Proficiency Testing of Therapeutic Drug Monitoring Techniques

To the Editor:

In this issue of the Journal, Jenny and Jackson-Tarentino *(1)* have carefully analyzed data from the New York State Department of Health therapeutic drug monitoring proficiency testing program to determine some causes of unsatisfactory performance. In regard to the Beckman Coulter SYNCHRON® Systems, it was noted that 9 results (out of 270) that were flagged "Out of Instrument Range" (OIR) were incorrectly reported as less than the reportable range when in fact they exceeded the range. A software change introduced in 1997 made the OIR flags more explicit by indicating OIR LO or OIR HI.

These authors note that the product precision claim is usually greater than that which a user would typically encounter. Most laboratories do not routinely perform precision runs, but use ongoing laboratory quality-control data to determine whether the instrument is performing satisfactorily. I'm not sure what benefit the customer would derive from a tighter advertised precision claim.

Reference

1. Jenny RW, Jackson-Tarentino KY. Causes of unsatisfactory performance in proficiency testing. Clin Chem 1999;45:89–99.

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Early Detection of Leptomeningeal Metastasis by PCR Examination of Tumor-derived K-*ras* DNA in Cerebrospinal Fluid

To the Editor:

Leptomeningeal metastasis (LMM) occurs in 3–8% of all cancer patients. Of the solid tumors, breast cancer, lung cancer, and malignant melanoma are the most common to metastasize to the leptomeninges *(1)*. The prognosis for patients with LMM is poor: most individuals survive a median of only ~4 months. Early diagnosis may improve the clinical response to radiotherapy and (intrathecal) chemotherapy, and may lead to more effective palliation and prolonged survival *(1)*.

Traditionally, a definitive diagnosis of LMM requires cytological detection of malignant cells in the cerebrospinal fluid (CSF). Interpretation is often aided by immunocytochemical techniques. Unfortunately, these CSF samples often contain very few morphologically identifiable malignant cells. In these cases, no definitive diagnosis can be established, leading to "suspicious" or "atypical" diagnoses *(1)*.

Molecular detection of tumor-derived DNA in CSF can potentially improve early and sensitive detection of LMM because no intact cells are required for diagnosis *(2, 3)*. Here we report the detection of K-*ras* gene mutations in the CSF of two patients with clinical features of LMM and negative cytology.

Both patients (A and B) suffered from lung adenocarcinoma, which had metastasized to the cerebellum. Treatment consisted of resection of

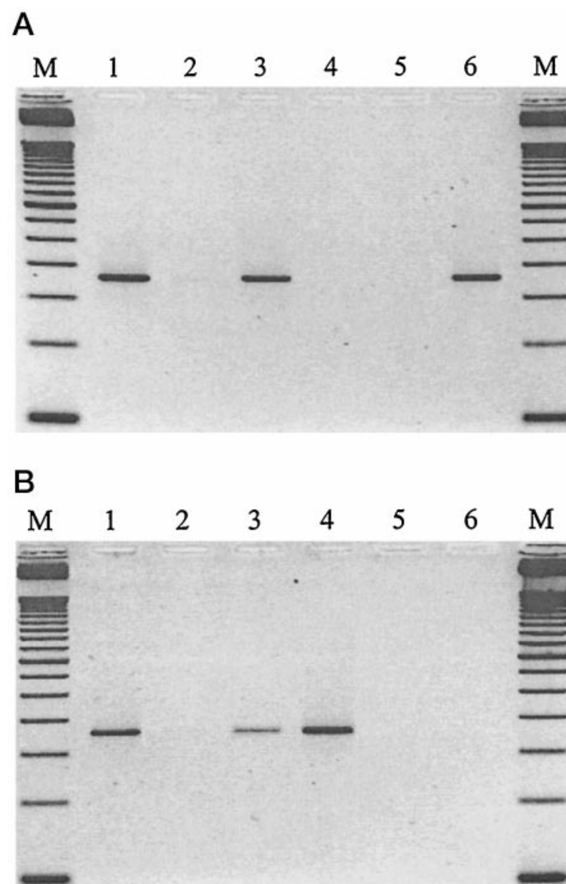

Fig. 1. Detection by MASA of mutant K-*ras* in the lung adenocarcinoma (*A*) and the cytologically negative CSF (*B*) of a patient with clinical features of LMM.

(*A*), MASA performed on DNA isolated from the tumor of patient B. *Lane 1*, amplification of wild-type K-*ras*; *lanes 2* and *3*, initial K-*ras* mutation screening using two PCR mixtures, each containing three MASA primers to detect all codon 12 mutations at nucleotide positions 2 and 1, respectively; *lanes 4–6*, split up of the three MASA primers specific for codon 12, nucleotide 1. (*B*), MASA performed on DNA isolated from the CSF of patient B (*lanes 1–3*) and a cell line containing K-*ras* wild-type alleles (*lanes 4–6*). Three different PCR forward primers were used for specific amplification of: wild-type K-*ras* (GGT, positive control; *lanes 1* and *4*), the AGT mutation (MASA specificity control; *lanes 2* and *5*), and the TGT mutation (*lanes 3* and *6*) as found in the tumor (Fig. 1A, *lane 6*). MASA forward primers were described by Hasegawa et al. *(6)*. The reverse primer was always 5′-ACTCATGAAAATGGTCAGAGAAACCTTTAT-3′. PCR products were separated on agarose (2%) and stained with ethidium bromide. *M*, 50-bp DNA ladder.

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