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Viewpoint

Precision medicine and the chaos theory in rheumatoid arthritis

Clément Triaille[1,2,*], Patrick Durez[1,3], Josef S. Smolen[4], Iain B. McInnes[5], Bernard Lauwerys[1], Nisha Limaye[6]

[1] *Pôle de pathologies rhumatismales systémiques et inflammatoires (RUMA), Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels, Belgium*
[2] *Service d'Hématologie, Oncologie et Rhumatologie pédiatrique, Cliniques Universitaires Saint-Luc, Brussels, Belgium*
[3] *Service de Rhumatologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium*
[4] *Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria*
[5] *College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK*
[6] *de Duve Institute, Université catholique de Louvain, Brussels, Belgium*

Predicting what the future holds is a quintessentially human aspiration. Beyond the purview of mystics, pragmatic prognostication has long preoccupied physicians. In the fifth century BC, Hippocrates stated: 'The best physician is one who can prevent and *predict*'. Some 2500 years later, the concept of 'precision medicine', ie, the ability to tailor treatment decisions based on accurate biomarkers, remains the holy grail in many medical specialties including rheumatology [1]. Disappointingly, despite intensive efforts, this concept has proven challenging to translate into practice in the field of inflammatory rheumatic diseases (iRMDs). As therapeutic options have increased over the 3 last decades across a variety of iRMDs and modes of action [2], the notion of '*the right drug for the right patient at the right time*' has attracted increasing interest—with enhanced expectations—from physicians and patients alike. Enticed by breakthrough advances in oncology, the rheumatology community has expended tremendous work and resources into gathering clinical, serologic, radiologic, pharmacologic, histologic, genetic, epigenetic, transcriptomic, metabolomic, proteomic, and other data to build predictive models. As these highly effective new therapies interfere with general inflammatory principles (rather than truly separate mechanisms operating in different patient subsets), precision medicine continues to be a challenge [3].

Rheumatoid arthritis (RA) provides a salutary exemplar. Blood and synovial tissues from patients with RA have been analysed with increasing granularity using technologies ranging from advanced imaging to spatial and single-cell transcriptomic profiling. Progressively, well-designed studies on large patient cohorts have replaced smaller-scale, exploratory work, with machine learning methods and comparative multiomics approaches now routinely employed [4–9]. Multiple studies have provided statistically significant data, leading to legitimate initial enthusiasm. However, absent validation has been a growing concern [10–12]. Major limitations have gradually become apparent in the quest for 'precision decisions' in iRMDs; some are summarised in Box 1. Few findings have proven either reliable and/or sufficiently applicable, and of sufficient predictive value, to be translated into daily clinical practice. Indeed, predictors of outcomes routinely assessed in clinical practice have hitherto not been surpassed by other molecular predictors.

These results are reminiscent of challenges encountered in systems research fields from meteorology to economics: characteristically, variables are so numerous, and their interactions and hierarchy so complex, that accurate prediction at the level of the individual becomes extremely elusive. Small, sometimes nonobvious—perhaps unidentifiable—differences in initial conditions can have seemingly disproportionate effects on ultimate measured outcomes. This has been referred to as 'chaos theory', or mechanistic chaos: the system under study is so intricate and dynamic that long-term prediction, or modelling, of its behaviour proves extremely difficult or even impossible, although it is governed by mechanistic laws (as opposed to stochastic events). Illustrative examples of this phenomenon are the movements of stock markets, (medium term) weather forecasts, and (by and large, with the exception of those with certain high-penetrance genetic variants [13]) prediction of lifetime cancer risk in individuals. Another common illustration of the chaos theory is the widely known metaphor of the 'butterfly effect': in a

*Correspondence to Dr Clément Triaille. (C. Triaille).
E-mail address: clement.triaille@uclouvain.be (C. Triaille).
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Box 1 Some major limitations learned in the quest of predictive biomarkers

- The immune system (with its myriad components) is incredibly dynamic, with considerable plasticity in both the short (a few hours) and long term (several months to years).
- Established determinants of response to therapies in a given individual include genetic susceptibility, unpredictable and variable environmental factors, and patient- and drug-specific factors.
- Each of these determinants seems to be associated with low effect size, and they are likely interdependent.
- Remission is not a stable state, and metrics of clinical response are composite scores with intrinsic limitations, eg, dependence on baseline disease activity, reliance on subjective factors with interobserver variability, and patient expectations.
- The right therapeutic choice for a given patient is not just a drug that induces remission, but also a drug that the patient agrees to take, is associated with an *a priori* tolerable risk/benefit balance, does not induce unacceptable side effects, and takes patient comorbidities into account.
- At present, the biotechnologies and resources necessary to combine and integrate the complexity of treatment response mechanisms are unlikely to (1) return results in an acceptable time frame, (2) be cost-effective, and (3) become widely accessible, *in the short-to-medium term*.

mechanistic, yet nonlinear system, a butterfly flapping its wings in South America could be the cause a tornado in Australia. Existence of such chaotic dynamics is increasingly recognised in biology, eg, in NF-κB (Nuclear Factor kB) transcription factor activity and the transcriptomic response of *Escherichia coli* to oxidative stress [14–16]. It has been postulated that chaotic response dynamics provide a selection advantage to a bacterial or a cell population (such as immune cells) in a complex environment by increasing the spectrum of different responses and ultimately, the adaptability of the organism to this environment.

We would do well to recognise, and respect, the potential for 'chaos' to impact biomarker development in RA. Numerous 'pathologic influencers' could impact tissue evaluation. Epigenetic, comorbid (eg, obesity) and exposome (eg, infection, vaccines, pollution, smoking, alcohol, and diet) dependent factors will likely be critical and yet are very difficult to include in primary blood or synovial biomarker studies. Even if one focuses on the primary articular 'RA lesion', one should consider the pronounced plasticity of immune cell phenotypes (and likely resident stromal cells in their niche) responding dynamically to internal (eg, intercellular interactions) and external (eg, therapeutic agents) stimuli. Immunologic migration to lymphoid tissues (mimicked by ectopic germinal centres in synovium) further complicates interpretation: do circulating, lymph node, or synovial immune cells reflect RA pathogenesis, the disruption caused by immune-targeted intervention, or an active immune response to an incidental, possibly irrelevant, recent infectious insult? Therefore, unsurprisingly, it has become increasingly clear that the determinants of individual clinical response to a given drug in RA are numerous, dynamic over time, and likely interdependent [17–19]. Whereas a technically accessible, cost-effective biomarker test would no doubt be rapidly and widely implemented, the complexity, time, cost, and variable accessibility of the (bio)technologies currently tested in RA represent a significant obstacle to reliable interpretation, validation, and ultimately, transition into daily practice.

The most robust predictive factors in RA have been known for a long time and are routinely assessed in clinical practice: high disease activity, seropositivity for anticitrullinated protein antibodies and rheumatoid factor, obesity, baseline bone erosions, smoking, and failure of a previous drug are all associated with lower probability of favourable outcomes under therapy [7,20–23]. Note the continuing utility of weighted scores such as the Disease Activity Score, the Simplified Disease Activity Index, or the Clinical Disease Activity Index, conceived based on the mining of clinical data; indeed, baseline disease activity, and even more so, change in clinical disease activity over the first 3 months, has been shown to be one of the best correlates of future response [21,24]. These are not *predictive* biomarkers per se but rather qualify as markers of biologic processes or disease 'state/activity' that in turn influence therapeutic outcomes [7,8,24].

Let's not throw away the baby with the bath water. Many precision medicine studies are based on biologically plausible hypotheses and designed to answer highly clinically relevant questions. Although a given omics-based readout (or combination thereof) may allow for a broad stratification of patients for likelihood of response, falling well short of the highly stringent predictive demands of precision medicine [9,10,25], its promise remains beguiling. The substantial efforts of our community are necessary and must be acknowledged for the important and fundamental new knowledge—and hypotheses—they have generated on the pathologic (molecular and cellular) mechanisms operating in RA. We contend that novel tools (particularly those that incorporate the spatial evaluation of affected tissues with exquisite granularity), combined with a fresh perspective (human and/or artificial intelligence generated!) may provide more accurate predictive risk scores [26–28]. Whether these can be quickly and cheaply implemented (and surpass current clinical predictors!) will in large part determine their real-world utility.

Both European Alliance of Associations for Rheumatology recommendations and American College of Rheumatology guidelines acknowledge the unpredictability of treatment response in RA: once the most accessible, cheap, and safe treatment (namely methotrexate) has failed, any targeted synthetic or biologic disease-modifying antirheumatic drug can legitimately be chosen for high-risk patients (based on clinical, radiological, and biological criteria). This should not imply that treatments be selected at random. We suspect that chaos in the pathologic RA lesion and its antecedents may render precision an unrealistic medium-term goal. On the other hand, a pragmatic application of decision making based on patient profile, preferences, compliance, extra-articular manifestations, and serologic measures assessed in standard clinical practice, comorbidities, and comedications could form a baseline upon which to then build estimations of 'molecular state'. The latter could be defined by currently available biopsy and poly-omic approaches. Drug safety profiles, reimbursement policies, and costs should also frame therapeutic strategy. A strict treat-to-target therapeutic approach should be applied in early RA with poor prognostic factors, with particular attention paid to the follow-up of patients at risk of unfavourable outcomes (such as structural damage or difficult-to-treat RA [29]). This is how rational, pragmatic therapeutic choices should be made in RA, unless unexpected future discoveries emerge from the chaos!

CRediT authorship contribution statement

Clément Triaille: Conceptualization, Writing – original draft. **Patrick Durez:** Writing – review & editing. **Josef S. Smolen:** Writing – review & editing. **Iain B. McInnes:** Writing – review & editing. **Bernard Lauwerys:** Writing – review & editing. **Nisha Limaye:** Writing – review & editing.

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Orcid

Clément Triaille: http://orcid.org/0000-0001-9227-3820

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