Letter to the editor: economic analysis lacks external validity to support universal syndromic testing for suspected meningitis/encephalitis

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We read with interest the industry-sponsored economic analysis of FilmArray Meningitis Encephalitis (ME) panel testing by Duff *et al.* in *Future Microbiology*. The authors conclude that "greater economic benefits are achievable with syndromic testing of all cases, rather than [...] targeted syndromic testing..." toward patients with >5 white blood cells in cerebrospinal fluid (CSF). However, instead of including all children undergoing lumbar puncture for 'suspected' ME as the authors advocate should be tested using a universal approach, the study excludes a significant population that would ordinarily be tested. This exclusion results from requiring an ICD-9 code for ME as an inclusion criterion. These codes are assigned retrospectively and are not available at the time of diagnostic decision-making, so their use eliminates children from the test population that present with 'suspected' meningitis but have normal CSF and therefore are not coded as ME. Table 2 in their paper reveals this selection bias in that in the study population 76% of children undergoing lumbar puncture had abnormal CSF and 97.4% of tested children had an infectious pathogen identified. These inflated values demonstrate that the test population consists of children with 'confirmed' ME and excludes most children with 'suspected' meningitis but normal CSF. Indeed, the literature and our experience support that the vast majority of pediatric patients (over 90% of those under 60 days) [1] who undergo lumbar puncture for 'suspected' ME due to indications such as fever have normal CSF and do not have a viral or bacterial cause of ME identified by any testing. This selection bias alone challenges the external validity of the author's claim to cost-effectiveness of a universal testing approach.

Furthermore, the authors assume in their model that negative ME panel results alone are sufficient to avoid admission or initiate discharge. This approach assumes that ME panel-negative patients no longer warrant inpatient observation or antimicrobials (Supplementary Table 1). However, it is standard practice in children, particularly infants <28 days, undergoing lumbar puncture for suspected meningitis to concurrently culture CSF for bacteria including those not included on the ME panel and test non-CSF specimens to evaluate for bacteremia, urinary tract infection or HSV infection. As such, these patients warrant continued antimicrobials and hospitalization pending the results of these studies (typically 24–36 h for bacterial cultures), thereby reducing the clinical and economic impact of negative MEP testing.

We believe that these two issues have resulted in an underestimation of the proportion of children with normal CSF who do not have ME that would undergo ME panel testing using a universal approach, and an overestimation of the impact of negative ME panel results. As the underestimated group with normal CSF at low-risk for ME grows (see sensitivity analysis in Supplementary Table 8) and the impact of negative ME panel testing decreases, the cost-effectiveness of a universal testing approach is minimized. While some patient populations, such as young infants

or immunocompromised children, certainly warrant universal ME panel testing despite normal CSF white blood cell counts, limiting testing to patients with abnormal CSF has been found to be safe and cost effective [2,3]. Such nuanced diagnostic stewardship approaches, incorporating carefully considered patient factors and CSF indices, should direct ME panel testing toward higher pretest probability populations, maximizing clinical impact while avoiding overtesting and the potential for false positives due to testing low-risk patients with normal CSF, as advocated by the universal testing approach of Duff *et al.*

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