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Actionable Biosensing for Real-Time Monitoring and Decision Support in Inflammatory Rheumatic Diseases

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Abstract

Inflammatory rheumatic diseases exhibit dynamic and heterogeneous inflammatory activity, yet clinical monitoring remains episodic and temporally sparse, limiting early intervention and delaying treatment adjustment. Advances in biosensing technologies, wearable monitoring, and computational modeling offer opportunities to transition toward continuous, data-driven disease assessment. In this review, we synthesize evidence across rheumatology, immunology, biosensing, and digital health to examine how multimodal measurement approaches can support clinically actionable decision-making. We introduce a structured framework—the "Measurement Stack"—that links three components: biological signal domains (systemic, synovial, imaging-derived, and physiological), sensing platforms with distinct temporal and specificity trade-offs, and computational inference layers including feature extraction, multimodal data integration, and predictive modeling. We emphasize that the clinical value of biomarkers depends not on association alone but on actionability, defined by temporal sensitivity, repeatability, robustness to heterogeneity and signal noise, and alignment with clinical decisions. Key methodological considerations include feature engineering for sparse and continuous data, handling missingness and signal drift, calibration-aware validation, temporal and external validation, and decision-curve analysis for clinical utility. A decision-centric mapping aligns measurement and modeling strategies with clinical tasks such as early flare detection, differentiation of flare from infection, therapy switching or tapering, and monitoring of treatment response. By integrating biosensing advances with clinically grounded evaluation standards, this review outlines pathways toward interpretable, deployment-ready monitoring systems enabling proactive and personalized management of inflammatory rheumatic disease.

Keywords: inflammatory rheumatic diseases; disease monitoring; biomarkers; digital health; wearable devices; clinical decision support; flare prediction; precision medicine; multimodal data integration; predictive modeling

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1. Introduction: Framing the Measurement Bottleneck in Inflammatory Rheumatic Disease

Inflammatory rheumatic diseases are inherently dynamic disorders, characterized by fluctuating immune activity, variable tissue involvement, and heterogeneous clinical trajectories across patients and over time. Disease activity can evolve rapidly, often preceding overt clinical symptoms by days or weeks. Despite this temporal complexity, routine monitoring in rheumatology remains largely episodic and indirect, creating a fundamental mismatch between disease biology and clinical observation [1,2].

Current clinical practice relies primarily on infrequent blood tests, delayed or resource-intensive imaging, and composite disease activity scores derived from intermittent assessments. Systemic biomarkers such as acute-phase reactants provide only coarse snapshots of inflammation and often fail to reflect local joint pathology or imminent disease transitions, while imaging modalities, though informative, are typically deployed reactively rather than proactively and are impractical for continuous monitoring [3,4]. Composite indices, although valuable for standardization, aggregate delayed biological signals and clinical observations, causing them to lag behind the underlying immunological processes they aim to represent [5,6].

This measurement gap has tangible clinical consequences. Flares are frequently detected only after symptoms become clinically apparent, limiting opportunities for early intervention. Treatment adjustments are often delayed, resulting in prolonged disease activity, avoidable joint damage, reduced quality of life, and potentially broader systemic consequences associated with uncontrolled rheumatoid arthritis. In parallel, uncertainty in disease monitoring contributes to unnecessary imaging, repeated clinic visits, and excessive or prolonged steroid exposure, amplifying both patient burden and healthcare costs [7–9]. Together, these challenges highlight that many failures in disease control arise not from ineffective therapies, but from insufficient tools to deploy those therapies at the right time and in the right context.

Accumulating evidence suggests that a key limitation in contemporary rheumatologic care may not be the availability of effective immunomodulatory therapies, but the lack of measurement systems capable of translating biological signals into timely and actionable clinical decisions. As therapeutic options have expanded, the bottleneck has shifted toward measurement, interpretation, and decision support [10–12].

Rather than cataloging all candidate biomarkers or molecular associations, this review synthesizes emerging evidence from biosensing, biomedical engineering, and digital health research to examine how biomarker and biosensing systems can support clinically actionable decision-making.

While prior reviews have explored digital biomarkers, AI-enabled prediction, and wearable technologies in inflammatory rheumatic disease [1,13,14], these discussions are typically organized around individual technologies or data modalities. Such modality-centric approaches risk fragmentation, evaluating tools in isolation rather than within the full translational pathway from biological signal to clinical decision. Taken together, these observations highlight the need for a systems-level perspective that integrates biological signals, sensing technologies, and computational inference within the pathway from measurement to clinical decision. Taken together, studies in biosensing, wearable monitoring, and digital health increasingly indicate that disease monitoring involves multiple interacting measurement layers. These include biological signal domains in which disease-relevant information resides, sensing technologies capable of capturing those signals, and computational methods that convert raw measurements into clinically interpretable outputs. For clarity, this review refers to this layered architecture as the 'Measurement Stack'.

Within this integrated framework, biomedical engineering offers a powerful and underutilized pathway to address the measurement bottleneck. Advances in biosensing technologies, medical devices, and wearable systems now enable repeated and minimally invasive measurement of molecular, physiological, and behavioral signals. Data integration and computational modeling make it possible to combine heterogeneous inputs into clinically meaningful inferences, while decision-support systems can link these inferences directly to treatment actions [15,16]. Viewed through an engineering lens of sensing, inference, and action, recent advances in biosensing and computational modeling suggest new opportunities to move from reactive disease management toward proactive, real-time care.

In the following sections, we examine how actionable biomarkers and biosensing systems can be designed, validated, and implemented to support real-time management of inflammatory rheumatic disease. The literature increasingly explores engineering approaches that connect biological measurement to clinical decision-making, with the goal of enabling earlier detection of disease activity, more precise therapy adjustment, and more sustainable long-term care. Figure 1 illustrates the overall actionable biosensing pipeline that operationalizes the Measurement Stack concept described in this review.

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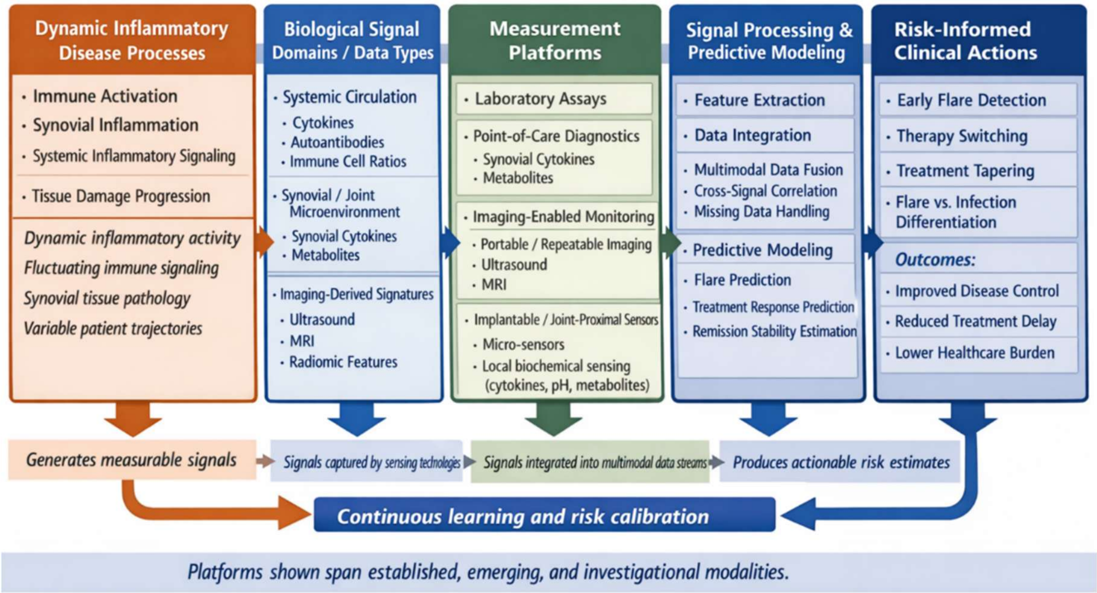

Figure 1. Actionable biosensing pipeline linking biological signals, sensing technologies, predictive modeling, and clinical decision support for real-time management of inflammatory rheumatic disease. Dynamic inflammatory processes generate measurable biological signals across systemic circulation, joint microenvironments, and imaging-derived domains. These signals are captured through laboratory assays, point-of-care diagnostics, wearable systems, and emerging implantable sensors. Signal processing and multimodal data integration enable predictive modeling for flare detection, treatment response prediction, and remission stability estimation. These outputs support clinical decisions including early flare detection, therapy switching, treatment tapering, and differentiation between inflammatory flare and infection, forming a continuous learning system for adaptive disease management.

2. What Makes a Biomarker Actionable? From Association to Clinical Utility

The literature on biomarkers in inflammatory rheumatic disease is extensive, yet relatively few proposed markers have meaningfully altered routine clinical practice. This gap reflects a persistent conflation between biomarkers that are biologically informative and those that are clinically actionable. Many biomarkers demonstrate statistical association with disease activity, prognosis, or treatment response, but fail to support timely or confident clinical decisions [17,18]. For biomedical engineering approaches to improve rheumatologic care, actionability—not association—must therefore be the defining criterion.

Synthesizing insights from biomarker development studies and clinical implementation research suggests that biomarkers capable of supporting clinical decisions generally share four practical characteristics. First, it must change before clinical deterioration or improvement becomes apparent. Biomarkers that rise only after joint swelling, pain, or functional decline are already evident offer limited opportunity for intervention. Actionable markers provide lead time, enabling clinicians to anticipate flares, detect early response to therapy, or identify loss of disease control before irreversible tissue damage occurs [19,20].

Second, an actionable biomarker must be measurable repeatedly and safely. Inflammatory rheumatic diseases require longitudinal monitoring over years, often in stable patients as well as during exacerbations. Biomarkers that depend on invasive procedures, high-cost imaging, or infrequent sampling are poorly suited for continuous disease management. Repeated measurement must be feasible in real-world settings without imposing excessive burden on patients or healthcare systems [14,21].

Third, actionable biomarkers must directly inform a clinical decision. The value of a biomarker lies not in its correlation with disease activity, but in its capacity to change what a clinician does within a defined therapeutic pathway. This includes decisions to initiate therapy, escalate or switch

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biologic agents, taper treatment during remission, or distinguish inflammatory flare from infection or non-inflammatory pain. Biomarkers that do not map clearly onto a decision pathway, regardless of their biological relevance, are unlikely to achieve clinical adoption [12,17,22].

Fourth, actionable biomarkers must maintain performance across patient heterogeneity and biological noise. Inflammatory rheumatic diseases encompass diverse phenotypes, comorbidities, treatment histories, and immune baselines. Biomarkers that perform well only in narrowly defined cohorts or under controlled conditions often degrade in real-world use. Robust actionability therefore requires resilience to inter-individual variability, fluctuating disease states, and measurement noise [23].

These criteria highlight why many widely used biomarkers remain insufficient for real-time disease management. Acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein, as well as autoantibodies used for diagnosis and risk stratification, provide valuable information but are limited by delayed kinetics, poor tissue specificity, and weak predictive power at the individual level [24–26]. Their utility is greatest for population-level assessment or retrospective confirmation rather than prospective decision-making.

These observations have led to increasing emphasis on biomarker actionability, shifting attention from simple molecular association toward measurement systems capable of supporting clinical decision-making. This perspective naturally favors engineering approaches that emphasize longitudinal sensing, signal integration, and decision thresholds over single-point measurements. Throughout this review, we adopt actionability as the central organizing principle, evaluating biomarkers and biosensing platforms not by their biological novelty alone, but by their capacity to enable timely, reliable, and clinically meaningful decisions in the management of inflammatory rheumatic disease.

To operationalize this definition, the four criteria for actionability can be translated into explicit engineering requirements and corresponding clinical implications. Framing actionability in this structured manner enables reproducibility, comparison across studies, and practical deployment. These criteria are summarized in Table 1.

Table 1. Engineering Criteria for Actionable Biomarkers in Inflammatory Rheumatic Disease.

Criterion	Engineering Requirement	Clinical Implication
Changes before clinical deterioration or improvement	High temporal sensitivity; ability to detect pre-symptomatic signal shifts; longitudinal sampling capability	Enables early intervention, flare prevention, and proactive treatment adjustment
Measurable repeatedly and safely	Low-burden sampling; minimally invasive or non-invasive acquisition; scalable workflow integration	Supports long-term monitoring without excessive patient or system burden
Directly informs a clinical decision	Clear mapping between measurement output and defined treatment actions; interpretable thresholds	Changes clinician behavior (start, switch, taper, escalate) rather than merely describing biology
Maintains performance across heterogeneity and noise	Robustness to inter-individual variability; calibration across subgroups; tolerance to missing data and signal drift	Reliable performance in real-world practice, not limited to ideal research cohorts

To organize these concepts within a systems-level framework, biosensing architectures can be conceptualized as a layered measurement stack that connects biological signal domains, sensing platforms, and computational inference. This layered architecture is illustrated in Figure 2.

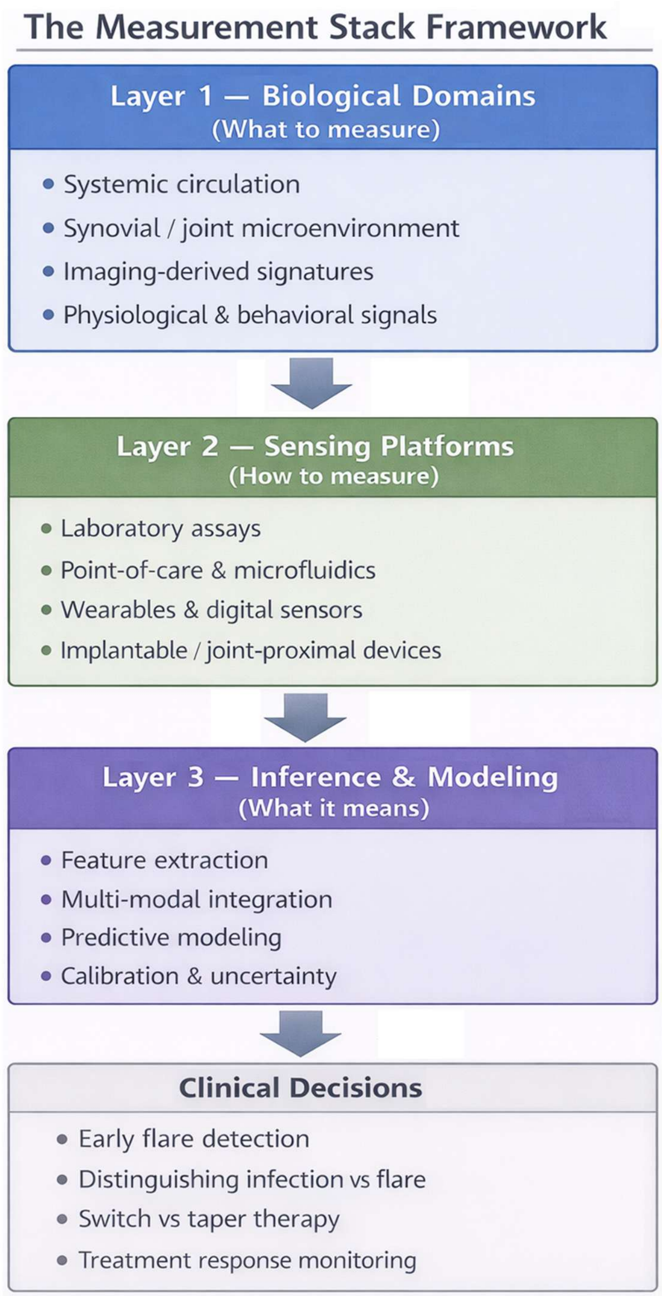

Figure 2. Layered Measurement Architecture for Actionable Biosensing in Inflammatory Rheumatic Disease. Layer 1 defines the biological domains in which disease-relevant signals reside. Layer 2 comprises the sensing platforms that acquire these signals with distinct trade-offs in specificity and temporal resolution. Layer 3 integrates signal processing and predictive modeling to generate interpretable outputs. Clinical decisions emerge from alignment across layers, linking biological measurement to actionable care.

3. Biological Domains for Measurement Defining Layer 1 of the Measurement Stack

Recent studies examining biomarker sources in inflammatory rheumatic disease indicate that biologically meaningful information arises from multiple anatomical and physiological compartments. Effective real-time management therefore depends on identifying where these signals reside and how they can be measured. Inflammatory activity is distributed across multiple compartments, each offering distinct advantages and limitations for measurement. As depicted in **Figure 2**, Layer 1 of the Measurement Stack defines the "what to measure" component of the

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framework, focusing on the biological domains from which disease-relevant signals can be acquired. No single domain fully captures disease dynamics; rather, each represents a different balance between accessibility, specificity, and clinical relevance [27,28].

3.1. Systemic Circulation

The systemic circulation remains the most widely used domain for biomarker measurement in rheumatology. Blood-based biomarkers include cytokines and chemokines, acute-phase proteins, autoantibodies, and immune cell ratios derived from routine hematologic profiling. These measures form the backbone of current clinical monitoring and research studies due to their familiarity and logistical convenience [29,30].

The primary strength of systemic biomarkers lies in their accessibility and standardization. Blood sampling is minimally invasive, broadly acceptable to patients, and compatible with repeated measurement over long periods. Assays for many circulating markers are well established, reproducible, and easily integrated into clinical workflows. This scalability has enabled large cohort studies and routine incorporation into disease activity assessment [28,30].

However, systemic circulation also presents important limitations as a measurement domain. Circulating signals represent an averaged and diluted reflection of inflammatory activity occurring across tissues, joints, and organ systems. Local inflammatory processes within affected joints may be weakly represented or temporally delayed in the bloodstream, reducing sensitivity for early or localized disease activity. In addition, systemic biomarkers are influenced by comorbid conditions, infections, metabolic status, and medications, introducing noise that complicates interpretation at the individual patient level [26,31].

As a result, while systemic biomarkers provide valuable contextual information and remain indispensable for baseline assessment, they often lack the specificity and temporal resolution required for early flare detection or fine-grained treatment adjustment. These limitations underscore the need to consider additional biological domains that more directly reflect joint-level pathology and dynamic disease processes [27].

3.2. Synovial and Joint-Proximal Microenvironments

The synovial and joint-proximal microenvironments represent the most disease-relevant biological domain in inflammatory rheumatic conditions. Synovial fluid and adjacent tissues are the primary sites of immune activation, cytokine production, metabolic remodeling, and tissue damage. Biomarkers derived from this compartment—including synovial proteins, metabolites, immune cell phenotypes, and extracellular vesicles—therefore offer a direct window into the pathological processes that drive symptoms and structural progression [32–34].

The principal advantage of synovial-based measurement is disease specificity. Unlike systemic circulation, synovial signals are minimally diluted and closely reflect local inflammatory burden, immune cell activation states, and tissue-destructive processes. Changes in synovial biomarkers may precede detectable alterations in blood markers, making this domain particularly valuable for early flare detection, differentiation between inflammatory and non-inflammatory pain, and assessment of local treatment response. From a biological standpoint, synovial measurements are often more tightly coupled to clinical outcomes such as joint swelling, pain, and erosion [35,36].

Despite these advantages, synovial and joint-proximal measurements pose significant engineering and practical challenges. Sampling synovial fluid is inherently more invasive than venipuncture, limiting feasibility for frequent or routine monitoring. Sampling success can vary across joints and disease stages, and repeated procedures may be poorly tolerated by some patients. In addition, standardization of synovial assays remains less mature than for blood-based tests, complicating cross-study comparison and clinical deployment [37,38].

These constraints create a fundamental tension between biological relevance and measurement practicality. While synovial biomarkers offer high specificity and mechanistic insight, their integration into real-time disease management requires innovations that reduce invasiveness, enable targeted or opportunistic sampling, or extract joint-proximal information through alternative sensing

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strategies. Addressing this tension is a central design challenge for actionable biosensing systems in rheumatology [39,40].

3.3. Tissue and Imaging-Derived Signatures

Imaging-based measurements provide a complementary biological domain that captures structural and functional changes within affected joints. Modalities such as ultrasound, magnetic resonance imaging, and power Doppler are routinely used to assess synovial hypertrophy, effusion, vascularization, and erosive damage. These techniques offer spatially resolved information that bridges molecular activity and clinical manifestations [4,41].

Ultrasound and power Doppler imaging are particularly valuable for detecting subclinical inflammation and synovial vascular activity that may not be evident on physical examination or systemic biomarkers. Magnetic resonance imaging provides high-resolution assessment of soft tissue, bone marrow edema, and early structural changes, offering sensitivity to disease processes that unfold before irreversible damage occurs. As such, imaging-derived signatures play an important role in diagnosis, prognosis, and evaluation of therapeutic response [42].

Beyond qualitative interpretation, imaging data can be transformed into quantitative biomarkers through radiomic analysis. Radiomics extracts numerical features from imaging data that describe texture, intensity, spatial heterogeneity, and temporal change. These features can be tracked longitudinally and integrated with other biological signals, converting imaging from a descriptive tool into a measurable and analyzable data source [43,44]. Quantitative imaging biomarkers hold particular promise for standardization, automated assessment, and integration into predictive models.

However, imaging-based measurement is constrained by cost, availability, and temporal resolution. Frequent imaging is impractical for most patients, and many modalities are deployed reactively rather than continuously. Interpretation can be operator-dependent, and variability across imaging platforms complicates large-scale deployment [45,46]. Consequently, imaging-derived biomarkers are best suited as intermittent but information-rich inputs within a broader measurement strategy, rather than as standalone solutions for real-time monitoring.

Together, synovial and imaging-based domains highlight the value of proximity to pathology, while underscoring the trade-offs between specificity, invasiveness, and feasibility. These trade-offs motivate the need for engineering frameworks that integrate information across domains, balancing biological relevance with practical deployment in routine care [47].

3.4. Physiological and Behavioral Signals

Physiological and behavioral signals constitute an increasingly important biological domain for measurement, particularly in the context of continuous and real-time monitoring. Variables such as physical activity, sleep patterns, skin or peripheral temperature, and heart rate variability capture downstream effects of inflammation on the nervous, metabolic, and musculoskeletal systems. While these signals do not measure immune activity directly, they provide indirect but high-frequency proxies of disease burden and functional impact [48,49].

The primary advantage of physiological and behavioral signals is their continuity. Wearable and ambient sensing technologies enable near-continuous data collection over extended periods, capturing fluctuations that would be missed by episodic clinical assessments. Changes in activity levels, sleep disruption, or autonomic balance may precede overt clinical flare or reflect subclinical disease activity, offering early warning signals that complement molecular biomarkers [19]. Because these measures are non-invasive and patient-centered, they are well suited for longitudinal monitoring in real-world settings.

However, physiological and behavioral signals are inherently indirect and context-dependent. They are influenced by factors such as mood, stress, comorbid conditions, medications, and lifestyle, which can confound interpretation [19]. As a result, these signals rarely provide sufficient specificity when used in isolation. Their greatest value emerges when integrated with molecular or imaging-based measurements, where they can enhance temporal resolution and support inference about disease dynamics without increasing patient burden.

From an engineering perspective, physiological and behavioral signals expand the measurement space beyond biology alone, enabling hybrid sensing strategies that trade biological specificity for temporal density. When properly contextualized, these signals can serve as scalable components of actionable biosensing systems, particularly for early detection of change and monitoring of treatment response over time [50].

3.5. The Synovial-First Versus Blood-First Design Choice

A central design question in rheumatologic biosensing concerns the choice between blood-first and synovial-first measurement strategies. This choice reflects a fundamental trade-off between scalability and specificity, and it shapes both the feasibility and clinical value of measurement systems [28,51].

Blood-first approaches prioritize accessibility and low burden. Blood sampling is familiar, scalable, and compatible with repeated measurement across large patient populations. These strategies favor standardization and broad deployment, making them attractive for population-level monitoring and integration into existing clinical workflows. However, blood-first designs often sacrifice tissue specificity, as circulating biomarkers may weakly or belatedly reflect joint-localized inflammation, particularly in early or limited disease [26,27].

Synovial-first approaches prioritize proximity to pathology. By targeting the joint microenvironment directly, synovial-based measurements offer higher specificity and stronger coupling to disease mechanisms and clinical manifestations. These approaches are particularly valuable for distinguishing inflammatory flares from non-inflammatory pain, assessing local treatment response, and resolving diagnostic ambiguity [27,36]. Their limitations lie in procedural burden, sampling frequency constraints, and variability in feasibility across patients and joints.

From an engineering standpoint, the synovial-first versus blood-first distinction is not binary, but represents a design trade-space defined by frequency, invasiveness, information content, and decision value. High-specificity measurements may justify lower sampling frequency if they resolve critical clinical uncertainties, while lower-specificity measurements may remain valuable if they can be acquired continuously and interpreted longitudinally. Hybrid strategies—combining frequent, low-burden signals with intermittent, high-specificity measurements—may offer the most effective balance [49,52].

Explicitly recognizing this design choice reframes biomarker selection as an optimization problem rather than a search for a single ideal marker. Actionable biosensing systems must be engineered to align measurement modality with the clinical decision they are intended to support, accounting for patient burden, resource constraints, and the temporal demands of disease management [53].

4. Biosensing and Measurement Platforms Defining Layer 2 of the Measurement Stack

Advances in biosensing and diagnostic technologies have expanded the range of platforms capable of capturing biological signals relevant to inflammatory rheumatic disease. These developments highlight the importance of understanding how different measurement technologies acquire and translate biological information in practice. Biosensing and measurement platforms translate biological signals into data streams with distinct trade-offs in information content, temporal resolution, scalability, and clinical usability. No single platform is sufficient across all contexts; instead, actionable monitoring emerges from matching platform capabilities to the biological domain and clinical decision they are intended to support [19].

4.1. Laboratory-Based Assays

Laboratory-based assays remain the most mature and information-dense measurement platforms in rheumatology. These include multiplex immunoassays for cytokines and chemokines, targeted proteomic and metabolomic panels, transcriptomic profiling, and immune cell phenotyping through flow cytometry or single-cell approaches. Such platforms offer high analytical sensitivity and breadth, enabling simultaneous interrogation of multiple biological pathways from a single sample [54,55].

The principal strength of laboratory-based assays is their information content. They are well suited for baseline characterization, mechanistic insight, and detailed assessment of treatment response. Standardized protocols and quality controls support reproducibility, and advances in multiplexing continue to increase throughput while reducing sample volume requirements. For discovery and validation of candidate biomarkers, laboratory assays remain indispensable [55,56].

However, these platforms are constrained by limited temporal resolution. Sample processing, centralized testing, and result turnaround times make frequent measurement impractical in routine care. As a result, laboratory assays often capture delayed snapshots of disease activity rather than real-time dynamics. Cost, infrastructure requirements, and the need for trained personnel further limit their suitability for continuous monitoring [57,58]. Within the Measurement Stack, laboratory-based assays therefore function best as high-information but low-frequency inputs, anchoring interpretation rather than driving real-time decisions on their own.

4.2. Point-of-Care and Microfluidic Platforms

Point-of-care and microfluidic platforms address many of the temporal and logistical limitations of centralized laboratory testing. These systems enable rapid assays at the clinic, bedside, or joint side, delivering results within minutes to hours rather than days. Microfluidic technologies allow precise handling of small sample volumes, integration of multiple assay steps, and potential multiplexing within compact devices [55,59].

The defining advantage of point-of-care platforms is decentralization. By bringing measurement closer to the patient, these systems reduce delays between sampling and decision-making, supporting more timely treatment adjustments. For rheumatologic care, point-of-care assays are particularly attractive for scenarios requiring immediate clarification, such as distinguishing inflammatory flare from infection or assessing response during therapy initiation or modification [60,61].

Despite their promise, point-of-care and microfluidic systems face ongoing challenges. Assay panels are often narrower than those available in centralized laboratories, and maintaining analytical performance outside controlled environments can be difficult. Standardization across devices and sites remains an active area of development, as does integration with electronic health records and decision-support tools [62]. Nevertheless, as engineering advances continue to improve robustness and multiplexing capacity, point-of-care platforms are poised to play a central role in actionable, near–real-time monitoring strategies.

Together, laboratory-based and point-of-care platforms illustrate a key principle of Layer 2: measurement technologies must be evaluated not only by what they can detect, but by when, where, and how reliably they can deliver information that supports clinical action [63].

4.3. Wearable and Continuous Sensing Systems

Wearable and continuous sensing systems represent a rapidly expanding class of measurement platforms with particular relevance for real-time disease management. These systems capture physiological and behavioral signals such as physical activity, sleep patterns, skin or peripheral temperature, and heart rate variability, generating high-frequency data streams that reflect the functional consequences of inflammation over time [19,64]. Although these signals do not directly measure immune activity, they provide continuous context that is unavailable through episodic clinical testing.

The primary contribution of wearable systems lies in their ability to generate digital biomarkers—quantitative features derived from longitudinal data that can be used to infer disease activity, detect early deviations from baseline, and predict impending flares [19,65]. Changes in activity levels, sleep disruption, or autonomic balance may precede clinical deterioration and prompt earlier clinical evaluation or intervention. From an engineering perspective, the value of wearables

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arises from temporal density rather than biological specificity, enabling detection of trends, patterns, and anomalies at a scale that laboratory or imaging modalities cannot match.

Despite these advantages, wearable sensing platforms face important challenges. Patient adherence varies over time, and data quality may degrade with inconsistent use or device fatigue. Signal drift, hardware variability, and environmental influences can introduce noise that complicates longitudinal interpretation [66,67]. In addition, physiological signals are influenced by numerous non-disease factors, necessitating careful modeling, personalization, and contextualization to avoid false alerts. As a result, wearable-derived biomarkers are most effective when integrated with molecular or imaging data rather than used in isolation.

4.4. Implantable or Joint-Proximal Sensing Concepts

Implantable and joint-proximal sensing platforms represent emerging engineering directions aimed at bridging the gap between biological specificity and temporal resolution. By positioning sensors closer to sites of pathology, these systems seek to capture local biochemical, mechanical, or physiological signals with greater fidelity than systemic or external measurements [68]. Conceptual approaches include implantable micro-sensors, injectable sensing elements, and joint-adjacent devices capable of detecting inflammatory mediators, metabolic changes, or mechanical stress.

The potential advantage of joint-proximal sensing lies in its specificity and immediacy. Local measurements may reflect disease activity more directly and with less dilution than systemic biomarkers, offering opportunities for earlier detection of flares and more precise assessment of treatment response [69,70]. When combined with wireless data transmission and low-power operation, such platforms could support continuous or semi-continuous monitoring without repeated sampling procedures.

However, these approaches raise substantial engineering, safety, and regulatory considerations. Long-term biocompatibility, device stability, and resistance to biofouling are critical challenges, particularly in inflamed tissues. Power supply, data transmission reliability, and failure modes must be carefully addressed to ensure patient safety [71,72]. Regulatory pathways for implantable diagnostic devices are complex, and clinical acceptance depends on demonstrating clear benefit relative to procedural risk and cost.

At present, implantable and joint-proximal sensing systems remain largely investigational, but they illustrate the direction of future innovation in rheumatologic biosensing. As materials science, microelectronics, and regulatory frameworks evolve, these platforms may become viable components of hybrid measurement strategies that combine continuous local sensing with less frequent systemic or imaging-based assessments [68].

5. Signal Processing, Modeling, and Prediction in Layer 3 of the Measurement Stack

Studies in digital health and computational medicine increasingly emphasize that measurement alone is insufficient to generate clinically actionable insight. Biological signals acquired from diverse domains and platforms must be transformed into interpretable outputs that support clinical decisions. Layer 3 of the Measurement Stack addresses this transformation by focusing on signal processing, data integration, and modeling strategies that convert raw measurements into clinically meaningful inferences. In the context of inflammatory rheumatic disease, this layer is essential for bridging the gap between heterogeneous data streams and real-time disease management [19,50].

5.1. Feature Extraction and Data Integration

Biosensing platforms generate data that vary widely in scale, frequency, and reliability. Molecular assays provide sparse but information-rich snapshots, imaging delivers spatially structured data at intermittent intervals, and wearable systems produce continuous streams of indirect physiological signals. Feature extraction is the process by which these raw inputs are converted into quantitative descriptors that capture relevant aspects of disease activity while reducing dimensionality and noise [49].

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Effective feature extraction requires domain-specific considerations. For molecular data, this may involve normalization across batches, aggregation of correlated markers, or derivation of composite scores that reflect pathway-level activity. Imaging data can be transformed through radiomic features that quantify texture, intensity, and temporal change. Wearable-derived signals often require temporal summarization, trend analysis, and detection of deviations from individual baselines rather than reliance on absolute thresholds [19,44].

Data integration extends feature extraction across modalities, enabling multi-modal data fusion. Combining molecular, imaging, and physiological features can enhance sensitivity and specificity by leveraging complementary information. Integration strategies range from simple rule-based approaches to more complex statistical and machine learning models that learn relationships across data types [73,74]. Crucially, integration must preserve interpretability and align with clinical decision-making, rather than producing opaque outputs that lack actionable meaning.

A persistent challenge in real-world data integration is missingness and noise. Sensor dropout, irregular sampling, and patient non-adherence are common, particularly for longitudinal monitoring. Robust modeling frameworks must accommodate incomplete data without biasing predictions or generating spurious alerts [75,76]. Approaches such as imputation, uncertainty-aware modeling, and adaptive weighting of data sources can mitigate these issues, but they require careful validation. Addressing missingness and noise is therefore not a technical afterthought, but a central design consideration for actionable biosensing systems.

By emphasizing feature extraction and integration as foundational steps, Layer 3 reframes biosensing as a systems-level problem. The goal is not to maximize data volume, but to extract stable, interpretable features that can be reliably combined to support downstream prediction and decision-making [77].

5.2. Predictive Modeling

Predictive modeling is the core mechanism through which integrated features are translated into forward-looking clinical insight. In inflammatory rheumatic disease, the goal of modeling is not merely to classify current disease state, but to anticipate change—particularly the onset of flares, loss of treatment response, or sustained remission [19,78,79]. This requires careful alignment between model design and clinical intent.

A critical distinction in this context is between early warning models and confirmation models. Early warning models are designed to detect subtle deviations from baseline that may precede clinical deterioration, prioritizing sensitivity and lead time. These models are valuable for proactive monitoring and may trigger closer surveillance or preemptive intervention. In contrast, confirmation models aim to validate whether a suspected flare or response is occurring, emphasizing specificity and confidence over early detection [19,80,81]. Conflating these two objectives can lead to inappropriate performance expectations and clinical dissatisfaction. Clear specification of model purpose is therefore essential for actionable deployment.

Another key consideration is the choice between population-level models and personalized baselines. Population-level models leverage large datasets to identify generalizable patterns across patients, offering scalability and robustness to sparse data. However, inflammatory rheumatic diseases exhibit substantial inter-individual variability in immune tone, symptom expression, and treatment response [78,82]. Personalized models that learn from an individual's longitudinal history can better capture deviations that are clinically meaningful for that patient, even when absolute values fall within population norms. Hybrid approaches, in which population-level models provide priors that are adapted to patient-specific baselines, may offer the most practical balance [83,84].

Model evaluation must therefore extend beyond traditional accuracy metrics to include measures of clinical utility, such as lead time to flare detection, stability of predictions over time, and performance across diverse patient subgroups [85–87]. Without this alignment, even technically sophisticated models risk remaining disconnected from real-world decision-making.

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5.3. Calibration, Uncertainty, and Trust

For predictive models to influence clinical practice, their outputs must be not only accurate, but trustworthy. Calibration—the alignment between predicted probabilities and observed outcomes—is a fundamental requirement for clinical acceptance [88–90]. Poorly calibrated models may generate confident but misleading predictions, undermining clinician confidence and increasing the risk of inappropriate intervention.

Uncertainty is intrinsic to biological systems and to the data used to model them. Actionable biosensing systems must therefore communicate uncertainty explicitly rather than obscuring it. This includes accounting for measurement noise, missing data, and model limitations [88]. From a clinical perspective, understanding the degree of uncertainty associated with a prediction is as important as the prediction itself, particularly when decisions involve escalation or tapering of immunosuppressive therapy.

Managing the trade-off between false positives and false negatives is central to model design. Excessive false positives can lead to unnecessary clinic visits, imaging, or treatment escalation, increasing patient burden and healthcare costs. Conversely, false negatives risk missed flares and delayed intervention, with potential for irreversible joint damage [91–93]. The acceptable balance between these errors varies by clinical context and decision type, underscoring the need for decision-specific modeling strategies.

Defining decision thresholds that clinicians can rely on requires close integration between modeling and clinical workflows. Thresholds should be chosen based on downstream consequences, patient preferences, and resource constraints, rather than purely statistical criteria [91,94,95]. Transparent threshold selection, ongoing model monitoring, and iterative refinement are essential for sustaining trust over time.

By foregrounding calibration, uncertainty, and trust, this section emphasizes that predictive modeling in rheumatology is not an abstract computational exercise, but a decision-support function embedded within clinical care. Framing modeling in this way positions biosensing and inference as enabling technologies for better decisions, rather than as replacements for clinical judgment [96,97].

Evaluation frameworks such as cross-validation, temporal validation using forward-chaining approaches, external validation in independent cohorts, and decision-curve analysis should be systematically incorporated to ensure robustness under real-world deployment. Internal validation alone is insufficient for models intended to guide treatment decisions. Performance must be examined under temporal shift, heterogeneous clinical settings, and evolving therapeutic practices. Incorporating these validation layers strengthens generalizability, reduces overfitting, and aligns predictive modeling with real-world clinical risk management.

To further operationalize computational rigor within the Measurement Stack framework, evaluation of predictive biosensing models should extend beyond discrimination metrics alone. Models must be assessed according to decision-relevant, calibration-aware, and deployment-oriented performance criteria. Table 2 summarizes recommended computational evaluation metrics aligned with actionable clinical objectives.

Table 2. Computational Evaluation Metrics for Actionable Biosensing Models in Inflammatory Rheumatic Disease.

Modeling Objective	Recommended Metric(s)	Why It Matters Clinically
Early flare detection	Lead time to event; time-dependent AUC	Determines whether the model provides a clinically actionable window for intervention before symptom escalation
Binary classification (flare vs no flare)	Sensitivity, specificity, positive/negative predictive value	Balances false positives and false negatives according to clinical risk tolerance
Probability estimation	Calibration slope, calibration-in-the-large, Brier score	Ensures predicted risk reflects true event probability and supports clinician trust
Decision utility	Decision curve analysis; net benefit	Quantifies clinical value relative to standard care and threshold-based decision-making
Longitudinal stability	Prediction drift metrics; temporal validation performance	Prevents model degradation and over-alerting during long-term deployment
External validation	Performance across independent cohorts and care settings	Demonstrates generalizability and robustness beyond development dataset

Explicit reporting of these evaluation dimensions shifts model assessment from technical accuracy toward clinical utility. By incorporating calibration, decision analysis, temporal validation, and external generalizability, biosensing systems can be evaluated according to their real-world performance under deployment conditions rather than retrospective dataset optimization.

6. Mapping Measurements to Clinical Decisions from Biomarker to Bedside Action

The ultimate test of any biomarker or biosensing system is whether it improves a clinical decision. In inflammatory rheumatic disease, many proposed biomarkers fail not because they lack biological relevance, but because their outputs are poorly aligned with the decisions clinicians must make in real time [98–100]. A decision-centric framework reframes measurement as a means to an end: enabling specific, timely actions that alter disease trajectory and patient outcomes.

Rather than evaluating biomarkers in isolation, this framework starts with the clinical question and works backward to define the measurement requirements needed to answer it. Different decisions impose different constraints on biological domain, sensing platform, and performance characteristics. Recognizing these distinctions is essential for designing actionable measurement systems [98,100].

Early flare detection represents one of the most pressing unmet needs in rheumatology. The relevant clinical objective is not confirmation of active disease, but advance warning that disease control is deteriorating. This decision favors measurements that change before symptoms escalate and can be acquired frequently. Physiological and behavioral signals, supplemented by systemic biomarkers, are often well suited to this task due to their temporal density [19,48,101]. Required performance emphasizes lead time and sensitivity, with acceptable trade-offs in specificity if alerts trigger low-risk follow-up rather than immediate treatment escalation.

Distinguishing inflammatory flare from infection or non-inflammatory pain demands a different measurement strategy. Here, specificity is paramount, as incorrect classification can lead to

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inappropriate immunosuppression or delayed antimicrobial therapy. Joint-proximal or synovial biomarkers, point-of-care molecular assays, and imaging-derived signatures are particularly valuable in this context [102–104]. Measurement frequency may be lower, but accuracy and interpretability are critical, and cost is justified by the high stakes of the decision.

Deciding whether to switch biologic therapy or taper treatment during remission requires reliable assessment of sustained disease control. This decision benefits from integrated longitudinal trends rather than single-point measurements. Systemic biomarkers, imaging at strategic intervals, and personalized predictive models can collectively inform whether observed stability reflects true remission or masked disease activity [105–107]. Here, robustness across patient heterogeneity and low false-negative rates are prioritized, as premature tapering carries significant risk.

Monitoring treatment response without months of delay highlights the value of intermediate markers that change earlier than clinical outcomes. Point-of-care assays and laboratory-based multiplex measurements can provide early indications of therapeutic efficacy or failure, allowing adjustments before prolonged exposure to ineffective treatments [108–110]. Performance requirements emphasize responsiveness and reproducibility, while cost and invasiveness must remain compatible with repeated use during therapy transitions.

Across these scenarios, the same biomarker may be highly actionable for one decision and marginal for another. Actionability therefore emerges from alignment between the clinical question, the biological domain measured, the sensing platform employed, and the performance characteristics required [98,111]. This decision-aligned architecture is summarized in Figure 3.

Figure 3. Decision-Centric Mapping of Measurement to Clinical Action. Major clinical decisions in inflammatory rheumatic disease are mapped to their corresponding biological domains, preferred sensing

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platforms, and performance requirements. The figure illustrates that actionability depends on alignment between the clinical question, measurement source, technology platform, and decision-specific performance criteria.

This decision-centric perspective also clarifies why no single biomarker or platform can address all aspects of disease management. Instead, effective real-time care will rely on coordinated measurement systems in which different modalities are deployed strategically according to the decisions they are best equipped to support [111,112].

7. Benchmarking and Validation Standards Explaining Why Many Biomarkers Fail Translation

A recurring reason why promising biomarkers fail to influence clinical practice is not lack of biological relevance, but insufficient validation against the realities of clinical decision-making. Many studies report statistically significant associations or strong performance metrics under controlled conditions, yet provide limited information on how these biomarkers behave across heterogeneous patient populations, longitudinal timelines, and real-world clinical workflows [78,113,114]. Without standardized benchmarks and transparent reporting, it becomes difficult to determine whether a biomarker is truly actionable or merely informative.

To address this gap, several methodological considerations can be used to guide reporting standards for biomarker and biosensing studies in inflammatory rheumatic disease. These standards are not intended to constrain innovation, but to ensure that reported results can be meaningfully interpreted, compared across studies, and translated into practice. By aligning evaluation with decision-level performance rather than retrospective association alone, these benchmarks aim to accelerate clinical adoption and reduce translational failure.

First, cohort characteristics and treatment background must be reported in sufficient detail to contextualize biomarker performance. Biomarker behavior is strongly influenced by disease subtype, disease duration, comorbidities, and ongoing therapies, particularly biologic and targeted synthetic agents [115–117]. Without explicit characterization of treatment exposure and disease stage, reported performance metrics cannot be generalized or reliably reproduced across clinical settings.

Second, studies should provide explicit and reproducible definitions of clinical events, particularly disease flares. Flare definitions vary widely across studies and often combine subjective symptoms with laboratory, imaging, or physician-assessed criteria [118,119]. Ambiguity at this level undermines both internal validity and cross-study comparison, limiting the interpretability of predictive performance claims.

Third, sampling frequency and monitoring duration must be aligned with the biological and clinical processes the biomarker is intended to capture. Biomarkers proposed for early warning or real-time monitoring require frequent and sustained sampling, whereas confirmation or stratification tasks may tolerate lower temporal resolution. Reporting only aggregate or sparsely sampled data obscures whether a biomarker can realistically support the clinical decision it is proposed to inform.

Fourth, handling of missing data and measurement noise should be explicitly described. Longitudinal biosensing inevitably encounters incomplete data due to missed visits, sensor dropout, technical failure, or variable patient adherence [120–122]. Models that perform well only under complete-case assumptions are unlikely to translate into routine care. Transparent reporting of missingness patterns and mitigation strategies is therefore essential for evaluating robustness.

Fifth, calibration and external validation are essential for assessing reliability beyond the development dataset. Many biomarker and prediction models exhibit acceptable discrimination but poor calibration, leading to overconfident or misleading predictions when deployed outside controlled cohorts [88,92,95]. External validation across independent populations and care environments provides a more realistic assessment of generalizability and clinical reliability.

Finally, and most importantly, studies should report decision-level endpoints rather than relying solely on statistical performance metrics. Relevant outcomes include lead time to flare detection, reduction in cumulative steroid exposure, avoidance of unnecessary clinic visits or

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imaging, and improvements in treatment adjustment timing. These endpoints directly reflect clinical value and provide a common basis for comparing diverse biosensing and modeling approaches.

Adoption of these benchmarking standards would shift the field from fragmented proof-of-concept studies toward cumulative, comparable evidence. By emphasizing transparency, reproducibility, and decision-level relevance, these criteria recast biomarker evaluation as an engineering discipline focused on performance under real-world constraints. In doing so, they establish a foundation for actionable biosensing systems that can be reliably integrated into the management of inflammatory rheumatic disease.

To facilitate reproducibility and cross-study comparison, these benchmarking principles can be operationalized into a minimum reporting framework. **Table 3** summarizes recommended reporting domains, corresponding minimum standards, and their relevance to clinical translation. Adoption of such standards would enable consistent evaluation of biosensing systems and accelerate movement from proof-of-concept studies to decision-ready technologies.

Table 3. Minimum Benchmarking and Reporting Standards for Actionable Biosensing Systems in Inflammatory Rheumatic Disease.

Reporting Domain	Minimum Standard	Why It Matters
Cohort characteristics and treatment background	Explicit reporting of disease subtype, duration, comorbidities, and concurrent therapies	Ensures performance is interpretable and generalizable across real-world populations
Clinical event definition (e.g., flare)	Clear, reproducible definition including objective and subjective components	Enables cross-study comparison and accurate assessment of predictive validity
Sampling frequency and duration	Transparent description of monitoring intervals and follow-up period	Determines whether measurement aligns with intended decision timeline
Missing data handling	Explicit reporting of missingness patterns and mitigation strategies	Prevents biased performance estimates and improves real-world robustness
Calibration and external validation	Assessment of model calibration and validation in independent cohorts	Establishes reliability beyond development dataset
Decision-level endpoints	Reporting of clinically meaningful outcomes (lead time, steroid reduction, visit reduction)	Links statistical performance to tangible clinical benefit

8. Implementation, Regulation, and Sustainability from Prototype to Practice

Many biomarker and biosensing innovations demonstrate technical promise yet fail to progress beyond pilot studies because implementation challenges are addressed too late or not at all. Translation into routine rheumatologic care depends not only on analytical performance, but on usability, workflow compatibility, regulatory clarity, and economic viability. Addressing these dimensions explicitly is essential for moving actionable biosensing systems from prototype to practice.

Usability and patient adherence represent primary determinants of real-world performance, particularly for wearable and longitudinal monitoring systems. Devices that are uncomfortable, burdensome, or difficult to maintain are unlikely to generate reliable long-term data. Adherence

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tends to decline over time, introducing bias and missingness that can undermine predictive models [75,120,123]. Engineering design choices that prioritize passive data collection, minimal user interaction, and robust performance under variable use conditions are therefore critical for sustained clinical impact.

Successful deployment also requires seamless integration into clinical workflows. Biosensing outputs must align with how clinicians receive information, document decisions, and manage time constraints. Systems that generate excessive alerts, require manual data interpretation, or operate outside existing electronic health record infrastructures face substantial barriers to adoption [124,125]. Actionable biosensing platforms should deliver concise, interpretable outputs at clinically relevant moments, supporting rather than complicating decision-making.

Reimbursement and health economics further shape feasibility. Even highly informative measurement systems may remain unused if they lack clear reimbursement pathways or demonstrable cost-effectiveness. Payers and health systems increasingly require evidence that new diagnostic tools reduce downstream costs, such as hospitalizations, imaging utilization, or cumulative steroid exposure [125,126]. Decision-level endpoints that capture these benefits are therefore essential not only for clinical validation, but also for economic justification.

Regulatory considerations are particularly salient for biosensing systems that incorporate predictive algorithms or machine learning. Diagnostic software that influences treatment decisions may be classified as medical devices, triggering requirements for validation, post-market surveillance, and ongoing performance monitoring [127,128]. Regulatory expectations increasingly emphasize transparency, robustness to data drift, and mechanisms for updating models safely over time. Early engagement with regulatory frameworks can reduce translational friction and clarify design constraints.

Equity and access represent additional, often underappreciated dimensions of implementation. Technologies that rely on expensive devices, frequent imaging, or specialized infrastructure risk exacerbating disparities in care. Scalable, low-burden biosensing approaches may improve access for patients in resource-limited settings, particularly when paired with telemedicine and decentralized care models [129–131]. Open-access dissemination of frameworks, validation standards, and performance benchmarks further supports equitable adoption and global relevance.

Finally, sustainability considerations align biosensing innovation with broader healthcare goals. Earlier detection of disease activity and more precise treatment adjustment can reduce unnecessary imaging, clinic visits, and overtreatment, lowering both economic and environmental costs [132–134]. By shifting care from reactive to proactive management, actionable measurement systems have the potential to improve outcomes while reducing long-term resource utilization.

Together, these implementation, regulatory, and sustainability factors underscore that translation is not an afterthought, but a design requirement. Embedding these considerations early in biosensing development aligns technological innovation with clinical reality, advancing solutions that are not only effective, but adoptable and enduring.

9. Limitations of the Measurement Stack Framework

While the Measurement Stack framework provides a structured conceptual model for integrating biosensing technologies with clinical decision-making, several limitations should be acknowledged.

First, the framework is primarily conceptual rather than empirically validated. Although it synthesizes insights from biosensing research, digital health studies, and computational modeling, prospective clinical studies are required to determine whether integrated measurement architectures improve clinical outcomes in inflammatory rheumatic disease.

Second, many sensing technologies discussed in this review remain at early stages of development or translational testing. Wearable monitoring systems, implantable sensors, and multimodal predictive models show considerable promise, yet large-scale validation across diverse patient populations and healthcare environments remains limited.

Third, real-world deployment of biosensing ecosystems depends on factors extending beyond analytical performance. Regulatory approval pathways, reimbursement structures, clinician workflow integration, and patient adherence may substantially influence adoption and long-term sustainability of these technologies.

Finally, predictive modeling approaches depend heavily on data availability and quality. Longitudinal biosensing systems frequently encounter missing data, sensor dropout, and variability in patient engagement, which can influence model performance and generalizability.

Future work should therefore focus on prospective clinical implementation studies that evaluate how layered biosensing architectures perform under real-world conditions, including their effects on clinical decision-making, patient outcomes, and healthcare system efficiency.

10. Future Directions Toward Integrated Biosensing Ecosystems

The next phase of progress in inflammatory rheumatic disease management will be driven by integration rather than replacement. Single biomarkers or isolated sensing platforms are unlikely to meet the diverse temporal and decision-specific demands of clinical care. Instead, future systems will combine complementary measurement modalities into coordinated biosensing ecosystems that balance specificity, frequency, and practicality. This integrated architecture is illustrated in Figure 4.

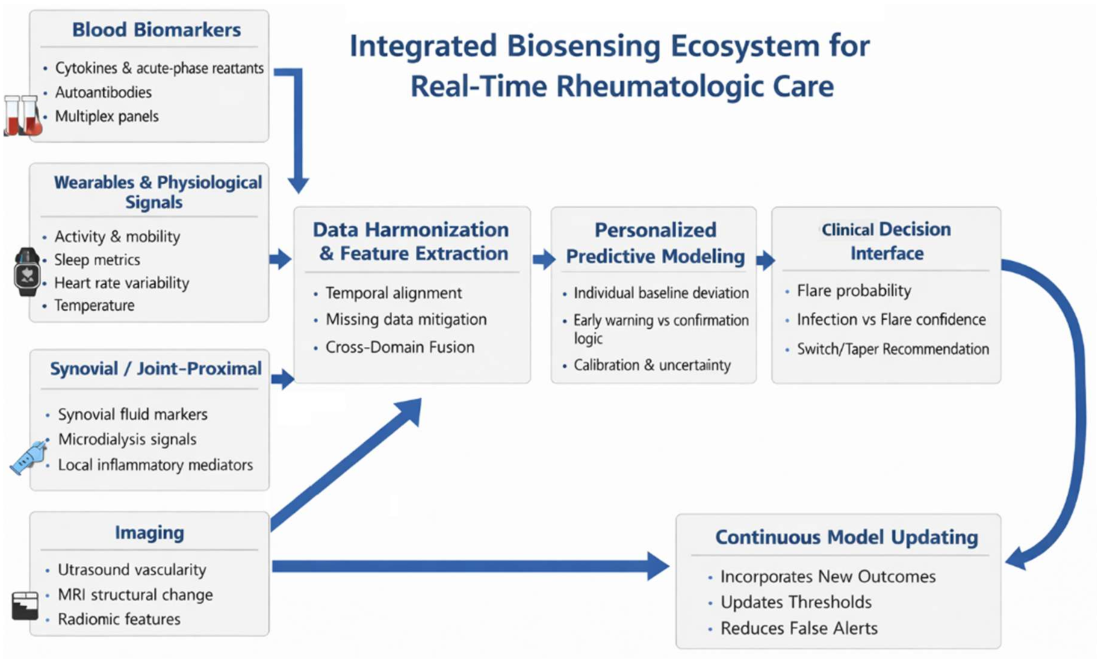

Figure 4. Systems-Level Architecture of an Integrated Biosensing Ecosystem for Real-Time Rheumatologic Care. The diagram illustrates coordinated integration of multi-domain biological inputs—including systemic blood biomarkers, wearable-derived physiological signals, synovial or joint-proximal measurements, and imaging-derived features—into a unified data harmonization and feature extraction layer. These processed features feed personalized predictive modeling that estimates flare probability, differentiates inflammatory flare from infection, and supports therapy adjustment decisions. A clinical decision interface translates model outputs into actionable recommendations. Continuous model updating incorporates longitudinal outcomes to recalibrate thresholds, reduce false alerts, and improve performance over time, reflecting an adaptive, learning healthcare system.

One promising direction is the development of hybrid monitoring systems that integrate systemic blood-based biomarkers with continuous wearable signals and intermittent synovial or joint-proximal measurements. Such systems can leverage the scalability and low burden of frequent physiological sensing while anchoring interpretation with higher-specificity molecular or imaging

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inputs [19,125,135]. Hybrid designs enable flexible deployment, reserving invasive or costly measurements for moments when uncertainty is highest or decisions carry greater risk.

Another critical advance will be the adoption of patient-specific baselines. Inflammatory rheumatic diseases exhibit substantial inter-individual variability in immune tone, symptom expression, and treatment response. Rather than relying solely on population-derived thresholds, future biosensing platforms will increasingly model deviations from an individual's longitudinal baseline to identify clinically meaningful change [19,125,136]. Personalization enhances sensitivity to early deterioration and reduces false alarms driven by stable inter-patient differences.

AI-assisted clinical decision support is likely to play a central role in operationalizing integrated measurement. Machine learning and statistical inference methods can synthesize heterogeneous data streams, estimate uncertainty, and present concise recommendations aligned with clinical workflows. Importantly, successful decision-support systems will emphasize transparency, calibration, and human interpretability rather than opaque automation, reinforcing clinician trust [12,79,137].

Realizing these advances will require sustained industry–clinic collaboration. Engineering innovation benefits from early exposure to clinical constraints, while clinical adoption depends on solutions that are robust, interoperable, and economically viable. Partnerships between device developers, data scientists, clinicians, and health systems can accelerate validation, clarify regulatory pathways, and align technology development with real-world needs [14,138].

Taken together, these directions point toward biosensing ecosystems that are modular, adaptive, and clinically grounded. By integrating multiple measurement domains, personalizing interpretation, and embedding inference within care pathways, future systems can move beyond episodic monitoring toward truly proactive management of inflammatory rheumatic disease. Over the next decade, progress in rheumatologic care is likely to be driven less by the discovery of new therapeutic targets than by the ability to sense, interpret, and act on disease dynamics in real time.

11. Conclusions: Measurement Is the Next Therapeutic Frontier

Therapeutic options for inflammatory rheumatic disease have expanded substantially over the past two decades, with targeted biologic and small-molecule agents offering unprecedented control of immune-mediated pathology. Yet improved therapies alone have not eliminated disease flares, treatment failure, or long-term tissue damage. As this review has argued, the limiting factor in contemporary care is increasingly how disease activity is measured, interpreted, and acted upon, rather than the availability of effective treatments.

Without real-time, actionable measurement, even the most potent therapies are deployed reactively and imprecisely. Episodic assessments, delayed biomarkers, and coarse composite scores fail to capture the dynamic nature of inflammatory disease, leading to late intervention, unnecessary treatment escalation, or prolonged exposure to ineffective regimens. These limitations reflect a measurement gap rather than a therapeutic one.

Advances in biomedical engineering increasingly provide practical approaches for addressing this measurement gap. By integrating biosensing platforms, data processing, and decision-support systems, engineering approaches can transform biological signals into timely and reliable clinical insight. Taken together, the evidence reviewed here highlights the importance of aligning biological measurement domains, sensing technologies, and computational inference with specific clinical decisions.

Advancing from prototype to practice will require continued focus on validation standards, implementation realities, and sustainability. However, the convergence of sensing technologies, computational modeling, and clinical need creates a timely opportunity to redefine disease management. By prioritizing actionable measurement as a core component of care, biomedical engineering may help shift rheumatology from reactive disease control toward proactive, precise, and enduring management. In this sense, the next major advance in rheumatology may arise not from discovering entirely new therapies, but from developing measurement systems capable of sensing disease dynamics early enough to deploy existing treatments with true precision.

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Abbreviations

RA – Rheumatoid arthritis
MRI – Magnetic resonance imaging
AI – Artificial intelligence
AUC – Area under the curve
CRP – C-reactive protein
EHR – Electronic health record
ESR – Erythrocyte sedimentation rate
DMARD – Disease-modifying antirheumatic drug

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