DNABII proteins that stabilize extracellular DNA crosslinks within the biofilm matrix, leading to collapse of the biofilm and restoration of bacterial susceptibility to antibiotics and host immunity [25]. They are species-agnostic and exhibit broad-spectrum antibiofilm activity against more than 20 tested Gram-positive and Gram-negative species, encompassing all ESKAPEE pathogens. Intravenous TRL1068—a fully human anti-DNABII monoclonal antibody (mAb)—was safe across escalating doses in a phase 1 hip and knee PJI trial and demonstrated preliminary reductions in bacterial burden and increased culture negativity at the explanted prosthesis during two-stage revision (ClinicalTrials.gov: NCT04763759) [26]. A phase 2 trial is now recruiting to evaluate TRL1068 in conjunction with debridement, antibiotics, and implant retention (DAIR) for hip and knee PJI (ClinicalTrials.gov: NCT06621251). CMTX-101, a humanized anti-DNABII mAb, completed phase 1 intravenous dose-escalation safety testing in healthy volunteers and is in an ongoing phase 1b/2a trial in individuals with cystic fibrosis chronically infected with *Pseudomonas aeruginosa* (ClinicalTrials.gov: NCT06159725).

Bacteriophage therapy presents a mechanistically novel treatment against bacteria with high potential for efficacy due to the variety of naturally occurring bacteriophages and their specificity for interacting with bacteria. Unlike conventional

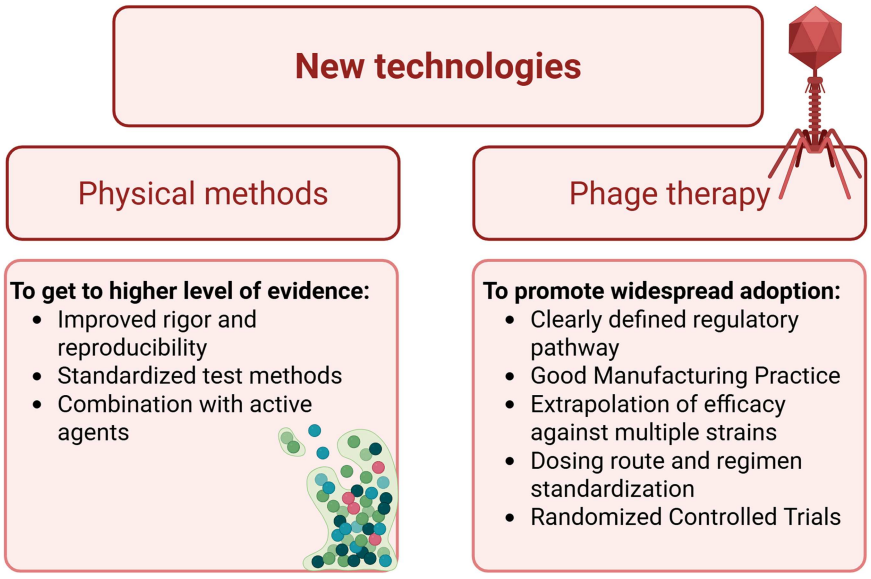

FIGURE 5 | New technologies. Emerging technologies for biofilm management, highlighting physical methods and bacteriophage therapy.

antibiotics, it is not impacted by the global challenge of antimicrobial resistance. There is growing interest in the application of bacteriophage therapy for the treatment of MSKI, as reflected by the establishment of dedicated phage therapy centers worldwide, and targeted funding initiatives such as the **S**trategies for **H**ealing **I**mplant-associated Infections and **E**nhancing **L**ongevity in **D**evices (SHIELD) doctoral network [27, 28] and multiple related questions raised during the ICM 2025 conference (G57, G58, G95). Despite its promise, the approach is accompanied by several uncertainties that must be addressed before widespread clinical adoption is feasible. A challenge is the absence of a clearly defined regulatory pathway to produce bacteriophages under Good Manufacturing Practice (GMP) conditions [29]. Another is the lack of clarity on how efficacy data obtained for a specific bacteriophage against a single pathogen can be extrapolated to the broader spectrum of pathogens and infection types encountered in clinical practice. Furthermore, optimal routes of administration and dosing regimens remain poorly defined, and the potential for host immune responses, particularly the development of neutralizing antibodies during treatment, raises additional concerns. The clinical evidence base remains limited [30, 31]. Although published low-level clinical reports are generally positive, some larger trials outside of musculoskeletal infection conducted in the past have failed to demonstrate a clear therapeutic benefit [32]. Thus, despite the exciting prospect of bacteriophage therapy as a novel and effective tool against biofilm, the prioritization of answering the most clinically relevant safety and efficacy questions is crucial. There is a pressing need for adequately powered randomized controlled trials (RCTs) to rigorously assess efficacy.

The general lack of direct clinical evidence of antibacterial effects of new technologies using active agents is partly due to the absence of rigorous and reproducible assays to evaluate the dosing, pharmacokinetics, pharmacodynamics of the proposed agent(s) and their efficacy against biofilm. However, now that appropriate experimental systems are discussed and minimal datasets for diagnostic (B4), therapeutic (B5), and clinical (B12) claims have been agreed upon by ICM2025, a more rigorous and critical evaluation of mature technologies can be performed. The recommended follow-on questions are listed in Table 4.

TABLE 4 | Clarification of efficacious clinical strategies and evaluation of the feasibility of novel treatments: Recommended follow-on questions.

- Is there standardized guidance for RCT outcomes for evaluating antimicrobial efficacy?
- Is there a harmonized set of outcomes in clinical and preclinical studies for antimicrobial efficacy?
- Is there a minimum set of outcomes that registries should collect/report for MSKI?
- Are there clinically relevant endpoints/outcome measures in preclinical (in-vivo) studies regarding antimicrobial safety?
- Are there clinically relevant endpoints/outcome measures in preclinical (in-vivo) studies regarding antimicrobial efficacy?
- Are there clinically relevant endpoints/outcome measures in in-vitro studies regarding antimicrobial safety?
- Are there clinically relevant endpoint measures in in-vitro studies regarding antimicrobial efficacy?

3.7 | Translational Barriers

While it was apparent that the efficacy of many device strategies was strongly supported against infections in vitro and in preclinical studies, for example, regarding new technologies such as smart antibiotic carriers (B30), there is a significant gap in the translation of these strategies to the clinic. This gap is caused by both the lack of predictive algorithms for the clinical impact of preclinical results and regulatory barriers to translation. Of the more than 1000 orthopaedic devices approved for clinical use in the US by the Food and Drug Administration (FDA) through the 510 K and premarket approval (PMA) mechanisms in 2024 and 2025, there are only a handful addressing infection and 16 combination products. Those that were approved for use via the 510 K pathway are largely antibiotic-eluting cement and those that were approved for use via PMA are bone grafts. Only 2 devices were approved by the DeNovo designation; ELEOS Limb salvage system with NanoCept technology (Onkos Medical, NJ), which is a "Limb and joint salvage device with coating for bacteria reduction" and Orthobond Mariner pedicle screw system (Orthobond, NJ), which is a "spinal fusion system with 12-methacryloyloxydodecyl pyridinium bromide coating" designed to reduce bacterial contamination. There is also one investigational drug; VT-X7 (Osteal Therapeutics, TX), which is a combination of the antibiotics tobramycin and vancomycin delivered into the joint via an irrigation pump. All these devices were approved for use in infected revisions and limb salvage while no anti-infective devices for prevention of infection in primary surgeries were approved in the same period. The current portfolio of devices indicates that there is a preference towards incremental advances rather than novel therapeutics and devices due to the challenges of the regulatory process and the large investments needed to develop these products, whose efficacy can take many years, many sites, and tens of thousands of patients to demonstrate, especially for infection prevention.

For this reason, the most effective use of resources is in prioritizing "high-risk" patients first for novel strategies, as this approach provides sufficient patient volume to power such studies and significantly reduces cost requirements. Identifying "high-risk" patients and standardizing study protocols remains a challenge and there is a gap in the conceptual understanding and methods of the evaluation of the risk of treatment failure for proposed technologies. More standardized, clinically relevant, accurate and cost-effective methods of evaluating the benefit-to-risk ratio of anti-infective devices/treatments and incorporating realistic regulatory considerations into research activities at the study design stage [33] are important research and clinical priorities.

The testing guidance and methods that regulatory agencies rely on are often developed by standards organization, such as the International Standards Organization (ISO) or the American Society for Testing and Materials (ASTM). These organizations develop standard guidance and methods based on the input and

consensus of the stakeholders in the area of interest, including industry, academic research, and regulatory agencies. Although there are specific tests for determining the antimicrobial efficacy of surfaces that are commonly used such as ASTM E-2149 and ISO 22196, there is an increasing need for test methodology specific to implantable medical devices in the context of biofilm and guidance on how to use existing methods for a comprehensive evaluation. Only by establishing methods of strong preclinical support can the widespread use of MSKI treatment strategies be successfully enabled. Increasing the clinical relevance of in-vitro testing strategies with better clinical performance predictions can reduce long-term follow-up requirements for clinical studies and can make a considerable impact in reducing the investments for drug and device development without increasing the risk for patients. This shift is imperative to also guide research efforts in the most efficient direction in treating infections and away from the production of strategies and products that cannot be cleared for safe and effective clinical use. Recommended follow-on questions are listed in Table 5. In the next sections, we present the biggest opportunities in overcoming translational barriers and providing successful ways of minimizing MSKI.

TABLE 5 | Translational barriers: recommended follow-on questions.

- Is there a minimum cohort of patients to confirm
  - antibacterial efficacy in prophylaxis?
  - antibacterial efficacy in treatment?
- Is there a known set of risks associated with
  - antimicrobial MSKI prevention?
  - antimicrobial MSKI treatment?
- Is there a preclinical and clinical method of quantifying resistance risk for novel antibacterial treatments?
- Is there guidance for the evaluation of
  - The safety risk of new antimicrobial technologies in MSKI treatment?
  - treatment failure of new antimicrobial technologies in MSKI treatment?
- Should there be a defined clinical indication while reporting the in-vitro testing of new technologies?

3.8 | Opportunities: Enhancement of Reproducibility and Rigor (Figure 6)

The previous consensus meeting in 2018 identified the need for clear definitions related to clinical PJI and emphasized the need for these definitions to be based on and supported by what is known about the biology of biofilms. While the previous ICM efforts established a clear definition of PJI based on clinical diagnostic plasma and synovial fluid markers supported by tissue culture, there are still gaps in our knowledge of bacterial diagnosis and characterization in the clinic in a timely and accurate manner. Addressing these gaps can enable the more accurate determination of antibiotic selection, dosing, and duration of treatment as well as more accurate evaluation of efficacy for existing and novel treatments and technologies.

Improvement is needed both in the quality of clinical outcome studies to be more informative for research studies and in the predictive value of in-vitro methods of biofilm characterization and treatment. This gap is due largely to the lack of standardization/harmonization of outcome measures and the lack of high level of evidence, both in preclinical and in clinical studies. For example, clinical studies often rely on clinical measures such as ranked pain scoring or probabilistic outcomes such as infection rate, which do not provide direct feedback to in-vitro or preclinical work. Addressing the gap requires a

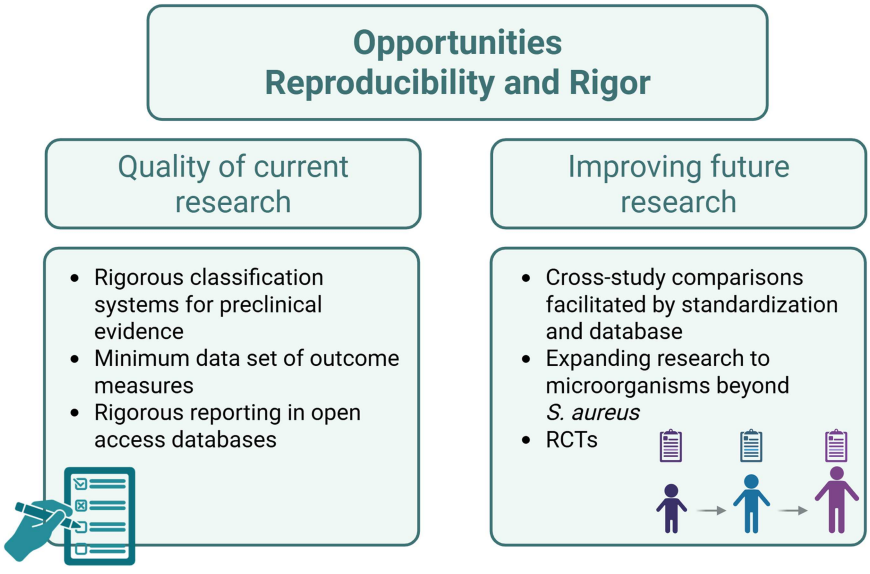

FIGURE 6 | Opportunities for reproducibility and rigor: Strategies to improve the quality and consistency of biofilm research. Enhancing current studies involves standardized data reporting and classification systems, while future directions include expanding beyond *Staphylococcus aureus* and promoting cross-study comparisons and randomized controlled trials (RCTs).

multi-pronged effort. First, the field must adopt rigorous classification systems for preclinical evidence, analogous to clinical hierarchies, and enforce standardized definitions of efficacy. Second, journals and funders should require a minimum data set of outcome measures, including inoculum quantification, infection verification, appropriate controls, burden measurement, imaging, and histology, to ensure reproducibility (B11). Third, implant studies must move toward protocol standardization in animal models (species, inoculum size, bacterial strains, outcomes). Finally, the creation of a shared, open-access database of infection model outcomes (similar to GEO for OMICS) will allow benchmarking, cross-study comparisons, and more robust meta-analyses. Only by embedding rigor, harmonizing reporting, and ensuring transparency can the gap between preclinical findings and clinical outcomes be bridged.

As mentioned above, preclinical research needs to systematically expand the range of pathogens to increase clinical relevance. Models should incorporate Gram-negative bacilli, polymicrobial infections, host-specific pathogens, and fungi to reflect the true clinical diversity of orthopaedic infections. It is also essential for clinical strains to be publicly available for sequencing and characterization to facilitate access, reproducibility, and comparability across studies. Additionally, publication standards must evolve to require quantitative documentation of pathology in bone and soft tissue for each tested strain. To enable and facilitate such broad and equitable access to clinical strains and their characterization, it is a priority to establish nation/regionwide repositories (e.g., ATCC (www.atcc.org) or CCUG (www.ccug.se). By broadening the microbial landscape and standardizing strain documentation, the field can generate more clinically relevant data and better anticipate therapeutic challenges. Furthermore, the construction of these resources can minimize translational barriers as FDA guidance suggests an even wider array of microorganisms, such as *Pseudomonas aeruginosa* and *Candida* spp., that should be considered in antimicrobial testing.

While there are clinical reports that generally describe positive outcomes for several technologies, there is a pressing need for adequately powered randomized controlled trials (RCTs) to rigorously assess their efficacy. The economic burden of MSKI is tremendous and increasing and all the stakeholders in this field have the responsibility to decrease the burden of this condition on patients by demonstrating the efficacy/inefficacy of available treatments and by improving the flexibility and accessibility of treatments. There is a need to highlight this field on a "consortium" level with the engagement of multiple research and clinical groups to enable standardization of methods and to improve the rigor and reproducibility of all preclinical and clinical studies. The ongoing lack of consortium efforts to bring together large sets of patients often necessary for sufficiently powered efficacy studies for infection is a major factor preventing the widespread availability of novel technologies for patients undergoing surgery for musculoskeletal conditions.

3.9 | Opportunities: Artificial Intelligence and Machine Learning (Figure 7)

Despite the wide range of topics addressed at the 2025 ICM on Orthopaedic Infections, artificial intelligence (AI) and machine learning (ML) were not emphasized as part of the prioritized research agenda. However, the meeting did include a dedicated question (G98) examining whether AI/ML has a role in the management of orthopaedic infections. The response acknowledged that AI holds potential advantages in data mining, systematic information collection, and the development of predictive, diagnostic, and treatment tools, with promising applications across prediction, prevention, diagnosis, treatment, and prognosis. Nonetheless, the consensus highlighted that current research remains limited, with significant barriers related to external validation, generalizability, and utilizing the "black box" nature of many ML models, ultimately assigning a low level of evidence to its use. Thus, while AI/ML are starting to be discussed within the field, their absence from the core list of research priorities underscores that orthopaedic infection research remains at an early stage of engaging with digital health innovations. Unlike other medical domains where AI applications are rapidly advancing, the field has yet to recognize these tools as immediate priorities. This reflects both the complexity of the clinical problem and the gap between technological development and clinical applicability. There is currently no integration of AI or ML in vitro or in preclinical research with unrealized opportunity for harmonizing between laboratory discovery, translational pathways, and clinical implementation. This limitation for AI or ML utilization for MSKI research is further challenged by low quality data [34, 35] a substantial barrier, as robust, high quality data sets are the foundation on which this technology must be built. However, these fundamental challenges that hinder meaningful translation into clinical practice, including small and imbalanced data sets, a lack of universally accepted diagnostic standards, difficulties in integrating data from multiple centers, and emerging regulatory hurdles, should be addressable going forward based on the ICM's mandated minimal datasets for diagnostic (B4), therapeutic (B5), and clinical (B12) claims. Thus, efforts to create shared, accessible datasets for integration into AI/ML development is a priority.

3.10 | Opportunities: Prioritization of In-Vitro Models (Figure 8)

NIH recently announced the award of contracts for establishing the Standardized Organoid Modeling (SOM) Center, prioritizing

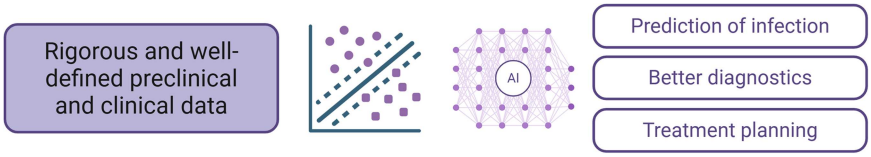

FIGURE 7 | Integration of artificial intelligence. The role of artificial intelligence (AI) in leveraging robust preclinical and clinical datasets for infection prediction, improved diagnostics, and treatment planning, emphasizing data quality and standardization as key prerequisites.

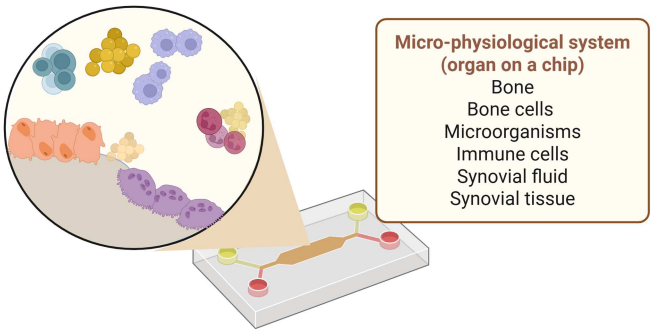

FIGURE 8 | Micro-physiological systems (organ-on-a-chip). Schematic representation of an organ-on-a-chip model integrating bone, synovial tissue, immune cells, and microorganisms. This system aims to mimic complex environments in vivo to study host-pathogen interactions and biofilm-associated infection mechanisms.

research that uses human-based technologies and models and reducing reliance on animal research [36]. This effort aims to utilize animal research when scientifically appropriate, justifiable and with proper animal oversight as well as to guide the direction of biomedical research towards innovation in in-vitro models with increased clinical relevance. The announcement states that funding opportunities will necessitate complementing animal studies with human-focused approaches, such as real-world data. This direction is also in line with our prioritization of approaches to close the gap between in-vitro and preclinical findings and their clinical interpretation and utility.

While the NIH SOM Center will first focus on heart, lung, liver, and intestine, this initiative is a great opportunity for musculoskeletal researchers to work towards developing musculoskeletal organoid/organ-on-a-chip models and those in which medical associated infections can be tested in a more clinically relevant manner. While bone organoids have been proposed for producing healthy and diseased musculoskeletal tissue models [37] and few models for osteomyelitis [38], a full in-vitro model of the infection environment of the joint including the synovium and synovial fluid does not exist. The construction of a synovial joint organoid model is an opportunity to enhance the in-vitro testing environments while aligning with the goal of improving the clinical relevance of preclinical testing. Ultimately, gaining a better understanding of the dynamics of synovial fluid biofilms will be crucial for developing diagnostics and therapies targeting these elusive, non-surface-attached biofilm forms.

The construction of advanced in-vitro micro-physiological systems, such as a synovial joint organoid model, is an important opportunity to enhance the in-vitro testing environments while aligning with the goal of improving the clinical relevance of preclinical testing. These models should ideally incorporate not only host and bacterial cells but also the relevant physical environment including flow conditions and incorporate sensors for real-time monitoring and feedback of micro-physiological stimuli [39]. For example, advanced imaging and molecular techniques can be leveraged to elucidate bacterial aggregate size, structure, and metabolic states, along with host cell response. Importantly, micro-physiological models can enable high- throughput screening of technologies and facilitate reproducibility across laboratories, generating high-quality, robust data sets. In turn, this will accelerate the integration of artificial intelligence as a new tool for improving orthopaedic infection prevention, diagnosis, and treatment, and contribute to the establishment of international standards for clinically relevant testing.

TABLE 6 | Opportunities: recommended follow-on questions.

- Is there an international standard (ASTM or ISO) for clinically relevant testing the antibacterial properties of implantable medical devices?
- Is there a shared, open-access database of infection model outcomes?
- Is there a known set of clinical factors to be included in the design of a synovial joint organoid?
- Is there a known set of clinical factors to be included in the design of an infected bone organoid?
- Is there data from animal models of infection that can be replaced by testing in an organoid?

The recommended follow-on questions are listed in Table 6.

4 | Conclusion and Outlook

Musculoskeletal infections, especially implant-associated infections, continue to present a significant burden to all stakeholders including, first and foremost, the patients and their caregivers, and the healthcare system. By bringing together the expertise of orthopaedic surgeons, infectious disease specialists, biofilm researchers as well as those who work in medical device development, clinical consensus meetings offer an opportunity to define the status quo and identify knowledge gaps. Here, we have presented an expert interpretation of our current knowledge of biofilm-related fields, identified immediate research priorities and recommended potential questions to be asked at the next consensus meeting. The most promising opportunities lie in *organizing, analyzing, and sharing the vast amount of data* that can be collected using advanced technologies such as various 'omics'-approaches and AI/ML, as well as in enabling *multi-center clinical studies with large and comprehensive cohorts* and *standardized techniques* which subsequently *inform preclinical testing to increase clinical relevancy*. Such efforts are essential for the much-needed improvement of rigor and reproducibility, in the identification of effective interventions and treatments (including devices) and in defining a more rigorous framework for introducing new technologies by better assessing risk and benefit.

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