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Review

Challenges and prospects for biomarker research: A current perspective from the developing world ☆

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ABSTRACT

Majority of deaths due to communicable and non-communicable diseases occur in the low and middle-income nations (LMNs), mainly due to the lack of early diagnoses and timely treatments. In such a scenario, biomarkers serve as an indispensible resource that can be used as indicators of biological processes, specific disease conditions or response to therapeutic interventions. Evaluation, diagnosis and management of diseases in developing world by following/extrapolating the findings obtained on the basis of the research work involving only the populations from the developed countries, could often be highly misleading due to existence of diverse patterns of diseases in developing countries compared to the developed world. Biomarker candidates identified from high-throughput integrated omics technologies have promising potential; however, their actual clinical applications are found to be limited, primarily due to the challenges of disease heterogeneity and pre-analytical variability associated with the biomarker discovery pipeline. Additionally, in the developing world, economic crunches, lack of awareness and education, paucity of biorepositories, enormous diversities in socio-epidemiological background, ethnicity, lifestyle, diet, exposure to various environmental risk factors and infectious agents, and ethical and social issues also cumulatively hinder biomarker discovery ventures. Establishment of standard operating procedures, comprehensive data repositories and exchange of scientific findings are crucial for reducing the variability and fragmentation of data. This review highlights the challenges associated with the discovery, validation and translational phases of biomarker research in LMNs with some of their amenable solutions and future prospects. This article is part of a Special Issue entitled: Biomarkers: A Proteomic Challenge.

1. Introduction

Burden of both communicable and non-communicable diseases is massive in developing countries [1]. While ethical and social issues, lack of awareness and ineffective international research collaborations are collectively obstructing clinical research and management in the developing world; certainly, the major hindrances are the paucity of financial support for establishment and maintenance of advanced research infrastructures and extreme biological diversities [2]. Over the last few decades, the emergence of 'omics' techniques has accelerated biomarker research by providing platforms suitable for screening large number of biomolecules in a rapid fashion, facilitating the identification of valuable biomarkers in a short period of time without the requirement of any prior in-depth knowledge into the mechanism of disease progression [3–9]. Although initial findings of potential biomarkers from the "omics" discovery phase are very promising, unfortunately their ultimate clinical translation is found to be very rare [10]. A plethora of biomarkers for a number of diseases have emerged, however only a few have received approval for clinical use by FDA [11–13].

In spite of the massive burden of disease related morbidity, the initiative of biomarker oriented research is prevalent in developed countries with only about 10% of global research dedicated to address the concerns of the developing world [1]. This review provides an inclusive discussion of various challenges associated with the conventional biomarker discovery pipeline with an emphasis on the major obstacles for clinical research encountered by the developing countries. Additionally, amenable solutions for some of the existing limitations and notable global initiatives in the field of omics research for development of

Abbreviations: DELSA, Data-Enabled Life Alliances; EGP, Estonian Genome Project; EuPA, European Proteomics Association; FDA, Food and Drug Administration; HUPO, Human Proteome Organization; IGS, International Genomics Consortium; LMNs, Low- and Middle-income nations; MIAPE, Minimum Information About a Proteomics Experiment; MDG, Millennium Development Goals; NCDs, Non-Communicable Diseases; NCI, National Cancer Institute; PPP, Plasma Proteome Project; PRIDE, Proteomics Identification Database; PSI, Proteomics Standards Initiative; P3G, Public Population Project in Genomics; SOPs, Standard Operating Procedures; TCGA, The Cancer Genome Atlas; WHO, World Health Organization

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standard operating procedures (SOPs) and quality assurance protocols for introducing uniformity in sample processing, data acquisition, analysis and interpretation are also discussed.

2. Generic hurdles in transition of biomarkers utility from bench to bedside

During the last two decades, tremendous efforts have been made in the discovery of biomarkers using high-throughput omics approaches. However, the numerous obstacles that lie along the biomarker establishment path pose diverse challenges to translate biomarkers in clinical settings (Table 1). Experimental design including, inclusion/exclusion criteria for subject selection, type of sample, collection and handling procedure, storage, accurate data acquisition, analysis and documentation are the major issues that need to be addressed for a successful biomarker discovery and validation program [11,14–19]. The next step after the biomarker discovery is development of assays [13] to test the clinical sensitivity and specificity of biomarkers. Safety, ease of

Table 1
Challenges associated with different stages of biomarker discovery pipeline.

Challenge/limitation	Description	Amenable solution/recommendation/global initiatives
1. Pre-analytical variations and lack of SOPs	• Sample collection Venepuncture, phlebotomy, blood source, sample collection device, anticoagulant (for plasma), coagulation process (for serum), tube additives • Sample processing Intrinsic proteolysis, addition of protease inhibitors/stabilizers, processing time and environment, dilution of samples, centrifugation condition, fractionation • Sample storage Shipping condition, elapsed time before freezing, storage temperature and duration, storage device, number of freeze/thaw cycles [88,89]	• Establishment of standard operating procedures (SOPs) and quality assurance protocols • Well planned and standardized experimental design • Uniform sample collection, handling and storage procedure [89] • Documentations of viabilities • Human proteome organization-proteomics standards initiative (HUPO-PSI) [90,91] • Minimum information about a proteomics experiment (MIAPE) [62]
2. Biological diversities[a]	• Sociodemographical background Age, gender, ethnicity, lifestyle, diet • Clinicopathological background Stage of infection, medication, pregnancy, previous history of diseases, existence of co-infections, exposure to environmental risk factors and infectious agents, and hormonally-related variables • Determination of sample size [92]	• Implementation of stringent inclusion and exclusion criteria • Analysis of suitable controls • Meticulous documentation of subjects' background • Analysis of bigger clinical cohorts • Analysis of specimens from different populations for cross-validation
3. Disease heterogeneity	• Changing patterns of diseases pathobiology, clinical manifestations and epidemiology • Lack of consideration of genetic and proteomic variation while profiling and researching a disease [9,92] • Lack of global initiative in sequencing projects like TCGA for diseases predominant in developing countries [93] • Negligence of intra tumor variation and clonal evolution [85]	• Clinical trial strategies to screen disease heterogeneity [93] • Global incentive to collaboratively study disease heterogeneity of diseases plaguing the world • Establishment of consortia for data sharing and bioinformatic analysis of population-wide variables [93]
4. Technical limitations, variations and data analysis	• Insufficient sensitivity and dynamic range of the detection technology • Extreme complexities of biological samples [9] • Variation of findings among different technological platforms and lack of reproducibility • Lack of uniformity in data acquisition and analysis process [4,94,95] • Lengthy experimental process and high cost	• Application of next-generation high-throughput and sensitive technologies • Reduction of complexities of biospecimens by using pre-fractionation techniques • Sharing of scientific data among different research groups across the world
5. Validation and clinical trials	• Technological approaches implemented in biomarker discovery are generally not suitable for validation [10] • Lack of high-throughput validation approaches • Difficulties in immunoassay-based validations of huge number of potential targets identified in discovery phase • Discrepancies between the findings of discovery and validation phase	• MS-based targeted proteomic approaches; particularly, selected reaction monitoring (SRM) or multiple reaction monitoring (MRM) are emerging [96]
6. Lack of resources/funding[a]	• Paucity of active financial supports; neither suitable governmental grants, nor any philanthropic/charity funding for long-term research ventures [7] • Lack of infrastructure for advanced multidisciplinary biomarker discovery processes	• Changes in trends of resources/funding for clinical research • Beside governmental funding, active support from "private sectors" (including pharmaceutical companies, R&D, NGOs), angel investors, regional authorities, charities • Commercialization of biomedical research [97]
7. Lack of stable biorepository[a]	• Lack of stable biorepositories in developing world [52] • Sample obtaining process from existing biobanks is not well organized [76] • Resources are not open for sharing • Ethical issues regarding long-term use of biospecimens, confidentiality and social implications [51,76,86]	• Next-generation biobanking in developing countries [1] • Establishment of high-quality uniform standards • Nationalization of individual stand-alone biorepositories [52] • Establishment of the national and international societies to address the technical, legal, ethical, uniformity and quality assurance issues [52] • Setting up nationwide biorepositories in developing world with access to third party data-miners to facilitate collaborative research across the globe [53]
8. Ethical, social and political issues[a]	• Bio-safety and quality control • Maintenance of confidentiality of the subjects • Disclosure of incidental unusual findings leading • Concerns regarding data ownership and sharing [53,75,87,98]	• Dissemination of awareness and education [99] • Establishment of institutional review boards (IRBs) • Stringent regulatory laws by the government • Intervention by international independent bodies for debating any possible violation of ethical issues

[a] Challenges prevailing in low and middle income nations (LMNs) of the developing world.