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HIPPOCRATES: improving diagnosis and outcomes in psoriatic arthritis

Oliver FitzGerald ✉ *and Stephen R. Pennington*

Combining the diverse expertise of clinical and scientific researchers from across Europe as well as patient representatives and pharmaceutical industry partners, the HIPPOCRATES consortium aims to characterize the molecular pathways underlying psoriatic arthritis in order to improve early diagnosis and precision treatment strategies for the disease.

Despite many years of progress in understanding the molecular pathways underpinning psoriatic arthritis (PsA) and in the management of this disease, it is evident that considerable clinical needs remain unmet[1]. HIPPOCRATES, a new European research programme funded by the Innovative Medicines Initiative, aims to address these needs by investigating the mechanisms and biomarkers associated with PsA, with the intention of improving diagnostic and therapeutic options for people living with the condition. In this commentary, as coordinating partner, we represent the views of the HIPPOCRATES consortium.

Unmet clinical needs in PsA

PsA is a chronic immune-mediated inflammatory disease that, together with skin involvement, affects joints and other components of the musculoskeletal system, in an estimated 1–2% of the general population[2]. PsA is associated with an increase in mortality and a reduction in quality of life, both likely to be related to the burden of inflammatory disease and to comorbidities[3].

Current approaches to diagnosis and treatment of PsA can result in poor short-term and long-term outcomes. As there are no diagnostic criteria or tests available, patients commonly experience a delay in diagnosis, which in turn contributes to a delay in establishing effective treatment. A delay in diagnosis of as little as 6 months, compared with an early diagnosis, is associated with worse radiographic outcomes and increased functional disability[4]. Thus, the early identification of those patients with psoriasis who are developing features of PsA is an important unmet need, as is the diagnosis of PsA in patients with early, undifferentiated inflammatory arthritis. Improved tools are also required to predict the emergence of PsA in patients with psoriasis, as the validation of candidate biomarkers and the development of a combined risk model for progression to PsA (including clinical, genetic and molecular risk factors) is a critical step for the development of a strategy aimed at PsA prevention. The ability to identify at baseline those patients with PsA whose disease will progress is also needed for the development of a stratified treatment approach. To date, there are no validated biomarkers or clinical algorithms that predict which patients with PsA will develop bone or joint damage.

Despite the emergence of new treatments for PsA that target a variety of molecular pathways, overall response rates have not improved; ~40% of participants in randomized controlled trials (RCTs) of such treatments fail to achieve an ACR20 response, and only ~25% meet more stringent disease response measures, such as ACR70 response, low disease activity or remission[5]. For a patient with active PsA, their disease might progress while the treating rheumatologist, without any reliable clinical or biochemical markers to guide them, tries one treatment after another. The identification and validation of biomarkers that predict an individual patient's response to treatment will underpin future precision treatment strategies.

The HIPPOCRATES approach

The ambitious, overarching aim of HIPPOCRATES is to characterize the key pathophysiological mechanisms that contribute to the development of PsA in patients with psoriasis and that define outcomes in patients with PsA. We anticipate that an improved, more detailed description of psoriatic disease endotypes and a better understanding of the molecular pathways resulting in these endotypes will enable individual patient profiles to inform therapy choice.

A key element of HIPPOCRATES is that it brings together and provides access to the largest and highest quality PsA cohorts in Europe, including 25,000 patients with psoriasis who will participate in a prospective, observational study. Also accessible will be data, images and biosamples provided by the HIPPOCRATES European Federation of Pharmaceutical Industries and Associations (EFPIA) partners (for example, from the OPAL Broaden (NCT01877668) and OPAL Beyond (NCT01882439) studies of tofacitinib for PsA, which involved more than 700 study participants). With these combined datasets, HIPPOCRATES can address a major shortcoming of previous PsA research, in which dataset sizes were not large enough to account for the

Conway Institute for Biomolecular Research, School of Medicine, University College Dublin, Dublin, Ireland.

✉*e-mail: oliver.fitzgerald@ucd.ie*

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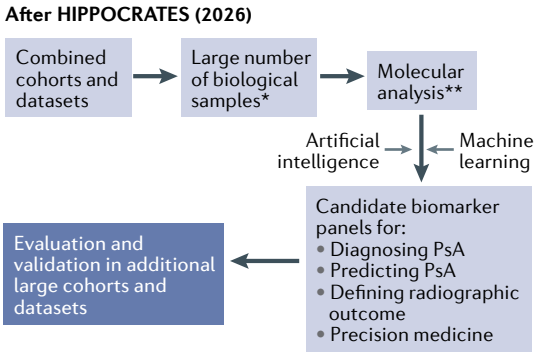

Fig. 1 | **Progress in psoriatic disease biomarker development after HIPPOCRATES.** To date, most biomarker discovery research in psoriatic disease is performed in cohorts from one centre, with no candidate biomarkers sufficiently evaluated or further validated. By the time the HIPPOCRATES project is completed in 2026, we aim to have moved the state-of-the art such that data from multiple, large cohorts will have been curated and combined with subsequent molecular analyses interrogated using artificial intelligence and/or machine learning statistical methods. This approach should yield candidate biomarker panels for areas of key unmet clinical need, which can be validated in other large datasets. *With consideration of pre-analytical variables. **Including quality control measures. PsA, psoriatic arthritis.

heterogeneity of the disease and hence support robust conclusions and implementable solutions. A centralized database is being established that will facilitate data integration and provide a unique opportunity, for both HIPPOCRATES investigators and future research programmes, to address areas of unmet need at scale.

Another important feature of HIPPOCRATES is that a wide range of cutting-edge analytical technologies will be deployed by experts at partner research centres to produce new molecular data. To identify relevant molecular pathways, patients with psoriasis and patients with PsA at various disease stages will be deeply phenotyped using biofluids and tissue; the biofluids will be used for 'omics'-based discovery, which will focus on epigenomics, proteomics, metabolomics and lipidomics, and tissue samples will be used for a range of analyses, including toponomics and single-cell analysis (for example, CyTOF and EpiTOF). All participants in these deep-phenotyping studies will be genotyped so that the results can be stratified according to genotype data.

The use of machine learning and artificial intelligence tools to interpret complex datasets should enable the identification of endotypes and the generation of important new insights, new diagnostic algorithms and prototypes of both diagnostic and therapeutic decision support tools (FIG. 1).

Central to the HIPPOCRATES ethos is that patients contribute to defining the research priorities and to the interpretation and implementation of the results that are obtained. From its initial conception, HIPPOCRATES has had direct, active and ongoing engagement with highly experienced patient research partners (PRPs), who are represented on the HIPPOCRATES management team and on each of the work packages, in addition to forming a patient advisory council. By demonstrating the pervasive benefit of the patient voice, HIPPOCRATES will be an example to future health research projects.

Critical to long-term success will be the ability to validate diagnostic and outcome algorithms in large, independent cohorts. Although the integrated HIPPOCRATES database might be used for such purposes, we have also reached out to investigators beyond the HIPPOCRATES partners through the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which has access to such cohorts. GRAPPA is now registered in Europe (GRAPPA-EU[6]) thus facilitating such access and providing some funding.

The way forward

By meticulously combining and sharing information from some of the most extensive and well-studied PsA cohorts across Europe and integrating diverse skills, the transdisciplinary HIPPOCRATES consortium has an exciting opportunity to address key research questions at scale and to validate biomarkers for clinical implementation (FIG. 1)[7]. This important opportunity will be enhanced by aligning HIPPOCRATES with international research efforts, including a complementary Accelerating Medicines Partnership-Autoimmune and Immune-Mediated Diseases (AMP-AIM) programme in psoriatic disease[8].

In summary, by integrating the strongest PsA clinical and research teams from across Europe, with the engagement, support and skills of EFPIA partners, the experience of PRPs and connection and integration with other international efforts, HIPPOCRATES should maximise the opportunity to extract critical clinical and molecular data from patient cohorts, thereby enabling development of diagnostic and prognostic tools to support patient stratification for precision treatment strategies.

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