Real-world Experience of Using *HLA-B*27* Tag-single-nucleotide Polymorphism Assay to Screen for Axial Spondyloarthritis

To the Editor:

We previously published an analytical validation of the *HLA-B*27* tag-single-nucleotide polymorphism (SNP) assay in *The Journal*¹ based on the initial identification of the *HLA-B*27* tag-SNP by the International Genetics of Ankylosing Spondylitis Consortium². Our tag-SNP assay is much cheaper than the traditional *HLA-B* locus testing, and has been implemented at the Provincial Medical Genetics Laboratory of Eastern Health (St. John's, Newfoundland, Canada) since August 1, 2016. The data on the use of this assay have been systematically collected.

Currently, *HLA-B* locus testing is the gold standard for determining *HLA-B*27* status, but it is rather expensive as a first-line test³. With an analytical sensitivity of 97.6% and specificity of 99.9%, the cheaper *HLA-B*27* tag-SNP assay (rs116488202) could offer a less expensive yet rigorous testing option. Specifically, the *HLA-B*27* tag-SNP assay could be ordered as a first-line screening test for patients with inflammatory axial pain who are suspected of having axial spondyloarthritis by primary care doctors, with the *HLA-B* locus assay reserved for rheumatologists for the rare circumstance when a patient has a negative tag-SNP test result and strong clinical suspicion of *HLA-B*27* positivity remains.

We evaluated the cost savings from this hybrid strategy for the period between August 1, 2016, and July 31, 2017, in the province of Newfoundland and Labrador, Canada. *HLA-B*27* testing was requested on 510 individuals. The cost of testing these 510 patients with the *HLA-B*27* tag-SNP assay was Can\$1673 (with average cost per test of \$3.28). Among those who tested negative using the *HLA-B*27* tag-SNP assay, 2.3% (~10 patients) would potentially be falsely diagnosed negative, based on our analytical validation. As a result, the *HLA-B* locus test would likely be ordered in half of these patients after medical history was reviewed by a rheumatologist. Hence, the total cost of testing 510 patients with the *HLA-B*27* tag-SNP assay could reach \$1963. In our data, only 2 individuals had repeat testing. The reason was a strong clinical suspicion of *HLA-B*27* positivity, due to a history of uveitis in 1 patient and family history in another patient. In both instances, the *HLA-B*27* tag-SNP assay called the genotype correctly (i.e., both patients were *HLA-B*27*-negative with the *HLA-B*27* tag-SNP assay and the *HLA-B* locus assay).

We estimated the total annual cost of using the *HLA-B* locus for 510 patients to be \$30,600, at an average cost of \$60 per test. Consequently, cost savings from using the *HLA-B*27* tag-SNP assay instead of the *HLA-B* locus tests were \$28,600 for this sample of 510 patients. This yielded a 94% reduction in costs relative to the case in which all patients were tested with *HLA-B* locus tests.

Notably, the number of tests ordered after the introduction of the hybrid strategy in Newfoundland and Labrador remained similar to that in previous years (about 525 tests annually). In other words, the availability of a cheaper test did not result in its overuse. The frequency of *HLA-B*27* positivity among all individuals tested (17.5%) was also similar to previous years in our population (average of 98 samples or 18.7% annually).

To account for variability in cost per test (cost per test dependent on the number of samples per run), we conducted 1-way sensitivity analyses in which we varied the cost per test for *HLA-B*27* tag-SNP from \$2.89 to \$4.61 and for *HLA-B* locus assay from \$55 to \$65. The resulting cost savings were estimated to range from \$25,000 to \$31,000, equivalent to a reduction of 91–95%.

Therefore, substantial cost savings can be realized by switching from the traditional *HLA-B* locus testing to the hybrid strategy to test for *HLA-B*27* status among suspected patients with inflammatory back pain. There are also intangible benefits such as reduced turnaround time for physicians who received the report sooner because of more samples being tested in each run. Importantly, no concerns were raised by the clinicians regarding the interpretation of the new test.

Given the excellent technical performance of this assay, and significant cost savings that can be realized, use of this hybrid strategy should be evaluated in a larger, more cosmopolitan population. With a larger population admixture, the performance of the test may be slightly lower, particularly among an Asian population; however, its overall clinical utility may still be maintained, and needs to be formally assessed in a more heterogeneous population.

HAIR V. NGUYEN, PhD, School of Pharmacy; DARREN D. O'RIELLY, PhD, Discipline of Genetics, Faculty of Medicine; PROTON RAHMAN, MD, FRCP, MSc, Discipline of Genetics, Faculty of Medicine, Memorial University, St. John's, Newfoundland, Canada. Address correspondence to Dr. P. Rahman, Professor of Medicine and Rheumatology, Memorial University, 154 LeMarchant Road, St. John's, Newfoundland A1C 5B8, Canada. E-mail: prahman@mun.ca.
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