Foreword

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Biomarkers in Medicine

Companion diagnostics at the intersection of personalized medicine and healthcare delivery

"The revolution in biology and high-throughput technology has provided an opportunity to develop a new generation of companion and complementary diagnostics…"

Keywords: clinical trials • companion diagnostics • detection • evidenced-based medicine • Food and Drug Administration • individualized and targeted therapy • prediction • prognosis • screening

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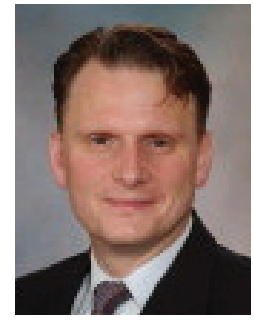

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Progress in understanding biological circuits, advances in enabling technologies including the high-throughput platforms of genomics, proteomics and metabolomics, the evolution in drug target discovery and the development of companion diagnostics set the healthcare enterprise on the verge of personalized disease management [1]. This revolution in clinical care is dependent on molecular diagnostics that predict and prevent disease, enabling the diagnosis and treatment of individual patients and populations [2]. Diagnostic biomarkers are quantifiable disease characteristics that provide information about underlying molecular processes to define disease progression or predict treatment response. Familiar diagnostic biomarkers include traditional measurements (heart rate and blood pressure), imaging techniques (chest x-ray and mammograms) and protein measurements (PSA and CEA). The revolution in biology and high-throughput technology has provided an opportunity to develop a new generation of companion and complementary diagnostics, including single-nucleotide polymorphism analysis, genomic and proteomic profiling, epigenetic profiling and gene expression profiling [3]. In turn, these diagnostics increase disease-specific sensitivity and specificity, contributing to the accuracy of personalized disease management.

This advancing wave of innovation has induced the next generation of biotechnology to capture the use of companion diagnostics for the application of specific therapeutic agents to the clinical care of individuals and populations [4]. Yet, as pointed out in this issue by Milne *et al.*, the potential of biomarker technologies, in the form of companion and complementary diagnostics, to revolutionize clinical care has not been fully realized, reflecting a disconnect between the emergence of discovery technologies and models for their validation, early adoption and application across disease populations [5]. These limitations in the validation of molecular diagnostics have raised considerations regarding approval and marketing by regulatory agencies. Moreover, as highlighted in this issue by Cohen *et al.*, the paucity of biomarker validation serves as a considerable obstacle to the adoption of companion diagnostics by healthcare providers and payors [6]. The evolving regulatory and reimbursement environments, in conjunction with the central importance of analytic validation and clinical qualification, has resulted in barriers to adoption that have restricted the full impact of companion diagnostics in clinical practice [5,6].

The emergence of analytic technologies for evaluating nucleic acids and proteins, which are associated with the deconvolution of the human genome, provided the technological push to develop molecular biomarkers for disease management [7]. Conversely,

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advances in our understanding of the molecular mechanisms contributing to pathogenesis have yielded an abundance of drug targets to individualize therapeutic care, providing the associated pull for development of companion diagnostics [8]. At first, companion diagnostics developed in the model of classical biomarkers, as single elements related to the response of a patient to a specific therapeutic agent. Their clinical utility was enhanced by the evolution of rapid next-generation nucleic acid sequencing technologies coupled with mutation-specific PCR supporting high-throughput analyses. These initial small steps have dramatically expanded to encompass systems-level dysregulation of the complex molecular circuits contributing to pathophysiology [9]. Panels of genetic markers and their disease-specific mutations have been cataloged and their value in predicting responses to targeted therapeutics is being established. Beyond genetics, molecular assessment of transcriptomes, single-nucleotide polymorphisms, methylation and the proteome are poised to inform the best therapeutic strategies, as exemplified in this issue in breast cancer [10].

> "While companion diagnostics reflect the envisioned future for individualized therapies, their potential has yet to be realized..."

While companion diagnostics reflect the envisioned future for individualized therapies, their potential has yet to be realized, reflecting issues of technologies, clinical validation and mechanisms. Technologies supporting companion diagnostics have not been systematically transitioned from engines of discovery to diagnostics platforms supporting robust assay performance consistent with mainstream applications in general clinical laboratories. Similarly, as pointed out by both Milne *et al.* and Cohen *et al.* in this issue, these platforms have not undergone rigorous analytic validation, providing defined value for the therapeutic management of disease in the form of clinical qualification [5,6]. Furthermore, diagnostic analytes may be evaluated by different technologies that have not been cross-validated, reducing cross-platform interoperability [10]. In turn, the absence of assay performance standards with rigorous analytic validation and standardization across laboratories and platforms contributes to diagnostic irreproducibility. In addition, quantitative and qualitative relationships between analytes and therapeutic management do not always undergo rigorous clinical qualification, and the evidence linking a companion diagnostic with clinical outcomes may not be confusing, as highlighted by Cohen *et al.* [6]. The clinical utility of companion diagnostics should be defined in appropriately powered prospective blinded and randomized clinical trials and validated in follow-up trials to provide unambiguous guidance on the utility of targeted therapies.

Companion diagnostics influence clinical decision-making, which can substantially impact on the economics of patient care. Indeed, as highlighted in this issue, companion diagnostics that quantify the expression of Her2 receptors in breast cancer identify patients who respond to costly monoclonal antibody therapies directed to that target [10]. Similarly, in this issue, Fong *et al.* highlight the utility of companion diagnostics for thiopurine methyltransferase in making clinical decisions concerning the use of thiopurines in a range of diseases, from cancer to rheumatologic disorders [11,12]. Moreover, as discussed in this issue, using companion diagnostics at the earliest stages can improve the success rate of drug development programs, ultimately lowering the costs of these programs and the therapeutics they produce [13]. In this context, the profit margins for companion diagnostics are justified by the argument that they direct the application of expensive therapeutics selectively to patients who will benefit in an era of constrained healthcare dollars [5,6,13]. However, the emergence of companion diagnostics specifically, and molecular biomarkers generally, as high-profit products has been one of the engines driving the boom in biotechnology [14]. Their success depends on whether these products address robust markets and direct decisions regarding expensive, complex or dangerous therapeutic interventions. At stake is a US$5 billion market growing at 25% annually.

Historically, the path for developing diagnostics included obtaining approval for the marketing of test kits from the US FDA, which would then be distributed by local clinical laboratories. However, molecular diagnostics can forego FDA approval and achieve implementation in central laboratories [14]. Obviating the need for FDA approval and offering diagnostic tests through a central laboratory permits more rapid development timelines and reduces costs. However, these higher development efficiencies are associated with a reciprocal reduction in the pursuit of definitive studies analytically validating and clinically qualifying diagnostics. It is this paucity of clinical validation that creates uncertainties in their value to healthcare economics and to clinical decision-making for therapeutic application, which contributes to restricted integration of companion diagnostics into patient management paradigms by payors and practitioners [5,6].

As highlighted in this issue, companion diagnostics offer a path from the current empiric model of healthcare to the development of deterministic personalized medicine [5,6,10,13]. However, their integration into practice management paradigms will only come about with the generation of data that clearly demonstrate

their value proposition for both healthcare economics and clinical practice [5,6]. Indeed, in this issue, Lee *et al*. highlight that the development and clinical application of companion diagnostics should have an established basis of evidence, reflecting clinical trial design, analytical methodologies and statistical rigor [15]. Moreover, there may be benefits in centralizing federal regulatory oversight of approval, marketing and quality control in application in the FDA and/or Centers for Medicare and Medicaid Services. In this context, efforts should be focused on collaborations across the public and private sectors to facilitate the discovery and application of companion diagnostics that will support the application of molecularly targeted therapeutics to achieve a truly personalized approach to healthcare.

Financial & competing interests disclosure

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References

1 Waldman SA, Terzic A. Knowledge cycle transforms therapeutic innovation. *Clin. Pharmacol. Ther.* 91(1), 3–8 (2012).

2 Waldman SA, Terzic A. Systems-based discovery advances drug development. *Clin. Pharmacol. Ther.* 93(4), 285–287 (2013).

3 Waldman SA, Terzic A. Translational medicine individualizes healthcare discovery, development and delivery. Foreword. *Biomark. Med.* 7(1), 1–3 (2013).

4 Waldman SA, Terzic A. Information hierarchies optimize patient-centered solutions. *Clin. Pharmacol. Ther.* 93(1), 3–7 (2013).

5 Milne C-P, Bryan C, Garafalo S, McKiernan M. Complimentary versus companion diagnostics: applies and oranges. *Biomark. Med.* 9(1), 25–34 (2015).

6 Cohen JP. Roadblocks preventing personalized medicine from reaching its potential *Biomark. Med.* 9(1), 5–8 (2015).

7 Waldman SA, Terzic A. Molecular insights provide the critical path to disease mitigation. *Clin. Pharmacol. Ther.* 95(1), 3–7 (2014).

8 Waldman SA, van der Graaf PH, Terzic A. Systems approaches evolve clinical pharmacology. *CPT Pharmacometrics Syst. Pharmacol.* 2, e68 (2013).

9 Waldman SA, Terzic A. Advancing pharmacometrics and systems pharmacology. *Clin. Pharmacol. Ther.* 92(5), 535–537 (2012).

10 Advani PP, Crozier JA, Perez EA. HER2 testing and its predictive utility in anti-HER2 breast cancer therapy. *Biomark. Med.* 9(1), 35–49 (2015).

11 Fong SCM, Blaker PA, Arenas-Hernandez M, Marinaki AM, Sanderson JD. TPMT testing for azathioprine therapy: progress in the clinic. *Biomark. Med.* 9(1), 51–65 (2015).

12 Relling MV, Gardner EE, Sandborn WJ *et al.* Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing: 2013 update. *Clin. Pharmacol. Ther.* 93(4), 324–325 (2013).

13 Rubinger DA, Hollmann SS, Serdetchnaia V, Ernst DS, Parker JL. Biomarker use is associated with reduced clinical trial failure risk in metastatic melanoma. *Biomark. Med.* 9(1), 13–23 (2015).

14 Licking EF, Longman R. The new diagnostics companies. *Start-Up* 12–19 March 2006.

15 Lee EY, Shen H-CJ. Regulatory considerations for companion diagnostics. *Biomark. Med.* 9(1), 67–75 (2015).