

Call for Correspondence

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Letters should be no more than 400 words, with no more than 5 references if included. Please include the full names, degrees, and affiliations of all letter authors and a phone number or e-mail address for contact.

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Re: “Clinical Sequencing Contributes to a BRCA-Associated Cancer Rediagnosis That Guides an Effective Therapeutic Course”

To the Editor: With great interest we read the case report “Clinical Sequencing Contributes to a BRCA-Associated Cancer Rediagnosis That Guides an Effective Therapeutic Course” by Chapman et al,¹ which shows the application of next-generation sequencing to cancer diagnostics. The authors present a case of a woman with an abdominal tumor that was initially diagnosed as pancreatic adenocarcinoma. However, subsequent mutational profiling and comparison with trans-cancer data from The Cancer Genome Atlas prompted the authors to rediagnose this tumor as ovarian adenocarcinoma, which was eventually confirmed through further clinicopathologic workup.

Although we find the idea of using molecular profiling to improve the accuracy of tumor diagnostics appealing, we would like to comment on the authors’ statements that histologic diagnoses are often incorrect and that, in the case they present, molecular profiling was necessary to render the correct diagnosis of ovarian adenocarcinoma. Despite the suggestive radiologic findings, the small cytological image the authors provide in their paper clearly shows 3-dimensional papillary cell aggregates primarily suggestive of papillary adenocarcinoma of the lung or the ovary,^{2,3} whereas a pancreatobiliary primary appears less likely from a pathologic point of view. Although we contend that a definitive diagnosis would not rely on morphology alone but would require immunohistochemistry, the morphology should have prompted considering ovarian carcinoma as one of the top differential diagnoses. Further tumor typing through immunohistochemical staining of the transcription factors WT1 and PAX8 (which, according to Chapman et al,¹ was performed afterward to confirm the molecularly based suspicion of ovarian origin) would then have provided strong support for ovarian and against pancreatobiliary adenocarcinoma according to the criteria of current WHO tumor classification.³

To evaluate how a larger group of pathologists would assess this particular case, we performed a Web-based survey among pathologists at the Institute of Pathology of the Charité Medical University Berlin. In the survey, we presented the clinical information of a 54-year-old female patient with abdominal pain and the cytological image available in the paper, including the immunoprofile used at the initial diagnosis. We offered the answer choices: (a) gastric cancer, (b) pancreatobiliary cancer, (c) colon cancer, (d) ovarian cancer, and (e) endometrial cancer. The 16 participating pathologists were unaware of the case report (ie, blinded to the context of the data provided). Twelve pathologists (75.0%) chose ovarian carcinoma as the most likely diagnosis, whereas 2 pathologists (12.5%) believed the tumor cells to be of gastric origin, and the remaining 2 (12.5%) favored a pancreatobiliary primary. Most participants commented that they would have requested further immunostains, including WT1 and PAX8. Therefore, although most pathologists had already suspected the correct diagnosis based on morphology alone, they—and also the pathologists in favor of gastric or pancreatobiliary carcinoma—would have used additional immunostains that would have led them to the same (correct) diagnosis.

Finally, although we strongly agree with Chapman et al¹ that molecular profiling, in addition to providing important clinical information on actionable mutations beyond histology, might in certain morphologically and immunohistologically ambiguous cases help classify tumors in the future using the approach they present, we would like to point out that correct tumor typing in the present case would have been rather straightforward with conventional morphological assessment and a few additional standard immunostains without any further molecular profiling. Although it is evident that molecular profiling will play an increasing role in cancer precision medicine in the coming years,^{4,7} we believe that these time-consuming and costly methods should be carefully integrated with the current standards of histo-/cytomorphological and immunohistochemical workup to optimize diagnostics and patient care.

Cont. on page lxviii.

March 2016

Cont. from page lxvi.

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The Authors Respond

Dear Drs. Klauschen et al: Thank you for your interest in our report and for your thoughtful comments.

Although the expertise of the academic and community pathologists initially involved in this case contributed greatly, the treating clinicians were unaware of the correct diagnosis at the time therapeutic decisions were necessary. The molecular characterization we performed here identified a hereditary gene mutation that not only guided treatment, but also informed the care and monitoring of the patient's immediate family. In our report, we sought to illustrate the utility of orthogonal evidence to help resolve diagnostic ambiguity and, more importantly, to identify a therapeutically actionable genomic lesion that also illuminates prognosis and guides genetic counseling of the index patient's family.

Your comments regarding the patient's initial immunohistochemistry evaluation are both reasonable and understandable in retrospect. Nevertheless, disease presentations are inherently variable and unpredictable, so we feel strongly that limitations of conventional diagnostic testing should be acknowledged and, when possible, improved upon for the benefit of patient care. In this regard, panel-based or unbiased DNA sequencing and other emerging diagnostic technologies, in addition to immunohistochemistry, offer great promise. Our community now faces the challenge of learning how to best use these technologies effectively, not to supplant existing methodologies, but to complement them. This view is supported by the United States' national "moonshot" initiative to support the development of novel, multidisciplinary approaches to improve cancer diagnostics and therapeutics and to generate new ideas and new breakthroughs in the care of patients with cancer.¹

In summary, we wholeheartedly agree that orthogonal molecular methods should be thoughtfully integrated with current approaches to inform all aspects of cancer care, an approach illustrated by our case report.

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