ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Personalized Medicine in Inflammatory Bowel Disease

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G&H What is personalized medicine, and how does a personalized medicine approach impact the diagnosis of inflammatory bowel disease?

DM Personalized medicine has been defined as customized healthcare informed by an individual's unique genomic, clinical, and environmental information. Many gastrointestinal physicians will argue, correctly, that they have been practicing personalized medicine with their inflammatory bowel disease (IBD) patients for many years by making decisions about treatment choices based on past disease behavior and smoking history, among other factors. However, we are on the verge, I believe, of being able to incorporate other molecular parameters into our patient evaluation and adding these to existing knowledge of clinical and demographic factors.

With regard to diagnosing IBD, IBD-associated serologic markers are the most widely utilized molecular parameter. However, despite impressive sensitivities and specificities, these factors are not sufficient on their own to make a diagnosis of IBD. The differential diagnosis of a person presenting with an altered bowel habit with or without rectal bleeding is wide. Definitive exclusion by endoscopy is required in some conditions, including colorectal cancer, irrespective of the serologic profile. A similar case is made for genetic variants, as the odds ratios for the genetic variants associated with IBD are of the order of 1 to 2.

However, these molecular markers are likely to play an increasing role in personalizing our approach to the management of IBD, especially as we see an evolution from the traditional diagnoses of Crohn's disease and ulcerative colitis. The IBDs are very heterogeneous conditions, and we are now beginning to understand some of the molecular variation underlying the clinical variability observed in the clinic. In the future, a diagnostic workup may include information on genetic variants that may define a particular subtype of disease. A more molecular-based disease classification will likely be an increasingly important part of understanding IBD and caring for our patients.

G&H What genetic markers have been identified that may characterize a particular subtype of disease?

DM The past few years have seen a rapid expansion of our knowledge of genetic markers that underpin IBD. Research has identified over 160 independent IBD susceptibility loci. The majority of these are shared between Crohn's disease and ulcerative colitis, although they may have differential effect sizes. Interestingly, most loci are also shared with several other immune-related conditions, such as spondyloarthropathy, type 1 diabetes, and psoriasis.

The first IBD susceptibility gene identified was the Crohn's disease–associated *NOD2/CARD15*. This gene is strongly associated with small bowel disease location

and stricturing disease behavior. A meta-analysis of *NOD2* variants confirmed consistent associations with small bowel disease location and stricturing phenotype in populations with European ancestry. Some, but not all, studies have suggested that *NOD2*-positive Crohn's disease patients are more likely to have postoperative recurrence. Although we are not yet defining a subtype of disease according to *NOD2* variants, in the near future, this genetic information may be combined with other markers to define a subset of disease.

In contrast, genetic associations within the major histocompatibility complex region are associated with colonic disease location in Crohn's disease and a more extensive and aggressive disease phenotype in ulcerative colitis.

There have been several attempts to combine these and other markers into composite scores to test for clinical utility in terms of predicting the severity of disease, the time until surgery among patients with ulcerative colitis, or the time until complications develop in Crohn's disease. These studies suggest that it may be possible to distinguish between more and less aggressive disease using multimodal composite scores, although it is clear that further validation is needed before we can integrate these findings into clinical care.

G&H Is it difficult to determine when a marker is validated and ready to enter the clinical arena?

DM Because much of the data suggesting the utility of integrating genetic and other markers into the diagnosis and treatment of IBD are relatively recent, there are several remaining hurdles before these markers can be considered ready for widespread use. Many true and valid associations may have no clinical use. To confirm an association, we have recognized thresholds, as with any scientific or clinical investigation, thereby minimizing the risk of false-positive results. A marker or composite score that achieves appropriate statistical thresholds should be validated in independent cohorts and, ideally, also in prospectively collected cohorts. There are prospective cohorts that have been followed for some time now. Over the next several years, there should be the opportunity to validate some of our retrospective findings in these prospective studies. If a marker is validated in this way and is deemed to be clinically useful, then it may be ready for introduction into the clinic.

G&H How might the identification of genetic or other markers influence treatment decisions in IBD?

DM Molecular markers may provide useful information in deciding which therapies are the most appropriate for a given patient in a number of ways. First, the likely severity of natural history "predicted" by a molecular signature might influence the treatment strategy. Second, a molecular signature may identify a pathway that is particularly pertinent to an individual's disease and suggest that a therapy targeted to that pathway may be the most appropriate approach. Finally, molecular variation may identify individuals at risk of adverse events to a particular drug.

Several studies have shown that patients positive for the serologic marker perinuclear antineutrophil cytoplasmic antibodies (pANCA) are less likely to respond to an anti–tumor necrosis factor (TNF) agent. This association appears to be true in both ulcerative colitis and Crohn's disease, although the mechanism is unclear. Although this characteristic of pANCA may not have been routinely used in clinical practice to date, this phenomenon may become increasingly relevant as alternatives to anti-TNF drugs, such as vedolizumab (Entyvio, Takeda Pharmaceuticals), become more widely available.

Another, more-established example of molecular associations with therapeutic outcome is the use of thiopurine methyltransferase (*TPMT*) polymorphisms to avoid bone marrow toxicity in patients treated with either 6-mercaptopurine or azathioprine. The majority of gastroenterologists routinely test for these markers, and such testing is recommended by the US Food and Drug Administration (FDA) prior to starting a patient on thiopurine therapy. Researchers have attempted to extend our understanding of the thiopurine pathways. A recent study has identified another gene, *NUDT15*, which appears to have a stronger effect than *TPMT* in predicting bone marrow toxicity in patients with Korean ancestry. This explains, in part, the higher prevalence of myelotoxicity associated with azathioprine or 6-mercaptopurine in Korean patients, even though they are less likely to carry *TPMT* mutations, compared with individuals with European ancestry. This *NUDT15* polymorphism is rare among patients with European ancestry, but it is still associated with bone marrow toxicity in this population.

G&H Are many genetic markers linked to ethnicity?

DM When considering the clinical utility of genetic markers in IBD, it is very important to understand the ethnicity of each patient, as different polymorphisms may have different effects or effect sizes in different populations. In addition to the *NUDT15* polymorphism discussed above, other variants may be particularly pertinent to the Asian population. Polymorphisms in the TNF superfamily 15 (*TNFSF15*) gene are associated with the development of IBD in both European and Asian populations. However, *TNFSF15* is the "dominant" gene for IBD among the Asian population, with a very strong association with Crohn's disease and an effect size that is far greater than that of other genes. The gene is

also associated with more severe disease and the development of fibrosis in Crohn's disease. *TNFSF15* is a good therapeutic target. If we can identify individuals whose genetic background suggests that this pathway might be important in their IBD development, then those patients might benefit from a treatment targeted at this gene. If we can prove this principle, then we might be able to develop a treatment for more severe diseases among European and Asian patients, in particular in this latter group because of the very strong association.

G&H Are patients asking about genetic testing?

DM Yes. The Human Genome Project and advances in IBD genetics are well documented in the popular press and by patient groups, and patients frequently raise the question as to whether they should undergo genetic testing. Because people can now obtain their own genetic profile from direct-to-consumer providers, physicians and other healthcare professionals need to understand both the potential uses and limitations of such information, as it is likely that patients will increasingly bring their own genetic data to the clinic for the clinician to interpret.

G&H What are the potential pitfalls?

DM A patient finding out that he or she is a carrier of a particular genetic variant associated with a severe disease can result in serious psychological consequences. Individuals providing this information need to be appropriately trained to handle such reactions, and people who receive genetic information should have access to genetic counselors. The FDA has become very concerned about this area and has, therefore, recently been scrutinizing some of the direct-to-consumer companies that are providing genetic information.

Another issue is that genetic variants will potentially only be one component of a very complex composite score. A number of groups, including our own, are trying to create simpler tools that combine genetic data with serology, along with clinical and demographic parameters (and it is likely that other "-omic" datasets will be added to this in the future) using simple visual readouts. Hopefully, clinicians and patients can then use these readouts to better understand the risks and benefits of any therapeutic decision. Ideally, these tools would be available on desktop computers or even as smartphone applications.

G&H What other measures are now being investigated that may lead to a more individually tailored approach to IBD prevention, diagnosis, and treatment?

DM A great deal of research is ongoing in other potentially relevant areas. These include gene expression, the microbiome, and the metabolome. Our datasets on risk, response, and other pertinent issues are only going to become more complex, so we will also need to develop better tools to make the information digestible and of practical use to both clinicians and patients.

Dr McGovern has no relevant conflicts of interest to disclose.

Suggested Reading

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