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Companion diagnostics at the intersection of personalized medicine and healthcare delivery.

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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.[1-3] 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.[4-6] Diagnostics biomarkers are quantifiable disease characteristics which provide information about underlying molecular processes to define disease progression or predict treatment response.[7] Familiar diagnostic biomarkers include traditional measurements (heart rate, blood pressure), imaging techniques (chest X-ray, mammograms), and protein measurements (PSA, 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 (SNP) analysis, genomic and proteomic profiling, epigenetic profiling and gene expression profiling. In turn, these diagnostics increase disease-specific sensitivity and specificity contributing to the accuracy of personalized disease management.[2,3,5,6]

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 .[8] Yet, as pointed out in this issue by Milne 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 (Milne et

al).[9,10] These limiations in the validation of molecular diagnostics has raised considerations around approval and marketing by regulatory agencies.[4,7,11,12] Moreover, as highlighted in this issue by Cohen, the paucity of biomarker validation serves as a considerable obstacle to the adoption of companion diagnostics by healthcare providers and payors (Cohen). The evolving regulatory and reimbursement environments, associated with the importance ofanalytic validation and clinical qualification, has resulted in barriers to adoption that has restricted the full impact of companion diagnostics in clinical practice.

The emergence of analytic technologies for evaluating nucleic acids and proteins, associated with the deconvolution of the human genome, provided the technological “push” to develop molecular biomarkers for disease management.[3-5,7] Conversely, advances in understanding molecular mechanisms contributing to pathogenesis have yielded an abundance of drug targets to individualizetherapeutic care, providing the associated “pull” for development of companion diagnostics.[13] At first, compnaion diagnostics developed in the model of classical biomarkers, as single elements related to the response of a patient to a specific therapeutic agent.[14] 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 complex molecular circuits contributing to pathophysiology.[13-15] 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, SNPs, methylation, and the

proteome are poised to inform the best therapeutic strategies, as exemplified in this issue in breast cancer (XYZ).

While companion diagnostics reflect the envisioned future for individualized therapies[1-5,7], their potential has yet to be realized, reflecting issues of technologies, clincial validation, and mechanisms.[9,10,16] Unfortuantely, 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 ponted out by both Milne and Cohen in this issue, these platforms have not undergone rigorousanalytic validation, providing defined value for therapeutic management of disease, in the form of clinical qualification (Milne, Cohen).[4,9,10,16,17] Further, diagnostic analytes may be evaluated by different technologies which have not been cross-validated, reducing cross-platform inter-operability.[4,7,17] Absence of assay performance standards with rigorous analytic validation and standardization across laboratories and platforms contributes to diagnostic irreproducibility.[7,13,17] Additionally, quantitative and qualitative relationships between analytes and therapeutic management do not always undergo rigorous clinical qualification, and the evidence linking a companion diagnsotics with clinical outcomes may not be confusing at best as highlighted by Cohen (Cohen)[9,10,18,19] 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.[9,10]

Companion diagnostics influence clinical decision-making which can substantially impact the economics of patient care.[1,18,19] 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 (XYZ). The profit margins for these 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 (Milne, Cohen). 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.[8] Their success depends on whether these products address robust markets and direct decisions regarding expensive, complex, or dangerous therapeutic interventions.[8] At stake is a $5 billion market growing at 25% annually.

Historically, the path for developing diagnostics included obtaining approval for marketing of test kits by the FDA that would then be sold to local clinical laboratories.[4,18,19] However, molecular diagnostics can forego FDA approval and achive implementation in central laboratories.[8] Obviating the need for FDA approval and offering diagnostic tests from a central laboratory, , permits more rapid timelines and cheaper reduced costs. However, these higher development efficiencies are associated with a reciprocal reduction in the pursuit of definitive studies analytically validating and clinically qualifying diagnostics.[7,9,10,17] It is this paucity of clinical validation, which creates uncertainties in their value to healthcare economics and to clinical decision making for therapeutic application, which contributes to restricted

integration of companion diagnsotics into patient management by payors and practitioners, respectively.[13,16,17]

As highlighted in this issue, companion diagnostics offer a path from the current empiric model of healthcare to the development of deterministic personalized medicine.[1,3,5,19] However, the integration of companion diagnostics into practice management paradigms will only come about with the generation of data that clearly demonstrates their value proposition for both healthcare economics and clinical practice. .[7,9,10,16] In that regard, the development and clinical application of companion diagnostics should have an established basis of evidence, reflecting clinical trial design, analytical methodologies, and statistical rigor. Moreover, there may be benefits in centralizing federal regulatory oversight of approval, marketing, and quality control in application, in the FDA and/or CMS.[9,11,12] In that context, efforts should be focused on collaborations across 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.[4,7,17-19]

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