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Case Report

Briefly Towards the Biomarker-Driven Development and Their Global Im-pact in The Evidence-Based Clinical Practice of Personalized and Precision Healthcare Services

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A B S T R A C T

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1. Introduction

Drug development continues to move in the direction of the development of clinical practice as applicable to Personalized and Precision Medicine (PPM), - where ideally the most effective therapy or treatment is determined by the genetic makeup of the patient. The area of PPM as an upgraded model of the healthcare services and thus an area of daily clinical practice, that involves the use of measuring biomarkers in clinical samples, is an area of high clinical interest. Tremendous efforts have been made to date to discover biomarkers of the next step generation for use in clinical practice, but, unfortunately, a rate of implementing of biomarkers into clinical practice is still rather low[1,2,3,4].

PPM uses upgraded clinical philosophy and innovative technologies to provide evidence-based and clinically valuable decisions in regard to the diagnosis and treatment, prediction and prognostication, prevention and prophylaxis of disease and/or any kind of disorders or pre-illness conditions. Increased utilization of molecular stratification of patients or persons at risks will provide medical professionals with evidence upon which to base canonical therapeutic strategies for individual patients or preventive and prophylactic manipulations for individual persons at risk. PPM thus has the potential to offer improved medication selection and targeted therapy being biomarker-based, reduce adverse effects, increase patient compliance, shift the goal of medicine from reaction to prevention and increase patient confidence post-marketing by approving novel biomarker-based and driven therapeutic strategies and altering the perception of medicine in the healthcare system.

In the realm of PPM as a modern healthcare, Hi Tech-related biomarkers have emerged as powerful tools, transforming the landscape of disease management and treatment[1,2,5-7,4]. These biomarkers, derived from various molecular entities such as genes, proteins and interactomes, hold immense potential in predicting and prognosticating individual responses to therapies and guiding personalized treatment strategies.

There are still many open questions in data-analytic research pertaining to biomarker development in the era of PPM, OMICS-technologies, Bioinformatics and IT-based resources and Big Data. Among them is the question of what constitutes best practice for the extraction of prioritized lists of candidate biomarkers to be used in the right way in daily clinical practice and drug discovery.

Biomarkers are considered to be essential and crucial for the development of PPM and PPM-based and PPM-driven technologies and can thus be used in the immediate clinical practice (such as determining what devices or drugs are the best fit for patients, depending on the presence or absence of certain biomarkers) as a generation of the ready-to-be-used monitoring tools, in a broad scope of clinical settings to facilitate medical product development and inform patient care decisions, as well as for drug development (for example, patient selection) in the drug design-inspired biotech-driven translational research and applications[5,3,8,9,6,7].

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. In this sense, among the main challenges to implementation of PPM into routine medical practice is a knowledge gap of professionals about biomarkers and biomarkers-driven tools to be used by the practitioners in their daily work. Moreover, biomarkers are useful for enrichment in regular clinical trials and identifying the “right” patients to enroll in clinical trials, whilst acting their crucial role as key contributors to drug design, drug discovery and drug development success as a whole. Biomarkers are used in drug development to help define mechanisms of action, drug target selection, stratification, patient selection, enrichment, dose selection, safety assessment, efficacy assessment, molecular pathways leading to disease and preclinical safety assessment[2].

The unique molecular and genomic heterogeneity of the living systems, including humans, constitutes a potentially rich source of candidate biomarkers. Screening for biomarkers as covariates within classic statistical models requires that error rates be controlled in a manner that accounts for test multiplicity[10]. In this sense, the refinement of a set of candidate biomarkers can be achieved through many different pipelines. But clearly, the identification of better candidate biomarkers at the beginning of the development pipeline will prove beneficial in the later stages of the process.

In general, biomarkers can indicate a variety of health or disease characteristics, including the level or type of exposure to an environmental factor, genetic susceptibility, genetic responses to exposures, markers of subclinical or clinical disease or indicators of response to therapy. Thus, a simplistic way to think of biomarkers is as indicators of disease trait (risk factor or risk marker), disease state (subclinical or clinical) or disease rate (progression)[11,4].

Conceivably relevant biomarkers can be used to define subgroups of patients and a patient’s subgroup affiliation can be incorporated into evidence-based medical decisions. Biomarkers such as prostate-specific antigen (PSA)and specific mutations in genes (e.g., genes, encoding BRCA1/BRCA2, raising breast and ovarian cancer risk), have been utilized in clinical practice for some time[12]. And thus expectations regarding the level of precision for such tools will likely be increased by the perception that Big Data and Data Banks (for example, clinical databases, high-throughput experimental datasets, IT-resources) can be translated into clinically relevant and useful information.

Biomarkers are extremely important in cancer research and Personalized and Precision Oncology (PPO); they are crucial for risk assessment, screening, differential diagnosis, prognosis determination, prediction of disease recurrence and response to therapy and progression monitoring[3,13,14]. With cutting-edge proteomic and genomic technologies, DNA and tissue

microarrays, gel electrophoresis, mass spectrometry and protein assays, as well as improved bioinformatics tools, the evolution of biomarkers to reliably assess the results of cancer mitigation and therapy is now possible. Looking forward, a urine or a serum test for each stage of cancer may possibly drive clinical decision making, complementing or even replacing presently available invasive methods[3,14].

Due to the individualization of cancer therapy, the identification of cancer- and oncology-specific biomarkers has become a foremost goal for cancer researchers[3,14]. The common usage of prostate-specific antigen (PSA) in prostate cancer screening has prompted investigators to look for appropriate biomarkers for screening other kinds of cancer. Targeted medicines, such as Iressa® (gefitinib), Gleevec® (imatinib) and Herceptin® (trastuzumab), are currently available and may benefit from a more targeted treatment based on diagnostic testing.

In the clinic, biomarkers may help identify individuals who are most likely to react to a medication, enable real-time monitoring of treatment effectiveness or detect early indications of drug toxicity. Furthermore, biomarkers are heavily used in go/no go decision making throughout the drug development cycle, from early discovery to preclinical assessment.

Meanwhile, with the emergence of more sensitive and specific technologies that are now able to be run in clinical settings and the ability to accurately measure biomarkers, there is a need to understand how biomarkers are defined and how they are used in conjunction with drug treatment or with the frame of protocols of clinical trials[8,9,6,7].

Innovative clinical trial designs are needed to address the difficulties and issues in the development and validation of biomarker-based personalized therapies. Designing trials of biomarker-guided therapy has many challenges, including: (i) being almost always unblinded, they are prone to bias; (ii) the control group, most frequently 'usual care' group, is open to contamination and has inevitably better outcome than in real non-trial 'usual care; (iii) being per essence 'strategy-trials' rather than simple intervention trials, causality is difficult to establish; (iv) therapy optimization as a result of change in the tested biomarker may be left to the decision of the investigator, only instructed to follow best guideline medical therapy or decided per-protocol using more or less sophisticated algorithms, which, although guideline-based, may vary according to the protocol[8,9,6,7].

Biomarker approaches have entered into early clinical trials and are increasingly being used to develop new diagnostics that help to differentiate or stratify the likely outcomes of therapeutic intervention. The utility of biomarkers in the evidence-based clinical decision and personalized therapy guidance seeks to improve the patient outcomes and decrease wasteful and harmful treatment. Efficient and validated biomarkers are crucial for the advancement of diagnoses, better molecular targeted therapy, along with therapeutic, prophylactic and rehabilitative advantages in a broad spectrum of various diseases or pre-illness conditions. Despite recent advances in the discovery of biomarkers, the advancement route to a clinically validated biomarker remains intensely challenging and many of the candidate biomarkers do not progress to clinical applications, thereby widening the innovation gap between research and application.

Biomarkers can be classified as antecedent biomarkers (identifying the risk of developing an illness), screening biomarkers (screening for subclinical disease), diagnostic biomarkers (recognizing overt disease), staging biomarkers (categorizing disease severity) or prognostic biomarkers (predicting future disease course, including recurrence and response to therapy and monitoring efficacy of therapy)[15].

In strategic sense, there are three key categories of biomarkers, including: (i) diagnostic biomarkers (to identify individuals with a disease or condition of interest or to define a subset of the disease), (ii) prognostic biomarkers (indicate the likelihood of a clinical event, disease recurrence or progression), (iii) predictive biomarkers (to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure), (iv) safety biomarkers; (v) pharmacodynamic (response) biomarkers[16]; (vi) monitoring biomarker; and (vii) susceptibility (risk) biomarkers **(Figure 1)**.

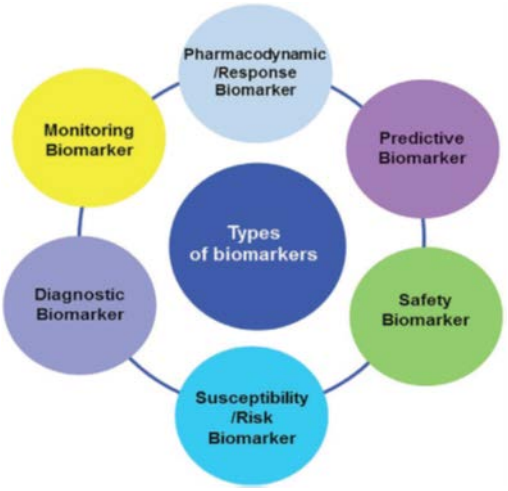

Figure 1: Classification of biomarkers based on its main clinical applications.

A canonical diagnostic biomarker is applied daily to identify individuals with a disease or condition of interest or to define a subset of the disease. A prognostic biomarker is used to estimate the outcome for a patient in the absence of a treatment. A predictive biomarker is used to estimate the benefit for a specific treatment, while being used to monitor the effectiveness of a prescribed treatment.

Analyzing and assessing the above-mentioned diagram, let me stress that predictive and pharmacodynamic biomarkers would play a crucial role in identifying patients or persons-at-risk who are more likely to respond favorably to specific treatments[1,2,5,8,9,6,16]. By unraveling the underlying molecular mechanisms associated with treatment response, these biomarkers pave the way for targeted interventions, optimizing treatment outcomes and minimizing unnecessary adverse effects. For instance, the identification of EGFR-related mutations in lung cancer, determines the response to EGFR inhibitors, leading to improved treatment efficacy and patient survival rates. The advent of those biomarkers has revolutionized the field of PPM, where treatments are tailored to individual patients based on their unique disease characteristics. By providing insights into the likelihood of treatment response, predictive biomarkers empower clinicians to make informed decisions and optimize therapeutic interventions[7].

In contrast to the fully validated and FDA-approved

biomarkers, many exploratory biomarkers and biomarker candidates have potential applications. Prognostic biomarkers are of particular significance for malignant conditions and monitoring cancer-related conditions. Similarly, canonical diagnostic biomarkers are important in autoimmune diseases. Disease severity biomarkers are helpful tools in the treatment for chronic inflammatory diseases. Identification, qualification and implementation of the different kinds of biomarkers are challenging and frequently necessitate collaborative efforts. This is particularly true for stratification biomarkers that require a companion diagnostic marker (theranosticums) that is co-developed with a certain drug. The latter in the future of PPM, being and serving as a valuable guidance, would play a crucial role in clinical practice since are possessing their accuracy to be crucial for the success of the therapeutic, preventive, prophylactic and rehabilitative choice.

All emerging treatments and associated biomarkers require clinical trials to confirm their properties and to inform and influence daily clinical practices, as well regulatory reporting before achieving approval for professional and/or commercial release.

Biomarkers can be used in clinical settings to facilitate drug repurposing and inform patient care decisions and can be incorporated into drug development through the drug approval process, scientific community consensus followed by regulatory acceptance and biomarker qualification.

The involvement of biomarkers in clinical practices will be more and more common in the next 5-10 years because of the development in medical-related biological and transdisciplinary research, as well as in Biodesign-inspired and biotech-driven translational applications. More clinical questions need to be answered about the biomarker and its role in disease process and therefore more biomarker-related clinical trials will be designed to answer those specific questions. More flexible trials serving multiple purposes are expected due to the intricate relation between biomarkers and the disease.

Meanwhile, a principally new generation of biomarkers is required that define all aspects of the variability of unified system indicators.

For instance, circulating microRNAs (miRNAs) are attracting interest in the burgeoning field of PPM and associated subfields, with data supporting their diagnostic, prognostic and predictive biomarker potential. Effective miRNA profiling calls for reproducible, sensitive and specific tools with turn-around times fast enough to support Biodesign-inspired translational research and applications into what can be a rapidly changing disease progression and treatment environment.

Moreover, following the clinical aims and objectives of the next step generation and having a complete understanding of a drug's pathway, interactome and network interactions could expedite the identification of sensitizing mutations, drug interactions or the risks of drug combinations to guide biomarker discovery, including simple, combinatorial and network-based biomarkers (NBBs) **(Figure 2A,B)**.

SLE is a heterogeneous autoimmune disorder, featuring with 90 (82 up- and 8 downregulated) differentially expressed genes (DEGs) common to female LN-, female LN+ and male LN+ using the GSE65391 and GSE49454 gene expression datasets from Gene Expression Omnibus database. The protein–protein interaction (PPI) network of 70 DEGs was constructed using STRING and cytoscape and the Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis showed that the PPI network was significantly enriched in defense response to virus, cytosol, protein binding and measles. Sixteen hub genes were identified from this PPI network and Literature Mining Gene Networks molecular of GenCLiP 2.0 showed strong interaction between STAT1, DDX58 and IFIT1. Enrichment analysis of hub genes in published literature showed the involvement of immune response and interferon-related genes in the pathogenesis of SLE. In addition, the transcription factors STAT1 and 2 and IRF6 and 9 had high Normalized Enrichment Score. The 70 DEGs with PPI network and 16 hub genes are potential biomarkers of SLE and can help improve diagnosis and develop individualized therapies. NBBs, network-based biomarkers.

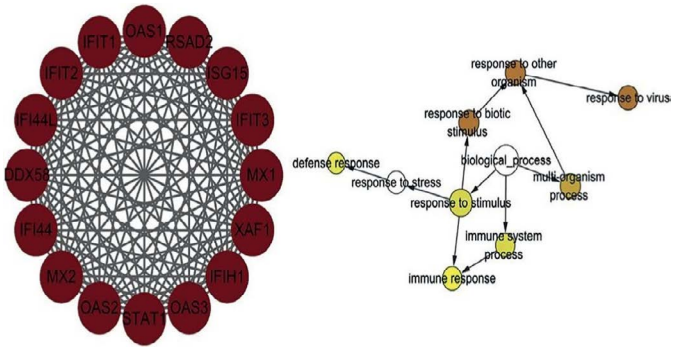

Figure 2A: Potential NBB-related protein biomarkers for systemic lupus erythematosus (SLE) determined by bioinformatics analysis.

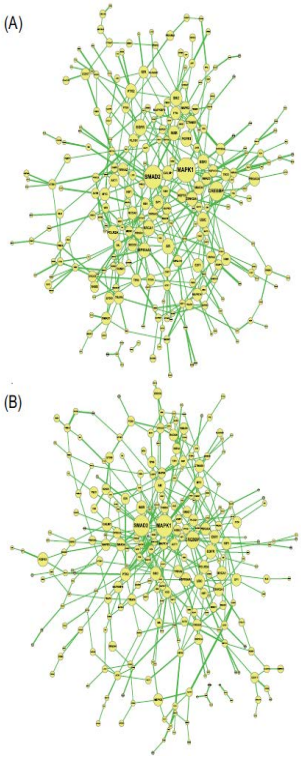

Figure 2B: The constructed network-based biomarker (A) Cancer protein association network (CPAN) (B) Non-cancer protein association network (NPAN).

The node size is proportional to the CRV for each protein and the edge width represents the magnitude of the association

ability between the two proteins. The figures are created using Cytoscape.

We may also identify specific pathways and interactome-based networks involved in diseases for which drugs have not yet been explored in appropriately designed trials. In this sense, NBBs help determine the probability of developing chronic pathologies or autoimmunity- or cancer-predisposed conditions. Key factors contributing to the growth of the global NBBs-related healthcare services market include high prevalence of chronic autoimmune diseases and cancer; rising adoption of biomarkers for diagnostic, predictive and prognostic applications; and increasing application in drug discovery and development.

A NBB using constructed protein association networks is a useful tool to highlight the pathways and mechanisms of the lung carcinogenic process and, more importantly, provides potential therapeutic targets to combat cancer. From a systems perspective, the constructed network-based biomarker further evaluated the targeted carcinogenic process by use of significant protein identification and diagnostic evaluation. More importantly, the significant proteins identified by the NBBs give mechanistic insights into the carcinogenic process and provide potential therapeutic targets to combat cancer in the real clinical practice.

Novel biomarkers may also identify specific pathways involved in risk, where drugs interrupting such mediator bio-targets have not yet been explored in appropriately designed trials[8,9,6]. Regarding biomarkers of the latest innovative trends, let me add that along with canonical antibodies (Abs) serving a crucial role as biomarkers in clinical settings, some of the Ab-based families proven to occur are Abs possessing with catalytic activity (catAbs or abzymes) and thus to belong to Abs with a feature of functionality **(Figure 3)**[5].

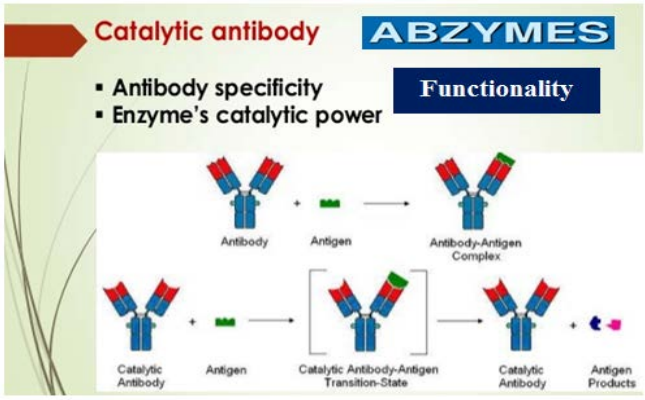

Figure 3A: Antibodies (Abs) possessing with catalytic activity (catAbs or abzymes) belonging to Abs with a feature of functionality.

The property is buried in the Fab-fragment of the Ig molecule and is appearing to sound as a functional property of the Ab molecule. In this sense, proteolytic Abs (or Ab-proteases) as a significant portion of the big family of abzymes represent Abs endowed with a capacity to provide targeted proteolytic effect.

CatAbs (or abzymes) are multivalent Igs, presumably of IgG isotype, endowed with a capacity to hydrolyze Ags. The enzymatic activity is located in the Fab fragment of the Ig molecule, which endows such antibodies with the ability to bind to specific antigens and hydrolyze them. Proteolytic Abs (or Ab-proteases) represent a significant portion of the family of abzymes that PPM uses to target specific Ags. Because of their Ag specificity, Ab-proteases also may be used as biomarkers able to control autoimmune disease progression to transform from subclinical into clinical stages and to predict complications. Moreover, sequence-specific Ab-proteases have proved to be greatly informative and thus valuable as biomarkers to monitor autoimmune diseases at both subclinical and clinical stages while demonstrating their predictive value for the development of the disorder[5,17,18].

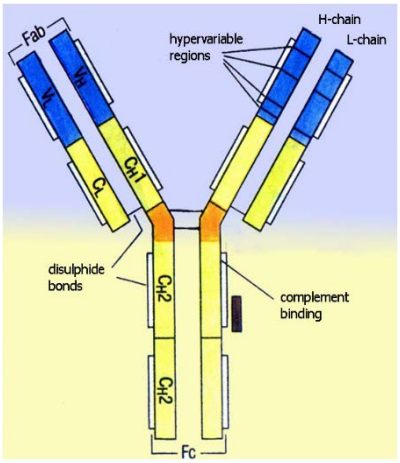

Figure 3B: CatAbs (or abzymes) are multivalent Igs, presumably, of IgG iso-type, endowed with a capacity to hydrolyze the Ag substrate.

You might see from the above-mentioned, that biomarkers can be used along with tools in clinical practice, as drug development tools and can be incorporated into drug development through the drug approval process, scientific community consensus followed by regulatory acceptance and biomarker qualification. This would offer a new way to optimize treatment, decrease rehabilitation costs and facilitate building new products and services in this area, viz. multimarker-based companion diagnostics.

For instance, biomarkers, defined as alterations in the constituents of tissues or body fluids, provide a powerful approach to understanding the spectrum of cardiovascular diseases and chronic autoimmune myocarditis with applications in at screening, diagnosis, prognostication, prediction of disease recurrence and therapeutic monitoring.

The unique diagnostic potential of specific biomarkers and its efficacy correlating with phenotypical expression, would cover neuroinflammation and neurodegeneration, including the applications of biomarker-based strategy in multiple sclerosis (MS), Parkinson and Alzheimer diseases.

A comprehensive understanding of the relevance of each cancer biomarker will be very important not only for diagnosing the disease reliably, but also help in the choice of multiple therapeutic alternatives currently available that is likely to benefit the patients. Cancer biomarkers are broadly categorized into three divisions based on the specific signature it is associated with: diagnostic, predictive and prognostic biomarkers. The therapeutic potential of different biomarkers and their use in clinical trials has also been discussed. Despite the recent advancements, a comprehensive approach on biomarker biogenesis is required to integrate the available information and to translate them as tools of prognostic and diagnostic potential.

Biomarkers of the future would be used for: (i) screening the general population or individuals at risk (panels of screening and

predisposition biomarkers); (ii) the detection of the presence of a particular type of cancer (panels of diagnostic and prognostic biomarkers); (iii) monitoring the progression of autoimmune inflammation and predicting the complications and outcome (panels of prognostic biomarkers); (iv) understanding whether a patient will benefit from a specific drug treatment (panels of predictive biomarkers); and (v) evaluating the drug's efficacy and optimizing the treatment, providing the tool to tailor treatment for individual autoimmunity-related patients or persons at risk (panels of pharmacodynamics biomarkers).

Meanwhile, a number of limitations of multimarker-based panels should be acknowledged. These include potential multiplexing and analytical challenges in assaying multiple biomarkers at once as well as the challenges of interpretation for the clinician due to different cut-offs for each of the separate markers[9]. Nevertheless, it can be anticipated that scoring calculators and algorithms will increasingly use circulating biomarkers in combination with clinical variables to allow appropriate surveillance and fully informed counselling of the patients, persons-at-risk, their families and other stakeholders in the process of patient care.

Anyway, biomarkers have gained immense scientific and clinical value and interest in the practice of PPM and PPM-related subareas. Biomarkers are potentially useful along the whole spectrum of the disease process. During diagnosis, a set of specialized biomarkers can determine staging, grading and selection of initial therapy. During treatment, they can be used to monitor therapy, select additional therapy or monitor recurrent diseases and complications. Advances in OMICS-technologies and molecular pathology have generated many candidate biomarkers with potential clinical value. In the future, integration of biomarkers, identified using emerging high-throughput technologies, into PPM-related evidence-based medical practice will be necessary to achieve 'personalization' of treatment and disease prevention.

A growing area of biomarker research in autoimmunity and cancer-related conditions is the search for biomarkers that can predict successful drug-free remission. Stratifying diseases classified according to phenotype is not the only way that biomarkers can be used to forge a molecular taxonomy of disease: they can do so also by breaking down the boundaries of current classifications. That is, biomarkers can be used to uncover molecular similarities between diseases thought to be distinct.

Biomarkers and PPM have introduced a novel way of thought processes, appraising diseases, in applying novel advanced technologies and emphasizing proactive and preventive medicines. Biomarkers are providing value across the entire drug development spectrum and the shift is impacting both the patients and the entire landscape of the healthcare system.

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