cell:plasma ratios. As recommended by the manufacturer, CZE was performed on the red blood cell pellet from the same sample. The additional fraction was no longer observed, confirming plasma protein interference.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

News & Views

Differentiating Germline vs Somatic Variants in Cancer Tissue: Are Large-Panel Genetic Tests Helping or Hurting the Cancer Patient?

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The increased use of next-generation sequencing (NGS)[2] and increased understanding of tumor genetics have led to the identification of safer and more effective anticancer therapies. Unfortunately, solid tumors are genetically diverse, limiting the efficacy of targeted therapies to subsets of patients having specific genomic profiles. As a result, comprehensive genetic testing using NGS gene panels is becoming more common to help clinicians select appropriate therapies. A recent article in *Science Translational Medicine (1)* suggests that testing only tumor DNA and not germline DNA may lead to inappropriate administration of cancer therapies, resulting in patient safety concerns and increased healthcare costs. This study assessed 815 tumor-normal paired samples using either exome sequencing or a targeted 111-gene panel from patients with 15 different tumor types. By testing only tumors, they found false-positive results (i.e., misinterpretation of germline alterations as somatic) in 31% of alterations using the 111-gene panel and 65% of alterations by exome testing. They also found that 3% of patients with suspected somatic changes harbored germline alterations in cancer-predisposing genes. The authors concluded that matched tumor-normal sequencing analyses are essential for precise identification and interpretation of genetic alterations for appropriate treatment of patients.

The majority of solid-tumor testing guidelines currently recommend individual gene or small gene panels to help clinicians determine whether specific drugs will have efficacy for a specific tumor type. These smaller gene assays, including "hotspot" or "targeted" NGS panels, assess important regions of the genome that should be well known to laboratories performing tumor-only tests. Clinical laboratories are less likely to misinterpret results from these panels because most detected variants are common and have known associations with specific therapies. Less commonly detected alterations with insufficient evidence to call pathogenic should be reported as variants of unknown significance (VUS). Testing laboratories and clinicians should not try to stretch VUSs into actionable mutations, because evidence-based therapies are driven by well-characterized mutations. Laboratories also need to state in their reports that NGS tumor-only assays cannot differentiate somatic vs germline variants and further testing may be necessary if a patient's clinicopathologic and/or family history is suggestive of a hereditary cancer syndrome. Therefore, for smaller gene panel testing, running a second matched normal-tumor test for all patients may add cost to the healthcare system without significantly improving testing accuracy. In addition, germline variant interpretation is not without difficulty, and overinterpretation of germline alterations can potentially harm patients.

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Received June 22, 2015; accepted June 23, 2015.
DOI: 10.1373/clinchem.2015.242768

[2] NGS, next-generation sequencing; VUS, variants of unknown significance.

The need for running matched normal-tumor testing becomes more relevant as one adopts larger gene panels/exome testing. In these instances, matched normal-tumor testing improves accuracy of somatic calls by subtracting germline alterations during bioinformatics analysis. Testing germline samples will identify pathogenic germline alterations in cancer predisposition genes that should be reported to the patient through appropriate genetic counseling. NGS testing is increasingly used in clinical laboratories and does help patients, but there are differences in the complexity of bioinformatics and interpretation of results based on the panel size and the list of specific genes being interrogated. With this complexity, it is imperative that both clinicians and laboratories communicate the pros and cons of different NGS panels and continue to learn from each other using data-driven decision-making tools to continue our mission of helping, not hurting, the cancer patient.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

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The Perils of Deprofessionalizing Laboratory Test Ordering: Are We Headed Down a Costly Path?

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Direct-access testing (DAT), in which the patient rather than the physician orders laboratory testing, continues to be a growing market. Demand has been driven by direct-to-consumer marketing, convenience, cost savings, and patient empowerment in managing his or her healthcare. In April 2015, Arizona passed House Bill 2645 (HB2645), which rewrites state law in regard to laboratory testing. HB2645 relaxes regulations related to DAT and allows individuals to (*a*) order any laboratory test without a physician's request or written authorization and (*b*) directly receive test results. The new bill does not require the patient to coordinate with a physician for consultation or interpretation of the results. Furthermore, healthcare providers are not liable for the failure to review or act on a laboratory test result that they did not authorize or order. Finally, HB2645 states that tests do not need to be covered by private insurance or abide by state cost-containment systems.

Those championing these changes argue that DAT will help contain healthcare costs by minimizing the burden on providers, reducing the cost of tests, and empowering individuals to take more interest in their own well-being. However, skeptics are concerned by the limited amount of peer-reviewed studies on the methodologies and performance of DAT and the increasing complexity of tests being offered at a growing number of pharmacies and online retailers. Proponents of HB2645 point out that CLIA regulations do not differentiate between physician-ordered testing and DAT; thus both are performed in CLIA-certified laboratories and must meet the same quality standards. Even so, there are inherent flaws with DAT. Healthcare providers correlate laboratory results with clinical presentation. Even common laboratory tests, such as those used to diagnose thyroid disorders, require interpretation of multiple test results in relation to each other and in conjunction with clinical symptoms.

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Received June 9, 2015; accepted June 17, 2015.
DOI: 10.1373/clinchem.2015.242222