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The Biodesign-Inspired Clinical Translational Applications Towards the Implementation of Biomarkers into Clinical Practice

Sergey Suchkov[1-6,9]*, Alan Wu[5,6], Shawn Murphy[7,8], Roger D Kamm[10], David Smith[11], Sabina Passamonte[9], Holland Cheng[11], Lidiya Kadyrova[13] and Philip D Cotter[12]

[1]*Russian University of Medicine, Russia*

[2]*The Russian Academy of Natural Sciences, Russia*

[3]*EPMA, Brussels, EU*

[4]*PMC, Washington, DC, USA*

[5]*AMEE, Dundee, Scotland*

[6]*AHA, Houston, TX, USA*

[7]*MGH, Boston, MA, USA*

[8]*Harvard Medical School, Boston, MA, USA*

[9]*University of Trieste, Trieste, Italy*

[10]*MIT, Cambridge, MA, USA*

[11]*T College of Biological Sciences, UC Davis, CA, USA*

[12]*ResearchDx and PacificDx, Irvine, CA, USA*

[13]*Department of Neurophysiology of Kazan State Medical Academy, Kazan, Russia*

***Corresponding author:** Sergey Suchkov, Russian University of Medicine, Moscow, The Russian Academy of Natural Sciences, Moscow, EPMA, Brussels, PMC, Washington, DC, AMEE, Dundee, AHA, Houston, TX, USA

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ABSTRACT

Biomarkers are indicators of typical biological processes, pathogenic processes, or pharmacological reactions to therapy. Biomarkers have been classified based on different parameters, including their characteristics, clinical applications, and finally, genetic and molecular biology methods. The application and identification of biomarkers in the medical and clinical fields have an enormous impact on society. Biomarkers are crucial in diagnosis, risk assessment, treatment guidance, and monitoring, with the potential to improve treatment outcomes. Biomarkers are clinically significant to a wide range of medical conditions, including cancer, cardiovascular diseases, autoimmune disorders, and neurodegenerative diseases. Biomarkers are a part of a relatively novel and ideal clinical tool in the diagnosis, prognosis, and treatment of canonical diseases (in patients) and preillness conditions (in persons-at-risk). There are considerable benefits of using biomarkers to study various aspects of diseases, drug development, and monitoring the potential effects of therapeutic interventions. Biomarkers would provide tests with greater sensitivity and specificity, improve the decision making process, and facilitate the development of therapies. To improve healthcare and produce cutting edge therapeutics, numerous efforts have been made to explore the biomarker frontier in search of new and/or better biomarkers. However, because the processes that lead to disease pathogenesis are frequently complex, it is easier to identify useful biomarkers for assessing drug response, making diagnoses, and tracking the development of diseases that better understand the underlying abnormalities associated with the disease and the mechanism of drug action. For clinical and basic pharmacologists, as well as other people involved in the identification of biomarkers, accumulating this information is a challenge. In this context, biomarkerguided

trials are crucial for advancing personalized and precision medicine (PPM) to guide clinical decisions, distinguishing between predictive and prognostic biomarkers, and improving patient outcomes. In a broad sense, biomarker is an indicative of the presence of an illness in the body or a molecule secreted by a tumor or a specific response of the body to the presence of the disorder.

It is usually identifiable or measurable in the blood, urine or other convenient body fluids by PCR, ELISA, and other conventional immune assays. In this sense, biomarkers can be categorized into genetic, epigenetic, proteomic, glycomic, and imaging biomarkers for disease-related diagnosis, prognosis, and epidemiology. In a narrow sense of biomarker, it is limited to biomolecule the most used to challenge in the clinical applications, especially in the CART therapy. Specifically, a cancer biomarker of the CART provides the most prominent signal of cancer cells for distinguishing from normal cells and the most effective target for immune recognition and destruction. Making the difference between a potential biomarker and a reliable biomarker, that can be universally used to guide critical clinical and commercial choices, is one of the main challenges in the field of biomarkers. An effective biomarker must influence clinical evaluation to improve patient care. Clinical decisions that are based on real test results, must be more beneficial than those that are based on false negatives or false positives. The effectiveness of a biomarker is determined by comparing it with an ideal biomarker and exploring its properties. Promising biomarkers have characteristics similar to those of ideal markers. Although many new biomarkers have been discovered, only a small number of them are clinically useful. To obtain promising results, researchers should use annotated clinical specimens, appropriate control groups, many samples, and standardized sample handling.

In the future, integrating biomarkers identified with emerging highthroughput techniques into medical practice will be required to achieve 'personalization' of treatment and disease prevention. New generation of biomarkers, particularly microRNAs, exosomes and network-based biomarkers (NBB) are gathering attention into the realm of PPM due to their diagnostic, prognostic, and predictive biomarker potential. Ultimately, the article emphasizes the significance of biomarker research in advancing PPM-guided interventions, improving patient outcomes, and reshaping the healthcare landscape.

Keywords: Biomarker; Biomarker Classification; Clinical Trial; Companion Diagnostics (CDx); Drug Development; Personalized and Precision Medicine; Personalized Treatment; Biodesign; Predictive Biomarker; Prognostic Biomarker

Abbreviations: PPM: Personalized and Precision Medicine; CFTR: Cystic Fibrosis Trans-Membrane Conductance Regulator; HLA: Human Leukocyte Antigen Allele; HIV: Human Immuno-Deficiency Virus; PSA: Prostate-Specific Antigen; COPD: Chronic Obstructive Pulmonary DisorDer; CRP: C-Reactive Protein; EGFR: Epidermal Growth Factor Receptor; PPO: Personalized and Precision Oncology; miRNAs: MicroRNAs; CTCs: Circulating Tumor; CPAN: Cancer Protein Association Network; PPI: Protein-Protein Interactions; NBBs: Network-Based Biomarkers; Abs: Antibodies; CatAbs: Catalytic Activity Antibodies; MS: Multiple Sclerosis

Introduction

The success in the management of disorders directly depends on the stage of the pathological process, and a wide range of biomarkers, due to their high specificity, can diagnose a disease and/or predict the risks of its development at the preclinical stage with almost 100% probability. A biomarker is a collection of genomic and proteomic signatures used to distinguish between healthy, preillness and diseased individual. These signatures can be in the form of DNA (ssDNA, dsDNA and retrotransposons), RNA (mRNA, miRNA, circRNA and lncRNA) or protein (antibodies and peptides) depending upon the site of secretion and isolation. The success of biomarker-based therapy can be attributed to the development of new sequencing strategies and characterization of tumor pathways with increasing knowledge about druggable targets and its predictive outcome. One of the earliest biomarkers to reach clinical practice was the identification of mutations in KRAS gene in some cancer types, which are predictive of therapeutic response towards anti-epidermal growth factor receptor (EGFR). Meanwhile, marker molecules are used to determine, in particular, the state of cell damage processes, a number of functionally important biomolecules, as well as the presence of metabolites or precursor proteins, which are detected thanks to innovative OMICS-technologies unveiling cellular and molecular mechanism of clinical pathologies (Figures 1A & 1B). PPM adopts a more nuanced strategy taking both genotypic and phenotypic differences into account to create a therapy or preventative method that may be used to benefit both populations and individuals.

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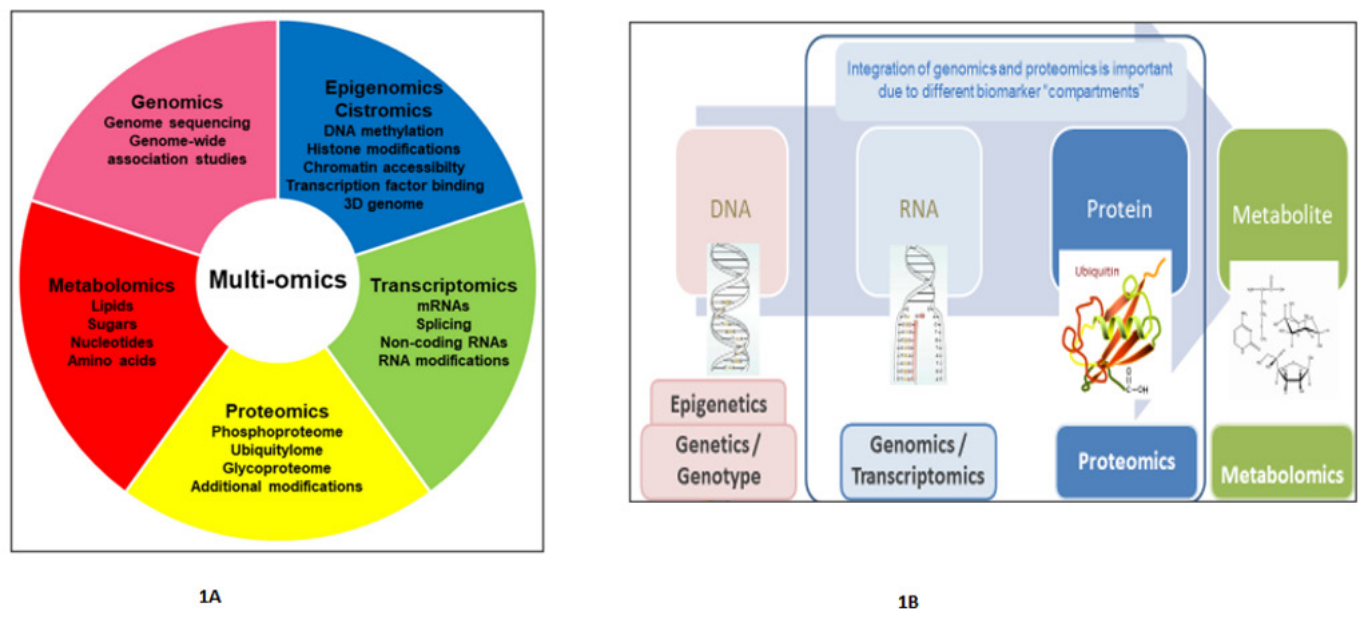

Figure 1:

A. Overview of OMICS approaches in PPM-guided clinical practice to revolutionize healthcare.

B. Multi-integrative OMICS technologies as applicable to biomarker development.

The progress in PPM is leading to tangible advantages, including the ability to detect illnesses at an early stage and create personalized treatment plans. Notably, the integration of highthroughput OMICS-driven typing with the widespread use of electronic health records presents an unparalleled opportunity for scientists to extract novel phenotypes from clinical and biomarker data. Highthroughput OMICS technologies that allow one to identify and quantify processes involved in these changes are now available and have been instrumental in generating a wealth of steadily increasing data from patient bios-amples. Extensive integration of these data have led to new biological insights into the origin and development of disease phenotypes and helped to unravel the molecular networks underlying this complex pathology. The comprehensive and quantitative analysis of a molecule class in a biological sample is named OMICS and multi-OMICS studies addressing different disease stages have been performed in recent years. The comprehensive investigation of these omics approaches and their integration into multi-omics analyses have led to a much deeper understanding of the molecular pathways involved in disease progression, and in response and resistance to therapies. PPM, personalized and precision medicine Over the past decade, the pace of progress in PPM has quickened due to advances in OMICS technologies that enable more precise characterization of biomarkers and targets. Biomarker identification and validation has been applied to a wide variety of therapeutic areas with the most predominant field of application in oncology.

The application of targeted cancer therapies fall under the rubric of predictive biomarkers, which address the potential response or insensitivity of the tumor to a particular therapy. In this case, companion diagnostic tests must be codeveloped with the drug through clinical trials in order to not only demonstrate drug efficacy but also validity of the predictive test. One of the best known examples of a predictive marker is the Her2/neu diagnostic test for treatment of Her2 positive metastatic breast cancer with Herceptin. Clinical pathology consists of a panel of OMICS-guided tests to detect, diagnose and monitor various disease related conditions (Figure 2). The integration of clinical parameters with clinical (digital) digital pathology image analysis, multi-OMICS data and 3D radiological & image analysis can provide a more comprehensive view that can be used for tissue subtyping, assessment of prognosis and predicting response to treatment. Clinical pathology being digitalized, can add an extra layer of information to help visualize in a spatial and microenvironmental context the molecular information of the mechanisms of the disorder. Using advanced digital image analysis, a larger spectrum of parameters can be analyzed as potential predictors of clinical behavior. Correlation between OMICS driven data, morphological features and host immune response can be also performed with therapeutic implications. Molecular imaging or the interface of radiological images and histology is another emerging exciting field which encompasses the integration of the latter with digital pathological images, OMICS and clinical data to portray a more holistic approach to understating and treating disease.

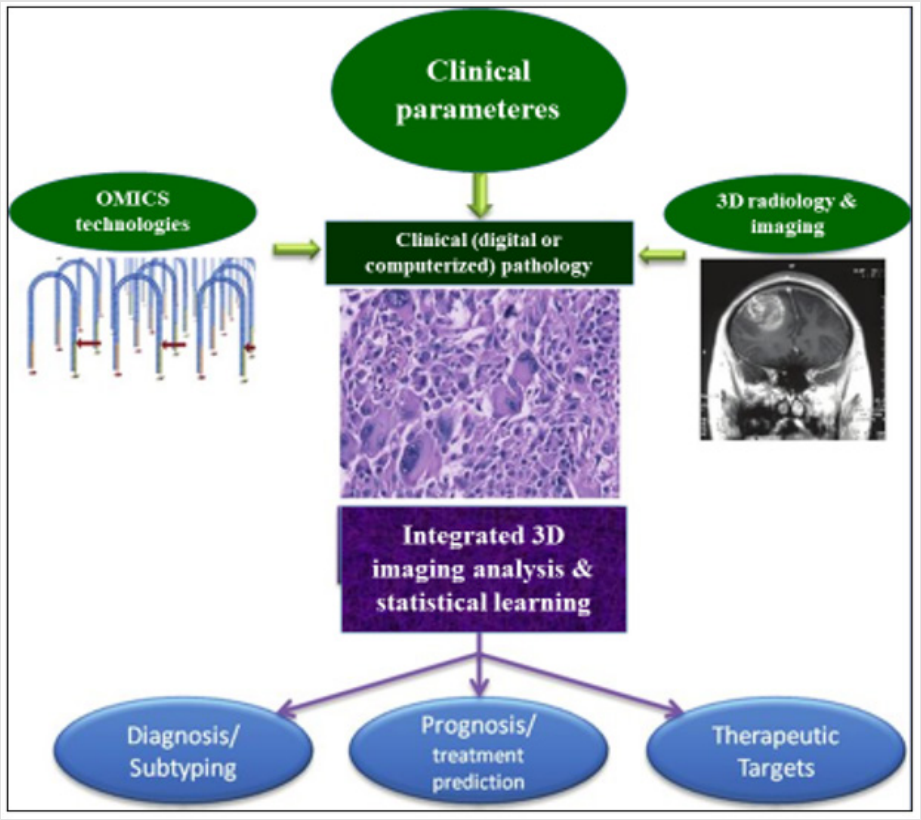

Figure 2: The integration of clinical parameters with clinical (digital) pathology image analysis, multi-OMICS data and 3D radiological & image analysis.

Entire procedure may involve a routine health check, a diagnostic test aimed at detecting a particular condition or disease, and follow-up tests to evaluate effectiveness of the treatment for a condition, which are often a series of easy to administer, convenient tests conducted at special laboratories to deliver quick and accurate results. Clinical digital pathology represents not only a promising tool for disease diagnosis, but also for high through put and quantitative data extraction and analysis for multipurpose biomarker discovery for translational research on a wide spectrum of diseases [Cooper LA, Kong J, Gutman DA. Integrated morphologic analysis for the identification and characterization of disease subtypes. J Am Med Inform Assoc 2012; 19:317–23; Kong J, Cooper LA, Wang F, Gutman DA, Gao J, Chisolm C, et al. Integrative, multimodal analysis of glioblastoma using TCGA molecular data, pathology images, and clinical outcomes. IEEE Trans Biomed Eng 2011;58: 3469–74]. Clinical digital pathology could enable the integration of biomarkers to enhance therapy effectiveness, potentially improving the capabilities of pathologists through AI and ML powered tools. In the context of biomarkers in clinical digital pathology, the parameters must meet the definition of a biomarker as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention. As one example of an area of expansion for biomarkers in clinical digital pathology, they can be applied to some stages (including subclinical ones) of cancer progression, where microsatellite instability (MSI), exosomes or circulating tumor cells (CTCs) are a predictive and/or prognostic biomarker (Figure 3). Molecular biomarkers have the potential to predict response to cancer therapy at an early time point. Integration of diverse types of biomarkers including clinic-pathological and imaging features, identification of mechanistic link to tumor biology, and rigorous validation using samples, which represent disease heterogeneity will allow to develop a sensitive and cost effective molecular biomarker panel for PPM and PPM driven oncology. Molecular biomarkers, either tissue or blood based, have the potential to predict response to therapeutic agents at an early time point with sufficient sensitivity and specificity, although to date none have yet reached the clinic. Most of studies evaluate one type of biomarkers, whether consisting of gene expression profiles, proteins, microRNAs, or other types, without an appreciation of their performance relative to other markers and with an insufficient sensitivity and specificity by themselves. Thus, there is a need to compare and integrate different types of biomarkers from multiple biomarker platforms, including clinicopathological and imaging features, side by side in the same sample sets to determine their comparative performance and the contribution of individual biomarkers to a robust panel.

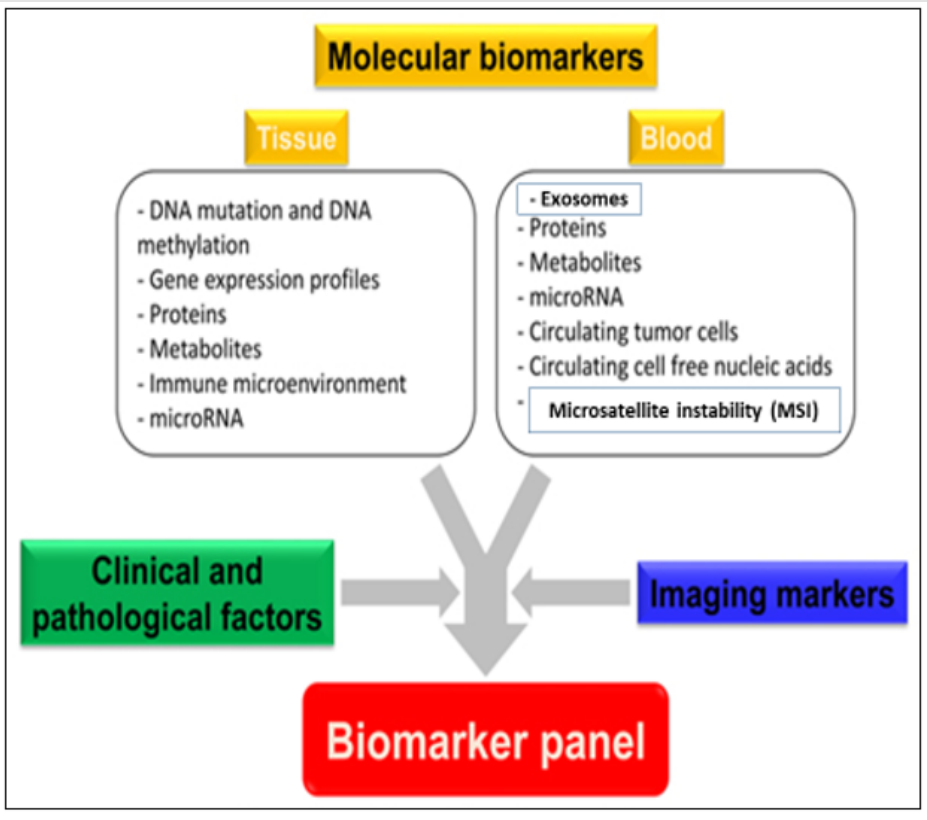

Figure 3: Molecular biomarkers in cancer.

Such an integrative approach will allow us to make the best choice of biomarkers to develop an optimal and reliable biomarker model. While this new field holds great promise for better understanding of disease pathogenesis, progression and response to treatment, the scale of large imaging data can be overwhelming and technically challenging. The role of biomarkers in the development of PPM provides a strategic opportunity for technological developments to improve human health and reduce healthcare cost. PPM as a concept concerns the adjustment of treatments to individual or subgroups of patients based on the use of disease-specific biomarkers. Biomarkers play a crucial role in understanding and monitoring the intricacies of the human body. They offer valuable insights into biological processes, disease diagnosis, treatment effectiveness, and patient outcomes, enabling researchers and clinicians to make informed clinical decisions. The identification of biomarkers to support decision-making is central to PPM, in clinical scenarios. The difference between a biomarker's prognostic and predictive value can be highly useful in charting a treatment plan for patients and determining treatment outcomes (Figure 4) Biomarkers are valuable for predicting prognosis and dose selection. Moreover, they may be helpful in detecting therapeutic and adverse responses and in patient stratification based on efficacy or safety prediction. Thus, biomarkers are essential tools for the selection of appropriate patients for treatment with certain drugs to and enable PPM, that is 'providing the right treatment to the right patient, at the right dose at the right time'.

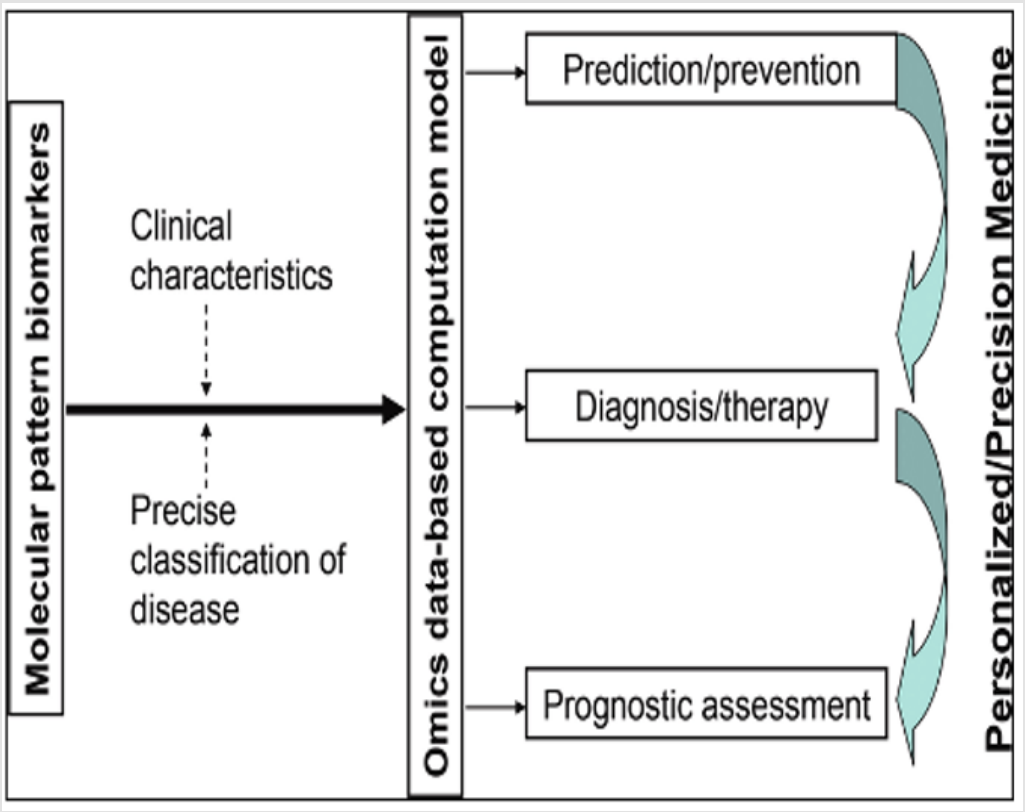

Figure 4: Application of pattern-related biomarker in personalized & precision medicine (PPM) [26].

Prognostic biomarkers are of particular significance for malignant conditions. Similarly, diagnostic biomarkers are important in autoimmune diseases. Identification, qualification and implementation of the different kinds of biomarkers are challenging and frequently necessitate collaborative efforts. PPM and PPM-guided modern (Hi Tech) clinical practice rely on validated biomarkers with which to better classify patients by their probable disease risk, prognosis and/or response to treatment. The challenge of PPM can be seen in two halves: identifying predictive biomarkers and prognostic markers. Identifying predictive biomarkers, which guide the development/use of tailored therapies among common predictive biomarkers, such as in cystic fibrosis transmembrane conductance regulator (CFTR) mutations that can identify patients who respond more favorably than others to particular treatments; human leukocyte antigen allele (HLA)–B*5701 genotype to evaluate HIV patients before the onset of abacavir treatment to identify patients at risk for severe skin reactions; [1]; breast cancer genes BRCA 1 and 2 mutations as a predictive biomarker to identify patients (women with platinum sensitive breast cancer), who are likely to respond to ADP ribose PARP inhibitors [2]. Identifying prognostic markers, which guide other aspects of care and clinical trial planning, i.e. prognostic markers can be considered as covariates for stratification – breast cancer genes, BRCA 1 and 2, as prognostic biomarkers that can help determine the likelihood of recurrence of breast cancer; prostate specific antigen (PSA) as a prognostic biomarker for assessing disease progression in prostate cancer patients; plasma fibrinogen can be used as a prognostic biomarker for patients with the chronic obstructive pulmonary disorder (COPD) to determine risk for exacerbation; Creactive protein (CRP) as a prognostic biomarker that can be used for patients with a history of myocardial infarction or unstable angina to identify risk of recurrent coronary artery disease [3].

It is necessary to distinguish between disease-related and drug-related biomarkers. Disease-related biomarkers give an indication of the probable effect of treatment on patient (risk indicator or predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case regardless of the type of treatment (prognostic biomarker). Predictive biomarkers help to assess the most likely response to a particular treatment type, while prognostic markers shows the progression of disease with or without treatment. In contrast, drug-related biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it. The "classic" biomarker in clinical practice is a laboratory parameter that the doctor can use

to help make decisions in making a diagnosis and selecting a course of treatment. For example, the detection of certain autoantibodies (autoAbs) in patient blood is a reliable biomarker for autoimmune disease, and the detection of rheumatoid factors (RAs) has been an important diagnostic marker for rheumatoid arthritis (RA) for over 50 years. For the diagnosis of this autoimmune disease the antibodies against the host citrullinated proteins are of particular value. These ACPAs, (ACPA stands for anticitrullinated protein/peptide Ab) can be detected in the blood before the first symptoms of RA appear. They are thus highly valuable biomarkers for the early diagnosis of this autoimmune disease. Owing to impressive advances in high-throughput technologies, multi-OMICS approaches are now being intensively pursued for in-depth studies of individual cancer types and their response to therapeutic regimens.

Spatial OMICS adds an additional degree of complexity by integrating data from the tumor microenvironment. Indeed, variabilities in gene expression profiles have already been observed in bios-amples and biopsies from selected areas of tumors, including normal and cancer areas, using spatial transcriptomic approaches. Taking into account the biomarker driven tumor ecosystem will much improve our future understanding of intercellular crosstalk and open new horizons in PPM. Recent findings derived from integrated multi-OMICS approaches include predictors of clinical response, identification of novel potential drug targets, profiling of compounds and mechanisms leading to drug resistance in different tissue (tumor, predominantly) types, and discovery of processes underlying cell plasticity. This is further complemented by recent advances in medical imagery, where the reliability of pathologic assessment has been much increased by refined molecular imaging techniques, and by artificial intelligence AI) and machine learning (ML) as well. Altogether, this steadily broadening knowledge about the intricacy and heterogeneity of tissues and pathological processes throughout individual disease stages will advance informed PPM driven strategies for patients and preillness persons-at-risk. Furthermore, it brings the additional hope that tailored prevention approaches will be available in the near future. Meanwhile, recent advances in computational methods for all these approaches will greatly help to unravel the interplay of the biological processes taking place and the mechanisms responsible for the switch from normal to cancerous phenotype.

This will provide innovative opportunities in the pre-early (subclinical) detection of the disease, risk stratification and decision on optimal treatment strategy. Many challenges, however, still remain due to heterogeneities among the OMICS technologies, the curse of data dimensionality with relatively few samples and a very large number of variables assessed, missing values in studies, and problems linked to the storage, annotation, interpretation and handling of substantial datasets. So, the rapid development of computation biology, systems biology, and multi-OMICS is driving the development of pattern recognition to discover reliable molecular pattern biomarkers for biomarker driven targeted treatment [4].

Biomarker Categories in Clinical Practice

To establish whether a marker is purely prognostic, it needs to be demonstrated that there would be a strong association between biomarkerrelated profile and the outcome, regardless of treatment. The latter can be used in diagnostics, as well as in assessment of disease severity, risk stratification, prediction, guide clinical decisions, and help pick appropriate treatment, modify therapy, and response to it. In a broader strategic sense demonstrating the evidencebased clinical value, there are key categories of biomarkers (Figures 5A-5C), including [5]: Biomarkers are critical to the rational development of medical therapeutics, but significant confusion persists regarding fundamental definitions and concepts involved in their use in clinical practice, particularly in the fields of chronic disease and nutrition. Clarification of the definitions of different biomarkers and a better understanding of their appropriate application could result in substantial benefits. The use of biomarkers as preearly (subclinical) warning systems in the evaluation of disease risk has increased markedly in the last decade. Biomarkers are indicators of typical biological processes, pathogenic processes, or pharmacological reactions to therapy.

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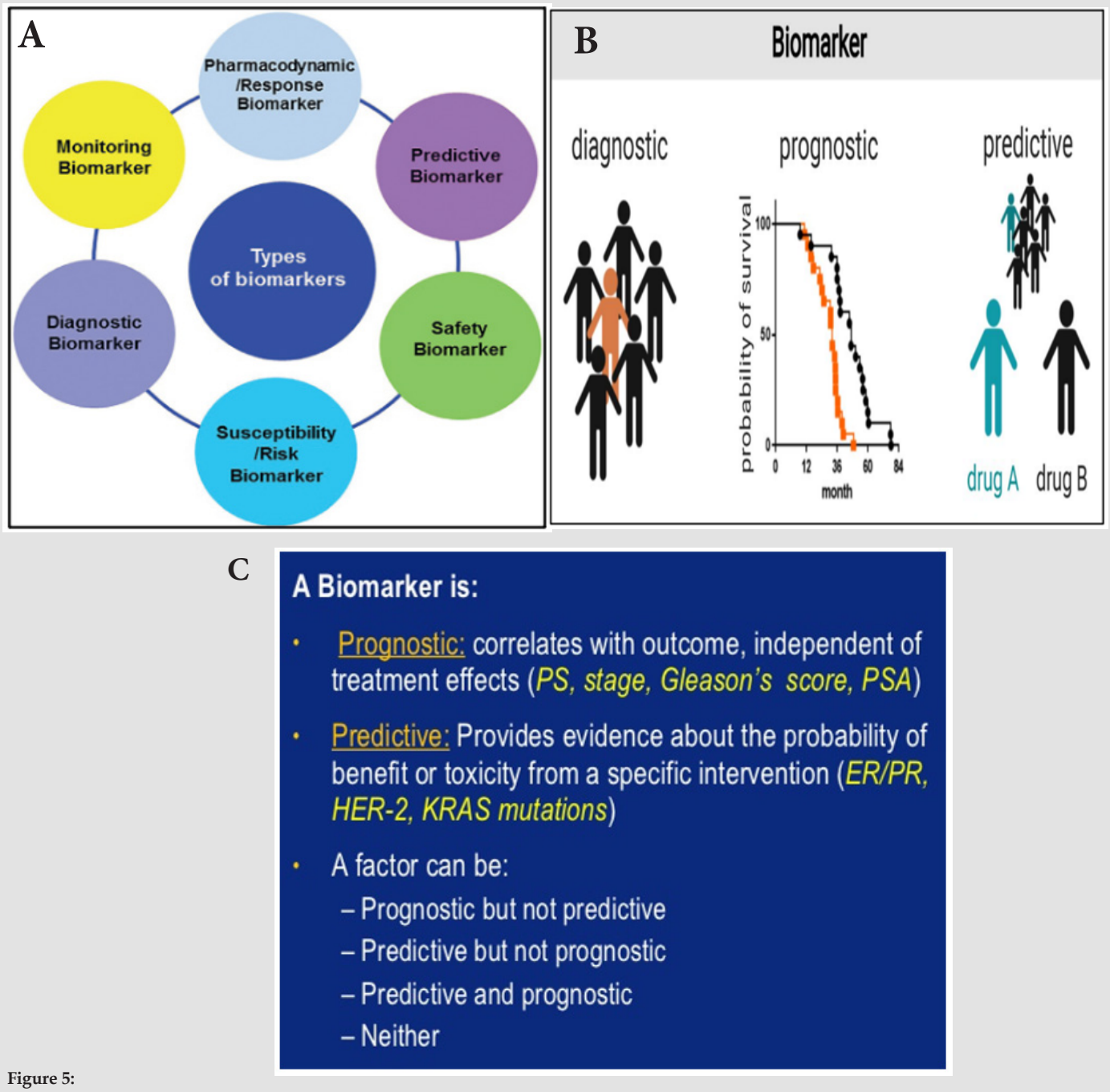

Figure 5:

A. Classification of biomarkers based on its main clinical application [4].
B. Predictive and prognostic biomarkers in personalized & precision medicine.
C. Prognosis & Prediction through the View of Targeted Biomarkers.

The application and identification of biomarkers in the medical and clinical fields have an enormous impact on society. Advancements in OMIVS technologies have opened up new possibilities to obtain novel biomarkers of different types, employing genomic strategies, epigenetics, metabolomics, transcriptomics, lipid-based analysis, protein studies, etc. Particular biomarkers for specific diseases, their prognostic capabilities, and responses to therapeutic paradigms have been applied for screening of various normal healthy, as well as diseased, tissue or serum samples, and act as appreciable tools in pharmacology and therapeutics, etc. Moving our focus from the treatment of late stage diseases to the monitoring and management of diseases caught at the pre-early stage, will perhaps move medicine from a curative model to one of prevention Biomarkers play an important role in the detection and management of patients and preillness persons at risk. For instance, prognostic biomarkers enable identification of patients with a more aggressive tumor evolution, while predictive biomarkers permit the identification of patients with a higher probability of responding or not to a specific treatment.

To demonstrate that a biomarker is predictive of treatment benefit, the study requires biomarker status on all patients as well as patients who were treated with the agent of interest and patients not so treated, preferably in the context of a randomized study. A formal statistical test of the treatmentbybiomarker interaction should be significant. To establish whether a marker is purely prognostic, it needs to be demonstrated that there is a significant association between the biomarker and outcome, regardless of treatment, and that treatment effects do not depend on the biomarker.

1) Diagnostic biomarkers: to identify individuals with a disease or condition of interest or to define a subset of the disease;

2) Prognostic biomarkers: indicate the likelihood of a clinical event, disease recurrence, or progression;

3) Predictive biomarkers: to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure;

4) Safety biomarkers;

5) Pharmacodynamic (response) biomarkers;

6) Monitoring biomarker;

7) Susceptibility (risk) biomarkers [6]; Selleck MJ et al., (2017). Making Meaningful Clinical Use of Biomarkers. Biomark Insights, 12:1].

Analyzing and assessing the abovementioned diagram, 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 [7]. 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 [8]. 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 (theranostic) that is codeveloped with a certain drug [9]. Theranostics is considered a fusion of diagnosis and medication. It helps to optimize the rationalization of safety, effective results and overall drug development. The latter in the future of PPM, being and serving as a valuable guidance, would play a crucial role in clinical practice since possessing their accuracy is crucial for the success of the therapeutic, preventive, prophylactic, and rehabilitative choice (Figures 6A & 6B). There is a growing paradigm within the frame of PPM about a shift toward integrating therapeutics and diagnostics rather than developing and deploying them separately. In this gradual move toward more effective and PPM guided medications, companion diagnostics are an intermediate stage. The next step may be "theranostics", in which single chemical entities are developed to deliver therapy and diagnosis simultaneously. This approach involves targeted and cell specific therapy, controlled drug release, personalized dosage forms, wearable drug delivery, and companion diagnostics. By integrating cutting edge technologies with drug delivery systems, greater precision can be achieved at the tissue and cellular levels through the use of stimuli responsive nanoparticles, and the development of electrochemical sensor systems. This precision targeting – by virtue of nanotechnology – allows for therapy to be directed specifically to affected tissues while greatly reducing side effects on healthy tissues.

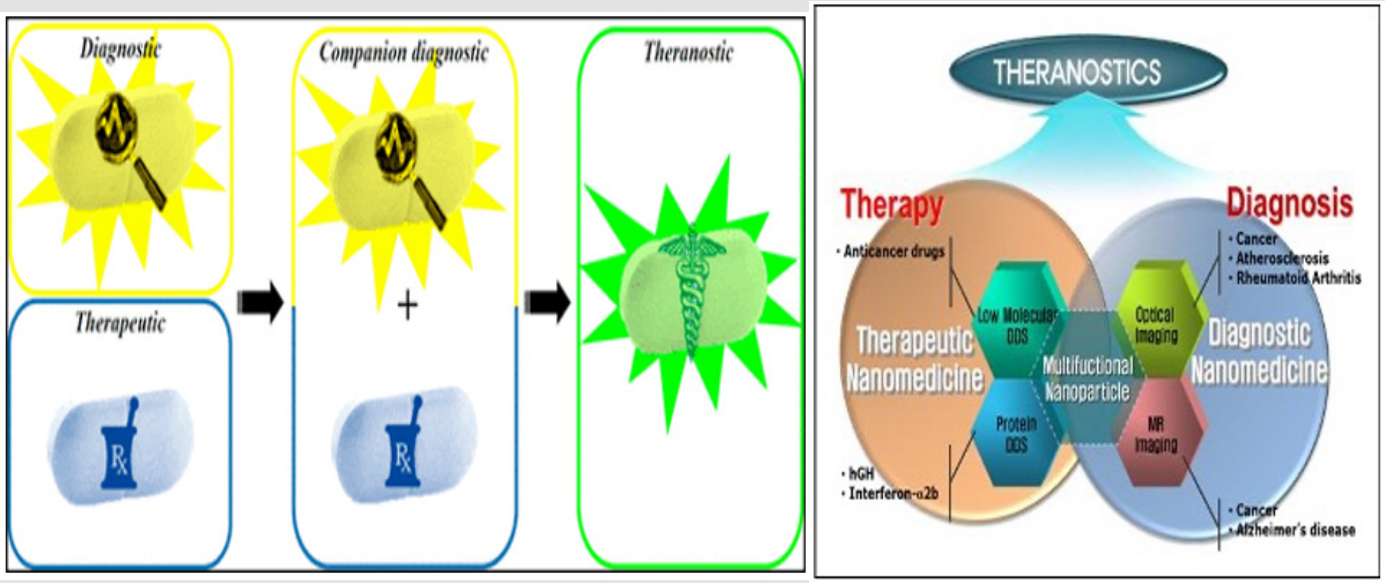

Figure 6:

A. From companion diagnostics to theranostics: a new avenue for personalized and precision-driven approaches [42].

B. From companion diagnostics to theranostics: a new avenue for personalized and precision-driven approaches [43].

Companion diagnostics enable efficient monitoring of treatment response, enabling customized adjustments to the treatment plan. The concept of the ranostics is well illustrated in PPM driven oncology and refers to the development of molecular diagnostic tests and targeted therapeutics in an interdependent, collaborative manner with the goals of individualizing treatment by targeting therapy to an individual's' specific disease subtype and genetic profile. This strategy will enable optimization of drug efficacy and safety and will assist in streamlining the drug development process. The importance of diagnostic approaches in drug development is highlighted by the rapidly expanding global cancer diagnostics market and the emergent attention of regulatory agencies worldwide, who are beginning to offer more structured platforms and guidance for this area. *In vitro* companion diagnostic assays and *in vivo* molecular diagnostic imaging continue to advance the field of PPM and are changing the way in which clinicians are treating cancer and other human diseases. Assays and imaging agents are being developed alongside therapeutics to stratify patients and maximize the potential treatment benefit of new oncology therapeutics. These approaches are not only changing the landscape of clinical trials, but are also contributing to important changes in drug development and treatment. With the discovery of new oncology targets and imaging tracers comes increased capabilities to probe, monitor, and evaluate cancer on a molecular level. It is clear that more widespread implementation of imaging diagnostic tools will advance oncology clinical trials and help support new drug approvals in this rapidly expanding therapeutic area. Efforts to discover next generation biomarkers for clinical use have been significant, yet their implementation remains low [10-12].

PPM leverages advanced biomarker driven technologies to inform evidence-based decisions across disease diagnosis, treatment, prediction, prevention, and prophylaxis. Utilizing molecular stratification, PPM enhances medication selection, reduces adverse effects, and shifts focus from reaction to prevention [13,9]. Biomarkers derived from genes, proteins, and interactomes play a pivotal role in predicting individual responses to therapies and guiding personalized treatment strategies. Questions persist regarding best practices for extracting prioritized biomarkers in PPM driven research, amidst the era of OMICS technologies and Big Data. Biomarkers are integral to the development of PPM driven technologies, aiding in clinical decision making, medical product development, and drug discovery. They serve as indicators of normal and pathogenic processes, contributing to drug target selection, patient stratification, and safety assessment in drug development [10,14]. The molecular heterogeneity of living systems offers a rich source of candidate biomarkers, necessitating controlled error rates in statistical models. Biomarkers can signify various health or disease characteristics, acting as indicators of disease trait, state, or progression. Relevant biomarkers define patient subgroups, informing evidence based medical decisions [15-17]. Expectations for precision tools like PSA and specific gene mutations are heightened by the potential of Big Data to translate into clinically relevant information [18].

Biomarkers and Personalized and Precision Oncology (PPO)

Biomarkers are extremely important in 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 [8,19,20]. In a broad sense, cancer biomarker is an indicative of the presence of cancer in the body or a molecule secreted by a tumor or a specific response of the body to the presence of cancer. It is usually identifiable or measurable in the blood, urine or other convenient body fluids by PCR, ELISA, and other conventional immune assays. In this sense, biomarkers can be categorized into genetic, epigenetic, proteomic, glycomic, and imaging biomarkers for cancer diagnosis, prognosis, and epidemiology. In a narrow sense of cancer biomarker, it is limited to proteins the most used to challenge in the clinical applications, especially in the CART therapy. With cuttingedge 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 drive clinical decisionmaking, complementing, or even replacing presently available invasive methods [10,21]. Predictive biomarkers help to optimize therapy decisions, as they provide information on the likelihood of response to a given chemotherapeutic.

Among the prognostic factors that identify patients with different outcome risks (e.g., recurrence of the disease), the following factors can be distinguished: somatic and germline mutations, changes in DNA methylation that lead to the enhancement or suppression of gene expression, the occurrence of elevated levels of microRNA (miRNA) capable of binding specific messenger RNA (mRNA) molecules, which affects gene expression, as well as the presence of circulating tumor cells (CTCs) in blood, which leads to a poor prognosis for the patient. Extracellular vesicles as biomarkers of cancer Among the many reasons for cancer therapeutics failure, one of them is the associated tumor heterogeneity and despite the new sequencing strategies developed, there are major challenges that need to be overcome. Studies have found that tumor cells secrete EVs such as exosomes and macrovesicles into the extracellular environment at a threefold higher rate than normal cells. These vesicles carry important genetic information such as DNA and RNA or protein fragments that act as signatures of the secretory cell type. Identification of EVs from patient's blood stream, urine or plasma provide important insights into the cells they originate from, their genetic constituent and molecular variants. Identification of EVs as potential biomarkers along with the advancement in techniques for their successful isolation has enabled new therapeutic targets for cancer treatment. EVs are isolated from the conditioned media of cells *in vitro* or from biofluids such as serum and plasma of patients.

Information carried by exosomes not only plays significant role in normal pathological processes, but are also a hallmark of aberrantly regulated pathways in different cell type associated malignancy. Exosomes have also been characterized as 'liquid biopsy' tools owing to their stability in secreted bodily fluids such as plasma, urine or saliva. Various exosomal markers such as CD63, TSG101 and Alix, among many are known and their detection from conditioned media of cancer cells or from patient derived tumor samples gives an indication of diseased process [Wang X, Huang J, Chen W, Li G, Li Z, Lei J. The updated role of exosomal proteins in the diagnosis, prognosis, and treatment of cancer. Exp Mol Med. 2022 Sep;54(9):13901400; Dai J, Su Y, Zhong S, Cong L, Liu B, Yang J, Tao Y, He Z, Chen C, Jiang Y. Exosomes: key players in cancer and potential therapeutic strategy. Signal Transduct Target Ther. 2020 Aug 5;5(1):145; Li C, Zhou T, Chen J, Li R, Chen H, Luo S, Chen D, Cai C, Li W. The role of Exosomal miRNAs in cancer. J Transl Med. 2022 Jan 3;20(1):6]. Overview of noncoding RNAs Noncoding RNA (ncRNA) is RNA transcript that do not encode for the protein. ncRNAs as a potential biomarker, providing rationales for the development of therapeutics targeted against or based on these ncRNAs, plays an important role in different biological processes and are often deregulated in cancer. Although noncoding RNAs have long been considered as nonfunctional "junk" RNAs, accumulating evidence in the past decade indicates that they play a critical role in pathogenesis of various cancers.

In addition to their biological significance, they are exploited as potential cancer biomarkers. In particular, microRNAs (miRNAs) (see the next Fig), a subclass of small noncoding RNAs that epigenetically modulate gene transcription, have become one of the most well studied substrates for the development of liquid biopsy biomarkers for cancer patients. Advances for quantifying lowly expressed RNAs in the circulation have facilitated robust identification of previously un-recognised and undetectable biomarkers in cancer patients. Of special interest is miRNAs (Figure 7) which are involved in several diseases like cancer. miRNAs are isolated from tumor tissue, saliva, blood, plasma, serum, etc., and then profiled for miRNA expression. miRNAs profiling helps in cancer diagnosis, cancer staging, and therapeutics. Often one microRNA affects more than one hallmark, with one prevailing tissue dependent mechanism. hough noncoding RNAs have long been considered as nonfunctional "junk" RNAs, accumulating evidence in the past decade indicates that they play a critical Urgency for pre-early cancer diagnosis and differentiating multiple cancer types is guiding the way for identifying microRNA signatures and monitor disease. Based on this evidence, numerous microRNAs have been suggested as potential cancer biomarkers for both diagnosis and prognosis. MicroRNA based therapies have also been tested in different cancers and have provided measurable clinical benefits to patients.

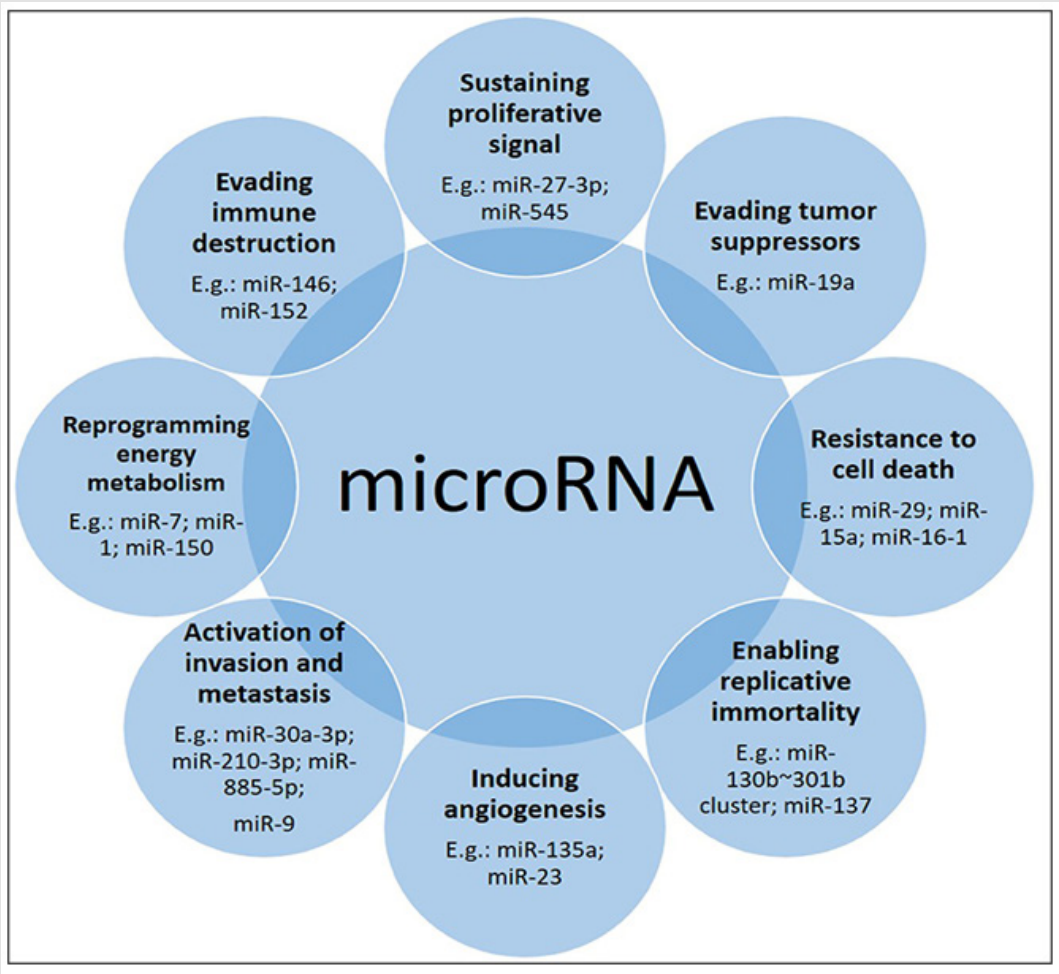

Figure 7: Micro-RNAs as cancer biomarkers: potential clinical applications and own- or up-regulation of microRNAs.

In addition, understanding miRNA biogenesis and regulatory mechanisms in cancer can provide important knowledge about resistance to chemotherapies, leading to more personalized cancer treatment. Effective miRNA profiling calls for reproducible, sensitive, and specific tools with turnaround times fast enough to support bio-design inspired translational research and applications into what can be a rapidly changing disease progression and treatment environment. Circulating miRNAs became one of the most promising biomarkers in oncology for early diagnosis, prognosis, and therapeutic response prediction [22,23]. The tight association of miRNAs with several cancer related processes makes them undoubtedly connected to the effect of specific cancer drugs inducing either resistance or sensitization. In this context, personalized medicine through miRNAs arose recently with the discovery of single nucleotide polymorphisms in the target binding sites, in the sequence of the miRNA itself, or miRNA biogenesis related genes, increasing risk, susceptibility, and progression of multiple types of cancer in different sets of the population. miRNA markers show that they can enable a wide range of diseases to be diagnosed before clinical symptoms are manifested, and they can help to assess a patient's response to therapy to correct and personalize treatments. And despite the lack of standardized protocols regarding the use of miRNAs in current clinical practice, they constitute a reliable tool for future use.

These molecules meet most of the required criteria for being an ideal biomarker, such as accessibility, high specificity, and sensitivity. Longnoncoding RNA (lncRNAs) are the RNA transcript that do not encode for proteins and do not have open reading frame (Figure 8). Long noncoding RNAs (lncRNAs) are major components of cellular transcripts that are arising as important players in various biological pathways. Due to their specific expression and functional diversity in a variety of cancers, lncRNAs have promising applications in cancer diagnosis, prognosis and therapy and have the potential to become biomarkers in cancers. LncRNAs can be noninvasively extracted from body fluids, tissues and cells, and can be used as independent or auxiliary biomarkers to improve the accuracy of cancer diagnosis or prognosis. Currently, the most well recognized lncRNA is PCA3, which has been approved for use in the diagnosis of prostate cancer. As biomark-

ers for cancer diagnosis and prognosis, lncRNAs can be extracted from tumor tissues, peripheral blood and urine samples of patients. In prognosis, they are correlated to patient's proliferation, metastasis, invasion or survival. A distinctive feature of lncRNAs is their high specificity in tumor tissues and cells, making it possible for them to be specific and accurate biomarkers. Compared to protein based antitumor drugs, lncRNA are more refined and less toxic, and the low expression of lncRNA means that only a small amount of inhibitors are needed to make a difference.

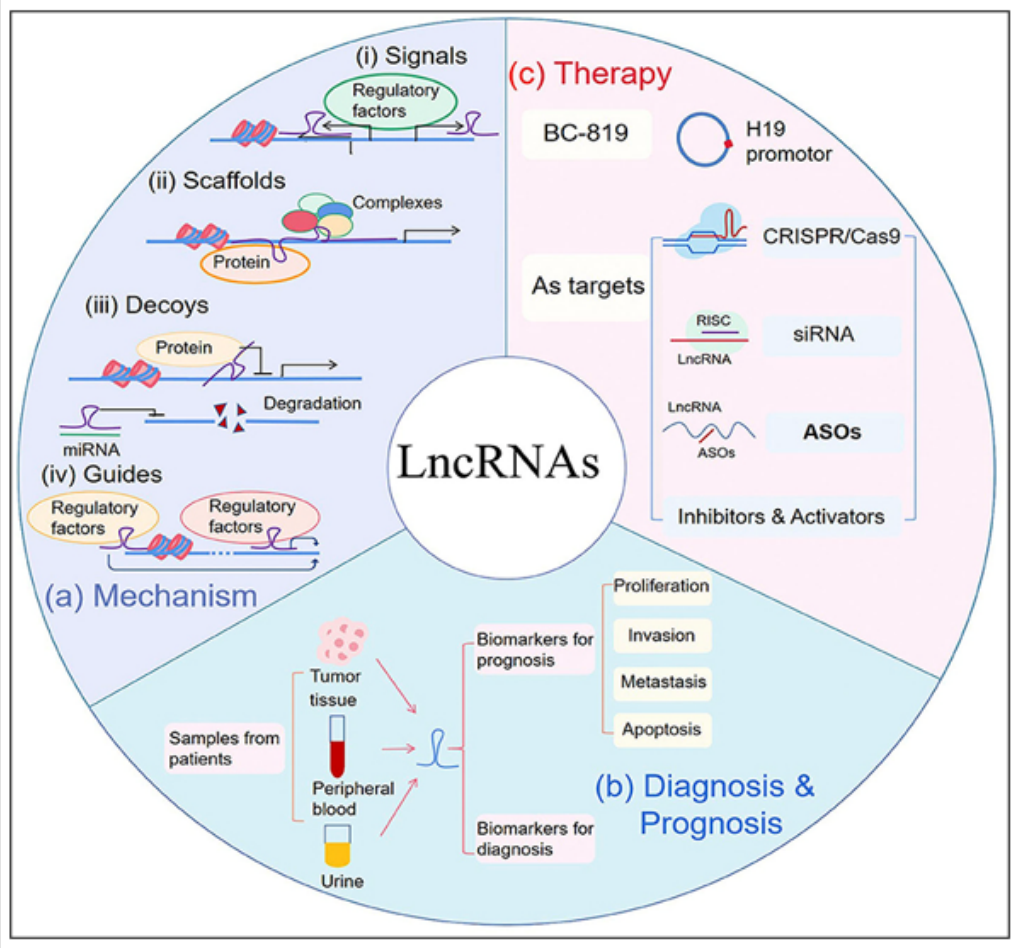

Figure 8: Long Non-coding RNAs as Cancer Biomarkers: Implications for Diagnosis, Prognosis, and Therapy.

Besides, computational tools provide new opportunities for lncRNA biomarker development and stimulate lncRNA based cancer applications towards upgraded cancer drug discovery and drugs targeting lncRNAs with useful clinical insights. Biomarkers for personalized oncology are used mainly in molecular diagnostics of chronic myeloid leukemia, colon, breast and lung cancer, and recently in melanoma. They are successfully used in the evaluation of the benefits that can be achieved through targeted therapy or in the evaluation of toxic effects of the chemotherapeutic used in the therapy [24,25] (Figure 9). Due to the individualization of cancer therapy, the identification of cancer and oncology specific biomarkers has become a foremost goal for cancer researchers [26,10]. The common usage of 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. Clinically, cancer related families of 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/nogo decision making throughout the drug development cycle, from early discovery to preclinical assessment. And thus development of oncologic therapies has traditionally been performed in a sequence of clinical trials intended to assess safety, preliminary efficacy, and improvement over the standard of care in homogeneous (in terms of tumor type and disease stage) patient populations.

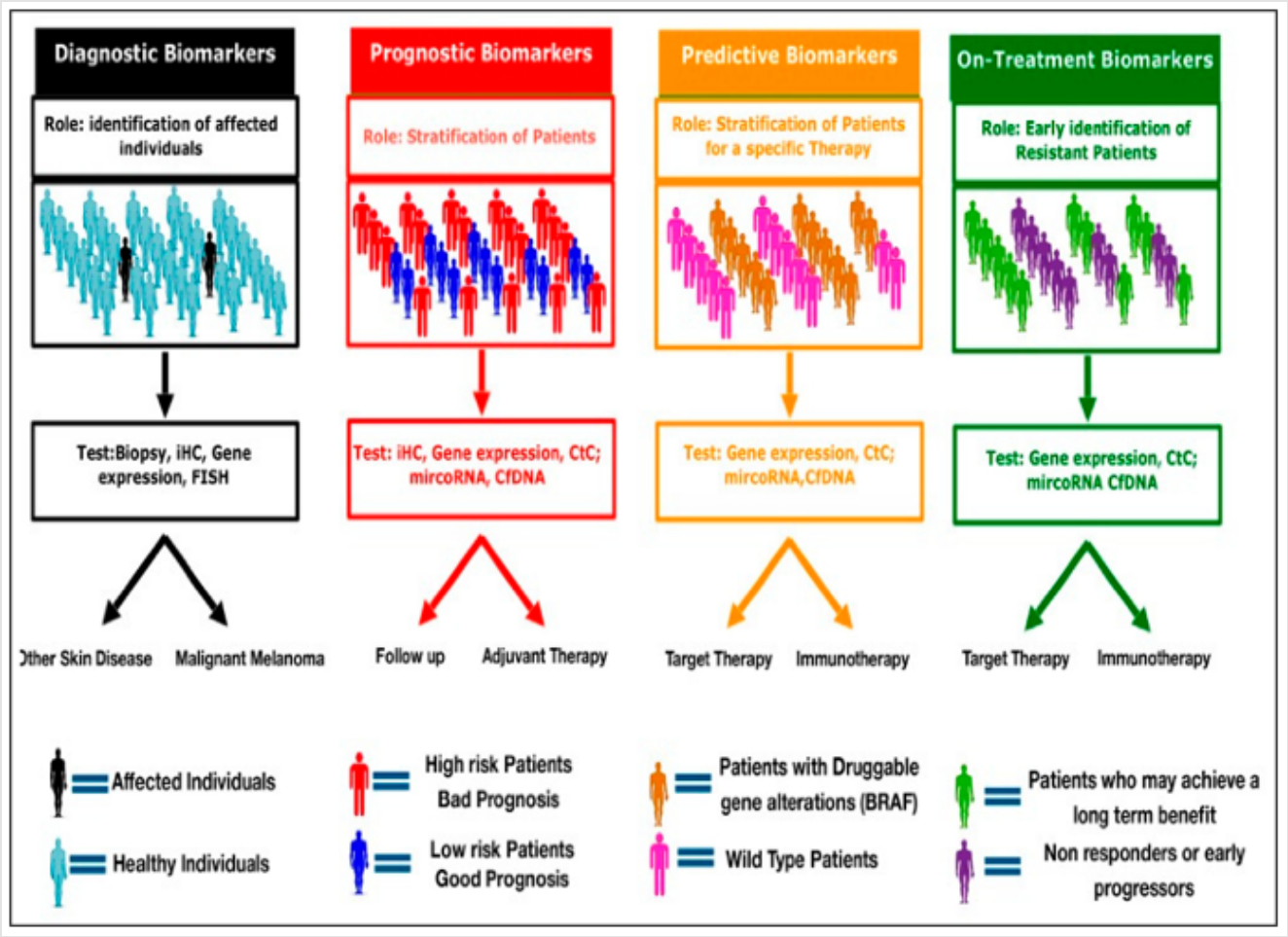

Figure 9: The use of various types of biomarkers on the example of melanoma [44].

As cancer has become increasingly understood on the molecular level, newer "targeted" drugs that inhibit specific cancer cell growth and survival mechanisms have increased the need for new clinical trial designs, wherein pertinent questions on the relationship between patient biomarkers and response to treatment can be answered. Currently, there are only a handful of FDA approved biomarkers in the market highlighting the present day challenges, starting from their diagnosis to clinical approval. Some examples of FDA approved biomarkers include:

(i) HER2 overexpression as a predictive marker to determine the survival status of breast cancer patients treated with anti-HER2 therapy;

(ii) Another example of FDA approved diagnostic maker include testing the patients suspected with prostate cancer for the prostate specific antigen (PSA) to test for malignancy of the associated disease (recent studies have found PSA screening to be in-consistent;

(iii) Measurement of 70gene expression analysis used to predict the recurrence of breast cancer after chemotherapy, is an FDA approved prognostic biomarker based assay.

Apart from the FDA approved biomarkers, there are various new approaches utilized towards personalized targeted therapy to bridge the gap between disease diagnosis and its clinical manifestation. And 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 [27]. In this context, for instance, NGS driven understanding of genes and their role in health and disease along with the increased testing capabilities have expanded the use of biomarkers across the research and care continuum. Biomarkers based on measurable levels of circulating markers in blood, plasma, and serum, as well as those identifiable on imaging, have been used for decades (Figure 10). Circulating biomarkers

provide numerous advantages in practice and could inform the clinician by aiding in diagnosis, directing treatment, and predicting outcomes. Circulating biomarkers have emerged as valuable surrogates for evaluating disease states in solid malignancies. Their relative ease of access and rapid turnover has bolstered clinical applications in monitoring treatment efficacy and cancer progression. The analysis of circulating tumor DNA (ctDNA), tumor derived cells (CTC, circulating tumor cells) or circulating microRNA (miRNA) in blood and other body fluids, have a great potential to improve different aspects of cancer management. The challenge now is to find which types of components, biofluids and detection methods would be the most suitable to be applied in the different steps of precancer and cancer detection and treatment. Circulating biomarkers such as nonspecific markers of disease burden and tumor markers have been used in the clinical setting to aid treatment monitoring.

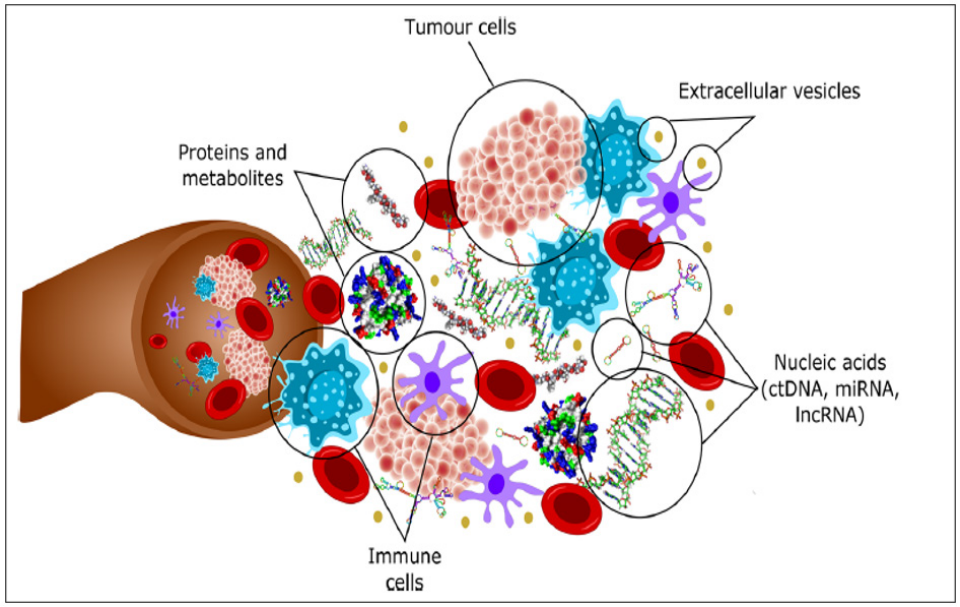

Figure 10: Circulating biomarkers.

OMICS based measures provide greater scope to identify individual differences in disease. This becomes particularly important in PPO, which, in turn, has been the leading therapeutic area in terms of biomarker development and use, setting the stage for biomarker adoption in other therapeutic areas. This includes new and adaptive designs focused on PPM and PPM guided PPO, where great progress has been made, providing along with patients precancer persons at risk with more effective treatments. Yet, opportunities remain to incorporate biomarkers, and particularly biomarker-based stratification, into PPOguided clinical trials to shorten trial durations and increase the chances of successful outcomes. In the recent years, knowledge about cancer biomarkers has increased tremendously providing great opportunities for improving the management of cancer patients by enhancing the efficiency of detection and efficacy of treatment. Recent technological advancement has enabled the examination of many potential biomarkers and renewed interest in developing new biomarkers. 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. Therefore, extensive research on various cancer biomarker profiles is important to understand their potential as therapeutic and diagnostic tools in different cancer types. Integration of biomarker discovery with other techniques such as imaging (labeling) of the specified tumor target site can provide information about the disease endpoint and offer a noninvasive way to monitor dose requirement.

Biomarkers of the Next Step Generation

Biomarkers play a critical role in improving the drug development process as well as in the larger biomedical research enterprise. Understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of normal, healthy physiology. Current biomarkers used in health care and health research are based on quantifying disease onset and its progress. Yet, health care should focus on maintaining optimal health, where the related biology is essentially differing from biomedical science. Meanwhile, health is characterized by the ability to continuously adapt in varying circumstances where multiple mechanisms of systems flexibility are involved. A new generation of biomarkers is needed that quantifies all aspects of systems flexibility, opening the door to real lifestylerelated health optimization, selfempowerment,

and related products and services. Discovery and clinical application of new biomarkers, is expected to play a significant role in reshaping life science research and life science industry, thereby profoundly influencing the detection and treatment of many diseases.

Moreover, a principally new generation of biomarkers is required that define all aspects of the variability of unified system indicators. For instance, miRNAs circulating are attracting interest in the burgeoning field of PPM and associated subfields, with data supporting their diagnostic, prognostic, and predictive biomarker potential. MicroRNAs (miRNAs) are small noncoding RNA molecules, which modulate genetic expression and which in recent years have emerged to have enormous potential as biomarkers. A schematic diagram showing miRNA biogenesis, modes of their secretion into body fluids, RNA extraction and quantitative approaches. In future, clinical decisions may be made based on the expression levels of miRNAs [17].

Circulating Tumor Cells (CTCs) in Clinical Practice

The attractive example of the next step generation biomarkers is circulating tumor cells (CTCs), illustrating subclinical stages and predictive risks as applicable to tumor progression [28]. CTCs as a biomarker of the latest generation would make up a minute fraction of the total number of cells circulating in blood. CTCs can be released from the primary tumour into the bloodstream and may colonize distant organs giving rise to metastasis (Figure 11) [22,29]. Analysis of circulating tumor cells (CTCs) collected from patient's blood offers a broad range of opportunities in the field of PPMdriven oncology. With new advances in profiling technology, it is now possible to demonstrate an association between the molecular profiles of CTCs and tumor response to therapy. CTCs are good candidates for generating preclinical models, making it possible to follow up the spatial and temporal heterogeneity of tumor tissues. This method is a noninvasive liquid biopsy that can be obtained at any stage of the disease. CTCs play a crucial role in metastasis and became an emerging topic in today's cancer research. In addition, the analysis of CTCs in liquid biopsies will be a valuable tool for prognosis prediction and real time therapy monitoring. The characterization of CTCs may open up a new field of treatment strategy to prevent metastasis or maintain a stable disease. Understanding CTC biology requires innovative technologies for the isolation of these rare cells. The analysis of CTCs is an outstanding tool to provide insights into the biology of metastatic cancers, to monitor disease progression and with potential for use in liquid biopsybased personalized cancer treatment. For instance, through singlecellresolution genomics and transcriptomics, it is becoming increasingly clear that CTCs are heterogeneous at multiple levels and that only a fraction of them is capable of initiating metastasis. CTCs adopt multiple ways to enhance their metastatic potential, including homotypic clustering and heterotypic interactions with immune and stromal cells. On the clinical side, both CTC enumeration and molecular analysis may provide new means to monitor cancer progression and to take individualized treatment decisions, but their use for early cancer detection appears to be challenging compared to that of other tumor derivatives such as circulating tumor DNA.

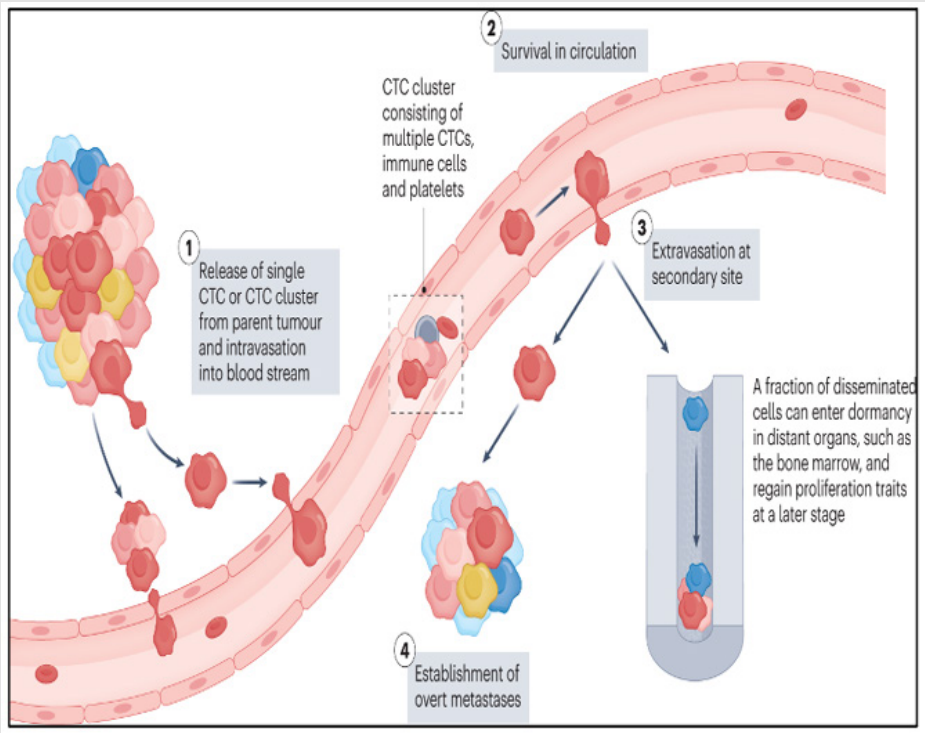

Figure 11: Key steps in the formation of metastases by CTCs [29].

CTCs as a kind of cellular biomarker that is detected in patients with early stage cancers and, owing to their association with metastasis, might indicate the presence of aggressive disease, thus providing a possible means to expedite diagnosis and treatment initiation for such patients while avoiding overdiagnosis and overtreatment of those with slow growing, indolent tumors. It is estimated that more than 90% of cancer mortality is caused by distant metastasis. Investigating CTCs provides important tumor information since these cells are already related to metastatic disease; broken free from the tumor mass, transited through interstitial tissues, and intravasated into the vasculature. Understanding and counteracting this process is essential to managing cancer. The utility of CTCs as an early diagnostic tool has been investigated and confirmed (Figures 12A-12C).

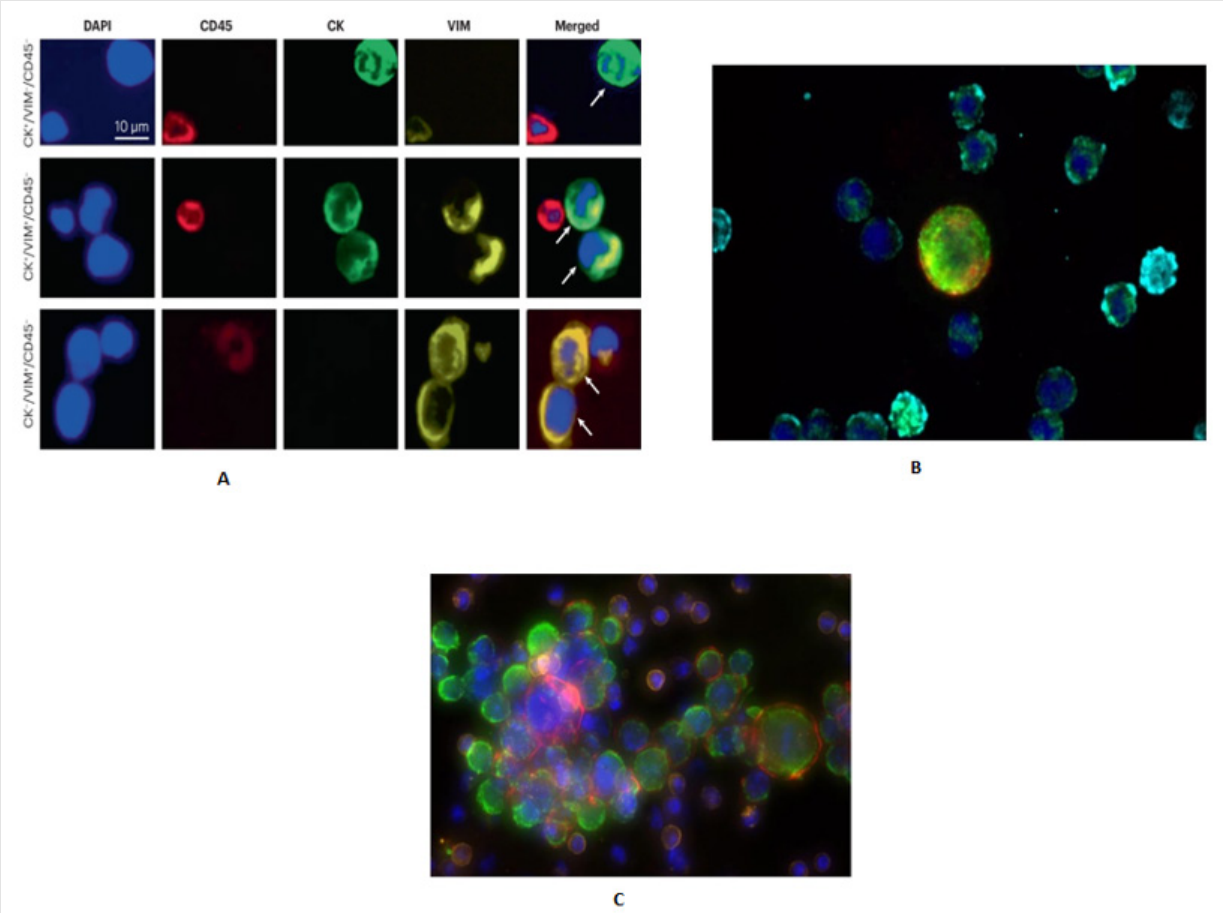

Figure 12:

A. Clinical applications of single-cell analysis of circulating tumor cells [29].

B. Clinical applications of single-cell analysis of circulating tumor cells (CTCs) CTC expressing HER2 / ER biomarkers [36].

C. Clinical applications of single-cell analysis of circulating tumor cells (CTCs) - highly sensitive CTC detection from triple negative breast cancer patient [36].

Catalytic Antibodies or Abzymes

Novel biomarkers may also identify specific pathways involved in risk, where drugs interrupting such mediator biotargets have not yet been explored in appropriately designed trials [27,30,21]. 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 Abbased families are Abs possessing with catalytic activity (catAbs or abzymes) and thus belong to Abs with a feature of functionality [31]. The immune system provides a highly evolved natural process to generate one class of complex biomarkersthe antibodies. A combination of the two could be exploited to generate new classes of molecules with novel functions. A catalytic antibody is a sort of natural artificial enzyme it is a natural protein synthesized by the usual biological processes and is intended to catalyze a reaction for which no real enzyme is available [32]. 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 Abproteases) represent a significant portion of the family of abzymes that PPM uses to target specific Ags (Figure 13). Catalytic antibodies made it feasible to develop new catalysts, which had previously been the subject of research. These antibodies are widely used in chemistry, biology, and clinical medicine.

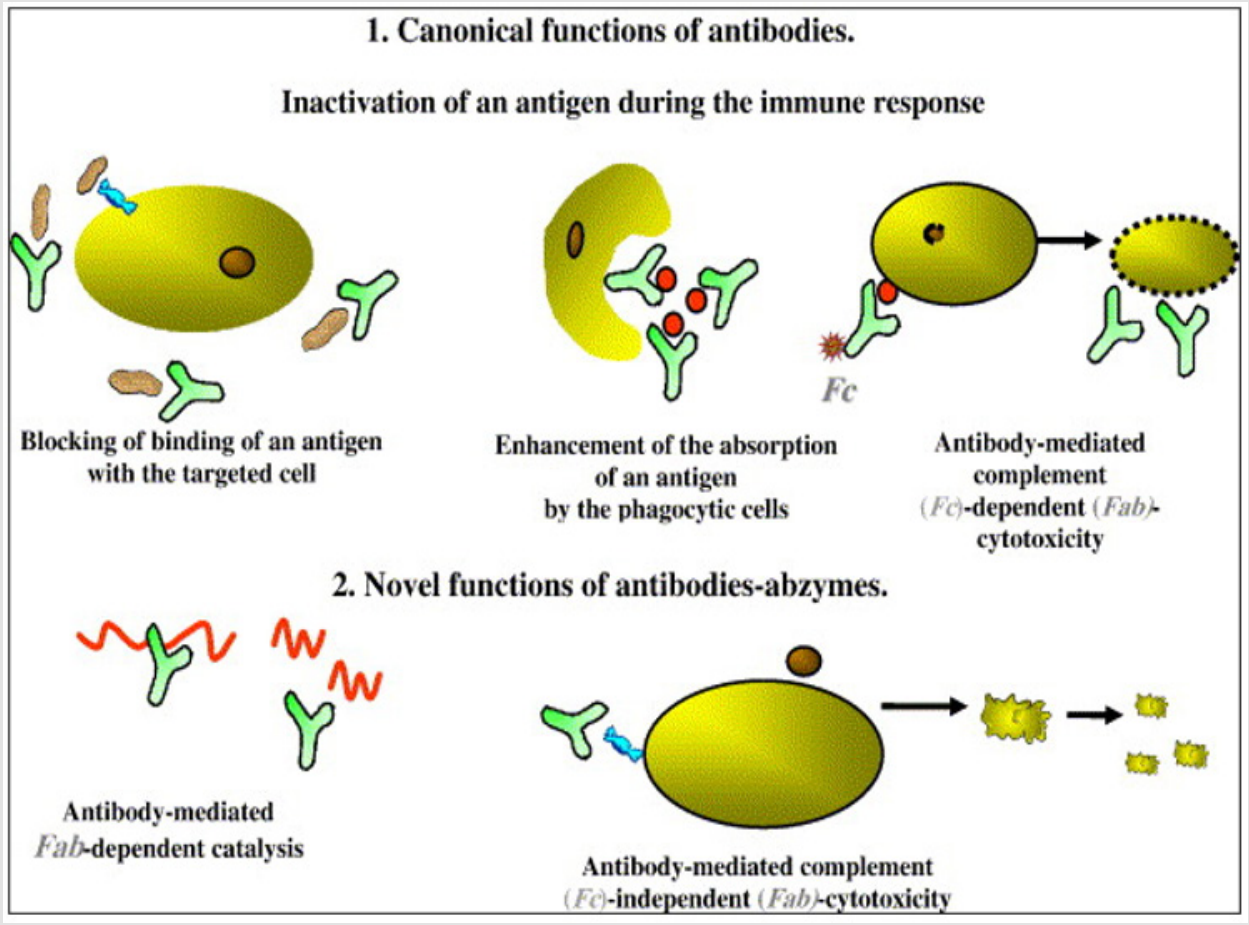

Figure 13: Antibodies possessing with catalytic activity (catAbs or abzymes) [40].

Catalytic antibodies can continue to play a role and even fully prevent the emergence of autoimmune disorders, especially in the field of infection and immunity, where the process of its occurrence and development often takes a long time. Natural abzymes with protolytic (protabzymes) and DNAhydrolyzing DNAabzymes) activity are of the greatest interest. The most impressive example of the catalytic activity of protabzymes is hydrolysis of specific proteins, revealed in patients with autoimmune diseases, such as bronchial asthma (vasoactive intestinal neuropeptide), autoimmune thyroiditis (thyroglobulin), multiple sclerosis (myelin basic protein), and autoimmune myocarditis (cardiomyosin). The pathogenic role of DNA abzymes is valuable for monitoring systemic autoimmune conditions, and they are present a powerful regulator of apoptosis and other cytotoxicity mechanisms in systemic autoimmune diseases and tumors. The most promising is use of abzymes as illness activity markers, and as therapeutic agents capable of catalyzing specific proteins or activating antitumoral chemotherapeutic preparations. The therapeutic and diagnostic uses of abzymes are currently being explored, and we expect that some of them will become major clinical resources in the future. Because of their Ag specificity, Abproteases 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 Abproteases 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 [33-35].

Network-Based Biomarkers (NBBs)

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). Today the experts may also identify specific pathways and interactome-based networks involved in diseases for which drugs have not yet been explored in appropriately designed trials, and being set up for: normal (physiological) and pathological conditions (Figures 14A & 14B). Great efforts have been undertaken in search of diagnostic biomarkers of leukemia. But individual molecules are not necessarily sensitive diagnostic indicators. Network biomarkers (NBBs) are considered to outperform individual molecules in disease characterization. The final network was further integrated with gene expression profiles to identify active modules with leukemia relevance. And the candidate NBB was evaluated for the diagnosing performance. A network of 97 genes and 400 interactions was identified for accurate diagnosis of leukemia. Functional enrichment analysis revealed that the network biomarkers were enriched in pathways in cancer. The NBBs could discriminate leukemia samples from the normal controls more effectively than the known biomarkers. The NBBs provide a useful tool to diagnose leukemia and also aids in further understanding the molecular basis of leukemia.

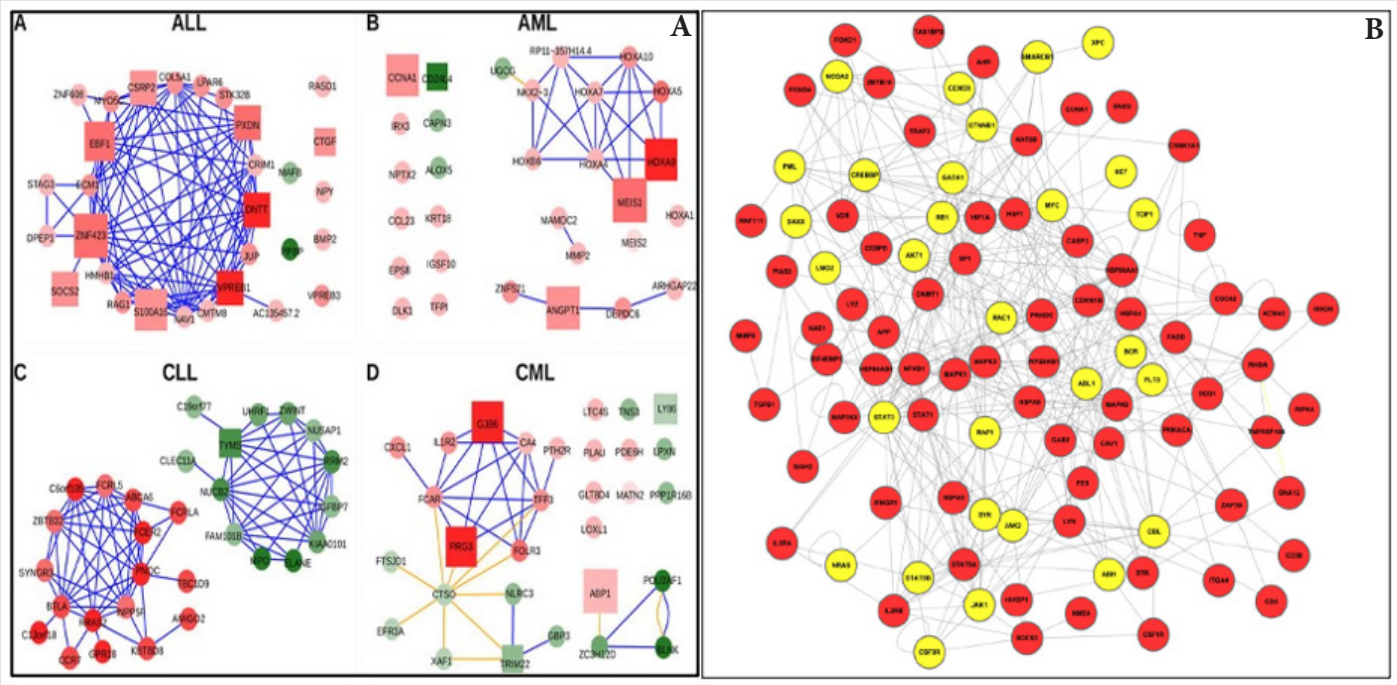

Figure 14: The interactome-based networks of leukemia [43].

Those networks may serve as sources of network based biomarkers (NBBs) to secure diagnostic, predictive, prognostic and monitoring related aims and objectives of the next step generation. In this sense, NBBs help determine the probability of developing chronic pathologies, autoimmunity, or cancer predisposed conditions. Key factors contributing to the growth of the global NBBsrelated healthcare services market include high prevalence of chronic autoimmune diseases and cancer; rising adoption of biomarkers for diagnostic, predictive, and prognostic applications, as well as 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 the 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 daily clinical practice of medicine [36].

Biomarker-Guided Clinical Trial Design

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:

1) Being almost always unblinded, they are prone to bias;

2) The control group, most frequently the 'usual care' group, is opened to contamination and has inevitably better outcomes than in real nontrial 'usual care';

3) Being per essence 'strategytrials' rather than simple intervention trials, causality is difficult to establish;

4) Therapy optimization as a result of a 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 guidelinebased, may vary according to the protocol [27,37].

5) Validated biomarkers are essential for improving diagnoses, molecular targeted therapy, and therapeutic benefits across various diseases. Despite recent progress, the path to clinically validated biomarkers remains challenging, often creating a gap between research and application. [38].

Clinical trials are necessary to confirm the properties of emerging treatments and associated biomarkers, influencing daily clinical practices and regulatory reporting before professional or commercial release. Biomarkers also play a role in facilitating drug repurposing and guiding patient care decisions within clinical settings and drug development processes. 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 the 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 relationship between biomarkers and the disease.

Future Applications of Biomarkers in Healthcare

Biomarkers are indicators of typical biological processes, pathogenic processes, or pharmacological reactions to therapy. And you might see from the abovementioned, 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. Numerous compounds have been tested as potential biomarkers for multiple possible applications within PPM-guided care but none is or will ever be sufficiently specific or sensitive for the heterogeneous syndromes of critical illness. New technology and access to huge patient databases are providing new biomarker options and the focus is shifting to combinations of several or multiple biomarkers rather than the single markers that research has concentrated on in the past. Biomarkers will increasingly be used as part of routine clinical practice in the future, complementing clinical examination and physician expertise to provide accurate disease diagnosis, prediction of complications, personalized treatment guidance, and prognosis. 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 involving screening, diagnosis, prognostication, prediction of disease recurrence, and therapeutic monitoring.

The unique diagnostic potential of specific biomarkers and their efficacy correlates with phenotypical expression, covering 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 are likely to benefit the patients. Cancer biomarkers are broadly categorized into three divisions based on the specific association with diagnostic, diagnostic, predictive and prognostic biomarkers. The therapeutic potential of different biomarkers and their use in clinical trials has also been discussed. Since the use of biomarkers as the preearly (subclinical or preillness) warning systems in the evaluation of disease risk has increased markedly in the last decade. And thus the application and identification of biomarkers in the medical and clinical fields have an enormous impact on society. Despite the recent advancements, a comprehensive approach in 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:

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) [38].

3) Monitoring the progression of autoimmune inflammation, and predicting the complications and outcome (panels of prognostic biomarkers) [39].

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 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 [20]. 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.

Conclusion

Biomarkers have gained significant scientific and clinical importance in the realm of PPM and related fields, offering potential benefits throughout the disease process. The oncology segment is the largest area for biomarker growth. Biomarkers can be used for early detection, estimate prognosis, guide selection of targeted therapies (companion diagnostics), and monitor response to treatment [40-43]. The increased demand for rapid and accurate diagnostic OMICS-tools, an increase in the global cancer burden, and an unmet need for more specific, personalized, therapeutic targets for cancer patients and precancer personsatrisk will continue to drive growth in the market, which is really growing. The current value of the global biomarkers market is estimated to be USD 43.1 billion, with an expected compound annual growth rate (CAGR) of 12.6% from 2021 to 2026 (Figure 15). The diagnostics segment of the global biomarker market is estimated to register the fastest CAGR over the forecast period [44-47]. The predicted growth is owed to advances in early diagnosis and improvement in the rate of the diagnosis From: Biomarkers Market, available at marketsandmarkets.com

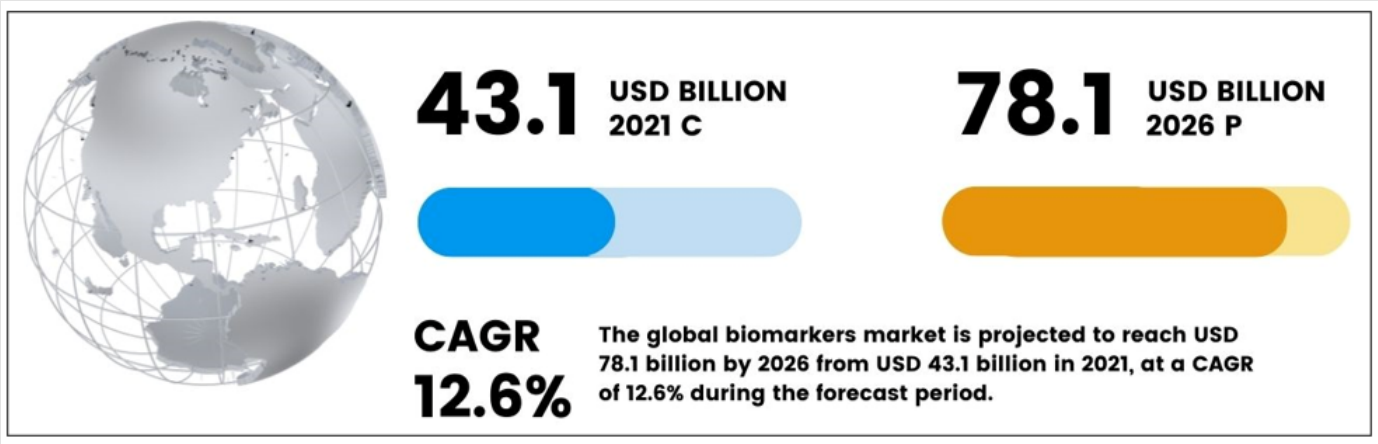

Figure 15: Global biomarker market size and growth forecast.

The key factors boosting market growth are:

(i) An ageing population and increasing prevalence of chronic diseases;

(ii) Advancements in the tools and OMICS technology used to discover and develop biomarker-based diagnostics.

Biomarkers play crucial roles in diagnosis, staging, treatment selection, and monitoring of diseases and their complications. Advances in OMICS technologies have led to the identification of numerous candidate biomarkers with clinical potential. Integrating these biomarkers into evidence-based medical practice using emerging highthroughput technologies is essential for personalized treatment and disease prevention. Additionally, biomarker research in autoimmunity and cancer is focused on identifying predictors of successful drugfree remission and uncovering molecular similarities between seemingly distinct diseases. Shifting focus from latest age disease treatment to early stage monitoring and prevention could transform medicine, with collaboration across academia, industry, and other sectors vital for realizing the full potential of biomarkers in personalized medicine.

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