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Precision medicine for inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory disease that affects the gastrointestinal tract and involves periods of relapse (flares) and remission. Patients cycle between feeling unwell with active disease, and relatively well with few or no symptoms. Time between disease flares varies depending on the severity of a patient's disease and the success of their treatment.

Crohn's disease (CD) and ulcerative colitis (UC) are the two main forms of IBD and are usually diagnosed between 15 and 40 years of age. Symptoms include stomach pain, cramps or swelling, diarrhoea, weight loss, tiredness, and less commonly arthritis, eye inflammation, and jaundice.

Genetic and environmental factors both contribute to IBD. Gut microbiota – microbes that live in the gut – and immune factors play a key role in IBD development and progression. Genetic factors can give clues to important disease processes and may predict how an individual will respond to treatment. In the future genetic testing may enable precision medicine approaches – more targeted treatments specific to a patient's disease – that could lead to better quality of life for IBD patients, although further work is needed in this area.

Summary

- IBD is a relapsing inflammatory disease that is increasing in newly industrialised countries
- Treatment decisions for IBD are currently based on trial and error, resulting in patient uncertainty and potential for uncontrolled disease
- Precision medicine approaches could inform treatment decisions and ensure the right patient gets the right treatment at the right time, increasing disease control and improving patients' quality of life
- Precision medicine for IBD is not yet ready for the clinic and requires further research and validation

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Inflammatory bowel disease

Crohn's disease and ulcerative colitis affect different parts of the gastrointestinal tract and have slightly different treatment pathways, with some shared treatment options. There are other forms of IBD, including very early onset IBD that affects children under six, but these have different causes and treatment considerations to CD and UC.

Inflammatory bowel disease is most prevalent in Western countries and incidence increases with industrialisation. The number of new cases in Asia has increased drastically in recent years – in Hong Kong around 30 people per million were diagnosed in 2014 compared to one per million in 1985 [1]. This is probably due to increased environmental risk factors, including stress, nonsteroidal anti-inflammatory drugs, vitamin D deficiency, pollution, westernised diet, and early-life antibiotics. Recommendations for the management and monitoring of IBD in Asia have been developed by the Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology.

Inflammatory bowel disease is a complex disease and its cause is not fully known. However, there are several biological processes that are altered. In healthy individuals, there is a physical barrier between the inside of the gut and the rest of the body, called the intestinal epithelial barrier. The gut microbiota is required for healthy gut function, and an intact epithelial barrier helps to protect it. Limited crossing of this barrier by the microbiota does happen, but in healthy individuals this is managed by anti-inflammatory immune cells so does not cause an inflammatory reaction.

In IBD, significant disruption to this barrier leads to 'leakage', meaning microbes can move into the body more easily. They are recognised by inflammatory immune cells, which are increased in number in IBD, causing gut inflammation and symptoms of IBD.

Genetics

Variants in genes involved in these processes can increase risk of CD or UC. Exact causal mechanisms remain uncertain for many genes, but they can help to understand the bigger picture leading to disease development and progression. Genes include those that [2]:

- Maintain the gut epithelial barrier (*CDH1* and *HNF4A*)
- Alter microbe recognition (*NOD2* and HLA alleles)
- Alter the immune response (*NOD2*, *ATG16L1*, *PTPN2*, and *IL23R*)

Genetic associations can differ between populations, for example *ATG16L1* is associated with risk in European but not Asian populations.

Precision medicine

Current treatment approaches

There is currently no cure for IBD but treatments are available, including: anti-inflammatory drugs; immunosuppressants; drugs called biologics, which target specific immune pathways; and antibiotics. Patients usually start on anti-inflammatories, but many do not respond and require a 'step-up' treatment approach with immunosuppressants, followed by biologics if they do not respond to immunosuppressants.

Precision medicine for inflammatory bowel disease

Treatment decisions – particularly for biologics – are broadly based on trial and error, although clinical expertise and patient preference play a role. Some patients try several treatments before finding one that works for them, living with active or poorly controlled disease during this time. Around 60-75% of CD patients require surgery in their lifetime due to insufficient disease control.

It has been suggested that reversing the treatment pathway and following a 'top-down' approach – starting with biologics and de-escalating when disease is controlled – may be helpful for some patients. The reasons this approach has not been adopted are:

- Biologics have not been proven to be beneficial in those with mild disease – evidence for their use is typically in those with moderate to severe disease
- Side effects tend to be more severe as treatments are escalated – some patients may get severe side effects unnecessarily if anti-inflammatories would have been sufficient
- Biologics are expensive – treatment escalation is generally accompanied by increased cost. Use of biosimilars, which are highly similar but cheaper versions of biologics, will help to reduce this
- It is not currently possible to identify who will respond to a given treatment – as many as 30-50% of patients stop a given biologic by 12 months due to lack of response or side effects [3]

Recognising that current approaches need improvement, IBD patients and healthcare professionals identified the optimisation of treatment strategies as a priority for research [4]. Precision medicine could be extremely valuable in improving patient's IBD treatment experience and outcomes.

Pharmacogenomics

A patient's genes can give clues to how they will respond to a specific drug. This can aid treatment decision making, an approach termed pharmacogenomics. Several genes – many involved in the immune response – show promise in IBD. Some of these associations seem intuitive; genes involved in TNF alpha pathways, which drive inflammation, are associated with response to biologics that block TNF alpha (anti-TNF therapies).

Genes associated with non-response to treatment have also been identified. For example, non-response to anti-TNF therapies has been associated with variants in the *PLIN2* gene, and treatment failure due to the production of anti-drug antibodies was increased in individuals with certain HLA alleles [5].

Other genetic variants have been associated with treatment side effects, a significant problem in IBD. HLA alleles can increase risk of acute pancreatitis – inflammation of the pancreas – following treatment with the immunosuppressant azathioprine. Variants in *NUDT15* and *TPMT* are associated with bone marrow suppression – reduced blood cell production – following treatment with azathioprine or mercaptopurine, another immunosuppressant.

Precision medicine for inflammatory bowel disease

Risk prediction

Another way to inform treatment decisions is to identify patients at high risk of severe disease, who could be given top-down treatment with biologics straight away, while those at low risk can have standard step-up treatment but still achieve disease control. Genetic risk scores are being investigated that could achieve this. Having high genetic risk for IBD has been associated with more severe disease, increasing risk of gut narrowing and surgery. Specific genes involved in microbial recognition or the immune response, including *MST1*, *MHC*, and *NOD2*, have been found to associate with age of onset and disease severity.

Investigation of gene expression has also been explored to inform treatment decisions. PredictSURE IBD™, a test marketed by PredictImmune, uses a gene expression signature in immune cells from blood to predict more aggressive disease at diagnosis. However, in February 2022 the National Institute for Health and Care Excellence in the UK concluded that there was insufficient evidence to recommend PredictSURE IBD™ for use by the National Health Service. This was largely because there was not enough evidence to show the benefit of altering treatment pathways. This is being investigated in a current clinical trial (PROFILE), which should provide this missing evidence.

Conclusion

Precision medicine has the potential to increase disease control, reduce uncertainty, and improve quality of life for patients with IBD. It may help healthcare professionals to make better informed treatment decisions. However, these approaches are not yet ready for clinic and need further research and validation to ensure they meet these aims and do not increase costs with little additional benefit.

References

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Published: August 2022

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