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The Functional Architecture of Personalized & Precision Medicine (PPM) Driven by Innovative Strategies to Secure the Clinical Implementation to Cancer Management: Brief Comments

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ABSTRACT

The medicine of the XXI century is personalized & precision medicine (PPM), by protecting and preserving human health throughout the life. Creating and maintaining a high level of public health and thus the wellness is a priority in the health sector. In this regard, an upgraded model of healthcare service, which includes the philosophy, principles and armamentarium of PPM and aimed at identifying the disorder at its early (subclinical) stage, is being created and set up. PPM focuses on predictive and preventive measures that contribute to the development of individualized strategies for managing a healthy lifestyle that stabilize morbidity rates and can help to improve the working capacity of the population. Against the background of the development of PPM, there was an explosion and the evolution of the concept of biomarkers (specific bio-indicators), whose combinations have been being studied, and their effectiveness and efficacy as working resources were being evaluated.

KEYWORDS

Personalized & precision medicine; Cancer management; Biomarkers

INTRODUCTION

Over the course of history, healthcare and thus healthcare philosophy have been focused predominantly on efforts to probe the already diseased individual by focusing down on a type of disorder (nosology) rather than on health or so-called pre-illness conditions. Much less effort has been placed on keeping individuals from developing disorders in the first place. PPM is expected to transform this situation giving healthcare professionals of tomorrow much more reliable control over morbidity, mortality and disabling rates, and significantly optimize the cost and

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efficacy of treatment for those who have fallen ill and already diseased, or are still persons-at-risk. PPM is a name for the grand new paradigm in healthcare management being based first on prevention, pre-clinical detection of the illness, and delivery of drugs to target tissues with exceptional levels of precision.

SCIENTIFIC AND WORKABLE PLATFORMS TO SECURE THE PPM PROGRESS

The grand challenge of PPM is to forecast, predict, prevent and treat exceptionally, is rooted in the most recent developments in systems biology, bioinformatics, nanomedicine and translational medicine. Each of those sciences is a separate niche activity that we hope to see unified to create a new healthcare continuum with great potential future impact on quality of life outcomes [1].

Systems Biology

Systems biology is already becoming well established in its own right. It is worth mentioning that the core information resources of systems biology are the "omics" sciences.

Genomics probes the general principles of the functional architecture of genomes. Currently, particular attention is being paid to the development of pathological genomics, which allows not only for molecular genetic diagnostics, but is also an important step to determining the intensity of RNA transcription and protein translation in relation to the onset and development of diseases. A clear example of promising developments in this field are results from translational genomics crystallized into DTC-testing aimed at precise and reliable diagnosis that can inform the implementation of disease preventive strategies and preventative manipulations.

If genomics is rooted in the development of DNA and RNA sequencing techniques, methods for the identification of individual proteins and antigenic determinants contained therein play a fundamental role in proteomics. Proteomics relies fundamentally on the use of kits, including immunochemical tests, protein micro-sequencing techniques, high performance liquid chromatography (HPLC) with mass-spectrometry, and on protein microchips for high throughput screening.

In addition, proteomics is now securing real time metabolomics to reflect the complexity of all metabolic pathways in cells at given points in time.

Thus, systems biology is helping profoundly to characterize the cooperative networks in cellular and intercellular systems, dynamics, control, and design principles. This information may then be employed to derive new models of practical medicine [1,2].

Bioinformatics (BI) and IT Technologies

The emergence of a large amount of unstructured information as a result of research is inconvenient. Such information overload is now being resolved by means of two unique technological platforms - BI and Artificial Intelligence (AI) for the analysis of big data being harvested from screening, scanning and assessment procedures. Those two platforms are expected to provide professional communities with the means to mine, integrate, store, process and interpret large quantities of data, as done never before.

A real bioinformatics challenge has been interpretation of data resulting from the sequencing of the human genome. Furthermore, with the most recent advances in DNA sequencing this field moves rapidly to integrate sequence information from individual patients in real time and to understand the latter through the view of digitalization.

With regard to practical advances gained with bioinformatics, this forms a particular ground for the revolutions in genomics, phenomics and exposomics, and the associated predictive analytics and thus the diagnostic,

predictive and prognostic technologies. A significant amount of data harvested from the body sources can be retained in even a single database to demonstrate connections and interrelationships for each body cell type. This has led to the impressive results accumulated in the fields of neurology, endocrinology of cardiology and oncology.

Thus, the BI-related armamentarium is becoming open and thus able to provide the newest technological support for the PPM health care model being implemented into the daily practice.

Translational Medicine (TraMed)

Within the framework of a PPM healthcare model, a special niche is occupied by the resources and tools for TraMed. The global main goal of TraMed is to bring together disciplines, resources, experience, and armamentarium within this niche in order to prompt laboratory innovations ahead to reach the practice and to thus improve prevention, prophylaxis, diagnosis, treatment and rehabilitation.

TraMed is considered today as interdisciplinary field of scientific and medical endeavor, linked with a deep knowledge of drug development, intellectual property, and regulatory issues, all to define optimal mechanisms for translation of the latest science and healthcare concepts from bench to bedside, and often involving the formation of spin out biopharma and biotech companies along the way. This is giving rise to a new philosophy and definition of a term of *interdisciplinarity* and communications to underpin an explosion of healthcare innovations in the very near future to come.

TraMed is also a binary concept that follows “from research to patient and persons-at-risk”, aimed at facilitating and implementing clinical trials involving new therapeutic strategies derived from the latest scientific research, and “from patient to research”, aimed at using clinical feedback to inform and then drive the innovation of even better, more appropriate therapeutic strategies into the clinic [2].

TraMed goal and a unique achievement of XXI century biomedicine

Currently, the principal priority of TraMed is to find potential and highly informative biomarkers with their subsequent selection. It is worth noting that the most important achievement of TraMed is the identification of biomarkers pathogenic pathway. Consequentially, such diagnostics, focused on molecular bioindicators of diseases, can secure both a more accurate illustration of the health status of a particular patient or a person-at-risk, and to develop a specific drug with the proper dose of the active substance, with potential benefits of increased clinical efficacy and individual safety. In addition, improved patient outcomes with the use of the biomarker tests must consider not only increased survival or quality of life, but also improved clinical decision support (CDS) and making leading to the avoidance of unnecessary therapy or toxicity captured within the rapid learning systematically revolutionize the public health service.

As a strategic product of translational applications, biomarkers, that gave impulse to the development of the concept of the precise diagnostic and targeted therapy, provide an opportunity to create tools belonging to the fundamentally new generation. Moreover, discovery and clinical application of biomarkers of the principally next-step generations are expected to play a significant role in reshaping life science research and healthcare biopharma and biotech, thereby profoundly influencing the detection, monitoring and curative effects in a broad scope of disorders including cancer in particular.

According to the trend-affiliated data, future challenges illustrating the biomarkers world would also include the development of combinatorial mathematical algorithms to

handle simultaneous analysis of many parameters (perhaps up to thousands even) illustrating the functional architecture of the interactome-based networks to aid the diagnosis be confirmed. And a comprehensive understanding of the relevance and validity of each (regardless to being *simple* or *combinatorial* ones) biomarker will be very important to efficiently diagnose the cancer condition and provide appropriate direction in the multiple therapeutic alternatives.

Precision therapeutic approaches

Whilst the above are a platform for the creation of a comprehensive personalized medicine approach to disease prediction and prevention, what about prospects for comprehensive precision therapeutic approaches (PTAs) for chronic disease treatment. We define such PTAs for chronic disease treatment as having the following basic elements.

Identification of disease target cells in situ

Potentially achievable through the application of advanced diagnostic imaging techniques such as magnetic resonance imaging (MRI), near infrared (NIFR) fluorescence or resonance Raman, used in appropriate combination with imaging nanoparticles (or theranostic nanoparticles [drug-delivery combined with imaging]).

Guidance of theranostic nanoparticles to disease target cells

Potentially made possible by the exogenous application of a tissue irradiation technique, such as image guided focused ultrasound (IgFUS), to direct theranostic nanoparticles (TNPs) to accumulate in disease target cells so as to clear disease state(s) there. Target-cell receptor specific targeting ligands may also be attached to TNPs in order to facilitate this process.

Confirmation of therapeutic effects

Potentially made possible by the accumulation of TNPs into disease target cells. Diseased cells should be visible for as long as cells survive and/or the disease state continues.

Such PTAs for disease treatment may be described as true image-guided approaches for treatment beginning with detection based on the use of bespoke imaging nanoparticles (or TNPs) for use in combination with advanced diagnostic imaging modalities such as MRI, NIFR and resonance Raman (as above) [but also computed tomography (CT) and nuclear medicine imaging techniques such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)]. Once disease target cells are visible to advanced diagnostic analysis, then personalized medicine (as described above) offers the detailed background information necessary to select the best choice of active pharmaceutical ingredient (API) for highly controlled delivery to diseased cells in vivo using bespoke TNPs under the influence of tissue irradiation (as noted above), giving rise to target-focused drug delivery, then highly effective treatment of a given patient under examination. Currently, the detection of disease target cells in situ has still to be perfected in the case of virtually all chronic diseases, so the advent of comprehensive PTAs for the treatment of chronic diseases is currently a future opportunity rather than a present reality, but not for long we would venture to hope [3].

«MUST-HAVE» KEY TO UNLOCK THE PERSONALIZED & PRECISION MEDICINE (PPM) AND ONCOLOGY (PPO)

Development trends of fundamentally new type of practical health care (personalized medicine) dictate new healthcare requirements. More than 11 million people are diagnosed with cancer every year. Biomarkers are therefore becoming invaluable tools for cancer detection, diagnosis, prognosis and treatment selection. These can also be used to predict the malignancy, to identify the subclinical stage, to localize the tumor and determine its

stage, subtype, and response to therapy. Identification of such signature in surrounding cells or at more distal and easily sampled sites of the body can also influence the management of cancer.

Diagnostic, predictive and prognostic biomarkers are quantifiable traits that help oncologists at the first interaction with the suspected patients or persons-at-risk. Those particularly aid in: 1) Identifying who is at risk; 2) Diagnose at the pre-early stage; 3) Select the best preventive and canonical therapeutic treatment modality, and 4) Monitor response to the manipulations. Those biomarkers mentioned exist in different forms covering a broad scope of:

- Cytogenetic and cytokinetic markers.
- Genetic and epigenetic biomarkers.
- Cells (CTCs, T-regulatory cells, cancer stem cells/CTCs, etc.) as biomarkers.
- Viral biomarkers.
- Cancer antigens.
- Heat shock proteins/HSPs.
- Mitochondrial markers.
- Metabolic biomarkers.
- Therapeutic biomarkers, etc.

A major challenge in cancer diagnosis is to establish the exact relationship between cancer biomarkers and the clinical pathology, as well as, to be able to non-invasively detect tumors at the pre-early (often subclinical) stage.

To achieve PPM-based treatment for cancer, a practitioner of the future would need biomarkers for securing predictive analytics and prognostic efficacy, for determining prognosis, predicting response to therapy, and predicting severe toxicity related to treatment. Biomarkers are therefore, an objective measure or evaluation of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Figure 1).

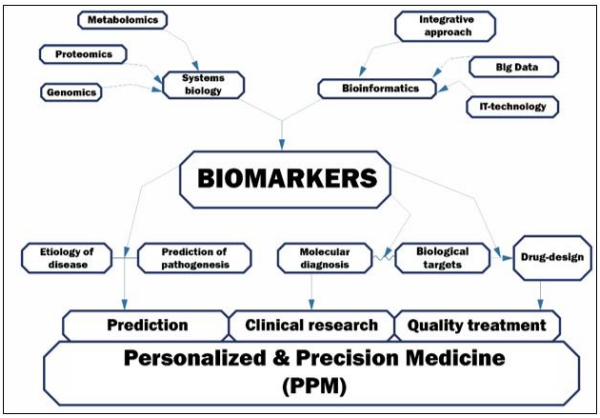

Figure 1: Biomarkers as «must-have» key to unlock the PPM and PPO.

A number of applications of PPM (e.g., a growing number of genomic markers of efficacy, adverse events and dosing of therapeutics) have been proposed and have contributed to oncology practice and healthcare as a whole at many points in an individual's (including patient's and person-at-risk') lifespan. So, we might stress that the translation of PPM and PPO into clinical care and health policy has lagged behind the pace of basic science discoveries.

STEP BY STEP ON THE WAY OF A GLOBAL CHALLENGE - TO SAVE OUR LIVES AND TO SECURE WELLNESS

"Being human means to be a fighter!" - wrote Johann W Goethe. Due to the increase in the occurrence of pathologies of unknown cause, in order to preserve and prolong life, it is necessary to take care of health as early as possible - even before the bright disease manifestations.

Therefore, a future challenge in the cancer research will be the discovery of novel biomarkers to get PPM and PPO fields re-armed! For instance, the biomarkers of the future would have to be used for: 1) Screening the general population or individuals at risk (panels of screening and predisposition biomarkers); 2) The detection of the presence of a particular type of cancer (panels of diagnostic and prognostic biomarkers); 3) Monitoring the progression of the disease, and predicting the tumor's outcome (panes of prognostic biomarkers); 4) Understanding whether a patient will benefit from a specific drug treatment (panels of predictive biomarkers); 5) Evaluating the drug's efficacy and optimizing the

treatment, providing the tool to tailor treatment for individual cancer patients or persons-at-risk (panels of pharmacodynamics biomarkers).

Thus, policy formation in the field of individual health promotion and protection is one of the priority tasks of national healthcare systems. To achieve the goals of value-based healthcare and the implementation of a PPM healthcare model, it is necessary to combine the assets of the latest advances in basic science with clinical medicine, followed by the introduction and promotion of translational capabilities.

PPM SEGMENTS AND THEIR FEATURES

The segment of predictive medicine provides procedures for disease prediction and for the prediction of consequences and complications. It should be noted that these arrangements are more suitable in healthy persons than in patients with a disease manifestation. As a result, the main idea of predictive medicine is to teach a healthy person the means to live in harmony with their body, genes and nature holistic ally.

As for the segment of preventive medicine, all efforts are aimed at promoting a healthy and active lifestyle. It goes without saying that preventive medicine is an alternative ideology and even methodology of healthcare, the essence of which is to manage the state of individual health and reserves of a particular organism in existing environmental conditions. The main task of preventive medicine is to extend healthy life and increase the size of working-age population, with simultaneous and timely detection of pathological changes in the body, and targeted measures aimed at preventing diseases.

By contrast, the segment of personalized medicine is a complex of medical and diagnostic measures for a particular patient, based on the results of fundamental research into individual genomes, proteomes and metabolomes and capable of becoming a program for managing own health.

Finally, the segment of precision therapeutics involves the development and implementation of innovative technologies to control drug administration such that drugs will essentially traffic to target tissues alone and nowhere else, thereby improving drug efficacies and minimizing drug use side effects potentially to a degree unheard of with huge potential impacts on standards of care.

All segments above gain from advances in cellular and biomolecular methods of diagnosis, prevention, treatment and rehabilitation. Creating and harnessing these advances is the main obstacle that stands in the way of general adoption of a full PPM healthcare model [4].

CONCLUSION

Each unit of personalized medicine is such an independent qualified segment, as a separate «specific brick» of a multidisciplinary functional system. Consequently, PPM-model can permanently work only with interaction between all segments. Creating a damage-proof base, these «bricks» piece together into unified whole, and a completely new technological model can be created, working for the benefit of society.

Based on an interdisciplinary basis, PPM and PPO are developing and producing scientific yield, which can be effectively used in daily clinical practice in the future. No less important is that such a multi-disciplinary alliance should be properly and correctly structured and adopted under real real-world environment.

In the conclusion, we would to note that a number of applications of PPM (e.g., a growing number of genomic markers of efficacy, adverse events and dosing of therapeutics) have been proposed and have contributed to oncology practice and healthcare as a whole at many

points in an individual's (including patient's and person-at-risk') lifespan.

The biomarker-based analysis is intended as a first step towards a more personalized and precision treatment and clinical utility. Our next-step objective is to study whether we could utilize the biomarker panels to identify individuals in high-risk settings for more thorough follow-ups. Such information has not been available before and we will evaluate the value of those results for care in follow-up studies. In addition, new generation of biomarkers is needed that quantifies all aspects of systems flexibility, opening the door to real lifestyle-related health optimization, self-empowerment, and related products and services.

Moreover, the key factors contributing to the growth of the global next-generation biomarkers market include high prevalence of chronic diseases (predominantly, cancer), high government funding for cancer research and clinical trials, rising adoption of biomarker for diagnostic applications, increasing application in drug discovery and development. Introduction of new technologies such as digital biomarker and rising adoption in PPM drive the market for NGBs.

Thus, PPM and PPO represent a paradigm shift in health care that is both maturing. There has been a rapid increase in the availability and use of biomarker-based tests and this growth is expected to continue. Accordingly, these upcoming changes will profoundly change the professional activities of medical communities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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