

FOCUS ON PSORIASIS: P4 MEDICINE

P4 medicine: Personalized, predictive, preventive, participatory medicine in a digital environment

HOW CAN THE INTERNATIONAL PSORIASIS COUNCIL CONTRIBUTE?

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As dermatologists, we know the heterogeneity of psoriasis, a polygenic, multifactorial disease with several comorbidities. For instance, some patients have a few localized plaques, whilst others have extensive involvement of the skin. In some patients, lesions are stable for years and can be controlled effectively with topical preparations until relapse many months later. Others have a course of frequent exacerbation and remission, and the lesions are characterized by active areas of inflammation. The locations of psoriasis may be the visible areas or hidden and localized areas of the body, which makes a difference to the burden of disease. Psoriasis is often accompanied by itch, although this may vary from patient to patient. The clinical phenotypes of psoriasis have been described and classified before, in a review by a task force of the International Psoriasis Council (IPC).¹

Comorbidities such as arthritis, metabolic syndrome, cardiovascular disease, depression, and anxiety may complicate psoriasis in many patients; however, their occurrence is variable. Awareness about comorbidities in psoriasis is now well established, and IPC has contributed to the appreciation and establishment of psoriasis as a systemic disease. In 2006, IPC held a multidisciplinary meeting on this subject in Rhodes, Greece, followed by a second one in Dallas, Texas, United States, in 2008. Thus, for many years, IPC has had the aspiration of evaluating

patients with psoriasis from a holistic, health-and-well-being perspective.²⁻⁵

The psychological impact of psoriasis is substantial. In particular, anxiety and stigmatization can be heavy burdens of the disease, but, again, there are large differences between patients.⁶

Several triggering factors have been suggested to be relevant to the course of psoriasis,⁷ such as medications, the Koebner phenomenon (development of psoriatic lesions in previously unaffected skin after trauma or injury), focal infections, and psychological stress. In addition, a variety of other potential triggering factors have been suggested, without epidemiological evidence. We learn from our patients about the personal relevance of some factors perceived by them as triggers that lack solid evidence from the literature.

Focusing on personalized care

Each patient has his/her own psoriasis. One of IPC's strategic aims is to "elevate the standard of care of those living with psoriasis with a focus on personalized care." This has implications for our research, patient care, and teaching. How can we as an organization make a significant contribution to this aim?

As professionals, we need a systematic approach to the appreciation of disease severity. The dimensions of disease severity assessment have been developed by the University of Manchester Centre for Dermatology Research as a three-integer approach: (1) the objective severity assessed, for example, by Psoriasis Area Severity Index, Body Surface Area, and Psoriasis Global Assessment; (2) the subjective severity as experienced by the patient, assessed, for example, by the Dermatology Life Quality Index; and (3) the historical severity assessed by responsiveness to previous treatments and episodes of erythroderma.⁸

The long-term course is actually what matters to most people with psoriasis. Patients experience remissions and exacerbations, but mostly we do not understand why a patient relapses, what the relevant disease-modifying

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factors in the individual are at any moment in time, and how treatment impacts the long-term course of the disease.

Due to the polygenic and multifactorial nature of psoriasis, there isn't a "one size fits all" answer. For example, in which patients is early active treatment of the most importance to change the long-term course of the disease? Striving for true disease modification instead of maintenance therapy may require a treatment strategy that is different from only realizing a quick-fix clearance. One of the major gaps in our understanding, as defined by IPC, is the natural history of psoriasis and to what extent early active intervention improves long-term modification, including skin manifestations, comorbidities, and overall health.^{9,10}

Over the years, a wealth of research data has been generated on psoriasis, including heredity, pathogenesis, epidemiology, quality of life, comorbidities, and responses to treatment. An important development has been evidence-based guidelines, based on high-quality research, fulfilling certain established quality criteria. The classic "evidence-based" research, however, has a well-known limitation of focussing only on a small number of variables. This reductionist approach to research does not do justice to what is most important for the individual patient in real-world practice. By this we mean sustainable disease control, triggering factors, and the risk management of comorbidities. Thus, an integrative whole-system approach is needed.

In practice, how do we take the right decision for the individual patient if the evidence is fragmentary? In real-world practice, patient history is important for revealing comorbidities, triggering factors, and disease-modifying factors, which are meaningful to the individual patient. Clinical experience with many patients helps us integrate these parameters to judge the best treatment for the individual patient at the right time.

An integrated approach to psoriasis

We are witnessing great innovations in health care that can integrate the multitude of factors that exist and influence the course of diseases. These factors can be classified under: biological systems including genomics, epigenomics, transcriptomics, and proteomics; the medical system, with

data from the medical record; and welfare, with a multitude of data regarding lifestyle, leisure activities, workload, and health apps.

Unfortunately, all these data are fragmented among electronic patient records that cannot "talk" to each other or are hidden due to privacy regulations. It is important that this information is stored in well-structured personalised clouds for each patient. Health care will make great progress as a result of "big data analytics," a digital process involving the application of machine learning to identify connections between a large number of triggering factors in very large patient populations. This development requires ethical reflection guaranteeing privacy on the one hand and enabling collective analyses on the other.

Relevant personal evidence will have to be provided for each patient on the basis of his or her individual characteristics. This development is specified as "computational medicine," "precision medicine," or, more accurately, "P4 medicine: personalized, predictive, preventive, participatory."¹¹

For example, can we predict which person with psoriasis will develop metabolic syndrome? Can we prevent the development of cardiovascular disease in a patient with psoriasis? In many other disciplines, this development is in progress.¹²⁻¹⁷

As the skin is, quite literally, right at the surface, dermatology in particular can play a leading role in this development. Skin imaging, subsequent pattern recognition by "machine-based learning" connected to systems medicine, and information on welfare in a digital environment will create a new form of evidence-based health care. On the one hand, the individual patient's data cloud will contribute to data collection. On the other, it will provide collective evidence for answers to relevant questions of the individual patient, reconciling multiple factors, questions such as:

- Is there a chance that this patient will develop severe symptoms of psoriasis?
- Will this patient develop comorbidities and, if so, which ones?
- To which treatments will this patient respond best?

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- Is this a patient who requires active and early intervention to prevent cumulative damage to his or her health and welfare?

We are moving from reactive medicine towards proactive medicine.¹¹

What can IPC contribute?

Dermatology as a discipline is on its way from the classical evidence-based approach to an integrated omics¹⁸⁻²² computational medicine using patient registries²³⁻³⁹ and lifestyle approaches.^{40,41} International collaborations using pooled data bases and bioresources will help the implementation of P4 medicine. This approach is being established in a number of institutions and national task forces, such as the stratified medicine consortium Psoriasis Stratification to Optimise Relevant Therapy (PSORT) in the United Kingdom, which has made important observations about predictors of response to therapy in psoriasis. The next step is to move from invention to innovation of health care. A highly variable, polygenic multifactorial disease such as psoriasis requires P4 medicine in a learning health care environment.

In several respects, IPC as a worldwide organisation can enhance P4 medicine. It is important that clinicians realise there is no turning back to the times of eminence and, to some extent, evidence-based medicine and the fragmented approaches by individual specialties. Open collaborations, data sharing, functional assays, and model organisms play a key role in the validation of -omics discoveries.⁴² A joint effort between relevant specialties, perhaps under the umbrella of “inflammation medicine,” can accomplish a new diagnostic approach and an individualized management plan according to the information retrieved from -omics investigations (eg, actionable mutations, novel therapeutic interventions). This collaboration is key in P4 medicine. Adequate registration of clinical data and harmonization of data collection are required.

For the patient of today:

- Awareness that psoriasis is a multi-faceted disease is needed in teaching programmes and in guideline development. A host of factors is important in the appreciation of disease severity, and multiple factors determine which treatment a patient receives, when the treatment should occur, and for how long. Knowledge about phenotyping and assessment of disease-modifying factors is important. In patient management, it is important to move away from fixed treatment paradigms.
- In describing degrees of disease severity, it is important to realise that there is no simple classification and that this is a linear scale. Professionals have to unlearn traditional dogmas of categories delineated by artificially uniform definitions, which only depersonalise care.
- Studies on treatment efficacy in special phenotypes — such as palmoplantar psoriasis, pruritic psoriasis, psoriasis at sensitive skin sites, scalp psoriasis — are crucial.
- Studies on intervention in the phases of the disease, in particular, early intervention, are needed.

For the patient of tomorrow:

- For systematic analyses of clinical data and data from welfare, it is important to design registration systems that facilitate a uniform collection of essential, relevant items of information.
- For a comprehensive availability of key components of biological systems, it is important to provide a laboratory platform for a collaborative approach on the different -omics.
- A platform for integration of patient registries will facilitate big data analytics worldwide.

The basis of P4 medicine is the holistic approach to the individual patient. We are cognisant that in many countries around the world the -omics technologies are not available. However, the principles of personalized, preventive, predictive, and participatory medicine still hold firm and are adapted and shaped by local circumstances. ■

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