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Short Communication

Improving pharmacoeconomic evidence of therapeutic drug monitoring for chronic inflammatory diseases across Europe

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Abstract

This manuscript aims to present the authors' position on the current evidence and identify key gaps in the pharmacoeconomic evaluation of therapeutic drug monitoring (TDM) for chronic inflammatory diseases (CIDs) across Europe. Specifically, it will address: (i) the clinical effectiveness and safety of TDM for pharmacoeconomic evaluation; (ii) available comparative analyses of TDM and their potential use in economic analyses; (iii) existing cost-effectiveness analyses (CEAs) of TDM; and (iv) budget impact analyses. By synthesizing these dimensions, the manuscript seeks to provide a foundation for more consistent, transparent, and policy-relevant economic evidence to support the implementation of TDM within European healthcare systems.

TDM can guide dose adjustment, continuation or discontinuation, changes to concomitant therapy, and next-line selection. To rationalize the use of high-cost biologics and improve access in low- and middle-income countries, TDM is policy-relevant, yet published CEAs are largely limited to older TNF-α inhibitors (mainly infliximab and adalimumab) and high-income settings. Available CEAs have also applied TDM inconsistently and assumed various direct effects, reflecting limited clinical certainty. Future work should standardize TDM algorithms, use comparative designs, include comprehensive costing, extend beyond TNF-α agents, and prioritize studies in low- and middle-income countries.

Keywords

Budget impact analysis, cost-effectiveness, pharmacoeconomic, therapeutic drug monitoring

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PENSOFT

Introduction

Chronic inflammatory diseases (CIDs), including conditions such as inflammatory bowel disease (IBD), rheumatoid arthritis, and psoriasis, represent a substantial clinical and economic burden across Europe (Anderson and Szefler 2019; Van Linschoten et al. 2021; Zhao et al. 2021). The increasing use of biologic therapies has markedly improved patient outcomes; however, variability in treatment response, drug exposure, and long-term effectiveness continues to challenge healthcare systems (Mamasaidov et al. 2025). In this context, therapeutic drug monitoring (TDM) has emerged as a promising strategy to optimize treatment by tailoring drug dosing to individual patient needs, thus aligning with the broader paradigm of personalized medicine (Peyrin-Biroulet et al. 2015). TDM is a significant advancement in the precise management of CIDs. By aligning biologic dosing with individual pharmacokinetic and pharmacodynamic variability, TDM has the potential to improve clinical effectiveness by promoting sustained remission, reducing loss of response, and shortening hospitalizations. TDM also improves safety by reducing adverse drug reactions, immunogenicity, and avoidable overexposure (Imamura 2019). These clinical gains directly translate into pharmacoeconomic value by reducing biologic drug expenditure, preventing costly treatment switches, and lowering healthcare utilization. Therefore, integrating TDM into routine care supports the sustainable, value-based use of biologic therapy, reinforcing its dual role as a clinical and economic optimization tool in the management of CIDs (Tachkov et al. 2023).

Despite growing clinical interest, the pharmacoeconomic evidence supporting TDM in CIDs remains fragmented and insufficiently robust. One of the key limitations is the lack of comparative studies directly evaluating patients managed with TDM versus those receiving standard, non-TDM care. This gap hampers the ability to generate consistent and generalizable economic conclusions, particularly for decision-makers who require comparative effectiveness and cost evidence to inform reimbursement and policy decisions (Pillai et al. 2017).

Given these challenges, there is an increasing need to incorporate comprehensive economic evaluation methods, including cost-effectiveness analysis (CEA) and budget impact analysis (BIA), into the assessment of TDM in CIDs. In particular, BIAs are essential for understanding the short- to medium-term financial consequences of implementing TDM at the healthcare system level (Ghabri and Mauskopf 2018). Moreover, beyond direct costs, it is critical to demonstrate that optimized treatment strategies contribute to improved productivity and health-related quality of life, thereby capturing the broader societal value of personalized approaches.

This manuscript aims to present the authors' position on the current evidence and identify key gaps in the pharmacoeconomic evaluation of TDM for CIDs across Europe. Specifically, it will address: (i) the clinical effectiveness and safety of TDM for pharmacoeconomic evaluation; (ii) available comparative analyses of TDM and their potential use in economic analyses; (iii) existing CEAs of TDM; and (iv) BIAs. By synthesizing these dimensions, the manuscript seeks to provide a foundation for more consistent, transparent, and policy-relevant economic evidence to support the implementation of TDM within European healthcare systems.

Clinical effectiveness and safety of TDM for pharmacoeconomic evaluation

TDM aims to individualize biologic therapy by maintaining serum drug concentrations within an optimal therapeutic window, balancing efficacy and safety. In theory, this approach could enhance therapeutic outcomes by accounting for interindividual variability in pharmacokinetics and pharmacodynamics—an especially relevant consideration in CIDs (Papamichael et al. 2023).

An important distinction should be made between reactive and proactive TDM. Reactive TDM is generally performed in response to loss of response, adverse events, or clinical uncertainty, whereas proactive TDM is applied at predefined intervals to prevent underexposure, overexposure, or immunogenicity. These strategies differ in clinical rationale, testing frequency, resource use, and expected economic consequences; therefore, they should not be treated as interchangeable in economic evaluations.

While the rationale for TDM in biologic therapy is well established, robust clinical evidence demonstrating clear benefits across CIDs remains limited and inconsistent. Associations have been observed between subtherapeutic drug levels, secondary loss of response (LOR), and immunogenicity; however, whether proactive TDM improves long-term outcomes compared with standard clinical management remains uncertain (Freeman et al. 2016).

Among available studies, evidence from IBD—particularly for TNF-α inhibitors—suggests potential benefits. The TAXIT trial reported numerically higher remission rates with proactive infliximab TDM (69%) versus empiric management (58%), although the difference was not statistically significant, and reduced unnecessary dose escalation (Vande Casteele et al. 2015). The primary outcome of TAXIT was not met because there was no statistically significant difference in clinical and biochemical remission rates at 54 weeks between the proactive TDM arm and the conventional arm. The authors consider that the design made it difficult to directly compare a proactive-only strategy with a reactive-only strategy. Similarly, in pediatric Crohn's disease, the PAILOT trial showed higher steroid-free remission rates with proactive adalimumab TDM compared with reactive monitoring (Assa et al. 2019). Nevertheless, these findings have not been consistently replicated in broader CID populations, and the strength of evidence remains moderate at best.

Proposed therapeutic thresholds, such as infliximab trough levels of 5–10 μg/mL or adalimumab levels above 7–8 μg/mL, have been derived largely from observational studies, and their applicability outside IBD is unclear (Papamichael and Cheifetz 2021). For newer biologics, including vedolizumab and ustekinumab, exposure–response relationships have been reported (Chaar et al. 2023), yet the clinical utility of applying fixed concentration targets through TDM has not been validated in randomized trials.

The suggested benefits of TDM—such as reduced hospitalizations, corticosteroid use, and surgical interventions—are based primarily on retrospective or real-world analyses, many of which are confounded by disease severity, treatment adherence, and local practice variations (Dreesen et al. 2019; Papamichael et al. 2019). Evidence that TDM directly enhances disease control or improves safety in CIDs as a class remains largely inferential rather than causal.

Although TDM could theoretically improve safety by preventing overexposure and underexposure to biologics, data confirming reduced adverse events are not definitive.

TDM may have particular relevance in subpopulations with altered pharmacokinetics, such as pediatric or older patients and those with organ dysfunction (Negoescu et al. 2020). However, even in these groups, evidence supporting routine proactive monitoring remains insufficient, and existing studies are often small or limited to specific biologics. Further studies are needed to distinguish the specific adverse outcomes affected by TDM.

From an economic standpoint, TDM has been proposed as a cost-saving strategy through optimization of biologic dosing and prevention of overtreatment. While models and some real-world analyses suggest potential savings (Roblin et al. 2015; Vande Casteele et al. 2015; Dreesen et al. 2019), these conclusions depend heavily on assumptions regarding test costs, assay accuracy, and the frequency of dose adjustments. Moreover, most pharmacoeconomic evaluations are restricted to TNF-α inhibitor therapy in IBD, limiting their generalizability to other CIDs.

Future developments, including model-informed precision dosing (MIPD) and point-of-care assays, may enhance the feasibility and real-time utility of TDM (Maier et al. 2021). However, until high-quality evidence confirms clear clinical and cost advantages, the role of TDM in CID management should be considered exploratory and applied selectively, guided by individual clinical context rather than as a standard of care. As the use of biologics expands across CIDs, the implementation of TDM-based treatment algorithms will likely become increasingly important for balancing therapeutic success with economic sustainability.

Available comparative analyses of TDM and their potential use in pharmacoeconomic analyses

Economic analyses compare the costs and results of available healthcare alternatives to inform decision-makers when selecting cost-effective alternatives and increasing the efficient use of healthcare resources (Drummond et al. 2015). There are many ways and criteria to estimate the "most efficient alternative" in a given context, e.g., the cheapest alternative, the most frequently used alternative, the most effective alternative, or the first-line recommendation in clinical guidelines (Kozma et al. 1993).

For the purposes of comparative analyses, the alternatives being compared are new (or innovative) technologies, products, or processes versus the closest alternatives in terms of results or efficacy (Ramsey et al. 2015). These are typically framed as "new" vs. "standard of care." In the case of TDM, when considering clinical outcomes, this framing allows the comparison to be grouped in terms of "application of TDM vs. non-application" (Kang and Lee 2009). Such a comparison will help evaluate the value added by TDM in monitoring medicine effectiveness or improving treatment efficacy.

In the era of biologic therapy and precision medicine, monitoring plasma levels seems to be of great importance because of the complexity of biologic medicines and the development of antidrug antibodies, which can compromise treatment results and increase costs (Smolen et al. 2023). Therefore, the importance of TDM increases alongside the need for comparative studies of TDM for the purpose of economic evaluation. The comparison here should be between the TDM and non-TDM groups.

In the classic NOR-DRUM trial, proactive TDM was compared with therapy without TDM (Syversen et al. 2021). The effectiveness of both approaches was compared during maintenance infliximab therapy in patients with CIDs. Proactive TDM was found to lead to sustained disease control over 52 weeks. A subsequent CEA was performed based on the results of the NOR-DRUM trial (Holly et al. 2025). Proactive TDM was a cost-effective treatment strategy compared with the strategy without TDM. The results of both studies led to the inclusion of proactive TDM in a clinical guideline to inform future treatment (Kawano-Dourado et al. 2024).

In a study by Gómez-Arango et al. (2021), adalimumab doses were tapered based on drug peak and trough levels during the treatment of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). The alternative for comparison was the standard of care. Both alternatives followed treatment guidelines. In addition to an improvement in clinical results, adalimumab dose tapering based on TDM improved the quality of life (QoL) of patients and proved to be cost-effective due to a reduction in direct medical costs in patients with stable disease. Dose tapering compared with non-tapering as a treatment approach was used in a study by Bastida et al. (2020) and compared with currently used empirical doses for RA treatment with tocilizumab. Precision dosing was achieved through dose tapering and led to cost savings. A testing strategy for patients who failed to respond to infliximab therapy was modeled and compared with empiric dose escalation (Velayos et al. 2013). The model confirmed the cost-effectiveness of the testing strategy due to its lower cost.

Proactive TDM based on pharmacokinetic modeling was used to personalize biologic medicine dosing in adult patients with Crohn's disease initiating infliximab therapy (Alizadeh et al. 2024). The alternatives for comparison were two dosing strategies: dose intensification based on symptoms, inflammatory markers, and infliximab concentration; and dose intensification based on symptoms alone. Proactive precision-guided TDM was estimated to be the most cost-effective therapy, providing clinical and QoL benefits by bringing patients into remission and avoiding treatment failure. These results were confirmed in a pediatric trial with adalimumab in which proactive TDM was compared with reactive TDM for Crohn's disease (Yao et al. 2021). Proactive TDM yielded more quality-adjusted life years (QALYs) at a lower cost to the healthcare system. In contrast, an earlier study for the same diagnosis, comparing proactive TDM with reactive TDM with dose escalation, found that the cost of infliximab should be reduced to give credence to the claim that the proactive monitoring strategy was more cost-effective (Negoescu et al. 2020). Finally, Dupenloup et al. (2025) conducted a comparative analysis of reactive TDM after proactive TDM in patients with ulcerative colitis receiving infliximab. The authors compared several alternatives, such as proactive TDM, reactive TDM, no TDM, and combinations of proactive and reactive TDM. It appears that 1 year of proactive TDM followed by reactive TDM is cost-effective for these patients.

Cost savings were reported when comparing TDM-guided dose de-escalation versus no de-escalation of infliximab doses in patients with Crohn's disease during the entire course of therapy (Attar et al. 2019). The model was tested in four different dosing cohorts, and the calculated savings amounted to more than €39 million. Similarly, Roblin et al. (2015) modeled the switch to another biologic therapy after loss of response. The two alternatives were a test-based strategy to determine anti-infliximab (anti-IFX) antibodies and empirical dose escalation over a period of 5 years. According to the results, the test-based strategy appears to be cost-saving due to the reduced cost of medicine therapy. TDM tests had no impact on the cost.

Other state-of-the-art approaches combine single measurements of drug levels with model-derived estimates to account for individual variability, the so-called MIPD. This approach has further potential to limit costs and improve the practicality of TDM. Minichmayr et al. (2024) reviewed how a single pharmacokinetic (PK) or pharmacodynamic (PD) measurement, when combined with patient-specific covariates and a population model, can be used for Bayesian forecasting. By introducing machine learning elements, these models become even more precise than the Bayesian estimates. The current tools available are considered sufficient to improve patient care. The question remains: which of them offers the best ratio of clinical outcomes to costs while also being easy to use?

Evidence is derived from heterogeneous sources, including randomized trials, observational studies, and model-based analyses, which should be considered when interpreting conclusions.

In summary, the comparative studies employ the following comparators:

- Dose tapering based on TDM vs. standard of care;
- Dose tapering based on TDM vs. currently used empirical doses;
- Proactive TDM based on pharmacokinetic modeling vs. two dosing strategies—dose intensification based on symptoms, inflammatory markers, and infliximab concentration; and dose intensification based on symptoms alone;
- Proactive TDM vs. reactive TDM;
- Proactive TDM vs. reactive TDM with dose escalation;
- Reactive after proactive TDM;
- TDM-guided dose de-escalation vs. no de-escalation;
- Test-based strategies vs. empirical dose escalation; and
- Single measurements of drug levels vs. model-derived estimates using MIPD.

Comparative studies generally support the potential pharmacoeconomic value of TDM for a variety of diagnoses, patient groups, and treatment strategies. The available evidence suggests that TDM may provide pharmacoeconomic value in selected populations and settings based on selected modeling studies. To enlarge the body of evidence, authors should organize observational or clinical trials according to patient, intervention, comparator, and outcome (PICO) elements. Patients with inflammatory diseases (P) receiving biologic or precision medicine therapy (I), evaluated through TDM with or without monitoring (C), with changes in treatment outcomes or QoL (O), seem to provide an ideal description of suitable studies. To be usable for the purposes of economic analyses, studies should collect information on the healthcare and non-healthcare resources used, monitoring costs, and treatment guidelines.

More studies comparing strategies with TDM vs. non-TDM are still needed from both clinical and economic perspectives, especially for precision medicines. Bearing in mind the high cost of precision medicines and the narrow group of potentially suitable patients, TDM might not only improve treatment results but also reduce costs for the healthcare system and society.

Cost-effectiveness of TDM for biologic treatment in inflammatory diseases

CEA helps determine whether a new intervention provides sufficient additional value in relation to the resources required to implement it. In healthcare systems with limited budgets, economic evaluation supports decision-making by identifying interventions that may improve health outcomes, reduce unnecessary costs, or use

available resources more efficiently (Russell et al. 1996). For technologies such as TDM, CEA is particularly relevant because the clinical benefit may arise not only from improved disease control but also from more efficient use of expensive biologic treatments, avoidance of ineffective therapy, dose optimization, reduced adverse events, and better selection of subsequent treatment. Therefore, economic evaluation provides a framework for assessing whether TDM-guided decisions are likely to be clinically useful and economically justified in routine care (Husereau et al. 2022).

A cost-effectiveness metric does not appraise or assign a value to life; it simply provides a basis for judging and selecting the therapy likely to make the most efficient use of current resources.

The estimated value of TDM may differ substantially depending on the analytic perspective adopted. From a payer or healthcare system perspective, the main drivers are drug acquisition costs, assay costs, administration costs, hospitalizations, treatment switching, and management of adverse events. From a societal perspective, additional elements such as productivity loss, absenteeism, caregiver burden, and patient time costs may become relevant. Future studies should clearly define the adopted perspective and justify which cost categories are included.

Systematic reviews on TDM cost-effectiveness (2021–2024)

Systematic reviews of CEAs of TDM published from 2021 to 2024 suggested that the TDM approach may be cost-effective or even dominant in some settings; however, the evidence was sparse and sometimes contradictory (Yao et al. 2021; Marquez-Megias et al. 2022; Dong et al. 2023; Tachkov et al. 2023; Zeraatkar et al. 2024). Studies in IBD and rheumatic diseases, focused mainly on TNF-α inhibitors, especially infliximab, reported that TDM generally appears cost-saving vs. empirical escalation and is often cost-effective, although formal CEAs remain few and heterogeneous. Clinically, TDM improves target attainment and can lower disease activity; proactive use during maintenance may support dose optimization, including tapering or discontinuation, without a higher relapse risk. However, effects on remission, radiographic progression, safety, and quality of life are small, mixed, or uncertain, with low-certainty ratings in some syntheses. Overall, the reviews concluded that TDM is promising for value and outcome optimization, but stronger trials and more robust model-based economic evaluations are still needed.

Cost-effectiveness analyses of TDM

Most available CEAs originate from high-income countries, particularly the US (Velayos et al. 2013; Negoescu et al. 2020; Yao et al. 2021; Dong et al. 2023; Alizadeh et al. 2024; Dupenloup et al. 2025), the UK (Krieckaert et al. 2015; Gavan 2017), the Netherlands (Hu et al. 2024), or Spain (Gómez-Arango et al. 2021).

CEAs focused on patients receiving maintenance treatment (post-induction responders) (Krieckaert et al. 2012; Krieckaert et al. 2015; Gavan 2017; Negoescu et al. 2020; Gómez-Arango et al. 2021; Tikhonova et al. 2021; Yao et al. 2021; Alizadeh et al. 2024; Dupenloup et al. 2025), patients with LOR (Velayos et al. 2013), or both (Freeman et al. 2016). Regarding the therapeutic area, five CEAs focused on Crohn's disease (Velayos et al. 2013; Freeman et al. 2016; Negoescu et al. 2020; Yao et al. 2021; Alizadeh et al. 2024), one on ulcerative colitis (Dupenloup et al. 2025), three on rheumatoid arthritis (Gavan 2017; Tikhonova et al. 2021; Krieckaert et al. 2023), and one study involved patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis combined (Gómez-Arango et al. 2021).

All CEAs focused on TDM for TNF-α inhibitors: infliximab (Velayos et al. 2013; Freeman et al. 2016; Negoescu et al. 2020; Alizadeh et al. 2024; Dupenloup et al. 2025) or adalimumab (Krieckaert et al. 2012; Krieckaert et al. 2015; Gavan 2017; Gómez-Arango et al. 2021; Tikhonova et al. 2021; Yao et al. 2021). In most CEAs, TDM measured both drug levels and antidrug antibodies, except for one study with drug-level TDM only (Alizadeh et al. 2024).

Six CEAs were sourced from controlled clinical studies in Crohn's disease maintenance (Negoescu et al. 2020; Yao et al. 2021; Dong et al. 2023; Alizadeh et al. 2024; Dupenloup et al. 2025) or rheumatoid arthritis maintenance (Krieckaert et al. 2015; Gómez-Arango et al. 2021). However, other CEAs relied on less robust sources, including expert opinion, assumptions, single-arm retrospective or prospective studies with TDM (Velayos et al. 2013; Hu et al. 2024), and studies that did not include TDM-guided treatment decisions (Krieckaert et al. 2012).

Using TDM was dominant (less costly and more effective) over usual care (Yao et al. 2021; Alizadeh et al. 2024), reactive-only strategies (Velayos et al. 2013; Gavan 2017; Negoescu et al. 2020; Gómez-Arango et al. 2021), or was cost-effective (Freeman et al. 2016; Gavan 2017; Tikhonova et al. 2021) in most CEAs. A few CEAs indicated that TDM was dominated (Tikhonova et al. 2021) or not cost-effective (Freeman et al. 2016; Dupenloup et al. 2025) compared with usual care. Proactive TDM was dominant over reactive TDM in one study (Yao et al. 2021) but was not cost-effective in others (Negoescu et al. 2020; Dupenloup et al. 2025).

Therefore, conclusions regarding the economic superiority of TDM should be interpreted as context-dependent rather than definitive.

Six CEAs indicated cost savings associated with the assessed TDM approach (Krieckaert et al. 2012; Velayos et al. 2013; Freeman et al. 2016; Gómez-Arango et al. 2021; Yao et al. 2021; Alizadeh et al. 2024), two indicated increased costs (Tikhonova et al. 2021; Dupenloup et al. 2025), and two indicated mixed results depending on the assessed strategy or variant (Gavan 2017; Negoescu et al. 2020).

Among the most reliable CEAs sourced from controlled studies (Krieckaert et al. 2015; Negoescu et al. 2020; Gómez-Arango et al. 2021; Yao et al. 2021; Dong et al. 2023; Alizadeh et al. 2024; Dupenloup et al. 2025), most indicated that the TDM approach was cost-effective compared with usual care; however, contradictory results were still observed. For example, a model-based evaluation based on the preliminary results of the controlled pragmatic INGEBIO trial indicated that the TDM approach was not cost-effective compared with usual care (Krieckaert et al. 2015), while a later-published CEA conducted alongside the INGEBIO trial indicated that TDM dominated usual care (Gómez-Arango et al. 2021).

The health outcomes of the included CEAs also varied substantially. Quality-adjusted life years (QALYs) gained with the introduction of TDM ranged from –0.31 (a decrease vs. no TDM [Krieckaert et al. 2012]) to 0.29 (an increase with proactive TDM vs. no TDM [Dupenloup et al. 2025]). However, most CEAs indicated little or no impact of TDM on QALYs.

Overview of BIA studies on TDM and personalized dosing

BIA is fundamental for public planning at the regional or national level. BIA can be seen as a complementary tool rather than a substitute for CEA (Sullivan et al. 2014; Ghabri and Mauskopf 2018). While cost-effectiveness indicates whether a new treatment or procedure is efficient compared with an existing one, BIA provides information on the yearly funding necessary to implement it. A new treatment can be cost-effective compared with an existing one because, despite increasing costs, it provides relevant benefits to patients. This does not automatically imply that a government should adopt it because it may require substantial resources for implementation. To this extent, BIA provides significant information on the adoptability of new treatments or procedures (Benucci et al. 2009; Watts 2023; Yi et al. 2025).

Cost-effectiveness does not guarantee affordability, and interventions may be rejected if their budget impact is excessive. Evidence indicates that decision-making should integrate cost-effectiveness, budget impact, and feasibility to ensure sustainable resource allocation (Groenland et al. 2022).

BIA represents an appropriate method to help governments decide whether to invest in TDM to treat CIDs. This method complements CEA by assessing affordability from the payer's perspective. While TDM may be cost-effective, large-scale implementation can strain health budgets. It builds on CEA by extrapolating per-person cost differences to the target population and then distributing total costs across payers (taxpayers or insurance members). Conducted from the payer's perspective, BIA uses a short time horizon, generally 1–3 years, aligned with budgeting cycles, avoids discounting, and accounts for uncertainties related to evolving technologies and demographic changes. BIA informs budgeting and planning by clarifying both financial feasibility and resource allocation (O'Mahony 2015).

Budget impact models are often developed to quantify the financial consequences of introducing lower-cost alternatives, such as biosimilars, into established treatment pathways. The budget impact of dose optimization through TDM might result from reduced drug wastage, fewer adverse events, shorter hospital stays, and less treatment switching or dose escalation. Under a fixed budget constraint, a structured approach is needed to ensure that:

- Total costs remain within the budget constraint;
- Interventions are ranked by the incremental cost-effectiveness ratio (ICER) or net monetary benefit (NMB);
- The threshold ICER is defined by the marginal funded intervention; and
- Adoption occurs only if the intervention is cost-effective and affordable within the budget.

TDM-guided dosing preserves clinical effectiveness while enabling dose reduction or interval adjustment. This strategy lowers direct healthcare costs. For high-cost biologics, TDM achieves budget savings through dose tapering without compromising efficacy (Gómez-Arango et al. 2021). TDM mitigates both overexposure, which increases toxicity and healthcare costs, and underexposure, which risks treatment failure and associated costs. A large study demonstrated that pharmacokinetically guided TDM reduced underexposure by approximately 39%, thereby enhancing treatment efficiency (Tikhonova et al. 2021). TDM-guided TNF-α inhibitor therapy was associated with higher rates of low disease activity and reduced relapse risk, with potential cost savings compared with empirically guided management in rheumatic diseases. However, no differences were observed in remission rates or several other outcomes (Tachkov et al. 2023). In summary, TDM-guided dosing can be economically favorable when drug costs are high, exposure variability is significant, and the clinical consequences of misdosing are costly.

Although these studies were not TDM-based, they illustrate how budget impact modeling is used to evaluate biologic treatment strategies and affordability.

Mirikizumab, an interleukin-23 p19 antagonist for the treatment of moderately to severely active ulcerative colitis (UC), was evaluated using a *de novo* budget impact model developed from a US commercial payer perspective to estimate the financial implications of its formulary introduction over a 3-year horizon. The model, applied to a hypothetical 1-million-member health plan, incorporated epidemiological inputs from published sources, market share projections informed by market research, and costs related to drug acquisition, administration, monitoring, and adverse event management, with discontinuation and dose-escalation rates derived from the literature. Scenario analyses indicated potential cost savings when mirikizumab substituted exclusively for ustekinumab, and deterministic sensitivity analyses

confirmed the robustness of base-case findings to parameter uncertainty (Stargardter et al. 2024).

TDM, which measures drug and antidrug antibody levels to guide treatment adjustments, has been linked to improved outcomes in patients with IBD receiving infliximab (IFX). A probabilistic simulation model estimated the incremental per-member-per-year budget impact of proactive TDM in the US in 2021 compared with reactive TDM and empiric dosing. The model simulated 161,781 IFX-treated patients over 2 years, with proactive TDM scheduled biannually, reactive TDM triggered by relapse, and no testing in the empiric scenario. Inputs were derived from published evidence, clinician interviews, and cost data updated to 2021. Findings indicated that proactive TDM generated average annual savings of $5,520 per member per year vs. reactive TDM and $9,229 per member per year vs. empiric dosing; despite higher monitoring and drug costs, savings were primarily obtained through reduced IBD-related healthcare utilization. These results suggest that proactive TDM can deliver net savings by optimizing dosing, reducing complications, and minimizing waste (Yi et al. 2025).

A BIA of baricitinib for rheumatoid arthritis (RA) management in Saudi Arabia applied models over 5 years. Patients were stratified by inadequate response to conventional synthetic DMARDs (csDMARDs), inadequate response to TNF-α inhibitor therapies, and the combined population. Inputs included drug acquisition, administration, and monitoring costs, with baricitinib market share assumed to be drawn equally from all comparators. Results showed net budget reductions in csDMARD-inadequate responders and in the overall population across all sectors, driven by lower administration and monitoring costs, while modest increases were observed in the TNF-α inhibitor-experienced group (Almodaimegh et al. 2020).

Similarly, a BIA in Italy assessed the introduction of rituximab (RTX) for rheumatoid arthritis patients eligible for second-line biologic therapy after TNF-α inhibitor failure. Using a Markov cohort simulation with 1-year cycles over 5 years, seven treatment sequences involving TNF-α inhibitors, RTX, and abatacept were compared. Direct medical costs, including drug acquisition, administration, premedication, and monitoring, were considered. Approximately 650 patients were eligible annually. Results demonstrated that adopting RTX as a second-line option yielded substantial savings compared with later-line use or exclusive reliance on TNF-α inhibitor therapies, reducing total costs by 33% at year 5. Early incorporation of RTX also increased patient-years on active biologic therapy per unit cost, underscoring improved efficiency and budgetary performance (Stargardter et al. 2024).

Finally, BIA has been applied to assess affordability and resource allocation, with several studies highlighting both barriers and enablers to implementation. In Finland, Purmonen et al. (2019) compared secukinumab, the first non-TNF-α biologic for AS, with adalimumab. Using a payer perspective and indirect comparisons of response rates, the model projected potential savings of €18.2 million over 5 years if patients switched to secukinumab. A BIA of proactive TDM was performed for IBD treatment with infliximab in the US setting (Dervieux et al. 2023). The results suggest that proactive TDM strategies in the US may be associated with 1-year savings compared with reactive TDM and empiric dosing.

Discussion

In this position paper, the available evidence that could be used in pharmacoeconomic evaluations of TDM was examined. The paper considered the necessary evidence on the clinical effectiveness and safety of TDM as a basis for pharmacoeconomic evaluation; available comparative analyses of TDM and their potential use in economic analyses; existing CEAs of TDM; and BIAs.

Available evidence indicates that personalized medicine approaches, including TDM, offer the potential to optimize dosing strategies by reducing over- or undertreatment. By identifying the minimum effective dose for individual patients, TDM may decrease overall drug consumption and associated pharmaceutical costs while maintaining or improving therapeutic outcomes. However, the extent to which these potential savings translate into measurable economic benefits across different healthcare systems in Europe has not been consistently demonstrated.

The available evidence indicates that neither comparative analyses nor CEAs are sufficient to build the necessary body of evidence, although TDM appears to be a cost-effective strategy, especially in CIDs.

The economic evidence on TDM is constrained by substantial heterogeneity in diseases, biologic agents, TDM approaches, outcome definitions, economic perspectives, and time horizons, which limits comparability across studies and precludes robust quantitative synthesis. Most published analyses relate to older TNF-α inhibitors in high-income settings; model-based evaluations often rely on weakly supported assumptions about the causal effects of TDM and cost inputs, and observational studies are vulnerable to confounding, selection bias, and secular trends. Reporting of cost data, model structure, parameter sources, and TDM implementation pathways is also frequently incomplete.

Overall, existing CEAs suggest that TDM may reduce the total cost of biologic therapy; however, the magnitude and even direction of its economic impact remain uncertain because the evidence is sparse, heterogeneous, and context-dependent. Reported savings are strongly influenced by how TDM is implemented (proactive vs. reactive, alone vs. combined with other management tools), the biologic monitored, study design quality, and whether key cost components (e.g., the cost of TDM and downstream treatments after TDM-guided changes) are fully captured—uncontrolled studies that omit such costs tend to yield implausibly favorable results. Taken together, these limitations mean that current estimates of the economic value of TDM should be interpreted with caution and underscore the need for standardized

TDM pathways, better-anchored models with comprehensive uncertainty analysis, and new studies from resource-constrained settings.

Although several available economic evaluations originate from non-European settings, their findings remain informative for European decision-makers because they illustrate key methodological issues, cost drivers, and implementation challenges related to TDM. However, direct transferability of these results to European healthcare systems is limited by differences in drug prices, biosimilar uptake, reimbursement rules, clinical pathways, assay costs, and willingness-to-pay thresholds. This highlights the need for country-specific or regionally adaptable economic models reflecting European clinical practice and payer perspectives.

The increasing availability of biosimilars may substantially modify the economic value proposition of TDM. When biologic acquisition costs decrease, the potential savings from dose optimization or treatment de-escalation may become smaller, whereas the relative importance of assay costs and implementation costs may increase. Economic evaluations should therefore explicitly account for biosimilar pricing, market penetration, and switching policies, as these factors may strongly influence whether TDM remains cost-saving or cost-effective in routine practice.

Successful implementation of TDM requires more than evidence of clinical or economic value. It also depends on the availability and standardization of assays, laboratory turnaround time, clinician familiarity with therapeutic thresholds, integration of TDM results into treatment algorithms, and reimbursement of both testing and follow-up decision-making. Without clear implementation pathways, TDM may generate additional monitoring costs without consistently improving treatment decisions or patient outcomes. Other factors that might influence the results include analytical variability among assays, timing of sampling, and differences in assay methodology, as these factors may affect the transferability of proposed concentration targets across studies and clinical settings.

Given the limited and imperfect clinical evidence underpinning current CEAs, future economic evaluations should be based on robust comparative data, apply standardized TDM algorithms with clear clinical use cases, and include comprehensive costing aligned with the chosen perspective and time horizon. Priority areas include extending evaluation beyond TNF-α inhibitors to high-cost biologics without biosimilars and understudied inflammatory diseases and generating evidence from low- and middle-income countries where rationalizing biologic use and improving access are most critical.

The limitations of TDM that could influence CEA lie in the expertise required for its appropriate implementation and interpretation. TDM, particularly when pharmacokinetic modeling is involved, requires familiarity with pharmacokinetic principles, model-based dose individualization, and the interpretation of model-derived estimates. The limited availability of professionals with such expertise may represent an important barrier to the reliable implementation of TDM and should be considered in the discussion.

Another critical issue concerns heterogeneity in patient follow-up practices, including inconsistencies in the timing and frequency of assessments before and after treatment initiation, as well as variability in the use of validated disease severity scales. Standardized longitudinal monitoring is essential not only for evaluating clinical outcomes but also for quantifying resource utilization and linking these outcomes to economic endpoints.

A further challenge lies in the absence of harmonized clinical and methodological guidelines for TDM implementation across European countries. Current practices vary significantly with respect to assay methods, therapeutic thresholds, and clinical decision algorithms. These inconsistencies limit comparability between studies and complicate the integration of evidence into health economic models.

In parallel, reimbursement criteria for TDM and biologic therapies differ substantially between countries, reflecting variations in national health technology assessment (HTA) frameworks, budget constraints, and policy priorities. Such variability underscores the need for robust and transferable economic evidence to support consistent and equitable access to optimized treatment strategies.

A limitation of this work is that it should be interpreted as a position paper rather than a systematic review. Its aim is to synthesize the authors' perspective on the current pharmacoeconomic evidence for TDM in CIDs, identify major evidence gaps, and outline priorities for future economic evaluations. Therefore, the manuscript does not attempt to provide a comprehensive quantitative synthesis of all available studies but rather highlights evidence areas that are most relevant for policy, reimbursement, and implementation decisions.

Future research should prioritize: first, pragmatic comparative studies assessing TDM-guided strategies vs. standard care; second, harmonized TDM algorithms with predefined therapeutic thresholds and decision rules; third, economic evaluations including both drug and testing costs as well as downstream treatment consequences; fourth, studies beyond infliximab and adalimumab, especially for newer high-cost biologics; and fifth, evidence from lower-resource European settings where biologic access and affordability remain major policy concerns.

Conclusion

TDM can guide dose adjustment, continuation or discontinuation, changes to concomitant therapy, and next-line selection. To rationalize the use of high-cost biologics and improve access in low- and middle-income countries, TDM is policy-relevant, yet published CEAs are largely limited to older TNF-α inhibitors (mainly infliximab and adalimumab) and high-income settings. Available CEAs have also applied TDM inconsistently and assumed various direct effects, reflecting limited

clinical certainty. Future work should standardize TDM algorithms, use comparative designs, include comprehensive costing, extend beyond TNF-α inhibitors, and prioritize studies in low- and middle-income countries. The current evidence suggests that TDM may support more efficient use of biologic therapies by guiding dose optimization, reducing unnecessary treatment escalation, and potentially improving the sustainability of care for patients with CIDs. However, the pharmacoeconomic value of TDM remains highly dependent on the clinical setting, monitored drug, healthcare system perspective, assay costs, and the availability of robust comparative evidence. Future research should therefore prioritize well-designed comparative studies and transparent economic models that integrate clinical outcomes, resource use, patient-relevant endpoints, and implementation costs across diverse European healthcare systems.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
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GP and PK were responsible for concepts, data validation, data collection, and writing. KT, PH, and EB were responsible for data collection, analysis, interpretation, and writing.

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Data availability

All of the data that support the findings of this study are available in the main text.