MAYO CLINIC

Individualized Medicine in Gastroenterology and Hepatology

Michael C. Stephens, MD; Lisa A. Boardman, MD; and Konstantinos N. Lazaridis, MD

From the Division of Gastroenterology and Hepatology, College of Medicine, Mayo Clinic, Rochester, MN.

CME Activity

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Learning Objectives: On completion of this article, you should able to (1) summarize the current status of genomic testing for inflammatory bowel disease, chronic cholestatic syndromes, as well as colon cancer and polyposis syndromes; (2) recognize the contribution of next-generation sequencing in the diagnosis of selected digestive diseases; and (3) apply genomic-based testing to the clinical subspecialty practice of gastroenterology and hepatology.

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Abstract

After the completion of the Human Genome Project, there has been an acceleration in methodologies on sequencing nucleic acids (DNA and RNA) at a high precision and with ever-decreasing turnaround time and cost. Collectively, these approaches are termed *next-generation sequencing* and are already affecting the transformation of medical practice. In this symposium article, we highlight the current knowledge of the genetics of selected gastrointestinal tract and liver diseases, namely, inflammatory bowel disease, hereditary cholestatic liver disease, and familial colon cancer syndromes. In addition, we provide a stepwise approach to use next-generation sequencing methodologies for clinical practice with the goal to improve the diagnosis as well as management of and/or therapy of the chosen digestive diseases. This early experience of applying next-generation sequencing in the practice of gastroenterology and hepatology will delineate future best practices in the field, ultimately for the benefit of our patients.

 ■ Mayo Clin Proc. 2017;92(5):810-825

Numerous human illnesses, including many gastrointestinal tract and liver disorders, are genetic in origin. For example, patients either inherit from their parents or are born with de novo genetic mutation(s) that could cause various diseases. What is evolving is our current ability to assess and interpret these genetic defects across the

human genome sequence in an accurate and timely fashion at a moderate cost. Specifically, next-generation sequencing (NGS) methods are currently available for clinical testing of either candidate gene panels or the entire human exome (ie, the portion of the genome translated to protein function). The results of such testing could inform practitioners on better ways to diagnose disease and to treat patients. Currently, many commercial and institutional laboratories across the United States offer College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA)—certified NGS-based tests for diagnostic purposes. Their cost ranges from $500 to $3000 for gene panel testing and from $7000 to $12,000 for whole exome sequencing (WES).

In this synopsis, we provide an update of the genetic basis of selected digestive diseases, namely, inflammatory bowel disease (IBD), hereditary cholestatic liver disease, and colon cancer and polyposis syndromes. Moreover, we provide an approach on how to apply these NGS methods aimed at improving the diagnosis and hopefully therapy of these conditions.

INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases, including ulcerative colitis (UC) and Crohn disease (CD), are chronic relapsing and remitting diseases that result in immune-mediated damage to the gut and other organs or systems. The incidence and prevalence of both CD and UC have increased significantly during the 20th century ($P<.05$).[1] For example, in Olmsted County, Minnesota, the incidence of CD increased from 5.8 to 133 cases per 100,000 person-years[2] and that of UC increased from 7.6 to 299 cases per 100,000 person-years between 1940 and 1991.[3] A more recent update has suggested that this increase has now plateaued.[4] Nevertheless, there is a considerable heterogeneity in the severity and behavior of IBD among patients. For example, some patients exhibit a stable inflammatory course whereas others have more complicated outcomes with penetrating (ie, fistula and abscess) or fibrotic (ie, stricture) behavior, leading to the need for surgery and significant morbidity.[5]

Gamut of IBD Presentations and Opportunities During the Genomic Era

Recent advances in understanding the pathogenesis of IBD have identified at least 163 genetic loci associated with this group of disorders.[6] It is believed that IBD occurs in an individual as a result of complex genetic, environmental, and microbial factors, leading to chronic inflammatory tissue damage.[7] With the recognition that IBD is a broad group of disorders with significant interindividual differences in etiology and disease behavior, it seems intuitive that genomic testing could be incorporated into clinical practice to stratify genetic causation or contribution of disease and to individualize treatment strategies. Currently, the main use of genetic testing in routine clinical practice for patients with IBD is limited to pharmacogenomics[8] and possibly to predict disease behavior.[9,10] Moving forward, studies that confirm the effectiveness of therapies designed specifically for subgroups of patients with IBD on the basis of genetic and other (ie, epigenome, microbiome, and metabolomics) factors will greatly expand the role of genomic testing in clinical management.

The use of comprehensive genomic testing for IBD (as opposed to targeted genotyping such as for thiopurine transmethyltransferase before the use of thiopurines) is already being incorporated into clinical practice in specific scenarios. This applies to specific groups of patients including those with very early onset inflammatory bowel disease (VEOIBD). These are patients with a family history of IBD that suggests Mendelian inheritance as well as IBD development with severe and refractory behavior. In such situations, genomic testing is used to search for monogenic disorders that have manifestations similar to those of typical IBD but will require a different therapeutic approach. The goal is to make a diagnosis owing to a specific genomic cause (as opposed to IBD) and thus to improve therapy. Very early onset inflammatory bowel disease (defined as onset of IBD by 6 years of age) is a particularly compelling example of how this approach can lead to more effective individualized therapies in patients who are usually extremely ill. These young children with manifestations of IBD tend to exhibit disease