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Towards the Biomarker-Driven Development and their Global Impact in the Evidence-Based Clinical Practice of Personalized and Precision Healthcare Services

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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. PPM, an upgraded healthcare approach that systematically uses patient and/or persons-at-risk da-ta to inform individualized treatment decisions, has emerged as potentially transformative – offering the promise of superior treatment outcomes for most of the clients, including patients and/or per-sons-at-risk. PPM-related resources are supported by significant advances in biomarker testing and then in the validation to be used further in daily clinical practice Figure 1. Yet, the promise of PPM cannot be realized if clients do not have access to the biomarker testing required to determine their eligibility for PPM-based treatments. 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 Figure 2.

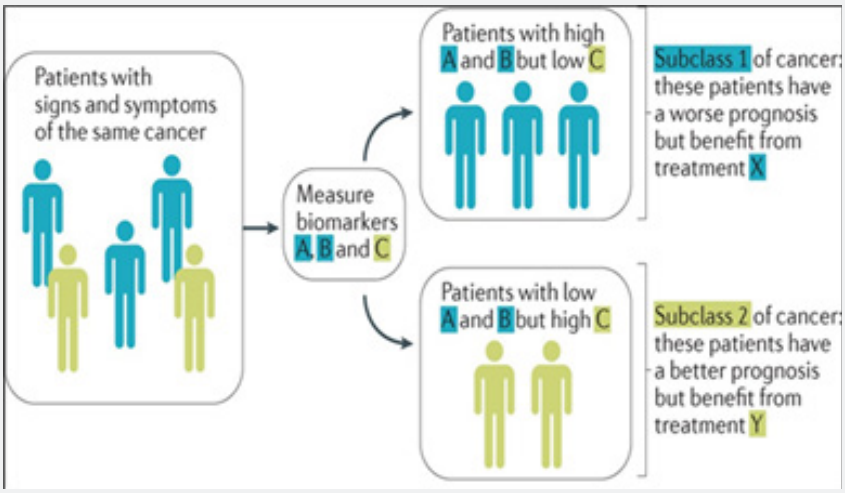

Figure 1: Biomarker development in the PPM-related era.

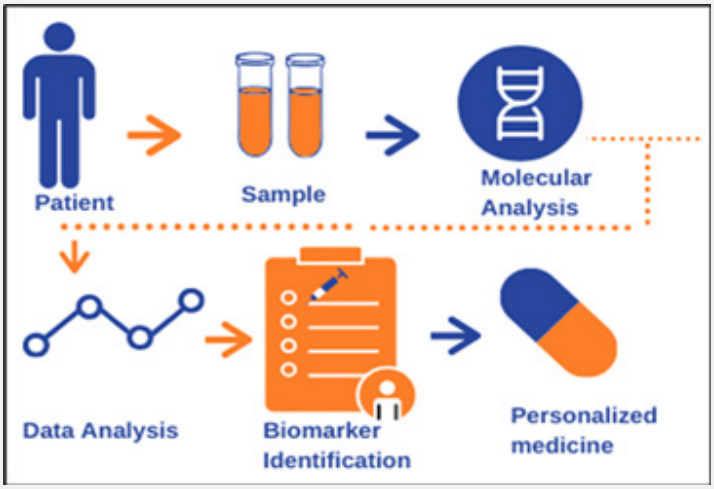

Figure 2: Role and impact of biomarkers in daily PPM-driven clinical practice.

Tremendous efforts have been made to date to discover biomarkers of the next step generation for use in clinical practice, but, unfortunately, the rate of implementing of biomarkers into clinical practice is still rather low [1-4]. 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 - and the assays used to detect, measure, and characterize them - are the cornerstone of PPM, which aims to match the right patient with the right drug at the right dose and time to optimize treatment impact and patient outcome. So, biomarkers are considered to be essential and crucial for the development of PPM and PPM-driven technologies, and can thus be used in the immediate clinical

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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 (endowing with diagnostic, predictive and prognostic resources) (Figure 3a,b), 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 de-sign-inspired biotech-driven translational research and applications [4-11]. The latter is much illustrated by explosive bursts at the global worldwide markets Figure 4.

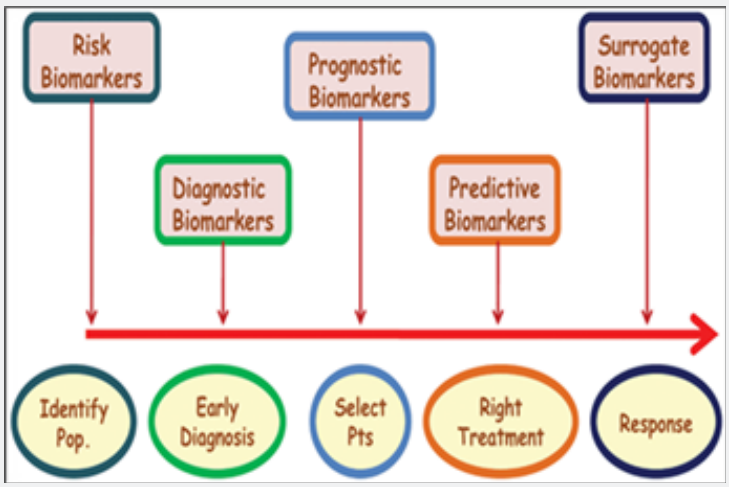

Figure 3A: Biomarkers as Diagnostic, Risk, Prognostic, Predictive, and Surrogate End-points.

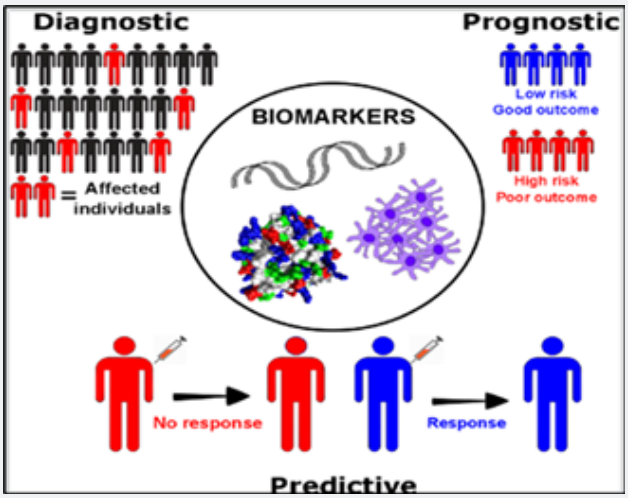

Figure 3B: Clinical applications of cancer bi-omarkers.

Modern diagnostic techniques are accelerating the shift toward PPM-related care for many ailments. With the aid of those techniques, physicians can identify and measure a variety of biomarkers to categorize patients and/or persons-at-risk into subgroups that differ in their tendency. This include client's vulnerability to develop a disease or pre-illness, their personalized mutation to develop a disease even after successful treatment, and their likelihood of responding to a particular treatment. And technological advancements in the development of biomarkers thus witnesses a rapid rise as the demand for PPM grows substantially. Thus, to ensure client (patient or persons-at-risk) access to the new technologies, a reimbursement framework needs to be put in place to reflect the changing healthcare landscape. This will potentially encourage manufacturers to invest in new products as reimbursement policies which have a direct impact on the development and growth of biomarker-driven families of diagnostic, predictive and prognostic tools.

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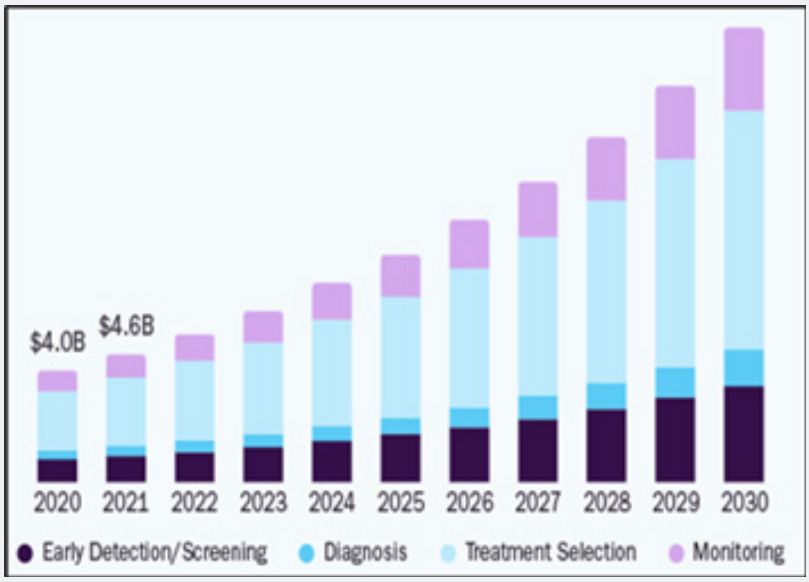

Figure 4: U.S. Personalized & Precision Bi-omarkers Market.

The value of biomarkers - characteristics that are assessed as indicators of physiological and/or pathogenic biological processes, or responses to an intervention - is broadly appreciated, but the number of qualified and validated biomarkers is small. 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, patient selection, efficacy assessment, molecular pathways leading to disease, etc. [2]. As the use of biomarkers continues to expand across the research and care continuum, therapeutic developers are tasked with integrating clinical design and execution with a clear biomarker-informed development plan Figure 5.

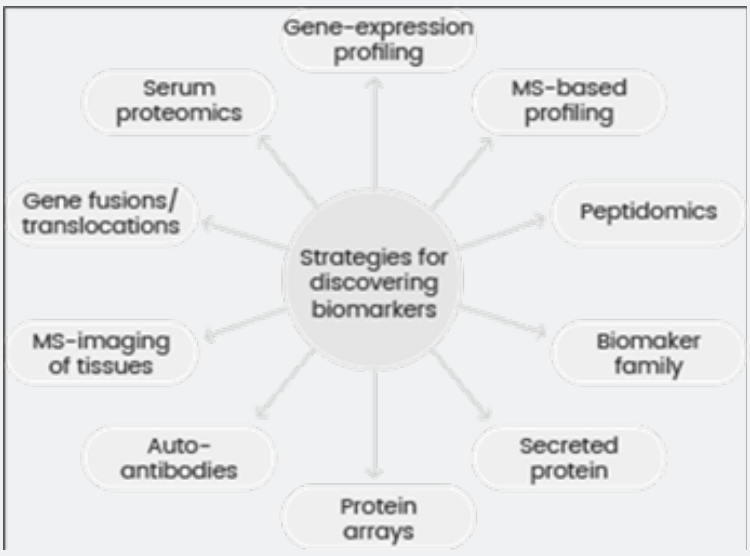

Figure 5: Strategy for biomarker discovery.

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A biomarker might be either a molecule secreted by a cell or a tumor, or it can be a specific response of the body to the presence of cancer. For instance, panels of genetic, epigenetic, proteo-mic, glycemic, and imaging biomarkers can be used for cancer diagnosis, prognosis and epidemiology. Consequently, biomarkers are not yet ready for routine use due to challenges in their clinical validation for pre-early (subclinical or pre-illness) disease detection, diagnosis and monitoring to improve long-term survival of patients. Molecular biomarkers are used together with clinical information to achieve PPM to customize prevention, screening, and treatment strategies to a group of patients with similar characteristics. As such, it is never too early to identify a defined pathway for taking an exploratory biomarker all the way through to diagnostic approval if data supports its use (Figure 6 a,b).

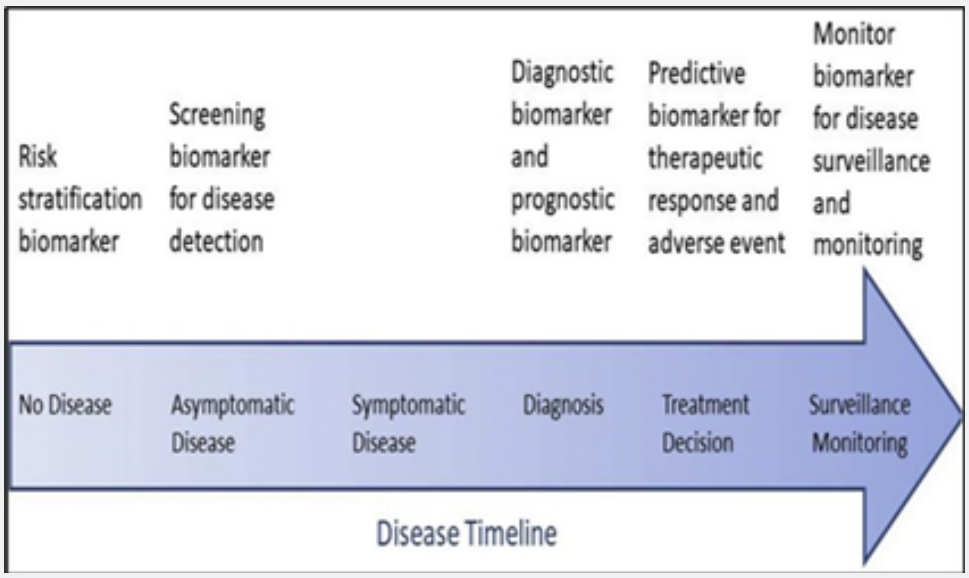

Figure 6A: Application of exploratory and use of biomarkers in relation to the course of disease.

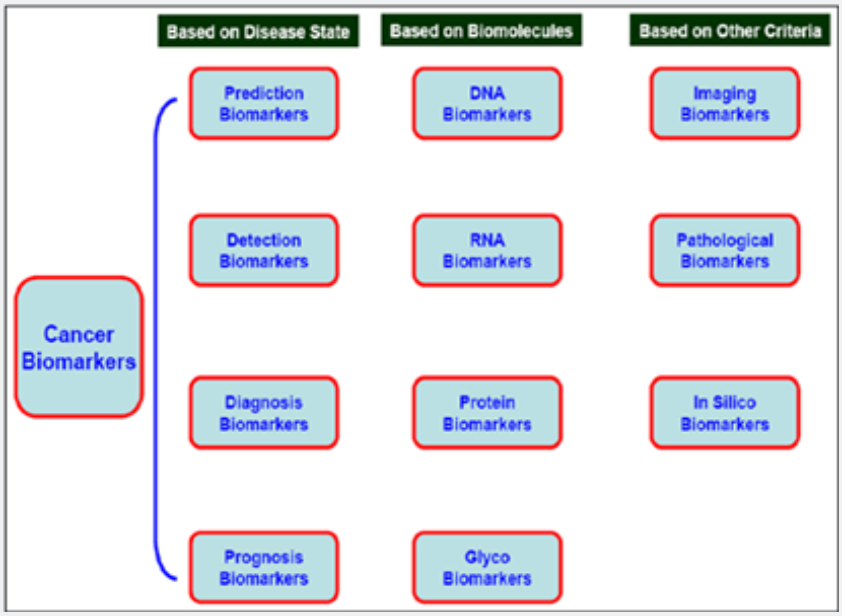

Figure 6B: Criteria-based classification of biomarkers.

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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) [4,12]. 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. The most common biomarkers are cancer-associated proteins, gene mutations, and extra copy numbers of genes. These molecules are sometimes secreted into the circulation and so may be detected by blood-based assay, whereas others are present in cancer cells and so require a biopsy to obtain tissue for testing.

The contribution of OMICS technologies to PPM is via the identification of relevant biomarkers. In a first step, OMICS technologies allow generating vast amounts of data on particular molecules in individuals with a specific condition. Data are then analyzed to determine whether particular biomarkers are associated with the occurrence of the disease or, perhaps, with a given prognosis, or even with a certain response to a defined therapeutic intervention. The human biomarker database can be accessed online, and the inter-disease relationships may be helpful in understanding the molecular mechanisms of diseases. To our knowledge, this is one of the first approaches to classify diseases based on biomarkers. And at the end of several rounds of analytical and clinical validation, biomarkers may be approved to be used in the clinic.

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 [6,13,14]. With cutting-edge OMICS-based 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 [6,14].

Due to the individualization of cancer therapy, the identification of cancer- and oncology-specific biomarkers has become a foremost goal for cancer researchers [6,14]. A wide array of potential cancer biomarkers is used to track disease development and progression or response to therapy Figure 7. Predictive biomarkers For instance, cancer biomarkers such as predictive ones indicate the likely effect of a specific targeted therapy on the patient and can guide treatment decisions. Among the latter: (i) HER2 positivity/activation which predicts response to trastuzumab in breast cancer; (ii) KRAS-activating mutations which are associated with resistance to EGFR inhibitors (e.g. cetuximab) in colorectal cancer (CRC); (iii) BCR-ABL1 chromosomal alteration, which can predict positive response to treatment with tyrosine kinase inhibitors (e.g. imatinib) in chronic myelogenous leukemia (CML).

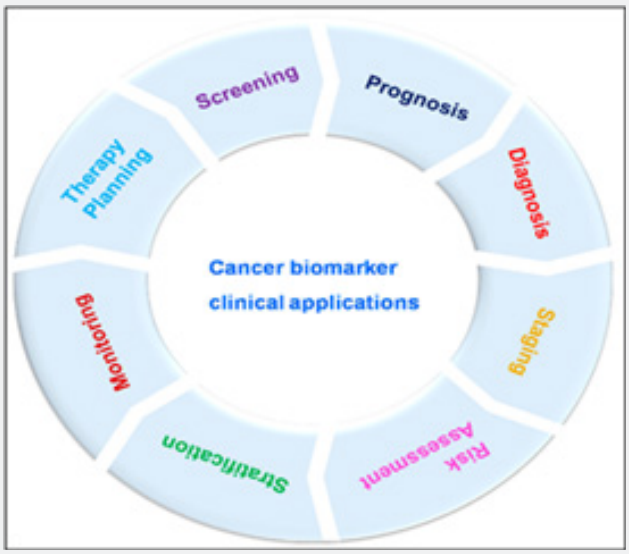

Figure 7: Cancer biomarker clinical applications.

Prognostic biomarkers Prognostic biomarkers don't typically trigger specific therapeutic decisions but inform physicians about the risk of clinical outcomes, such as recurrence or disease progression. Examples of prognostic biomarkers include: (i) prostate-specific antigen (PSA) levels which can indicate local and/or systemic prostate cancer disease progression; (ii)

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chromosome 17p deletions and TP53 mutations which predict poor survival in patients with CML; (iii) BRCA1 and BRCA2 gene mutations that increase the risk of breast and ovarian cancer in women and prostate cancer in men.

Moreover, hypermethylation of a gene promoter as a prognostic factor can lead to loss of gene expression, such as methylation of the HSBP1 gene in prostate cancer. Meanwhile, the presence of circulating tumor cells (CTCs) in peripheral blood which is strongly correlated with metastasis and the formation of secondary tumor foci, is considered as a prognostic factor as well. Diagnostic Biomarkers are broadly used to identify whether a patient has a specific disease condition and are expected to have high specificity and sensitivity. They include: (i) the Bence–Jones protein urine test which is often used as a diagnostic indicator of multiple myeloma; (ii) elevated levels of the CEA which is used in the surveillance of CRC patients; (iii) levels of PSA which are higher in patients with prostate cancer.

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 in prognostic sense. 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 and prognostic biomarkers empower clinicians to make informed decisions and optimize therapeutic interventions [10].

A Grand challenge for the development of cancer biomarkers is the nature of the cancer as being a heterogeneous disease. This heterogeneity may complicate the development of biomarkers. Detailed and comprehensive knowledge of cancer at the cellular and molecular levels has grown dramatically and exponentially in the past two decades and has resulted in significantly improvement in the characterization of human tumors which in turn has catalyzed a shift toward the development of targeted therapies, the basic concept for PPM. Therefore, it is postulated that the emergence of highly powerful "OMICS" technologies would contribute a lot into the backbone toward the discovery of novel biomarkers and/or panels, with distinct advantages over the currently used biomarkers. And the former concept of single biomarker discovery is expected to be replaced soon by multi-biomarkers discovery of panel of genes or proteins whereby, raising the query of whether the heterogeneous and multifactorial cancer may have single fingerprint.

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. So, the joint effort of clinicians, bio designers, researchers, bioinformaticians, and biostatisticians, in academia and industry will certainly make progress towards the development of sensitive and specific predictive, prognostic and diagnostic biomarkers. And the latter as a Grand Challenge and future prospective of biomarkers would determine trends in the biomarker development by facilitating the combination of therapeutics with diagnostics and would promise to play an important role in the development of PPM.

The intended use of a biomarker (e.g., risk stratification and screening) and the target population to be tested need to be defined early in the development process. The use of a biomarker in relation to the course of a disease and specific clinical contexts should also be pre-specified. The patients, persons-at-risk (pre-cancer clients) and specimens should both directly reflect the target population and intended use. And key considerations for conducting discovery studies using archived specimens are thus the targeted population represented by the specimen archive, power of the study, prevalence of the disease, the analytical validity of the biomarker test, and the pre-planned analysis plan. 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 [4,7-10]. And the unique molecular and genomic heterogeneity of the living systems, including humans, constitutes a potentially rich source of candidate biomarkers [15]. 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.

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 [4,7-10].

Identification, qualification and implementation of the different kinds of biomarkers are challenging and frequently necessitate collaborative efforts. But to fully realize the resources

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of PPM, two components are essential: (i) a targeted therapy and (ii) a companion test to identify a bi-omarker Figure 8(a,b). The latter is particularly true for stratification biomarkers that require a companion diagnostic marker (theranostics) that is co-developed with a certain drug Figure 9(a, b). The above-mentioned is considered to be the future of PPM, being and serving as a valuable guidance and playing 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.

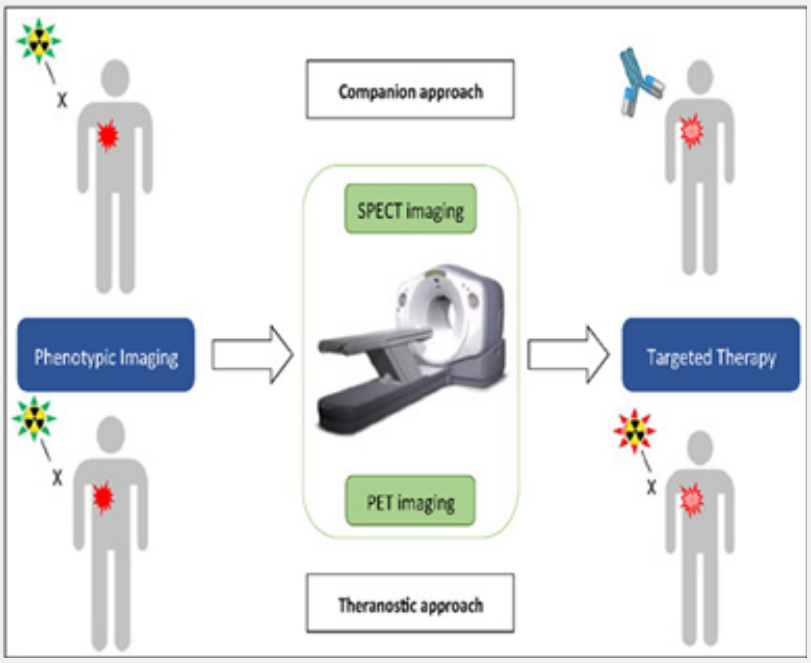

Figure 8A: Companion and theranostic approaches in PPM-driven nuclear medicine.

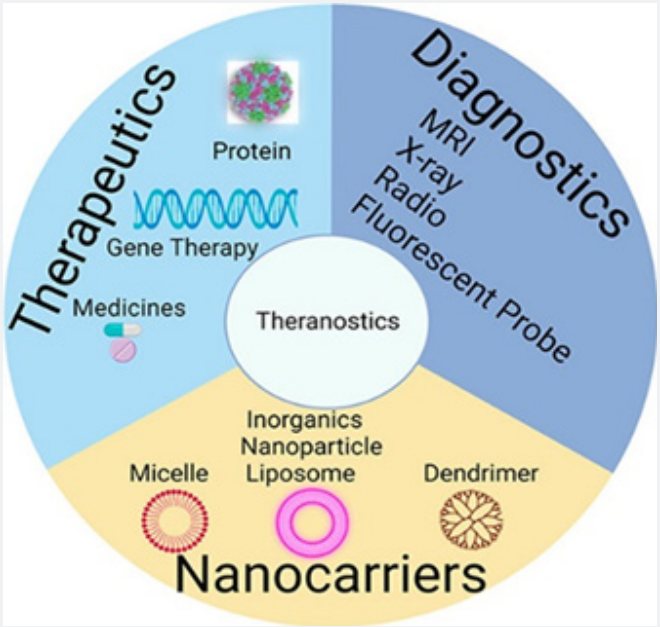

Figure 8B: Nanotheranostic platform for simultaneous targeted therapy and theranostics-driven diagnosis.

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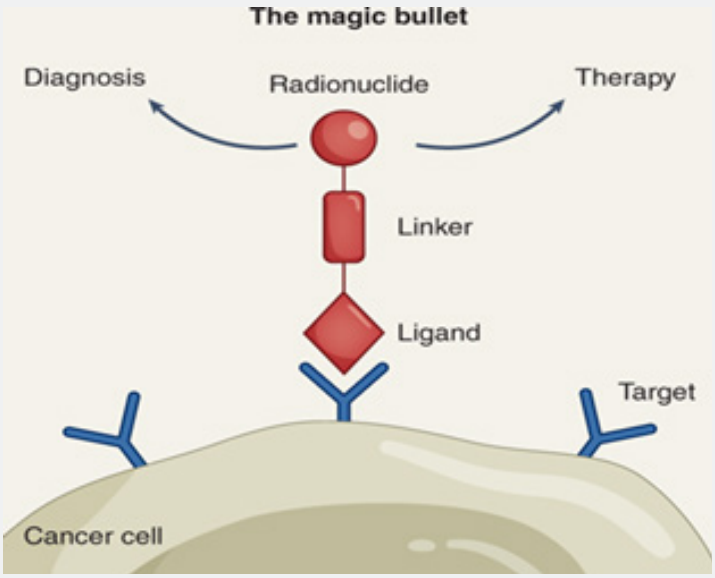

Figure 9A: Stratification biomarkers via a compan-ion diagnostic marker (theranostics).

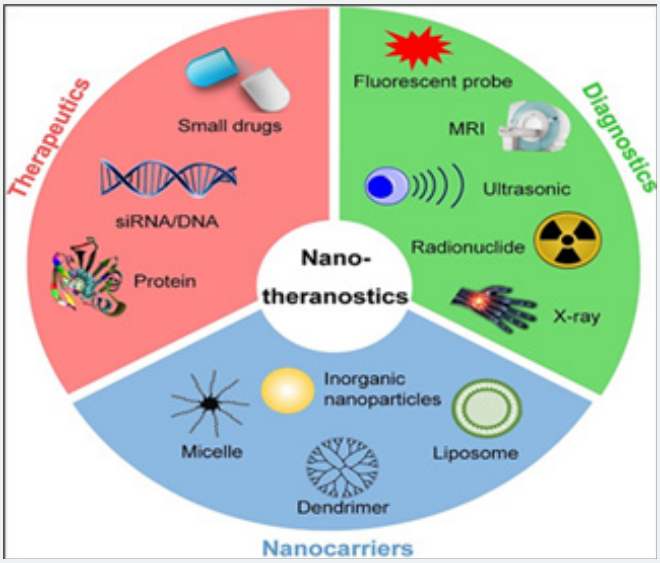

Figure 9B: Nanostructure-Based Theranostic Systems.

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. In this context, biomarker-adaptive signature designs (ASD) identify the most suitable target subpopulations, based on clinical observations or known biomarkers, evaluate the effectiveness of the treatment on that sub-population in a statistically valid manner, and combine the biomarker identification and classifier development to the selection of candidate patients and a statistical test for treatment effect on the selected patient subgroup for clinical trials. 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

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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 disease. Meanwhile, in a few areas related to human personalized nutrition and metabolism, biomarkers play important roles to predict health and functional outcome and are routinely used in clinical practice Figure 10.

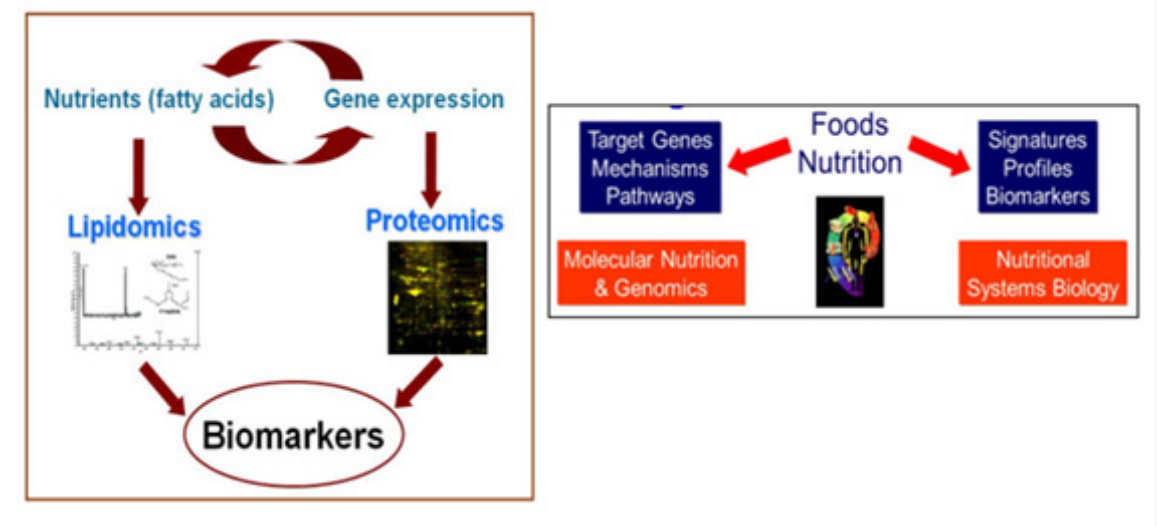

Figure 10: Nutraceutical biomarkers.

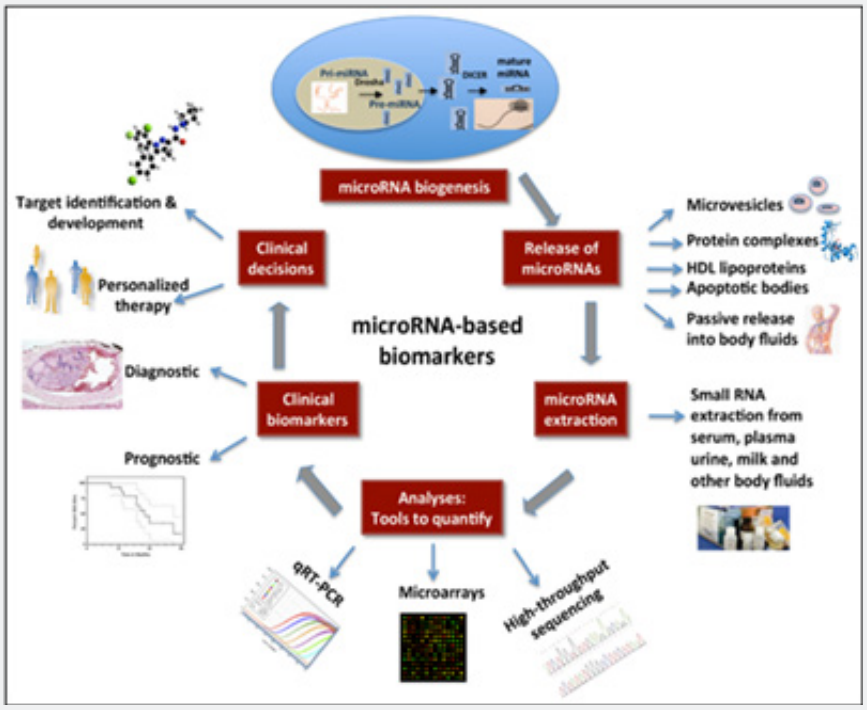

Figure 11: Circulating microRNAs as biomarkers.

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Therefore, intervention strategies are mostly still targeted at individualized and population levels and nutrio-, epi- and metagenomics biomarkers could play a crucial role in decision making, whilst influencing by dietary, lifestyle, and environmental factors, which contribute to the heterogeneity observed in humans. So, biomarkers of the next step generation which indicate the individual risk or benefit must not neglect the complexity of foods, lifestyle, and metabolic processes that contribute to health or disease and are significant challenges for personalizing dietary advice for healthy or diseased individuals. Meanwhile, in global terms, 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 Figure 11.

Effective miRNA profiling calls for reproducible, sensitive and specific tools with turn-around times fast enough to support Bio design-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 12a-c).

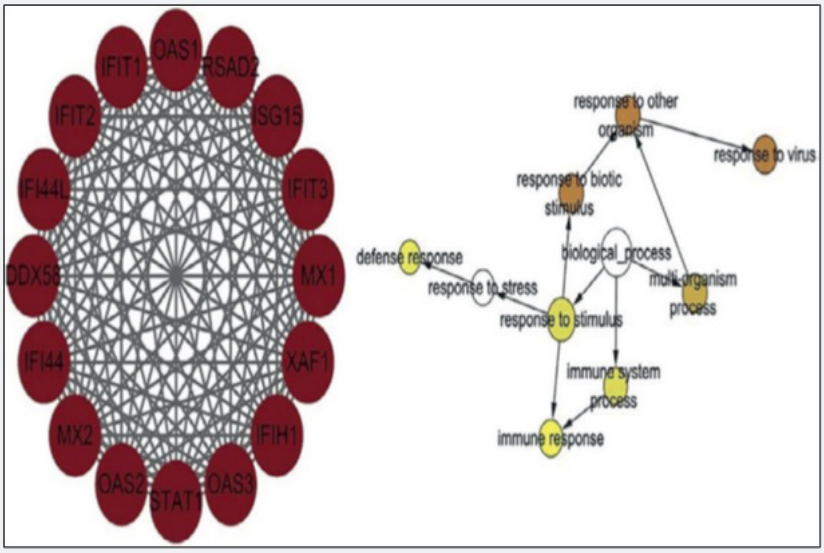

Figure 12A: Potential NBB-related protein biomarkers for systemic lupus erythematosus (SLE) determined by bioinformatics analysis.

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 Ex-pression Omnibus database. The protein–protein interaction (PPI) network of 70 DEGs was constructed using STRING and cyto-scape, 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 im-prove diagnosis and develop individualized therapies NBB, network-based biomarkers; SLE, systemic lupus erythematosus; PPI, protein–protein interaction Co-expression network of four major hubs in breast cancer tissue; purple nodes are hub genes of the network. Yellow lines indicate interaction between the hub genes CCNB2 has a significant role as a prognostic NBB in cancer progression.

The known cancer related genes in final network are marked yellow. Leukemia is highly complex and heterogeneous, involving interaction among multiple molecular components. Network biomarkers are considered to outperform individual molecules in disease characterization. The candidate NBB was evaluated for the diagnosing performance. A network of 97 genes and 400 interactions was identified for accurate diagnosis of leukemia.

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Functional enrichment analysis revealed that the NBBs were enriched in pathways in cancer. The NBBs provide a useful tool to diagnose leukemia and also aids in further understanding the molecular basis of leukemia.

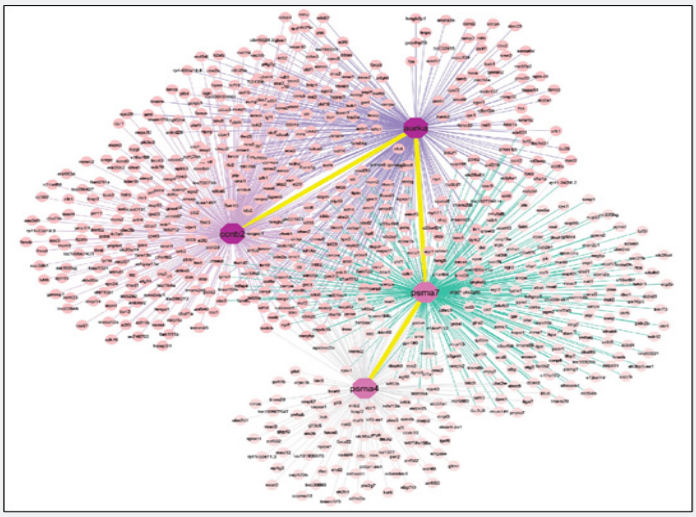

Figure 12B: CCNB2 as a Potential Non-Invasive Breast Cancer Diagnostic Biomarker in Peripheral Blood Mononuclear Cells Using the interactome approach.

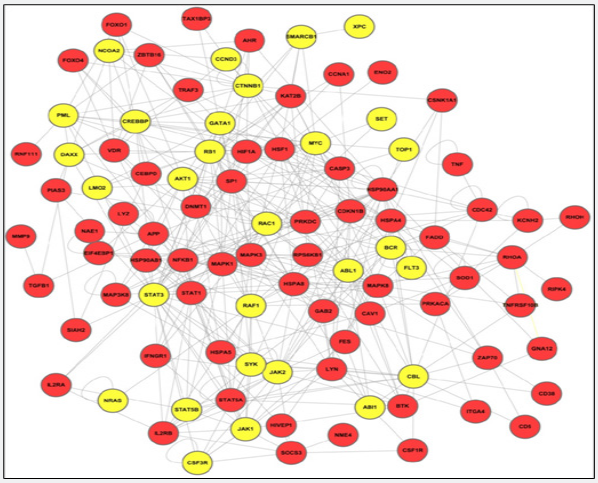

Figure 12C: The final network-based biomarker for leukemia.

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 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 [7-9].

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Regarding biomarkers of the latest innovative trends, let me add that along with canonical anti-bodies (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 13 [3].

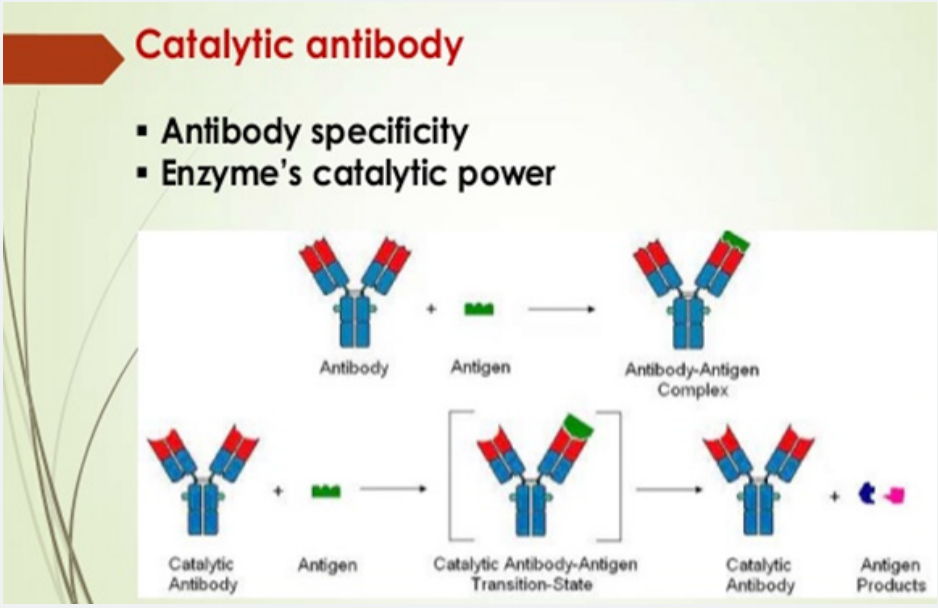

Figure 13: Antibodies (Abs) possessing catalytic activity (catAbs or abzymes) belonging to Abs with a feature of functionality.

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. Proteo-lytic Abs (or Ab-proteases) represent a significant portion of the family of abzymes 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].

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 and facilitate building new products and services in this area, viz. multimarket-based companion diagnostics. The latter is able to distinguish cancer from normal, benign disease states, and patients with other cancers. The model satisfies the requirements of an ideal screening test, being simple to use, and having a good diagnostic efficacy.

Moreover, the use of a panel of plasma biomarkers for the identification of women with ovarian cancer delivers a significant increase in diagnostic performance when compared to the performance of CA-125 alone [16]. The unique diagnostic potential of novel 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 trans-late them as tools of prognostic and diagnostic potential. However, to many the ultimate potential of biomarkers is to change disease management

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(reactive mode) into health management (preventive mode), in other words keeping healthy people healthy rather than curing diseased patients. Key drivers for such change are molecular biomarkers that allow earlier and more sensitive detection of onset of disease, better molecular classification of disease, improved personalized treatment, and improved monitoring of treatment effects.

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 cutoffs for each of the separate markers [15]. 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 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 [17].

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. This trend is to combine quantitative molecular biomarker data and clinical read-outs to provide a more detailed characterization of a disease state. This enables clinicians not only to diagnose diseases but also to specify the subtype or causal origin of pathophysiology, potentially leading to a more tailored treatment.

Within pharmaceutical development, biomarkers have matured from being a hype to becoming an intricate part of the decision-making process. Rather than trial-and-error, most if not all drug-development projects have key biomarker read-outs incorporated in their strategy to enable early risking of the chosen approach and selection of the best compound moving forward. In parallel and in line with the desire for PPM from society, there is a clear trend with oncology leading the way that new drugs have a companion diagnostic biomarker where possible. Supported by their increased economic power, the emerging countries currently invest heavily in biomarker development, aiming to improve existing therapeutic treatments and to generate more personalized drugs for their markets. This progress has dramatically changed the landscape of biomarker discovery and strongly increased the potential of identifying more specific and applicable biomarkers for PPM [18,19].

New strategies assisting in the early and pre-early identification of biomarkers also help to optimize clinical trial design through data informed decisions. Biomarkers identified in subclinical development can be translated into the clinic as companion diagnostics (CDx)-theranostics tan-dem, to stratify relevant patient populations for treatment. Those biomarker-driven approaches are fueling PPM resources to improve drug efficacy, patient safety, and to reduce the attrition rate of the newest therapeutics and nutriceutics. Biomarkers and PPM have introduced a novel way of thought processes, appraising diseases, in applying novel advanced technologies, and emphasizing proactive and preventive medicines. Looking ahead, focused biomarker development networks as outlined above are likely to boost the application of validated biomarkers in biodesign-driven translational and PPM. 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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