Tailored Testing for Celiac Disease

Celiac disease is a gluten-sensitive enteropathy occurring in genetically susceptible individuals and affecting almost 1% of the population. The small-intestine biopsy, currently the gold standard test, is a rather invasive and expensive test to serve as the initial step in the diagnosis of celiac disease (1, 2). Therefore, current guidelines recommend serologic testing for autoantibodies against tissue transglutaminase (TGA) or endomysium (EMA) as the first step (1, 2). Most studies have reported excellent sensitivity and specificity for these tests (3, 4), but some studies have reported unsatisfactory sensitivity, particularly among patients with mild intestinal damage (5, 6). The HLA types DQ2 or DQ8 are strongly associated with celiac disease, but few researchers have tested this association as a basis for diagnosis (7).

In this issue, Hadithi and colleagues (8) compared the test performance of HLA-DQ typing and serology for diagnosing celiac disease. Unlike participants in many previous studies, all participants in Hadithi and colleagues' study had duodenal biopsy as the primary diagnostic test. The investigators thereby avoided the selection bias inherent when physicians use a positive serologic test result to decide whom to refer for biopsy, which is one of the several limitations of many studies (4). Subsequent to the biopsy, all participants had serologic testing and HLA-DQ typing. The major strength of the study is the large number of unaffected participants, which provides a precise estimate of specificity for serologic tests. The specificity was 99% for TGA or EMA and 57% for HLA-DQ typing, both with narrow 95% CIs. By contrast, HLA typing had excellent sensitivity: 100% versus 81% for serology. The sensitivity of antigliadin antibodies (AGA) was inferior to EMA and TGA. These data show clearly that serologic tests and HLA typing perform quite differently as tests.

On the basis of these study results, a positive EMA or TGA result was 90.8 times more likely to be seen in a patient with celiac disease than in someone without celiac disease. With this positive likelihood ratio, a positive test result would increase a pretest probability of 5% to a posttest probability of 83%. Assuming the same pretest probability, the posttest probability would be only 11% after a positive HLA-DQ result, with its positive likelihood ratio of 2.3. However, HLA typing had a negative likelihood ratio of 0, which means that without HLA-DQ2 and HLA-DQ8, the posttest probability would be 0% regardless of the pretest probability. Despite its strengths, the study had only 16 celiac disease cases. This means that the estimate of sensitivity—when having either an HLA-DQ2 or HLA-DQ8 test result—was imprecise (the sensitivity was 1.00, but the 95% CI was 0.79 to 1.00), suggesting imprecise estimates of posttest probability. For instance, given a pretest probability of 20%, the posttest probability after a negative TGA-IgA test result can vary from 0 to the quite unsatisfactory 9%.

Hadithi and colleagues explored the possible use of the combination of HLA typing and serologic testing. They defined a positive result on the 2 tests combined in 2 ways: first, as a positive result on any serologic test *or* HLA typing, and second, as a positive result on any serologic test *and* any HLA test. With either definition, the sensitivity and specificity of the combination was no better than the sensitivity of HLA typing alone or the specificity of serologic testing alone. Moreover, by combining these rather different tests in panels, many patients will have discrepant results, leading to greater uncertainty that is largely due to the low specificity of HLA typing. By showing clearly that combination testing has no added value, Hadithi and colleagues have made a valuable contribution.

Instead of doing both tests routinely, we suggest that clinicians use serologic testing or HLA typing (but not both), depending on the clinical situation. It makes logical sense to use HLA typing—a high-sensitivity *rule-out* test—when there is high suspicion for celiac disease and to use serologic testing—a high-specificity *rule-in* test—when the suspicion is low. Herein, we describe some clinical situations where the use of HLA typing can be beneficial and discuss some of its potential restrictions.

The attraction of a test with very high sensitivity, such as HLA typing, is based on several potential ways that exclusion of the disease would benefit patients or physicians. These include avoiding worry about the possibility of disease in the future, preventing unnecessary and potentially lifelong therapy, and reducing the costs or impact of further testing. Human leukocyte antigen typing, with its inherent ability to rule out celiac disease, would be beneficial in clinical situations when the diagnosis of celiac disease remains obscure, perhaps because of discrepancy between histologic and serologic findings or failure of response to a gluten-free diet. In individuals already on a gluten-free diet but with an uncertain or unconfirmed diagnosis of celiac disease, the absence of HLA-DQ2 or -DQ8 would obviate the need for lifelong dietary treatment (9, 10). Human leukocyte antigen typing is also beneficial in screening for Down syndrome, Williams syndrome, and Turner syndrome (11–13) or in clinical circumstances, such as osteoporosis, iron deficiency anemia, or infertility, where there is an increased risk for celiac disease but not an increased prevalence of celiac disease–associated HLA genes.

Would a negative HLA typing result reduce the need for intestinal biopsy? This largely depends on whether celiac disease is the leading cause of malabsorption in the population. A negative test result for HLA-DQ2 or HLA-DQ8 does not rule out malabsorptive disorders, such as Whipple disease and tropical sprue, that are also diagnosed by mucosal biopsy. Moreover, even patients with less

clearly defined malabsorptive symptoms, such as dyspepsia, or patients with nutritional deficiencies, such as iron deficiency anemia, may still require endoscopic evaluation. Thus, HLA typing is one of several factors in making the decision to perform biopsy. It should not be the sole arbiter.

Despite the excellent sensitivity of HLA-DQ testing, its use may be restricted in several clinical situations. For example, family members of patients with celiac disease and patients with specific autoimmune disorders are at increased risk for celiac disease. However, about two thirds of family members of patients with celiac disease carry HLA-DQ2 or -DQ8 (14). Therefore, assuming a pretest probability of 10% for celiac disease in family members of an affected individual and a 66% carriage rate for predisposing HLA-DQ2 or -DQ8, the posttest probability of celiac disease after a positive test result will be only 15%. Screening patients with type 1 diabetes and thyroid disorders for celiac disease is also limited by a high prevalence of HLA-DQ2 and -DQ8 in these patients (15, 16). Thus, the efficiency of a rule-out test depends not only on its sensitivity but also on the prevalence of the susceptibility gene in individuals at risk. Moreover, HLA typing is a genetic test, which means it should be used with caution, especially in the context of determining family risk. Genetic counseling is advisable when testing in such a context. Even communicating a negative result can be challenging if an unaffected individual feels guilt when other family members are affected. Communication of positive genetic test results is much more challenging because of disease labeling, consequent discrimination by insurance companies, and potential negative psychological impact on patients and families. Nongeneticists must be aware that genetic testing can reveal unexpected paternity (17). Finally, clinicians need to recognize that there are rare exceptions to the rule that HLA-DQ2 or -DQ8 is always present in celiac disease (18).

The major contribution of the study by Hadithi and colleagues is the demonstration of less-than-perfect performance of serologic testing and the complementary role of HLA typing in a context where intestinal biopsy is the diagnostic test that determines treatment decisions. Hadithi and colleagues' study illustrates the importance of considering the pretest probability of celiac disease and the performance and limitations of each test when deciding which diagnostic tests to use for celiac disease. In most circumstances, physicians should use TGA-IgA but not AGA as the initial diagnostic test, referring patients who test positive and those with reasons to suspect other diagnoses for duodenal biopsies. The principal role of HLA testing is trying to rule out celiac disease in diagnostically challenging circumstances, such as discrepant serologic and histopathologic findings and refractory symptoms despite a gluten-free diet, or when patients with an uncertain diagnosis have already begun a gluten-free diet.

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