The Oncologist®

Commentary

# Completing the Translation

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

The successful development and translation of biomarkers into clinically actionable results have been well choreographed, beginning with demonstration of analytical and clinical validity, followed most importantly with demonstration of clinical utility [1]. Most current biomarker guidelines for clinical use by physicians, as well as reimbursement decisions by payers, are usually clear on these evidentiary requirements. Although well intentioned, the sanctity of this foundational process is consistently challenged by developments, in the laboratory and clinic, that continue to impede clinical progress and slow treatment benefit to patients.

This is especially true in oncology, where the biomarker landscape has changed rapidly and substantially in the past decade. Increasingly, patient care and treatment decisions are being driven by biomarkers commonly derived from a simple venipuncture (liquid biopsy) and not an invasive tissue biopsy [2]. Convenience, faster turnaround time, easy access to repeat testing, lower cost, and a more accurate reflection of a tumor's heterogeneity, or true biology, have prompted and accelerated this shift [3, 4]. Furthermore, biomarkers derived from a liquid biopsy continue to increase in type and number and now include nucleic acids (both DNA and RNA), proteins, circulating tumor cells, and fractions of tumor cells (exosomes), as well as normal cellular elements [5], guaranteeing continued biomarker opportunities and application to patient management.

In cancer, cell-free, circulating tumor DNA (ctDNA) is the principle mutation-based liquid biopsy biomarker in use today, with analysis predominantly by next-generation sequencing (NGS), as well as other technologies [5]. As a class of biomarkers, ctDNA has demonstrated decision-making potential along the entire continuum of patient care, from risk identification and early disease detection through drug targeting and response prediction in overt or metastatic disease [6]. The benefits of clinical management with ctDNA may best manifest in non-small cell lung cancer, where discovery of new driver mutations has led to new drugs and remarkably improved response rates in patients [7, 8]. Moreover, detection of ctDNA in other body fluids, such as urine and cerebral spinal fluid, further extends its potential diagnostic applications [9, 10]. This apparent clinical versatility is unprecedented when considered alongside past cancer biomarkers.

Unfortunately, this embarrassment of diagnostic riches in care and treatment of patients with cancer is not without consequences, encumbered by both technical challenges and administrative or reporting difficulties. Multiple sources have previously focused on technical comparisons among ctDNA technologies and laboratories, with ample evidence that significant differences in results exist between labs that question the validity and actionability of a result [11, 12].

At the other end of the diagnostic result spectrum is the actual report provided to the physician, translating the generated result into a clinical decision. Importantly, there has been little standardization in this arena. Indeed, for an average clinician not well versed in molecular genetics and without access to a sophisticated molecular tumor board, deciphering the results of a patient's next-generation sequencing report is akin to trying to read a novel written in hieroglyphics. In this issue of *The Oncologist*, Peng and colleagues present the results of their clever investigation into laboratories reporting NGS results to clinicians and offering result interpretation and treatment guidance [13]. Their focus here is much needed because their findings are alarming and require more attention by all stakeholders.

To address reporting practices across laboratories, Peng's group simulated (synthesized) ctDNA with known variants and allelic frequencies and shipped samples to 66 genetic testing laboratories with a devised case history form included. The returned reports were reviewed using 21 predefined criteria designed to reflect detection accuracy, report integrity, and supporting information.

In keeping with previous reports on technical discordance among laboratories, this study also found considerable discordance in reporting detected variants, with only 42% (28/66) of respondents scoring complete concordance. Generating valid results for ctDNA is challenging. Circulating tumor DNA is a minor component of the total circulating DNA, estimated in some cases to be as low as 0.01% [5]. The multistep process required to analyze this small fraction into an actionable result—collecting and processing blood, extracting the DNA and preparing libraries, generating sufficient sequences from ctDNA strands, and the bioinformatic interpretation of those sequences—all potentially add error to the result [5]. The lack of analytically validated controls and the continued push to identify variants at the extreme low end of an assay's range exacerbate this challenge and explain, in part, these findings [14].

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What was most surprising, and specific to the intent of this study, is that none of the laboratories scored 100% against the 21 predefined report criteria, with the majority of reports scoring between 50 and 70 points out of a total of 100 points (37/66, 56.0%). Reports from many participating labs were insufficiently annotated, lacking important information regarding technical performance metrics for technologies employed, quality control results to help guide result interpretation, and detailed clinical interpretation of all variants and possible drugs, including potential clinical trials as an option to gain access to a drug. ctDNA testing allows for panels of well over hundreds of genes to be analyzed simultaneously as a single test. Such capability allows exploration of all possible driver mutations in a patient's cancer and possible off-label use of a drug based on a common driver mutation. This biomarker-enabled therapeutic cross-walking greatly benefits clinical scenarios where treatment options are limited [15]. In all, 88% of participating laboratories lacked sufficient information for adequate interpretation of results and patient management.

This study is not without limitations. Most of the participating labs were based in China, and detail regarding the participating laboratories is minimal, making it difficult to draw more deeply on the study's conclusions. However, these limitations, as well as other technical limitations, do not diminish the significance of their findings, which contribute to a much bigger, developing message: Translating genomic biomarkers obtained from liquid biopsies or tissue biopsies into routine clinical use is far more than just generating a result.

As Peng et al. remind us, demonstrating that a biomarker has analytical validity, clinical validity, and clinic utility is not sufficient if the treating physician is not adequately informed about the interpretation of genotyping results, the implications and limitations of the results, and possible alternative treatment options for the patient if the results do not indicate a clear action [13]. Moreover, even though molecular tumor boards evolved in part to offer such assistance to treating physicians, they, too, require such guidance from the laboratory's report to avoid errors [15]. The interpretation of genomic signals is not always explicit and can be misleading [16, 17]. Biology remains one of the biggest challenges to reducing genotyping to routine practice, and more standards and guidelines for generating and, as this study indicates, reporting results are urgently needed.

Fortunately, many professional societies and action groups are moving in this direction. For example, the plethora of different reports from commercial and academic labs, replete with different reporting elements and styles, can be confusing to physicians. The College of American Pathologists (CAP) has made available standardized pathology reporting templates that can greatly harmonize with the information reported from liquid biopsy results [18], affording accurate and confident decision making. Moreover, a recent publication from CAP and the American Society Clinical Oncology critiqued the literature on published reports for ctDNA, focusing on tissue-based testing and controlling preanalytic variability in generating results. Their critical findings and recommendations on evidence generation are relevant to ctDNA from liquid biopsies as well [19]. Their recommendations join the chorus for more evidence development before introducing a new biomarker or technology into clinical use. Additionally, efforts are underway to substantiate commercially available quality control reagents to understand the true performance characteristics of a laboratory's ctDNA testing and allow cross-lab comparison of results and result interpretation [20].

What remains to be developed and implemented is a consensus on reporting requirements to complete the translation of biology to precision medicine. The wealth of potential biomarkers obtained through liquid biopsies appears endless. It is not too late to set the record straight.

## Disclosures

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**Editor's Note:**
See the related article, "From Somatic Variants Toward Precision Oncology: An Investigation of Reporting Practice for Next-Generation Sequencing-Based Circulating Tumor DNA Analysis," by Rongxue Peng, Rui Zhang, Martin P. Horan et al., on page 218 of this issue.


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