

# Personalised medicine in IBD: don't dispose of the sledgehammer just yet

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## Summary

Although personalised medicine offers a novel and exciting treatment strategy for our inflammatory bowel disease patients, there is still a long road ahead before it can be converted from a simple concept to the bedside.

Precision or personalised medicine (PM) is a form of medical management that uses information about a person's genes, proteins and their environment to prevent, diagnose and treat disease.<sup>1</sup> The ultimate goal of PM is the preferential selection of specific therapies based on an individuals' unique biology to individualise dosing such that therapeutic efficacy is maintained while simultaneously reducing risk of side effects. PM has become increasingly popular in the medical field since the advent of the human genome project, allowing researchers and clinician scientists to apply genomic data to cancer and other rare diseases, giving patients a more personalised diagnosis and care plan.<sup>2</sup> Oncology was one of the first specialties to use personalised therapy with the early example of screening for HER2 receptors in breast cancer with Herceptin treatment if positive, resulting in increased survival rates and reduction in side effects.<sup>3</sup>

The success of PM, however, hinges on the precise understanding of the underlying, molecular diagnosis.<sup>4</sup> Although there has been increased interest in applying PM to inflammatory bowel disease (IBD), the practical application is much more complex than originally postulated. First, the origins and aetiology of IBD is still not fully understood. And unfortunately, despite the recent advancements made in the understanding of its complex disease pathogenesis, including the role of genetics, immune function, microbiome,

and exposome, management decisions are still made using a 'one-size-fits-all' approach.<sup>5</sup> It could also be postulated that a precision approach in IBD may not be feasible when there are numerous variables contributing to disease activity; understanding and controlling for them all in an exposome that is constantly changing may not allow us to keep up with their impact on a patient's phenotype and consequently hinder a personalised approach.

Furthermore, there is a growing need for a 'multi-omic' approach to utilise PM successfully, where data from different disciplines are collected to advance our understanding of IBD pathogenesis, identifying new drug targets and biomarkers. This, however, requires significant patient data, biofluids and validation. It must be taken into consideration that a personalised approach makes validation processes increasingly difficult considering that the outputs of these 'omic' integrations are specific for individual patients and not necessarily applicable to other patients.

Cost must also be considered when utilising PM, particularly for less wealthy countries or countries that have privatised health care systems. To implement PM effectively, the right tools and infrastructure are needed, which will require heavy investments in technology to enable the sharing of large data and the ability to perform high throughput analysis.<sup>4</sup> Unfortunately, until the cost of utilising this technology becomes more widely available and affordable, this approach has the potential to widen healthcare disparities globally. Another financial factor to consider is pharmaceutical funding and support. This industry works by promoting a drug that works for a large number of patients. Thus, personalised

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approaches are unlikely to be an attractive option for many industry sponsors and may lead to a funding gap to further advancements in PM.

It is an unfortunate reality that equality in health-care and research is inadequate; as such, selection from previous studies and evidence-bases are built around generally specific cohorts with a noticeable lack of diversity in patient recruitment. Thus, it is an area of concern if these large data technology machines inadvertently exclude this vital information, which could further compound inequalities in PM, thereby worsening healthcare inequalities. As PM progresses, the importance of equality of access to therapies will become paramount.

Currently, we have slowly started to include a personalised approach into the care of our IBD patients. This can be seen in testing for infection exposure, including Epstein–Barr virus (EBV) (where seronegativity is associated with a small increased risk of lymphomas if treated with thiopurines),<sup>6</sup> prior to starting anti-TNF therapy due to risk of reactivation and disseminated disease,<sup>7</sup> testing for varicella zoster and advising vaccination regimes prior to starting biologics,<sup>8</sup> and undergoing therapeutic drug monitoring (TDM) in patients taking thiopurines and biologics. However, there are still many centres that continue to treat with thiopurines despite a negative EBV test, while numerous studies have not confirmed a benefit in inducing or maintaining clinical remission with TDM.<sup>9</sup>

On a genetic level, there have been some significant breakthroughs in PM. The first of these was the discovery that measurements of thiopurine S-methyltransferase (TPMP) activity could help predict those at risk of thiopurine toxicity.<sup>10</sup> A further breakthrough was made with the PANTS study which highlighted that HLA-DQA1\*05 allele was associated with a greater risk of anti-drug antibody production in those with Crohn's treated with Infliximab or Adalimumab.<sup>11</sup> Furthermore, the homozygous risk allele TL1A -358 C/C in patients with Crohn's disease who were treated with infliximab or adalimumab had a reduced risk of surgery compared with the heterozygous risk allele or homozygous protective allele TL1A -358 C/T + T/T.<sup>12</sup> This therefore shows that there is promise with PM and has prompted research into novel therapeutic drug targets such as the TL1A using the premise of

this working on precise targets for the right patients.<sup>13</sup>

Despite these breakthroughs, there is still a long road ahead before PM can be practically converted from a simple concept to the bedside, and certainly for the foreseeable future, treatment strategies will continue to need the sledgehammer. While there remain many reasons to be optimistic about the prospect of a personalised approach, there remains many barriers still making this into a beneficial reality for our patients.

### Author contributions

**Aditi Kumar:** Conceptualisation; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Matthew J Brookes:** Conceptualisation; Data curation; Writing – original draft; Writing – review & editing.

**Jonathan P Segal:** Conceptualisation; Data curation; Writing – original draft; Writing – review & editing.

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