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Translational medicine individualizes healthcare discovery, development and delivery

"In the present issue of Biomarkers in Medicine, the impact of translational medicine in revolutionizing disease management is highlighted."

Individualized patient management is rapidly expanding, fueled by unprecedented innovation that spans modern medical discovery, development and delivery [1,2]. This next generation 'd³' continuum is poised to radically transform the extent of healthcare solutions. Discovery is accelerating across the spectrum of biomedical specialties and, driven by high-throughput molecular technologies that support newfound knowledge in genomics, epigenetics, proteomics and metabolomics, offers previously unrecognized insights into the pathogenesis of human disease [2–5]. Integration across platforms enables informed development and delivery of healthcare paradigms aimed at elucidating the molecular pathophysiology underlying patient-specific disease and the deployment of targeted personalized diagnostic and therapeutic modalities ensuring optimal management. Accordingly, biomarker panels of disease risk, indices of prognostic outcomes, predictors of therapeutic responses and molecular signatures of adverse event susceptibility have become integral in the toolkit of healthcare providers [6,7]. Remarkably, deconstructing hierarchical signaling systems corrupted in disease refines molecular interventions targeting dysregulated circuits, thereby personalizing healthcare algorithms to maximize benefits while eliminating risk [8].

In the context of this revolution in the scientific underpinnings of health and disease, translational medicine has become the critical path to personalized patient care, positioned to realize the enormous value of national resource commitments that serve as the engine driving the modern biological revolution [9,10]. The emerging translational medicine community of practice, which integrates key knowledge domains across medical and scientific specialties, leads the vanguard of this scientific revolution, driving innovation in platform technologies that provide unexpected capabilities in areas beyond

traditional patient management in disease prediction, prevention and cure [11]. Indeed, translational medicine is primed to maximize science-driven healthcare paradigms that directly align clinical care strategies with individual patient and population requirements for optimum health and wellness [12]. In the present issue of *Biomarkers in Medicine*, the impact of translational medicine in revolutionizing disease management is highlighted.

Hyslop *et al.* focus on triple-negative breast cancer [13]. This disease, which often affects young women, is typically highly aggressive and notoriously difficult to clinically manage. Insights from enabling platform technologies have revealed disease heterogeneity, with at least six subclasses separated by subtle cellular and molecular signatures [13]. In turn, these signatures are undergoing translation into novel biomarkers that identify prognostic risk categories and predict therapeutic responses [13]. Moreover, these molecular advances are motivating the evolution of the regulatory framework at the level of the US FDA, with the addition of novel clinical outcomes, including pathological complete responses, and the incorporation of emerging molecular signatures as key correlative end points in biomarker adaptive approaches driving therapeutic trials in triple-negative breast cancer [13].

Recognition of translational medicine as one essential approach to maximizing health and wellness across the aging continuum, originating at the nexus of molecular discovery and patient management, underscores the fundamental need for a structure that spans the spectrum from knowledge generation to regulation and application [7]. In turn, this framework can transform novel molecular insights into patient-centered algorithms, evolving platform technologies into healthcare delivery systems, distributing best practices in translational medicine into populations and ultimately

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modulating behaviors that transform global healthcare [14].

The model of bench-to-bedside translation is highlighted by Magee *et al.*, who are developing novel immunotherapeutic approaches for patients with colorectal cancer anchored in the discovery of a key molecular marker that is selectively expressed in metastatic cancer cells [15]. Indeed, this molecular marker has been the focus of numerous clinical trials of its utility as a prognostic and predictive staging marker in colorectal cancer. More recently this marker has been positioned to enter clinical trials as a vaccine target for the secondary prevention of metastatic colorectal cancer [15]. Moreover, the deployment of this type of molecular innovation in translational medicine is being facilitated by essential key knowledge domains in comparative effectiveness and health services research, in the science of knowledge dissemination, and in the nucleation of multidisciplinary teams spanning disparate communities of practice [7,16]. This continuum of innovation in discovery and application, from the bench to the bedside and ultimately to the population, produces a flux of information across those communities, shaping and prioritizing strategies that are central to the implementation of translational medicine, ensuring deployment of optimum healthcare paradigms for clinical application [17].

Contemporary patient care is experiencing a dramatic evolution driven by the expansion of new knowledge at the nexus of discovery and application. In that context, translational medicine has advanced logarithmically, spurred on by enabling technology paradigms including the omics revolution, personalized therapies, precision medicine and the informatics sciences, including bioinformatics and clinical informatics, that provide unanticipated insights into the molecular structure underlying pathophysiology [18–20]. The development of these paradigms are illustrated by Rothstein and Jickling, who review the substantial impact that biomarker discovery and application is having on the clinical management of stroke [21]. Indeed, the development of a variety of novel molecular biomarkers and signatures is poised to permit the identification of patients at risk for ischemic stroke; discriminate different mechanisms of stroke with implications for management; evaluate the extent of damage to brain tissue to establish the prognosis of patients who have suffered a stroke; and permit the identification of optimum therapeutic management algorithms to maximize benefits

to patients [21]. Similarly, Balgkouranidou *et al.* highlight the impact of biomarker discovery, specifically in the area of epigenetics, on the management of lung cancer, the leading cause of cancer death worldwide [22]. Indeed, the frequency of DNA methylation aberrations in lung cancer and the platforms that quantify these modifications in specimens offers unique advantages compared with other species of biomarkers. Furthermore, the expanding list of genes exhibiting epigenetic changes in pathophysiology underscore the essential role of these alterations for diagnosis, prognosis and prediction of response to therapies in lung cancer [22]. Moreover, it is important to consider that epigenetic alterations represent disease-associated changes to the genome that are reversible, in striking contrast with genetic mutations. Thus, these diagnostic approaches are revealing essential drugable targets that have the potential to alter the management of this devastating disease [22].

Integration of these emerging enabling technology platforms defines one essential path forward to resolve the complex mechanistic processes underlying fundamental physiological programs that are corrupted in disease at the systems level [23]. In turn, identification of these maladaptive system adaptations provides previously unexpected insights, producing individualized diagnostic and therapeutic approaches, biomarkers of disease risk and prognosis and predictive markers of therapeutic responses, optimizing healthcare management paradigms for individual patients and populations. Defining these biological systems and signaling circuits underlying pathophysiology offers a framework to identify ideal drug targets and develop approaches that provide patient-oriented healthcare solutions. This complexity is illustrated by Pravica *et al.*, who highlight the critical interplay of systems in the pathobiology underlying multiple sclerosis [24]. Indeed, this multifactorial disease reflects the complex and variable interplay between genetics, the immune system and the environment [24]. Mechanistic insights evolving from efforts in translational medicine are identifying distinctive patterns of disease, permitting subsegmentation of patients with different prognostic risks [24]. In turn, the revolution of biomarker discovery and application is poised to completely redefine disease susceptibility to identify patients at risk [24]. Moreover, these platforms provide novel approaches for therapeutic response

assessment, to quantify the effectiveness of disease-modifying therapies [24].

The foregoing highlights the revolution in translational medicine established by emerging innovations in platform technologies, in which patient-centered outcomes are informed by the individualization of molecular diagnostics and therapeutics. This bench-to-bedside continuum is framed in this issue by the interview with Dr Richard Weinshilboum of the Mayo Clinic, (MN, USA) who discusses his career at the intersection of emerging platform technologies, development of novel insights into the genomic underpinnings of disease pathogenesis and drug responsiveness and the translation of these insights into better diagnostic tools that optimize therapeutic interventions across the disease spectrum [25]. This emerging paradigm in translational medicine is yielding insights and approaches that are extending from the laboratory into the healthcare marketplace. Moreover, global economics, political realities and limitations in

healthcare resources make it essential to establish the value of translational medicine, to ensure clinical benefits are maximized for patients, populations and societies worldwide [1].

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