Raoul Herbrecht,[1,2,3] Blandine Guffroy,[1,2,3] François Danion,[4] Aïna Venkatasamy,[3,5] Célestine Simand,[1,2,6] and Marie-Pierre Ledoux[1,2]

[1]Department of Hematology, University Hospital of Strasbourg, Strasbourg, France, [2]Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France, [3]Université de Strasbourg, Institut National de la Recherche Médicale, Unité Mixte de Recherche S1113/Interface de Recherche Fondamentale et Appliquée en Cancérologie, Strasbourg, France, [4]Department of Infectious Diseases, University Hospital of Strasbourg, Strasbourg, France, [5]Department of Radiology, University Hospital of Strasbourg, Strasbourg, France, and [6]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Illkirch, France

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Correspondence: R. Herbrecht, Institut de Cancérologie Strasbourg Europe, 17 rue Albert Calmette, 67033 Strasbourg, France (r.herbrecht@icans.eu).

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Reply to Herbrecht et al

To the Editor—We thank Herbrecht and colleagues for their valuable comments regarding application of the updated radiologic criteria of the revised and updated consensus European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) definitions for invasive fungal disease [1]. The authors point out that an important limitation of the first definitions in 2002 [2] and the 2008 iteration [3] was an overly strict definition of radiologic signs of pulmonary disease. In the most recent version of the definitions, the finding of a wedge-shaped, lobar or segmental consolidation was added to the existing criteria of dense, well-circumscribed lesion(s) with or without a halo sign, air crescent sign, or cavity, which, together with a host criterion and mycologic evidence, constitute probable invasive aspergillosis [1].

Herbrecht et al report the radiologic findings in a cohort of 727 patients with proven or probable invasive pulmonary aspergillosis, of whom 621 had initial computed tomographic (CT) imaging available. Using the revised radiologic definitions, 1 or more wedge-shaped, lobar or segmental consolidations were present in 23.7% of patients. Moreover, nearly one-third of patients with proven invasive aspergillosis presented with a consolidation pattern but without a nodule on initial CT scan. Indeed, nonneutropenic patients were more likely to have consolidation than neutropenic patients.

We applaud the authors for producing these data so soon after the EORTC/MSGERC definitions were published and welcome the fact that their findings support the radiologic definitions proposed [1]. Determining appropriate radiologic criteria for invasive fungal disease is challenging, as the radiologic lesions are nonspecific, especially among nonneutropenic patients [4, 5]. During our deliberations, we considered other radiographic findings such as bronchial thickening with tree-in-bud lesions, ground glass opacities, micronodules, and pleural effusions as diagnostic criteria. However, the consensus was to exclude these because of their lack of specificity for pulmonary aspergillosis. Nevertheless, more data such as those presented by Herbrecht et al are clearly needed as they will be instrumental in helping reevaluate the radiologic criteria and inform future revisions of the EORTC/MSGERC definitions.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of their institutions.

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John W. Baddley,[1] C. Orla Morrissey,[2] Cornelia Shaefer-Prokop[3] Sharon C.-A. Chen,[4] Peter G. Pappas,[5] and J. Peter Donnelly[6] for the Imaging Workgroup of the Revision and Update of the Consensus Definitions of Fungal Disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

[1]University of Maryland School of Medicine, Baltimore, Maryland, USA, [2]Alfred Health and Monash University, Melbourne, Australia, [3]Meander Medical Center Amersfoort and Radiology, Radboud University Medical Center, Nijmegen, The Netherlands, [4]Centre for Infectious Diseases and Microbiology, Laboratory Services, Institute of Clinical Pathology and Medical Research, Westmead Hospital, University of Sydney, Sydney, Australia, [5]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA, and [6]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

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Correspondence: J. P. Donnelly, Department of Hematology, Radboud University Medical Center, De Hoefkamp 1096, 6545 MD Nijmegen, The Netherlands (p.donnelly@usa.net).

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Utility of Metagenomic Next-generation Sequencing of Plasma for Infectious Pathogens

To the Editor—We read with interest the study by Hogan et al [1] and the accompanying commentary by Babady [2] on the utility of metagenomic next-generation sequencing (mNGS) of plasma for infectious pathogens. The Hogan et al study retrospectively evaluated "real-world clinical impact" of mNGS testing by reviewing 82 tests from 5 centers. We disagree with the authors' conclusion that such testing has very limited clinical impact.

The Hogan et al study equates "clinical impact" with "change in patient management." However, does this metric apply to the performance of a test, or to the judiciousness of the ordering physician? The Supplementary Data lists 73 cases (42 positive tests, 31 negative) in which tests were adjudged to have "no or limited clinical impact." There are at least 2 issues with these subjective determinations. First, in at least 20 instances of positive tests, mNGS testing confirmed results obtained through conventional microbiologic testing. In some of the cases in which new organisms were identified, therapy (either empiric or targeting another identified organism) that would be expected to cover the identified organism was continued. Is this a failure of the assay, or a failure of appropriate application of the assay? Second, in several instances of negative tests, other infectious testing was also negative, and a noninfectious diagnosis was subsequently made. In others, a negative test occurred after empiric treatment had been started and the patient was improving. Prior studies have shown the test is often negative in this setting [3]. Is it a limitation of the mNGS test to be negative in the setting of a noninfectious diagnosis? Should it have ever been sent on an improving patient on empiric treatment?

Any medical intervention, whether it be a test, a drug, or a procedure, should involve a careful assessment by the treating physician as to whether it can lead to some benefit to the care of the patient. Too often, however, providers become enamored with the "new thing," whether it be a drug, a test, or some other novel intervention. They may want to be the first to use it, or the first on their team to suggest it be used, potentially leading to lack of appropriate critical thinking about whether it is the correct thing to do for a given patient.

We agree with Babady that diagnostic stewardship should be considered for any testing, particularly when it applies most specifically to a given subdiscipline. However, appropriate stewardship of medical resources should be part of every physician's job, and any medical intervention should be undertaken with careful consideration of the possible outcomes and within the expertise of the provider, independent of cost. The higher reported utility of mNGS testing at our center [4] is likely heavily influenced by the active role ID takes in overseeing the use of the test, and includes both careful patient selection and proper timely utilization of the test. Juice is only "worth the squeeze" when someone first puts some thought into selecting the fruit.

Note

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William J. Muller[1,2] and Sonali Chaudhury[1,3]

[1]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, [2]Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA, and [3]Division of Hematology, Oncology, and Transplantation, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA

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Correspondence: W. J. Muller, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Avenue, Box 155, Chicago, IL 60611 (wjmuller@northwestern.edu).

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Reply to Muller and Chaudhury

To the Editor—We thank Drs Muller and Chaudhury for sharing their perspectives on our study evaluating the clinical impact of plasma metagenomic next-generation sequencing (mNGS) [1, 2]. There are several reasons why our studies reached diverging conclusions. First, in our study, we applied impact criteria based on the treating team's evaluation of clinical utility. Given that plasma mNGS is currently a send-out test and results are available after conventional microbiological tests, most providers did not consider mNGS to provide additional value when it simply confirmed conventional results. This contrasts with the definition of "clinical relevance" in their study, which included cases where mNGS confirmed conventional positive and negative test results rather than producing a new positive result or diagnosis [2, 3]. Indeed, had we applied our criteria across both studies, the overall conclusions would likely have been similar. Future studies