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Correspondence

PCR versus Immunohistochemistry for Microsatellite Instability

To the Editor-in-Chief:

In the paper by Watson et al,[1] the authors' conclusion that PCR for microsatellite instability is superior to immunohistochemistry (IHC) for mismatch repair proteins for the detection of hereditary nonpolyposis colorectal cancer/Lynch syndrome is not supported by their data. In the only direct comparison of the techniques (Table 3 of the paper), both techniques successfully identified the same 19 cases as mismatch repair deficient, the same 187 cases as mismatch repair proficient, and both techniques each missed one mismatch repair-deficient tumor. These are identical performance characteristics (although from an admittedly small sample).

In the original set of 1059 tumors, only PCR was performed on all of the tumors, whereas IHC was performed on the subset that was unstable. IHC as conventionally scored did not detect an abnormality in about 10% of these unstable tumors. However, given the results of Table 3, it is certainly possible that if IHC had been the initial test and PCR had been performed only on the tumors with abnormal IHC, then PCR would also have scored a minority of unstable tumors as stable. Thus, the conclusion that PCR is superior to IHC is not supported by these data as well.

Finally, the authors consider the requirement that nuclear staining be absent from all tumor nuclei to score a tumor as unstable by IHC as a "flawed definition." As stated above, this "flawed definition" showed identical performance characteristics as PCR in the authors' own direct comparison. It is only when staining heterogeneity is taken into account that IHC lacks specificity for instability. We may debate whether it is appropriate to review selectively the subtle staining patterns in hindsight, but it is very important that the utility of IHC not be compromised by changing extremely sensitive and specific criteria to accommodate anomalous results.

In our clinical laboratories, as in many others, we view PCR and IHC for microsatellite instability as complementary techniques. Whether one or the other may be superior for mass screening is not clear at the present time, but the answer is not established by this study.

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Reference

1. Watson N, Grieu F, Morris M, Harvey J, Stewart C, Schofield L, Goldblatt J, Iacopetta B: Heterogeneous staining for mismatch repair proteins during population-based prescreening for hereditary nonpolyposis colorectal cancer. J Mol Diagn 2007, 9:472–478

Authors' Reply

We thank Drs. Samowitz and Broaddus for their correspondence regarding our paper in which we reported heterogeneous staining for the expression of mismatch repair (MMR) proteins.[1] Although the results from immunohistochemistry (IHC) and microsatellite instability (MSI) testing showed excellent concordance (Table 3), it should be borne in mind that MSI status was compared against the IHC criterion of complete loss of MMR expression. As stated in our paper, our experience with IHC was that a high proportion (75%) of microsatellite stable (MSI−) cases showed heterogeneous patterns of MMR protein loss. While this observation should not pose a problem for clinical laboratories that perform both IHC and MSI techniques in parallel (usually specialist genetics laboratories), it presents a major obstacle to the introduction of population-based screening programs that are based on IHC as the initial test. The "anomalous" IHC results reported in our study (Figure 2) and by other workers cited in our paper imply that every case displaying a focal, heterogeneous, or weak staining pattern is potentially a mutation carrier and requires further testing by MSI. Since the majority of routine diagnostic pathology laboratories offer IHC but not MSI testing, it would seem more logical and cost efficient to perform MSI testing as the initial screen, preferably in a reference

molecular pathology laboratory. The small proportion (~7%) of cases found to be MSI+ and wild-type BRAF could then be further tested for loss of MMR expression, again preferably in a reference laboratory for IHC (Figure 3).

Our results suggest that approximately 10% of younger patients with MSI+ tumors and who are potentially MMR gene mutation carriers would be missed using IHC as the initial test in the absence of parallel MSI testing (Tables 1 and 2). Whether IHC, MSI, or a combination of both is used for mass screening is likely to depend on local expertise and historical and financial considerations. Although our work in Western Australia leads us to favor MSI as the initial screening test, we look forward to hearing the experiences of other researchers in this area.

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Reference

1. Watson N, Grieu F, Morris M, Harvey J, Stewart C, Schofield L, Goldblatt J, Iacopetta B: Heterogeneous staining for mismatch repair proteins during population-based prescreening for hereditary nonpolyposis colorectal cancer. J Mol Diagn 2007, 9:472–478