LETTER TO THE EDITOR

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Diagnosis of Preclinical Crohn's Disease: Hurdles, Challenges, and Hopes

Dear Editor:

We read with interest the paper by Taylor et al.[1] The authors calculated a risk score for asymptomatic first-degree relatives (FDR) of patients with Crohn's disease (CD) by combining the genetic risk score (a synthesis of 72 CD variants) and smoking status. Such score was used to identify FDRs in the lowest and highest quartiles of CD risk. FDRs were then invited to undergo video capsule endoscopy (VCE). They then built a model to predict inflammation at VCE that included several variables. Variable selection and regularization were carried out using different methods. The best predictive model according to elastic net included CD family history, genetic risk score, and fecal calprotectin (area under the curve, 0.8; confidence interval, 0.62–0.98); according to random forest, the 5 most important predictors were (1) fecal calprotectin, (2) genetic risk score, (3) high-sensitivity C-reactive protein, (4) interleukin-6, and (5) CD family history (area under the curve, 0.87; confidence interval, 0.75–1.00).

As of today, diagnosis of clinical CD occurs late in time when inflammation has already caused extensive mucosal damage and the appearance of symptoms. Such a late diagnosis is often associated with complications or poor response to medical therapy. We have shown in the single reported long-term follow-up case of a patient with preclinical CD that the interval between the biologic onset and symptoms is of several years.[2] Such a long period of time offers an excellent opportunity to prevent the symptomatic onset and to better understand the disease causes and pathogenesis. For example, aggressive therapy at biologic onset seems capable of healing the intestinal mucosa.[2] Testing individuals with preclinical disease has also raised the possibility that dysbiosis (widely considered a key factor in CD etiology/pathogenesis) could be a consequence rather than a cause of disease.[3]

This nice study by Taylor et al[1] is consistent with our early findings in FDR that underwent ileocolonoscopy and with older, unrelated studies showing a mild increase in stool markers in a large proportion of them.[4,5] However, one wonders how applicable this strategy is to screen individuals at risk. Multiple-relatives family history is already a well-known risk factor for CD. Fecal calprotectin and other blood and stool markers of inflammation are often not sensitive enough to even detect clinical small bowel disease.[6] The genetic risk score proposed by the authors is certainly a potentially helpful tool but it only seems to minimally improve the accuracy of the prediction model, notwithstanding that its inherent uncertainty might make it cost ineffective and might potentially generate undue expectations (as other commercial "genetic" tests have done). Finally, VCE is a potentially excellent tool to investigate small bowel inflammation. However, CD can also affect the colon in a considerable proportion of patients. Furthermore, VCE scoring should be developed and validated for this particular indication.

We are currently conducting a similar study whereby the FDRs are evaluated by the new panenteric ("Crohn's") capsule with reflex colonoscopy performed in positive cases to obtain tissue and confirm the diagnosis. Biomarker, genetic, and gene expression investigations are also run in parallel.[7] Others have chosen a retrospective but potentially effective approach to identify indicators of early disease.[8]

Ideally, in the future an accurate noninvasive marker could trigger the execution of diagnostic tests, such as VCE, in individuals at risk or even in the general population. However, before one can completely change the current dismal diagnostic algorithms and propose strategies to block disease evolution much data need to be gathered on CD natural history, the rate of progression, and the best interval to intervene. There is a long road ahead and the journey has just begun. However, there is little doubt that we are moving in the right direction.

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Conflicts of interest

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