

cleotide polymorphism genotype data obtained from the GWAS. In addition to the HLA genes, the major histocompatibility complex (MHC) region encompasses numerous genes related to immune responses, which could be promising candidates of causal origins of the diseases. Thus, it is important to assess whether the associations of the SNPs observed in the MHC region are independent from those of HLA alleles or not.⁷ Our study demonstrated that the GWAS signals observed in the MHC region between UC and CD could be attributable to the HLA risk haplotypes. Regrettably, our results would not support the previous studies reporting the risk of non-HLA genes in the MHC region with UC.⁸ Nevertheless, it would be difficult to conclude causality of the MHC region on the diseases solely based on the genetic association studies, and further investigations involving functional assessments would be desirable.

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- Okada Y, et al. *Gastroenterology* 2011;141:864–871.
- Asakura H, et al. *Gastroenterology* 1982;82:413–418.
- Futami S, et al. *Dig Dis Sci* 1995;40:814–818.
- Rivas MA, et al. *Nat Genet* 2011;43:1066–1073.
- Kumasaka N, et al. *PLoS One* 2010;5:e10207.
- Hashimoto M, et al. *Tissue Antigen* 1994;44:166–173.
- Okada Y, et al. *Arthritis Rheum* 2009;60:3582–3590.
- Seki SS, et al. *Tissue Antigens* 2001;58:71–76.

Conflicts of interests

The authors disclose no conflicts.

doi:10.1053/j.gastro.2012.01.026

Can Surrogate End Points From a First-Round Screening Be Reliable for Colorectal Cancer Screening?

Dear Sir:

Wilschut et al¹ use a simulation model that suggests that fecal immunochemical test was most effective with a 50 ng/mL cutoff level. Their simulation model used the detection rates obtained from robust randomized controlled trials comparing an immunologic test at various cutoff levels versus the guaiac test. These data reflect the results of first-round screenings, when the prevalence of adenoma or cancer is maximal in the screened population. The sensitivity and the specificity may not be constant for subsequent rounds. The lower sensitivity of higher cutoff levels of the immunologic method or of the guaiac test during the first round may be compensated by repeating the test in subsequent rounds. In contrast, the lower specificity of the cutoff level of 50 ng during this first round may be worse when repeating the test at subse-

quent rounds. The simulation model may not have accounted for variation in subsequent rounds of testing.

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- Wilschut JA, et al. *Gastroenterology* 2011;141:1648–1655.e1.

Conflicts of interest

The author discloses no conflicts.

doi:10.1053/j.gastro.2011.11.056

Fibroblast Growth Factor 19, an Anticholestatic Drug Produced by Human Liver

Dear Sir:

In a remarkably lucid study, Modica et al¹ conclude that activation of the nuclear farnesoid-x receptor (Fxr) in the intestine protects the liver from cholestatic injury. This seems to work fine in mice, but would it also work in humans? A word of caution seems warranted.

Interruption of the enterohepatic circulation disrupts the physiologic feedback regulation of hepatic bile salt synthesis. The consequences of cholestasis for bile salt metabolism in rodents and humans are different. In rodents, cholesterol 7 α -hydroxylase (Cyp7a1), the rate limiting enzyme of bile salt synthesis, is elevated on prolonged bile duct ligation.^{2–4} This means that bile salt synthesis increases in a condition where bile flow is impaired. In contrast, in humans with prolonged extrahepatic cholestasis, CYP7A1 is strongly down-regulated.⁵ This striking species difference is not only due to species differences in composition of the bile salt pool, but also to differences of expression of the regulatory hormones, Fgf15 (rodents) and FGF19 (humans). In rodents, Fgf15 is produced exclusively in the ileum, whereas in humans FGF19 is produced in ileum as well as liver, at least during cholestasis. Thus, interruption of the enterohepatic circulation by bile duct ligation in mice and rats leads to a deficiency of Fgf15. In humans with bile duct obstruction, the liver takes over and produces FGF19, which can be detected in high levels in plasma.⁵ Fgf15 and FGF19 are potent repressors of Cyp7a1/CYP7A1 expression. Binding of Fgf15/FGF19 to its receptor FGFR4 on the hepatocyte surface causes a strong and specific down-regulation of the Cyp7a1 gene.

Modica et al show that oral administration of obeticholic acid (INT 747), a strong FXR agonist, protects the liver in several mouse models of cholestasis.¹ The main mode of action of this drug is activation of Fxr and induction of Fgf15 in the ileum and the subsequent down-regulation of Cyp7a1 in the liver. Thus, in mice with interrupted enterohepatic cycling of bile salts, administration of obeticholic acid protects the liver from bile salt-mediated cytotoxicity. In contrast with mice, the human liver produces FGF19 during cholestasis. This hepatic FGF19 production most likely results from acti-