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Towards Personalized and Precision Oncology Through the View of Design-Driven Cancer Translational Research and Clinical Applications

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Annotation

PPM is now the recommended standard for oncology care. Individualizing treatment is thus becoming a core objective of the Personalized and Precision Medicine (PPM) and its valuable branch, entitled as Personalized & Precision Oncology/PPO). PPO is emerging as a complementary approach that aims to bridge the gap between genotype and phenotype by modelling

individual tumors in vitro. Those patient- and pre-cancer person-at-risk-derived ex vivo models largely preserve several tumor characteristics that are not captured by genomics approaches and enable the functional dissection of tumor vulnerabilities in a PPM-guided manner. Those trends and developments have opened exciting new avenues for PPO-guided clinical practice, with the potential for successful applications in contexts in which genomic data alone are not informative.

To really understand PPO, we would have to understand the various fields of translational applications that provide the tools to exploit and practice PPO and genomics- and phenomics-related tools, in particular! PPM and PPO along with the "OMICS-guided" diagnostic, predictive, prognostic and therapeutic manipulations are expressions used for this paradigm shift often interchangeably[1-16].

Multi-OMICS technologies provide profound insights into cancer biology and PPO-guided clinical practice. A fundamental computational approach for analyzing multi-OMICS data is differential analysis, which identifies molecular distinctions between cancerous and normal tissues. Such approaches offer a more nuanced understanding of cancer biology and are instrumental in pinpointing PPO-guided therapeutic strategies[17].

Genomic information, in particular, is increasingly being incorporated into clinical care. Genomic profiling can provide clinically relevant information regarding somatic point mutations, copy number alterations, translocations and gene fusions. Continued advancements in precision genomics promise to further expand the application of genomics-enabled medicine to a broader spectrum of patients and persons-at-risk, in particular[18].

The uptake of PPM, while advancing in cancer care, has faced several adoption challenges, including education, policy and practical factors. For instance, personalized cancer treatment in particular stands to highly benefit from PPO-driven therapies, since extensive variability between tumors presents a need to target each case in a personalized manner. At this point, personalized cancer therapy is considered to be a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that cancer biomarkers are associated with patient prognosis and tumor response to therapy. And personalized tumor molecular profiles (tumor biomarkers can be OMICS-profiles that predict therapy response) tumor disease site and other characteristics are then potentially used for determining optimum individualized therapy options[2-15,19,16,20].

Improved cancer patient (or pre-cancer person-at-risk) outcomes with the application of the biomarker tests must consider not only increased survival or quality of life, but also improved Clinical Decision Support (CDS) & making leading to the avoidance of unnecessary therapy or toxicity. So, bioinformatics, Artificial Intelligence (AI), Machine Learning (ML) and biostatistics will be crucial in translating those Big Data into useful clinical and pre-clinical applications, leading to improved diagnosis, prediction, prognostication and treatment[21-27].

The Editorial describes along modern modes and technologies of diagnostics, translational cancer therapeutics and the way forward from clinical and molecular diagnosis to treatment. Also, the Review concerns the role of bioinformatics and biostatistics, considering the Big Data analysis serving PPM and PPO approaches.

Facilitating the transformation toward PPM that will improve patient outcomes in the oncology setting requires a coordinated effort among policymakers, cancer agencies, health systems and industry. To implement PPM effectively in cancer practice requires an informatics solution beyond the legacy electronic medical record platforms currently available to clinical teams.

Therefore, the proposed Editorial demonstrates the successful evidence for the use of PPM-driven resources in the treatment of cancer and its future clinical perspectives as PPO-driven trends. The latter fills the gaps in cancer biology and oncology with its up-to-date content and well-designed sections. It will serve as a valuable resource for bio designers, general practitioners, oncologists, medical students and interdisciplinary researchers. And the concept of PPM and PPO as its branch appear to hold promising results, having potential benefits for the effectiveness of care, new disease taxonomy and population healthcare as a whole.

1. Introduction

NContemporary views of human disease (including cancer) and thus modern medicine, clinical oncology and global healthcare are based on simple correlation between clinical syndromes, pathological analysis and data rooted in the latest research and applications. In this context, the link that might exert reliable control over morbidity, mortality and disabling rates and to thus improve the healthcare services and to significantly optimize the efficacy of treatment for those who had fallen ill (patients) and for persons-at-risk is Personalized & Precision Medicine (PPM) (Figure 1).

PPM refers to the tailoring of diagnostics or therapeutics to individual patients based on their unique genetic and physiologic characteristics. Personalized medicine takes these differences and implements preventions/treatments tailored to the individual. Precision medicine identifies differences in individuals, categorizing based on environmental, biological and psychosocial factors[28,29].

PPM is one of the most promising approaches to tackling diseases that have thus far eluded effective treatments or cures. In particular, cancer, takes an enormous toll on individuals, families and societies as a whole. With regard to cancer, PPM most often means looking at how changes in certain genes or proteins in a person's cancer cells might affect their care, such as their treatment options. PPM holds promise for better personalization of care in the future.

PPM uses a patient's genetic profile to guide decisions about disease prevention, diagnosis and treatment. That is Genes, Genome Clusters and Genome Landscapes are really the core of PPM being assessed and analyzed by diagnostic, predictive and prognostic analytics tools, on one hand and presented to the practitioners, on the other one.

PPM as being the Grand Challenge to forecast, to predict and to prevent is rooted in a big and a new science generated by the achievements of:

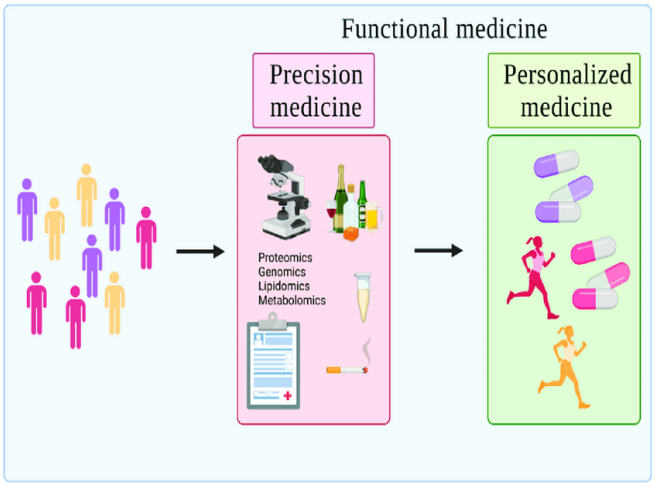

Figure 1: Personalized & precision medicine (PPM) as a Model of Healthcare Services of the Next-Step Generation.

Systems Biology[30-38] (Figure 2A)

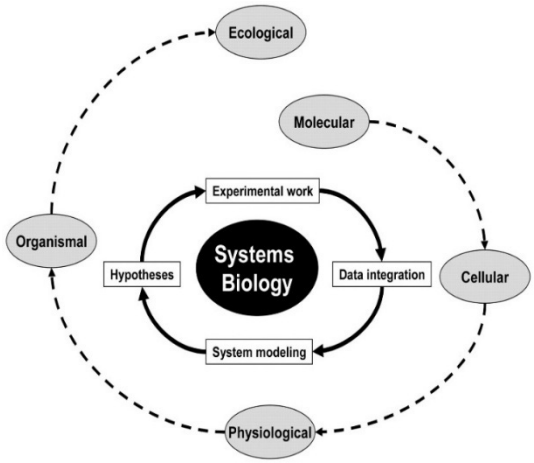

Figure 2A: Systems Biology in theory.

Systems biology is a comprehensive quantitative analysis of the manner in which all the components of a biological system interact functionally over time. Systems biology is a field of research that focuses on understanding whole biological systems, such as protein complexes, metabolic pathways or gene regulatory networks and it attempts to understand cells, tissues and organisms and how they behave and function from a systems perspective. Systems biology is an integrative discipline connecting the molecular components within a single biological scale and also among different scales (e.g. cells, tissues and organ systems) to physiological functions and organismal phenotypes through quantitative reasoning, computational models and high-throughput experimental technologies. In other words, systems biology is a computational and mathematical analysis and modeling of complex biological systems and a systemic view of biological issues means that the function of no organ is independent of the other so that the behavior of all components will affect the behavior of the whole system.

The masses of data generated by high-throughput technologies are challenging to manage, visualize and convert to the knowledge required to improve patient (including cancer patient and pre-cancer person-at-risk) outcomes. Systems biology integrates engineering, physics and mathematical approaches with biologic and medical insights in an iterative process to visualize the interconnected events within a cell that determine how inputs from the environment and the network rewiring that occurs due to the genomic aberrations acquired by patient tumors determines cellular behavior and patient outcomes. A cross-disciplinary systems biology effort will be necessary to convert the information contained in multidimensional data sets into useful specific (including cancer) biomarkers that can classify patient tumors by prognosis and response to therapeutic modalities and to identify the drivers of tumor behavior that are optimal targets for cancer therapy. An understanding of the effects of targeted therapeutics on signaling networks and homeostatic regulatory loops will be necessary to prevent inadvertent effects as well as to develop rational combinatorial therapies. Systems biology approaches identifying molecular drivers and biomarkers will lead to the implementation of smaller, shorter, cheaper and individualized clinical trials that will increase the success rate and hasten the implementation of effective therapies into the clinical armamentarium[30-35].

Integrative Medicine (Figure 2B):

Figure 2B: Integrative medicine.

Integrative medicine, as defined by the American Board of Integrative Medicine® (ABOIM) and the Consortium of Academic Health Centers for Integrative Medicine, is the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing.

Integrative health and medicine have emerged as a movement that focuses on the whole person, considering the individual in its physical, psychological, spiritual, social and environmental context and is inclusive of all professions and practices that use this approach. Integrative health and medicine stand for an evidence-informed integration of conventional biomedicine with traditional and complementary medicine (T&CM). All appropriate therapeutic approaches and healthcare disciplines are used to achieve optimal health and healing, while recognizing and respecting the unique contribution from many medical systems[39,40].”

Biodesign-driven translational research & applications (Figure 2C and D):

The impact of systems biology & fundamental biological discoveries is not reaching the clinical setting at a pace that was expected. In order to bridge this gap, the focus of biomedical researchers has shifted from OMICS-driven discoveries to “translating” only clinically relevant biological information. The change in focus has redirected the field of design-driven biotechnology toward what “translational research,” which is the

buzzword of the era. By definition, translational & applications is "an interdisciplinary branch of the biomedical field supported by three main pillars: bench-side, bedside and community," Stemming from translational biotechnology came system biology, bioengineering and so on. Combining such biomedical information from different layers of OMICS-data can ultimately help us in revealing the landscape of molecular mechanisms involved in highly prevalent complex diseases like cancer.

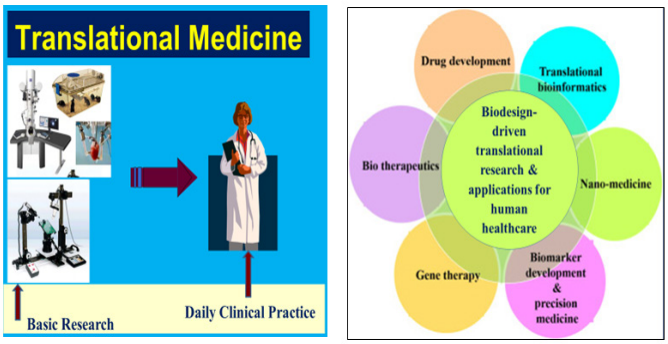

Figure 2C and D: Modern approaches towards biomedical translation: predicting translational progress in biomedical research & applications.

Translational medicine (also referred to as translational science) is a discipline within biomedical and public health research that aims to improve the health of individuals and the community by "translating" findings into diagnostic tools, medicines, procedures, policies and education. Translational medicine, area of research that aims to improve human health and longevity by determining the relevance to human disease of novel discoveries in the biological sciences. Translational medicine seeks to coordinate the use of new knowledge in clinical practice and to incorporate clinical observations and questions into scientific hypotheses in the laboratory. Thus, it is a bidirectional concept, encompassing so-called bench-to-bedside factors, which aim to increase the efficiency by which new therapeutic strategies developed through basic research are tested clinically and bedside-to-bench factors, which provide feedback about the applications of new treatments and how they can be improved. Translational medicine facilitates the characterization of disease processes and the generation of novel hypotheses based on direct human observation[41-43].

Whilst integrating platforms of OMICS-technologies (Figure 3).

Various types of systems data can be generated and integrated with the multi-OMICS integrative analysis. High-throughput OMICS technologies allow the retrieval of comprehensive biological information, whereas computational capabilities enable high-dimensional data modeling and, therefore, accessible and user-friendly visualization. In clinical settings, we need to timely model clinical and multi-OMICS data to find statistical patterns across millions of features to identify underlying biologic pathways, modifiable risk factors and actionable information that support early detection and prevention of complex disorders and development of new therapies for better patient care. OMICS analysis has identified clinically actionable mutations, gene and protein expression patterns associated with prognosis and provided further insights into the molecular mechanism's indicative of cancer biology and new therapeutics for PPO.

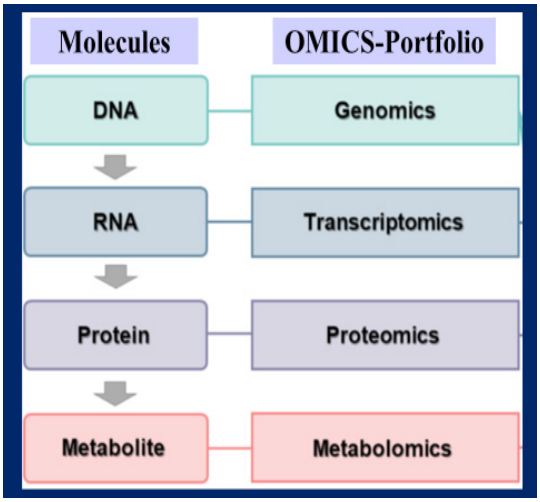

Figure 3: Multi-OMICS Portfolio: paving the path toward achieving PPM and PPO.

The integration of multiple biological layers of OMICS studies brought oncology to a new paradigm, from tumor site classification to pan-cancer molecular classification, offering new therapeutic opportunities for PPO and PPM. In this context, Mult-OMICS information leads to a global profiling of health and disease and providing new approaches for personalized health monitoring and preventative medicine[3-15,44-46].

PPM, personalized precision medicine; PPO, personalized precision oncology

Whose data is analyzed, integrated, mined and clinically interpreted by a set of algorithms and software of bioinformatics (Figure 4A and B).

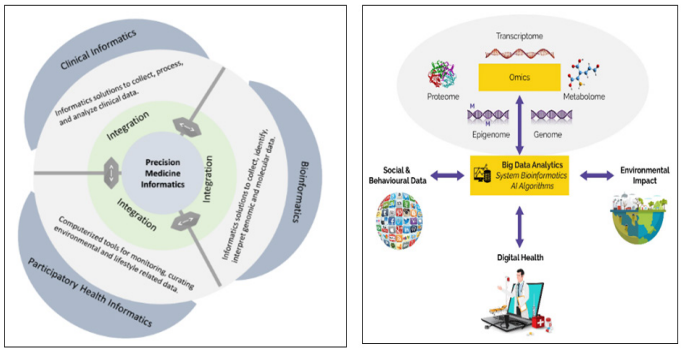

Figure 4A and B: PPM informatics & Big Data analytics.

(G) Classification of enabling tools and techniques in three areas of PPM-driven informatics: clinical informatics, biomedical informatics and participatory health informatics.

(H) Integrated Big Data accumulated from a variety of PPM-dependent sources, including OMICS data, social & behavioral data, environmental data and personal client data (including EMRs and disease story).

Nowadays, the increasing availability of OMICS and related data, due to both the advancements in the acquisition of translational application results and in systems biology simulation technologies, provides the bases for PPM. Success in PPM depends on the access to healthcare and biomedical data. To this end, the digitization of all clinical exams and medical records is becoming a standard in hospitals. The digitization is essential to collect, share and aggregate large volumes of heterogeneous data to support the discovery of hidden patterns with the aim

to define predictive models for biomedical purposes. Patients' data sharing is a critical process. In fact, it raises ethical, social, legal and technological issues that must be properly addressed. Meanwhile, fragmentation and heterogeneity of available data makes it challenging to readily obtain first-hand information regarding some particular diseases, drugs, genes and variants of interest. So, both medical professionals and IT experts across the globe have started to device computational infrastructural solutions to address the need of timely and precise decision on a patient health issue. It is a high time for both the informatics community and the medical community to collaborate with each other to make a combine effort for achieving the common goal of a better-quality patient care. To understand the IT-related viewpoint of how the PPM is implemented, we provided an overview of enabling tools and techniques in three potential areas: biomedical informatics, clinical informatics and participatory health informatics.

The integration of heterogeneous data sources allows to lay the foundations for a series of statistical assessments needed to answer more complex questions that can be used in a variety of fields, such as predictive and precision medicine. In particular, studying the clinical history of patients who have developed similar pathologies we could allow to predict or individuate marks allowing early diagnosis of possible illnesses[47-50].

PPM is a goal of upgraded healthcare of the nearest future to come, in which diagnostic and treatment decisions are informed by each person's unique clinical, OMICS-based, healthcare bureaucracy (medical records, etc) (Figure 5) and environmental (exposomics-related) (Figure 6) information.

Figure 5: Electronic and Sensory Health Records in Clinical Practice and Health Management.

Health care informatics focuses on collecting, using and analyzing data and refers to using data and information technology to improve clinical outcomes and improve both the patient and provider experience. The new applications of public health informatics contribute to more timely and accurate data for disease surveillance. Examples include electronic laboratory reporting of notifiable diseases, aided by new data transmission standards and vocabularies; personal digital assistants or handheld computers to collect data in the field that can be downloaded into a database with no further data entry requirements; geographic information systems integrated with satellite images to provide information about the spread of diseases; use of mobile telephones to report surveillance data from the field; and use of the Internet as an effective way to share surveillance data with health care professionals[51-53].

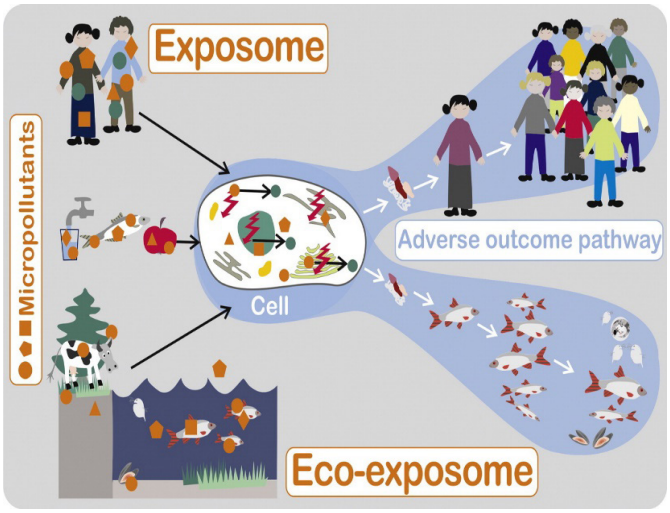

Figure 6: Exposome-driven human health.

Human health is determined by the interaction of our environment with the genome and microbiome, which shape the transcriptomic, proteomic and metabolomic landscape of cells and tissues. Precision environmental health is an emerging field leveraging environmental and system-level ('omics) data to understand underlying environmental causes of disease, identify biomarkers of exposure and response and develop new prevention and intervention strategies. The exposome is defined as the totality of internal and external exposures across the lifespan and their health effects. The external exposome includes diet, nutrients, water, chemicals, pollutants, toxins and other environmental and geospatial exposures. The internal exposome can be measured by untargeted metabolomics, encompassing the small metabolites resulting from all the metabolic processes. Exposomics intended to give a better account of the complex relationships between genes and environmental factors. As a complement to OMICS data, studies on drug-exposome interactions holds immense potential to elevate PPM to an unprecedented level[51-54].

2. PPM-Guided Clinical Oncology Practice Through the View of Biomarker-Driven Approaches

The global goal of PPM is to combine current medicine with molecular breakthroughs to target patients individually and increase the efficacy and effectiveness of the therapeutic strategy. Meanwhile, to secure therapeutic targetting which is crucially important and valuable for the latter, whilst implementing the key PPM-related resources into clinical practice, there is a strong need to develop a principally new approach based on biomarkers-driven targeting aimed at subclinical and/or predictive recognition of biomarkers long before the illness (e.g., cancer) clinically manifests itself[55-61] (Figure 7).

Molecular pathway maps indicate involvement of multiple molecular mechanisms and selected biomarker candidates reported as associated with disease progression are identified for specific molecular processes and disease-related stages, including risk factors, screening and diagnosis and prognosis covering the induction stage, latency (subclinical or pre-illness) and clinical manifestations[61-65].

This new biomarker-driven diagnostic and monitoring

technology will create a full digital fingerprint of patient samples that will be able to connect genotype, phenotype, diagnosis, treatment and outcome at the molecular level. Meanwhile, in PPO, one of the ways to improve the specificity is to move from a single to multiplex biomarkers, which can additionally provide significantly increased diagnostic, predictive and prognostic accuracy. Such multiplex biomarkers should include information from each level of systems biology bridging genomics, transcriptomics, proteomics and metabolomics. This approach would give a real opportunity to secure diagnostic, predictive and prognostic manipulations[66-72] (Figure 8A-C).

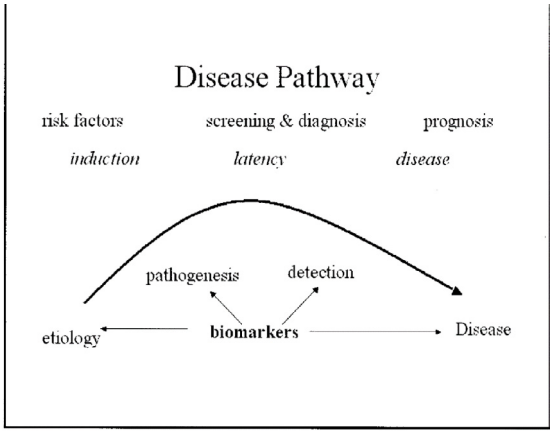

Figure 7: Disease Pathway Biomarkers.

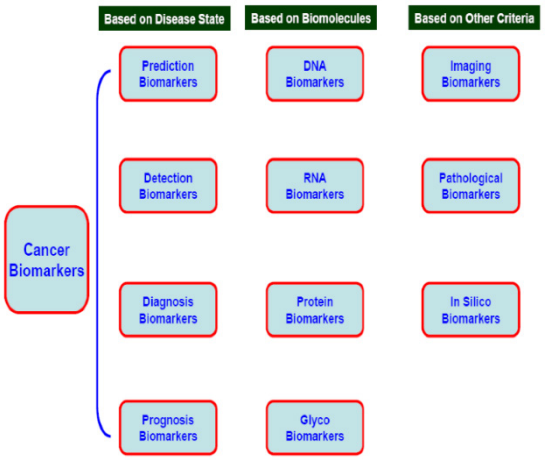

Figure 8A: Various roles of biomarkers in cancer treatment.

Cancer biomarkers are categorized into several segments based on their utility in various steps of oncology practice, including:

i. **Diagnostic:** for a confirmed diagnosis of cancer and its extent (are also useful to differentiate between the types of tumors like benign or metastatic tumors, primary or secondary site tumors, etc.);

ii. **Prognostic:** (help determine the aggressiveness of the detected tumor and how the tumor will respond to the selected therapy - helps physicians to plan and design a proper regimen for the patient);

iii. **Predictive:** help in the screening of cancer in a healthy patient and also could predict the risk of getting cancer in the future;

iv. **Pharmacodynamics:** the circulating biomarkers access the drug response like its metabolism and deposition in the body during a treatment course, whilst helping to understand the optimum effective dose of the drug;

v. **Recurrence:** are useful in predicting the recurrence of disease in patients who have undergone treatment and recovered from cancer - periodic screening using assays of the biomarkers helps understand the chances of disease recurrence;

vi. **Monitoring:** the response of treatment cycles in killing tumor cells -it helps to treat physicians to design future treatment goals[65,72-75].

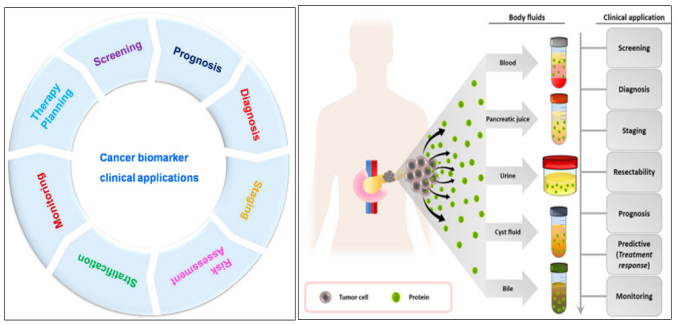

Figure 8B and C: Cancer biomarker and their clinical applications.

Cancer biomarkers are the key to unlocking the promise of PPO, selecting which patients will respond to a more personalized treatment while sparing non-responders the therapy-related toxicity. In cancer, a biomarker refers to a substance or process that is indicative of the presence of cancer in the body. A biomarker might be either a molecule secreted by a tumor or it can be a specific response of the body to the presence of cancer. Genetic, epigenetic, proteomic and imaging biomarkers can be used for cancer diagnosis, prognosis and epidemiology. Cancer biomarkers must be embedded in the real world of oncology delivery. Cancer biomarkers belong to a variety of bio elements such as DNA, mRNAs, proteins, lnc RNAs, miRNAs, exosomes, cellular metabolites and organic materials. Cancer patients and pre-cancer persons-at-risk must be placed firmly at the center of a cancer biomarker informed PPO-driven care agenda[76-81].

In this context, cancer biomarkers are any measurable molecular indicator of risk of cancer, occurrence of cancer or patient outcome. They may include germline or somatic genetic variants, epigenetic signatures, transcriptional changes and proteomic signatures. These indicators are based on biomolecules, such as nucleic acids and proteins, that can be detected in samples obtained from tissues through tumor biopsy or, more easily and non-invasively, from blood (or serum or plasma), saliva, buccal swabs, stool, urine, etc. Therefore, thousands of species of RNAs, proteins and metabolites are suggested as candidate tumor biomarkers alone or as constituents of multiplex signatures. If the patient is already diagnosed with a certain cancer, RNA or protein biomarker signatures may help to select a specific therapy or to predict the probability of a relapse. Mean-while, detection technologies have advanced tremendously over the last decades, including techniques such as next-generation sequencing, nanotechnology or methods to study circulating tumor DNA/RNA or exosomes.

Along with a significance of single or multi-faceted sets of biomarkers, annotated molecular networks offer new opportunities to understand diseases within a systems biology framework and provide an excellent substrate for network-based identification of biomarkers. The network biomarkers (NBBs) and dynamic network biomarkers (DNBBs) represent new types

of biomarkers with protein-protein or gene-gene interactions that can be monitored and evaluated at different stages and time-points during development of disease[82-88]. In this sense, clinical bioinformatics as a new way to combine clinical measurements and signs with human tissue-generated bioinformatics is crucial to translate NBBs and DNBBs into clinical application, validate the disease specificity and understand the role of biomarkers in clinical settings.

Clinical applications of biomarkers are extensive: much of the current PPM-related designed testing platforms are focused on the identification of protein biomarkers, which are distinct from genetic ones. They can be used as tools for cancer risk assessment, screening and early detection of cancer, accurate diagnosis, patient prognosis, prediction of response to therapy and cancer surveillance and monitoring response. They have the advantage that they make up the actual molecular phenotype of disease, as they are at the end of the DNA-to-RNA-to-protein progression from genotype to phenotype[89-94].

Biomarker-guided and PPM-driven oncology can make a big difference for patients with cancer and for pre-cancer persons-at-risk. If the clients are not being presented with biomarker-informed testing and treatment options, cancer patients are being unknowingly denied targeted therapeutic possibilities that could help them live longer, healthier lives. The same principle applies for pre-cancer persons-at-risk who, whilst being avoided biomarker-informed testing, would not be able to secure the cancer prevention.

In this context, novel technologies such as liquid biopsy, CTC screening and monitoring and companion diagnostics (theranostics) accompanied evolving trends in PPO and prognostic and predictive markers such as minimal residual disease[95-98]. Therefore, they can help to optimize making decisions in clinical practice. More-over, PPO is needed for newly developed targeted therapies, as they are functional only in patients with specific cancer genetic mutations and biomarkers are the tools used for the identification of these subsets of patients. So, PPO emerged as a new field encompassing small molecular inhibitors and biologics.

Cancer is a multifaceted and complex disease that results from the disruption of genetic, epigenetic and metabolic systems responsible for maintaining physiological conditions in the cell. Cancer is characterized by uncontrollable overgrowth of usually one particular cell type, which becomes a cancer cell and by spreading of these cancer cells to lymph nodes and other organs of the body, what is called metastatic disease. So, cancer heterogeneity provides a formidable obstacle to optimizing clinical protocols to achieve durable clinical responses. And the absence of reliable cancer-related biomarkers for the pre-early (subclinical) detection and progression monitoring results in the generation of complex cancer-related molecular pathways negatively impact anticancer immune-mediated responses. As a result, immunotherapy-based therapeutic modalities alone or in combination with other standard or targeted therapies provide limited clinical benefits for patients. Therefore, it is imperative to discover biomarkers suitable for selecting patients most likely to benefit from therapies[99-107].

Biomarkers are crucial for identifying the patients who are expected to derive greatest advantage from canonical targeted therapy and pre-cancer persons-at-risk who do need a special approach, including preventive therapeutic modes.

In case of cancer, tumor microenvironment plays a crucial role in the process of growth and spreading of cancer cells in the body (Figure 9).

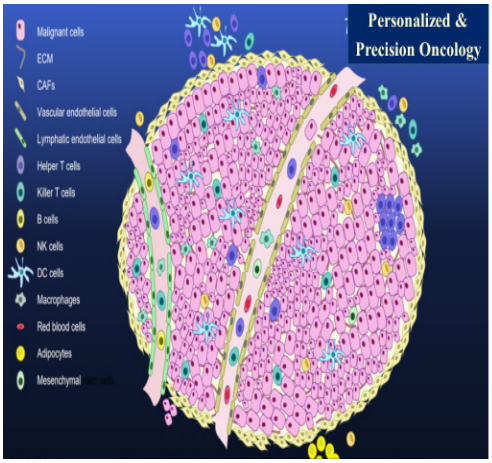

Figure 9: The Tumor Microenvironment.

This simplified illustration of the tumor microenvironment just some of the many different cell types typically present, including tumor cells, vascular cells, immune cells and others that may or may not be related to the tumor or have a role in tumor promotion or suppression. The patterns of relationships between these different cell types have been shown to correlate with different disease prognoses, with specific "spatial phenotypes" being recognized as characteristic of response to therapy or mortality risk.

In this context, PPO describes a diverse set of strategies in cancer medicine tailored to the unique biology of a patient's disease. The adaptability of cancer cells and their intricate interactions with the surrounding microenvironments add another layer of complexity to therapeutic outcomes. But aimed to find the optimal solution and solve the problem. This design of destroying cancer cells while leaving normal cells intact rapidly expanded to most of tumor types. Therefore, strategies range from the use of targeted and/or smart therapies to the use of data from genomic profiling to select treatments independent of cancer type and its microenvironment and hence go beyond traditional organ-based oncology[108-115,27].

The lack of reliable cancer-related biomarkers not only impedes pre-early (subclinical) detection of cancer but also complicates the assessment of treatment efficacy, necessitating multifaceted approaches for successful management. Therefore, cancer biomarkers are the key to unlocking the promise of PPO-guided trends, selecting which patients or pre-cancer persons-at-risk will respond to a more personalized treatment while sparing non-responders the therapy-related toxicity. We do emphasize the need for cancer biomarkers infrastructure to be embedded into PPM-driven and PPO-guided health systems of the next step generations. Cancer biomarkers must be embedded in the real world of PPO-guided delivery and testing must be implemented across the civilized medical systems, with the intended aim of narrowing, not widening the inequity gap for patients[19,16,20].

2.1. PPM-guided individualized strategy to optimize clinical oncology practice and design-driven cancer translational research

PPM-guided individualized strategy proves particularly useful in navigating the complexities of cancer cell inter-actions

with their microenvironment, thereby enhancing therapeutic results. Furthermore, PPM has the potential to revolutionize diagnostic procedures, especially for cancers that often go unnoticed in their pre-early stages. The use of targeted biomarkers could facilitate not only early detection but also a more nuanced evaluation of treatment effectiveness. So, PPM and PPO are thus mostly based on the high-throughput molecular profiling of tumors which allows for the identification of genomic modifications spotlighting appropriate research and therapeutic targeting. A comprehensive understanding of the landscape of genetic alterations in tumors will certainly further advance our understanding of the dynamic interactions between tumor cells and immune subpopulations, resulting in the development of rational combinatorial therapies[16].

In clinical settings, we need to timely model clinical and multi-OMICS data to find statistical patterns across mil-lions of features to identify underlying cancer-related biologic pathways, modifiable cancer risk factors and actionable information that support early detection and prevention of cancer and pre-cancer conditions and development of new therapies for better cancer patient care and pre-cancer prevention. Moreover, we are witnessing the transition toward understanding cancer as a continuum by capturing spatial and temporal tumor heterogeneity[103-105,116-123] (Figure 10).

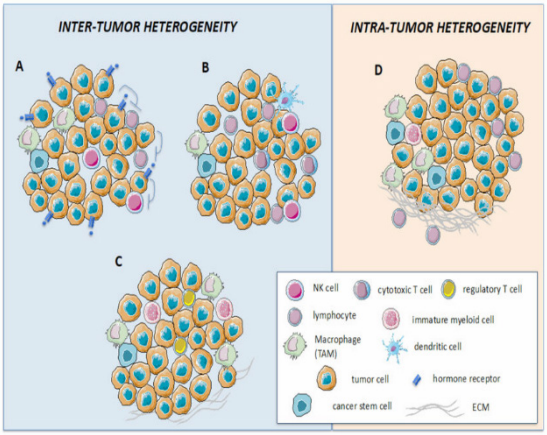

Figure 10: Inter-and intra-tumor heterogeneity dictates the response to HER2-targeted therapies.

Tumor heterogeneity is regarded as a major obstacle to successful PPM and PPO. The lack of reliable response assays reflective of in vivo tumor heterogeneity and associated resistance mechanisms hampers identification of reliable biomarkers. On-treatment biopsies may provide insight into intrinsic or acquired drug resistance. Subsequently, upfront combinatorial treatment or sequential therapy strategies may forestall drug resistance and improve patient outcome. During the course of disease, cancers generally become more heterogeneous. This heterogeneity might result in a non-uniform distribution of genetically distinct tumor-cell subpopulations across and within disease sites (spatial heterogeneity) or temporal variations in the molecular makeup of cancer cells (temporal heterogeneity)[124-126].

In this sense, individual cancer cells can differ with respect to a large number of capabilities, which are regulated at different levels by cell-intrinsic cues, including genetic, epigenetic and proteomic changes. Among the major intrinsic causes of intratumoral heterogeneity are cancer cell migration and invasion, genetic instability, epigenomic/transcriptomic and proteomic regulation, the degree of epithelial-to-mesenchymal transition (EMT) and cell plasticity, as well as the extent of stemness. Tumor microenvironment also contributes to intratumoral heterogeneity through cell-cell interactions and paracrine signaling - cancers describe a clonal increase in the number of cells that will cause a cell to lose control of itself against signals from its environment, allowing it to reproduce independently. One of the biggest reasons for this clonal increase is the genomic changes that occur in both proto-oncogenes and oncogenes.

Tumor heterogeneity, dominating as intratumor one, is considered today as a novel complex biomarker of tumor progression, metastasis and immune evasion and may foster tumor evolution and adaptation and hinder PPM-guided strategies that depend on the outcome from single tumor-biopsy samples. Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges in PPM and PPM-driven biomarker development. And the phenotypic consequences of genetic intratumor heterogeneity would form reflect genomic landscape of the tumor and form the current basis for most biomarker discovery and PPM-guided approaches. Intratumoral heterogeneity evolves in time and space, changes in response to therapy and the development of resistance and varies between different patients.

Intratumoral heterogeneity is central to the natural selection that drives the processes of carcinogenesis, metastasis and acquired resistance to therapeutic interventions (Figure 11).

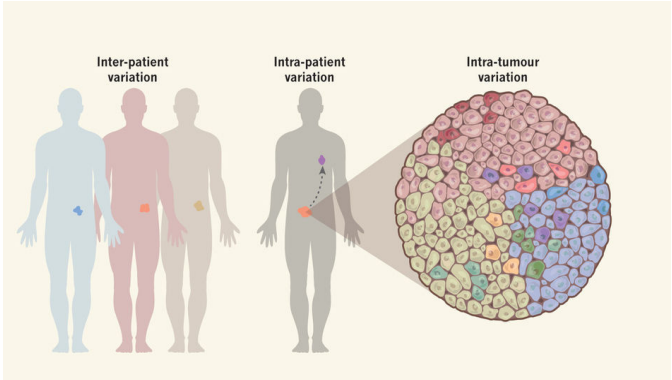

Figure 11: Cancer genetic heterogeneity occurs at multiple levels: between patients, be-tween primary and metastatic tumors in a single patient and between the individual cells of a tumor[127].

Intratumor heterogeneity may present profound regulatory and practical clinical challenges when considering such drug combinatorial approaches, faced with a restricted number of drugs active against defined actionable mutations compared with the bewildering potential for diversity within individual tumors. Today's diagnostic, predictive and prognostic technologies applied in hospitals could be implemented through collaborations with basic scientists, translational bio designers and clinicians and could help pathologists to diagnose tough samples to stage.

One of the challenges of modern precision pathology and PPM-guided oncology is to deal with increasing complexity of modern tissue diagnostics. This might require the analysis of:

Multiplex immunofluorescence or FISH screening of proteins and its associated spatially resolved genetic information even on a single slide,

The integration of other multi-OMICS information including

molecular data from next-generation se-quenching (NGS), the quantification of 3D-images and the integration of individual patient data from related are-as like radiology, liquid biopsies and the entire diagnostic portfolio.

In this context, precision cancer diagnosis is aiming at detecting individual cancer associated genetic changes amenable to molecularly targeted treatments. This requires first of all a diagnostic identification of the presence of cancer cells (circulating tumor cells-CTCs, cancer stem cells-CSCs, etc) in the liquid biopsy taken from the tumor bearing tissue. It also includes the typing and the subtyping of the tumor cell origin and its grading in terms of its likely behavior (Figure 12A and B).

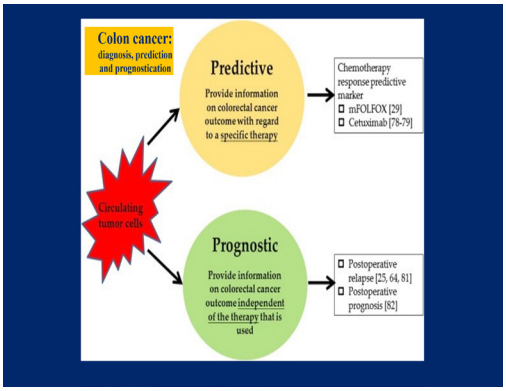

Figure 12A: Circulating tumor cells (CTCs) as a predictor and prognostic tool for metastatic cancer and cancer progression.

Modified from: Tariki MS, Barberan CCG, Torres JA, Ruano APC, Ferreira Costa DJ, Braun AC, da Silva Alves V, de Cássio Zequi S, da Costa WH, Fay AP, Torrezan G, Carraro DM, Domingos Chinen LT. Circulating tumor cells as a predictor and prognostic tool for metastatic clear cell renal carcinoma: An immunocytochemistry and ge-nomic analysis. Pathol Res Pract. 2024 Jan;253:154918. doi: 10.1016/j.prp.2023.154918. Epub 2023 Nov 10. PMID: 37995423

Detection of CTCs in patients with cancer and pre-cancer persons-at-risk is a feasible tool with prognostic potential since increased numbers of CTCs are associated with metastasis and disease progression.

Following the above-mentioned, we would have to stress that the unique example of the newest applications to illustrate subclinical and predictive risks as applicable to tumor progression is CIRCULATING TUMOR CELLS (CTCs). CTCs as a biomarker of the latest generation would make up a minute fraction of the total number of cells circulating in blood. And the newest again, Cell Search® method based on a surface expression of epithelial cell adhesion marker (EpCAM), would be able to get the procedure done![128]

The analysis of circulating tumor cells (CTCs) and CTC clusters in the blood can be used for the pre-early detec-tion of invasive colon, breast and lung cancer. CTCs represent an independent predictor of outcome in patients with metastatic cancer. Moreover, CTCs have a prognostic significance in the monitoring of a malignant disease or the response to targeted cancer therapy.

Modified from: Petrik, J.; Verbanac, D.; Fabijanec, M.; Hulina-Tomašković, A.; Čeri, A.; Somborac-Bačura, A.; Petlevski, R.; Grdić Rajković, M.; Rumora, L.; Krušlin, B.; et al. Circulating Tumor Cells in Colorectal Cancer: Detection Systems and Clinical Utility. Int. J. Mol. Sci. 2022, 23, 13582. https://doi.org/10.3390/ijms232113582

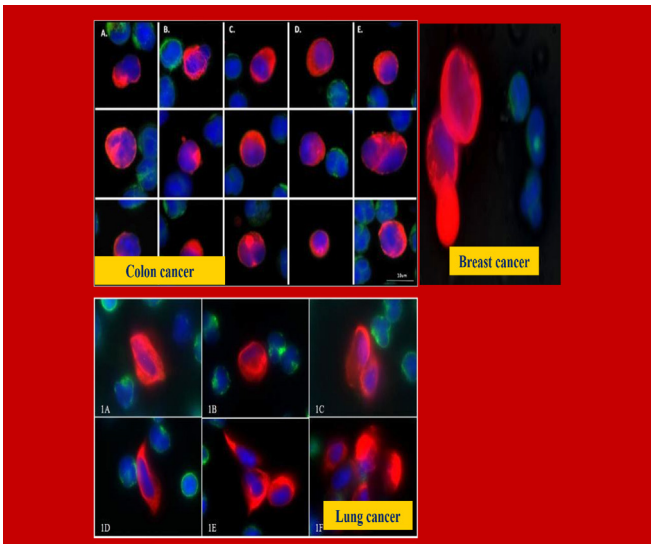

Figure 12B: Circulating tumor cells in colorectal, breast and lung cancer CTC detection: valuable tools and predictive biomarkers to refine prognosis.

Giuliano, M., Giordano, A., Jackson, S. et al. Circulating tumor cells as prognostic and predictive markers in met-astatic breast cancer patients receiving first-line systemic treatment. Breast Cancer Res 13, R67 (2011). https://doi.org/10.1186/bcr2907

Ivanova E, Ward A, Wiegmans AP, Richard DJ. Circulating Tumor Cells in Metastatic Breast Cancer: From Ge-nome Instability to Metastasis. Front Mol Biosci. 2020 Jul 16;7:134. doi: 10.3389/fmolb.2020.00134. PMID: 32766277; PMCID: PMC7378584

Tamminga M, de Wit S, Schuuring E, Timens W, Terstappen LWMM, Hiltermann TJN, Groen HJM. Circulating tumor cells in lung cancer are prognostic and predictive for worse tumor response in both targeted- and chemo-therapy. Transl Lung Cancer Res. 2019 Dec;8(6):854-861. doi: 10.21037/tlcr.2019.11.06. PMID: 32010564; PMCID: PMC6976367

Meanwhile, along with CTCs, cancer stem cells (CSCs) represent the other main target of the current efforts to eradicate cancer because of their ability to promote metastatic dissemination and to survive cytotoxic therapies. Whilst keeping in mind the role of the tumor microenvironment playing an active role in supporting tumor progression and greatest impact in the crosstalk between CSCs and the host immune system to allow for developing effective therapeutic strategies targeting the ability of CSCs to escape immune-surveillance through immune editing[129-132].

CSCs, a small subset of cells in tumors that are characterized by self-renewal and continuous proliferation, lead to tumorigenesis, metastasis and maintain tumor heterogeneity. Cancer continues to be a significant global disease burden (Figure 13A and B).

The analysis of circulating tumor cells (CTCs) and CTC clusters in the blood can be used for the pre-early detection of invasive colon, breast and lung cancer. CTCs represent an independent predictor of outcome in patients with metastatic cancer. Moreover, CTCs have a prognostic significance in the

monitoring of a malignant disease or the response to targeted cancer therapy[132,133].

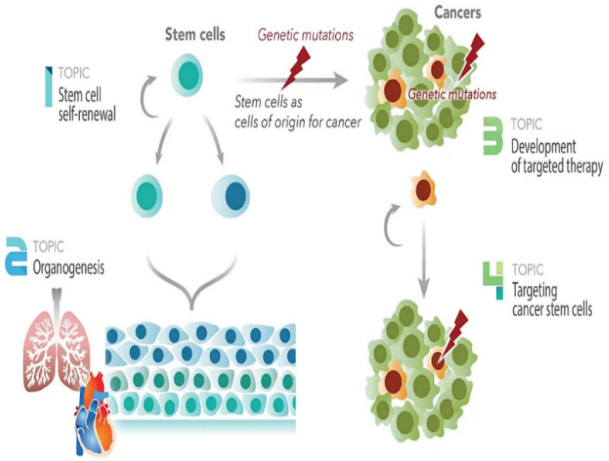

Figure 13A: Circulating tumor cells in colorectal, breast and lung cancer CTC detection: valuable tools and predictive biomarkers to refine prognosis.

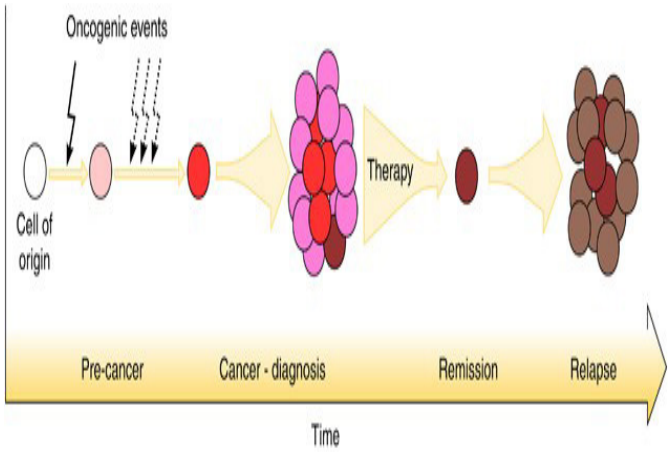

Figure 13B: The cancer stem cell (CSC) theory of tumor development and relapse initiation.

An initial oncogenic event (solid arrow) occurring in a normal cell may create a precancerous cell or directly result in malignant transformation. The oncogenic event is likely to require a number of supporting genet-ic/epigenetic events (hashed arrows). By the point of clinical diagnosis, the heterogeneous tumor contains cells which have or are able to activate their stem cell program and may be able to evade standard therapy. Any CTCs evading therapy are able to divide and differentiate to repopulate the tumor[132,133].

CSCs are a subpopulation of cancer cells with many clinical implications in most cancer type, including their role in cancer metastases and causing treatment resistance and recurrence in cancer. The discovery of CSCs has pro-vided many new insights into the complexities of cancer therapy: tumor initiation, treatment resistance, metastasis, recurrence, assessment of prognosis and prediction of clinical course. Thus, many different therapeutic approaches are being implemented for prevention and treatment of cancer recurrence. Commonly used methodologies for detection and isolation of CSCs include the use of different surface biomarkers. Overall, given their significance in cancer biology, refining the isolation and targeting of CSCs will play an important role in future management of cancer and development of PPO[133-138]. Thus, shedding light on this problem could contribute significantly to our general understanding of how tumors are formed and further the development of new treatment strategies[139,16].

As you might see from the above-mentioned, clinical evaluation of tumor heterogeneity is an emergent issue to improve PPM-guided clinical oncology, since this phenomenon is closely related to cancer progression, resistance to therapy and recurrences. A quantitative measure of genetic heterogeneity based on next-generation sequencing (NGS) data and mutant-allele tumor heterogeneity have been developed and applied to a Big Data set[166,194].

In particular, reliable and accurate NGS technologies have a very large promise to accelerate PPM and PPM-guided clinical oncology practice. Currently, NGS can speed up in the pre-early diagnosis of cancer and discover pharmacogenetic markers that help in personalizing cancer therapies. NGS holds the added advantage of providing more comprehensive picture of cancer landscape and uncovering cancer development pathways[27,140,141].

The latter would strongly request the proper feedback – would that measure correlate with clinical outcome or… not? From a practical point of view, analytical methods that are widely accessible today or will be in the near future, are evaluated to investigate the complex pattern of intratumor heterogeneity in a reproducible way for a clinical application. Moving forward, improved computational methods to better dissect clonal architecture and model tumor clonal dynamics, as well as studies examining tumors with finer resolution through the use of deeper sequencing depth, single-cell samples or multiple tumor regions, will help to elucidate the impact intratumor heterogeneity has on a tumor's features and potential. Continuing such studies will lead to an improved under-standing of the above-mentioned phenomenon and clonal dynamics, endowing us with the ability to more fully decipher the evolutionary history of a tumor as well as a greater understanding of which events are truly clonal and how a tumor may respond to therapy. This will potentially translate into novel bio design-driven therapeutic approaches and inform new ways to best stratify groups of cancer patients and pre-cancer persons-at-risk for maxi-mal treatment or preventive prophylactic efficacy.

By integrating multiple data sources (multi-OMICS), each case of cancer can be approached as if it represents a separate disease. The notion of PPO takes on new meanings as new levels of data are added to the understanding of cancer, from complex biological, digital, clinical, behavioral and environmental data[16].

Cancer induction and progression through the vies of PPO start from the symptoms and everything that can be seen with the doctor's naked eye and the resolution increases through the development of microscopy, biochemistry, cell biology and the birth of pharmacogenetics. And the cancer-related disorder begins to be reclassified starting from molecules to symptoms; it is the stage in which the notions of biomarkers and targeted therapies gain momentum. Precision in this period is based on deciphering the structure of DNA and the early stages of biotechnology development. Later, PPO is dominated by the development of high-capacity genomic sequencing technologies, with comprehensive genomic profiling, shifting the gears toward genomic medicine and modern biotechnology, which today underpins the development of most drugs. And, finally, in the latest version of PPO, the characterization of cancer will be of very high resolution (single-cell multi-OMICS); it

will be dynamic (the transition from pre-cancer to cancer will be predictable), comprehensive (multi-OMICS biomarkers, functional tests, multi-target drugs, hybrid pharmacological constructs) and data-driven (network medicine, IT assisted decision-making tools, etc) (Figure 14).

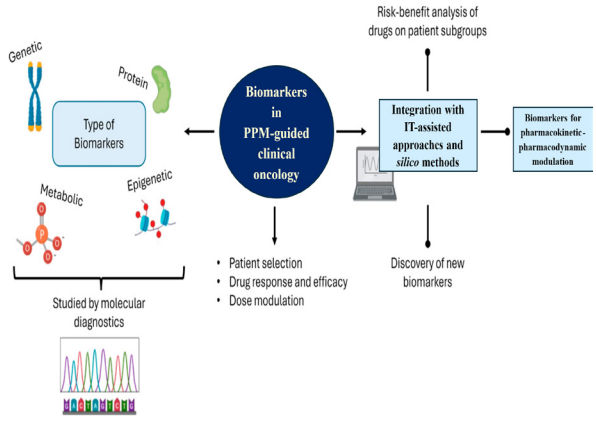

Figure 14: Biomarker integration in PPM.

Biomarkers are used extensively in PPM-guided practice for screening, diagnosing and characterizing diseases. Biomarker analysis has started the shift toward an individualized treatment for each patient and, as such, biomarker discovery is of high importance in this approach. http://biorender.com

The integration of OMICS technologies, biomarker-driven platforms and IT-assisted algorithms into healthcare presents a transformative potential for PPM and PPM-guided patient care. These methods offer numerous ad-vantages, such as improved diagnostic accuracy, tailored treatment plans and enhanced patient monitoring[16].

Among these methods, in silico approaches, which involve computer simulations and modeling, are gaining traction, reducing the need for time-consuming physical examination, speeding up drug development and enhancing disease understanding. They also hold promise for conducting virtual clinical trials, which can streamline the evaluation of medical interventions. User-friendly, seamless integration with existing healthcare systems and clear insights are crucial for broad adoption.

3. PPO as a New and Upgraded Field in Development of Ppm-Guided Clinical Oncology

The field of PPO is rapidly being transformed by emerging technologies based on IT algorithms and bio analytics approaches, that are enabling a more efficient and accurate analysis of large amounts of data sources with different modalities. Whilst assisting in identifying novel biomarker-driven therapeutic targets and predict treatment responses and leading to more PPM-guided treatment decisions for cancer patients and pre-cancer persons-at-risk (Figure 15).

PPM-guided cancer medicine or Personalized & Precision Oncology (PPO) is a multidisciplinary team effort that requires involvement and commitment of many. Building on the success of significant advances in precision therapy for oncological patients, future developments will be shaped by improvements in scalable OMICS diagnostics in which increasingly complex multilayered datasets require transformation into clinically useful information guiding patient management at fast turnaround times. Adaptive profiling strategies involving tissue- and liquid-based testing that account for the immense plasticity of cancer during the patient's journey and also include early detection approaches are already finding their way into clinical routine and will become paramount. A second major driver is the development of smart clinical trials and trial concepts which, complemented by real-world evidence, rapidly broaden the spectrum of therapeutic options. Tight coordination with regulatory agencies and health technology assessment bodies is crucial in this context. Multicentric networks are key in implementing precision oncology in clinical practice and support improving the ecosystem and framework needed to turn invocation into benefits for patients[138].

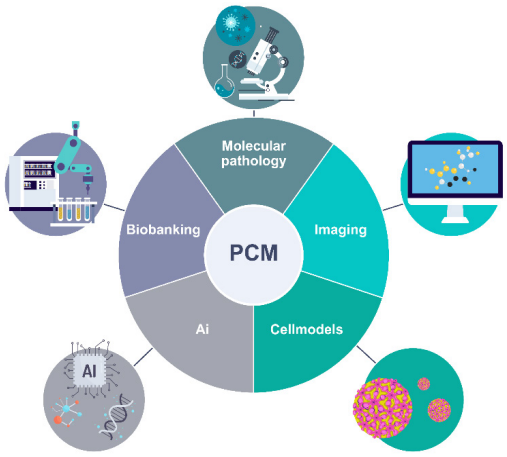

Figure 15: The main measures adopted with-in PPM-guided cancer medicine.

Meanwhile, establishing therapy options and managing cancer treatments in the context of data from multi-OMICS manipulations is believed to be urgently necessary and this view accelerates the implementation of PPM-related resources in oncology, resulting in PPO[142,72]. On a clinical PPO-related perspective, integrative analysis of multiple OMICS data gives a focus to functional targets being highly valuable for clinical translation. The integration of multiple biological layers of OMICS data brought PPO to a new paradigm, from tumor site classification to pan-cancer molecular classification, offering new therapeutic opportunities for precision medicine. On a more basic point of view, integrative data analysis heightens the OMICS fields, enables the oncogenic processes to be comprehensively interrogated, leading to a broader understanding of tumor biology and opening the way to integrative tumor model development, whilst dramatically accelerating the identification of robust biomarkers toward the development of tailored cancer therapy. The latter is an effective strategy to fight cancers by bridging OMICS technologies, IT resources and drug discovery trends to provide specific treatment for patients and preventive prophylaxis for pre-cancer persons-at-risk (both with different genetic characteristics). And not only efficacy but also the adverse effects of drugs on cancer patients or pre-cancer persons-at-risk should be taken into account during the treatment[143,144,27,16,72].

In this sense, PPO is evidence-based, individualized medicine that delivers the right care to the right cancer patient at the right time and results in measurable improvements in outcomes and a reduction on health care costs.

The essence of PPO lies in the use of biomarkers of different levels and specificities, obtained from tissue, serum, urine or

imaging. Those tools for implementing PPO resources based on molecular diagnostic and interventions will improve cancer prevention. Molecular diagnostics identify individual cancer patients who are more likely to respond positively to targeted therapies. The use of companion molecular diagnostics or theragnostic is expected to grow significantly in the future and will be integrated into new cancer therapies a single (bundled) package which will provide greater efficiency, value and cost savings. This approach represents a unique opportunity for integration, increased value in PPO.

Globally, PPM has revolutionized approaches to treatment in the field of cancer by enabling therapies to be specific to each patient and pre-cancer persons-at-risk. However, physicians encounter an immense number of challenges in providing the optimal treatment regimen for the individual given the sheer complexity of clinical aspects such as tumor molecular profile, tumor microenvironment, acquired or inherent resistance mechanisms, risks for the development of metastases, the limited availability of biomarkers and the choice of combination therapy. The integration of innovative next-generation technologies via bioinformatics-driven platforms has the potential to transform the field by supporting clinical decision making in cancer treatment and the delivery of precision thera-pies while integrating numerous clinical considerations.

The above-mentioned unique opportunity allowed for identification of areas where cancer patients, pre-cancer persons-at-risk, the parents and physicians are communicating effectively and also where there is a teachable gap in the profiled education. Furthermore, surveying physicians about the advantages and roadblocks they experience with biomarker testing provided valuable information on ways to improve the delivery of PPM-guided resources to provide personalized care and ultimately enhance care for canonical patients and pre-cancer persons-at-risk individually.

Globally, cancer patient and pre-cancer person-at-risk and physician responses indicated that a particular pair of clients are aware of basic tumor biology and treatments and thus are exposing their willingness to participate in personalized and precision care. It is of interest that physicians misjudged client responses and this may reflect an opportunity to improve the dialogue between cancer patients and pre-cancer persons-at-risk on one hand and physicians, on the other one. Regarding the latter, it is time to stress that in the future, the development of blood-based rather than tissue-based methods for the detection of tumor biomarkers may help increase the willingness of cancer patients and pre-cancer persons-at-risk to participate in personalized care even further. With much less invasive and more convenient testing procedures, both doctors and their cancer-related clients may participate more fully in personalized care.

The latter means that multi-faceted collaboration with healthcare professionals, educators and technology experts will be essential to developing systems that meet the needs of both clinicians and patients, as well as for persons-at-risk and their relatives. It also is essential for stakeholders to work collaboratively to navigate these challenges and create an environment that supports innovation while safeguarding ethical principles and patient rights.

In this context, high-throughput OMICS technologies and IT-assisted algorithms and tools allow the retrieval of comprehensive and holistic biological information, whereas computational capabilities enable high-dimensional data modeling and, therefore, accessible and user-friendly visualization. Rapid advances in high-throughput technologies of biomedical informatics aspects such as database storage and big data management, integration of OM-ICS within EHR and interoperability have the potential to increase the weight of PPO and PPM as a whole within clinical cancer practice. The proposed architecture could improve the potentialities of data routinely collected in many health information systems to form a patient-centered information environment[144,145,18,27].

Furthermore, bioinformatics has enabled comprehensive multi-OMICS and clinical data integration for insightful interpretation[145-147,27].

3. OMICS-driven and IT-supported Resources as Sets of Crucial Tools to Fight Cancer

The development of PPO-guided and OMICS-supported cancer care is predicted to lead to better outcomes and reduced risk of side effects for patients with cancer as well as reducing costs and improving efficiencies for healthcare systems[72].

In this context, genetic testing, profiling and enhanced genomic analysis have had a profound impact on the way in which tumors are evaluated and classified. A number of new drugs, including vemurafenib and dabrafenib, which target proteins that prevent the immune system attacking cancer cells, have been developed as a result of this dis-covery[148].

Among a variety of the alternative genetic tests, let me stress that predictive genetic testing is really a crucial and valuable type of testing used to look for inherited gene mutations that might put a person at higher risk of getting certain kinds of cancer. This type of testing might be suggested for:

i. A person with a strong family history of certain types of cancer;

ii. A person already diagnosed with cancer; and

iii. Family members of a person known to have an inherited gene mutation that increases their risk of cancer.

Prognostic biomarkers associate host and tumor variables with clinical outcomes independent of treatment, show-casing how aggressive a tumor is likely to be[149-151]. These biomarkers have an impact on the prognosis of cancer patients or pre-cancer persons-at-risk regardless of treatment, predicting the mean clinical outcome of a patient. They can be used to stratify randomization by disease risk, thus minimizing heterogeneity within the sub-group and maximizing heterogeneity across subgroups; to identify potential treatment targets; and to direct treatment to specific patient subgroups.

After the genetic information obtained and thus is available, the client (cancer patient or pre-cancer person-at-risk) would contact genetic counseling service for making the final CD making. Before and after genetic testing, genetic counseling can help you understand your risk of developing cancer and pre-select the options to minimize this risk. Moreover, family cancer centers can advise you about your risk of developing cancer, provide genetic counselling and medical advice and, in some situations, comprehensive genetic testing.

PPM-guided cancer practice is founded and has evolved largely on the basis of biomarker-directed predictive cancer therapy. The strength of this association has grown to such an extent that the use of predictive biomarker tests to guide the therapy for individual cancer patients has become the cornerstone of PPM. The implementation of PPM-guided cancer diagnostic technologies and PPO-related resources through OMICS-guided profiling technologies has increasingly been integrated with standard clinical-pathological evaluations to enhance diagnosis, prognostication and prediction of clinical outcomes (Figure 16).

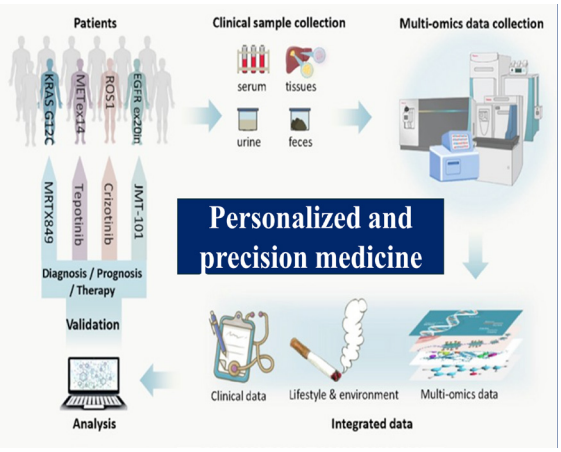

Figure 16: PPM-guided service in cancer practice.

Samples (e.g., serum/tissue/urine/feces) can be analyzed by multi-OMICS technologies. Blood informs on the systemic response to the disease, urine includes the host metabolites which are excreted from the body, stool samples show what the intestine is exposed to and resected tissue can give information on the response mounted at the site of disease. Information from multi-OMICS analyses, clinical reports, lifestyle and psychosocial characteristics can identify biomarkers for prevention, diagnosis, prognosis and surveillance and help to determine the most suitable therapeutic schedule for individuals presenting with a given disease[152].

Precision cancer pathology including immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for cancer biomarker analysis in routine pathology practice, has therefore become fundamental not only to inform on tumor diagnosis and prognosis but also to drive therapeutic decisions in daily practice.

In this context, pharmacogenomics (PGx) is one of the most important components of PPO, which focuses on the association between genetic variations and drug response. PGx can help oncologists decide drug selection, dose adjustment and treatment period and prevent adverse drug reactions. Specific genetic variations have been related to clinically significant changes in drug disposition between individuals, including vulnerability to adverse drug responses and therapeutic response or efficacy. There is a substantial amount of scientific evidence supporting the utility of pharmacogenomics testing in cancer patient management[153-158,72].

PGx testing (Figure 17) is aimed at tailoring cancer drug therapy at a dosage that is most appropriate for an individual cancer patient or a pre-cancer person-at-risk, with the potential benefits of increasing the clinical efficacy and individualized safety.

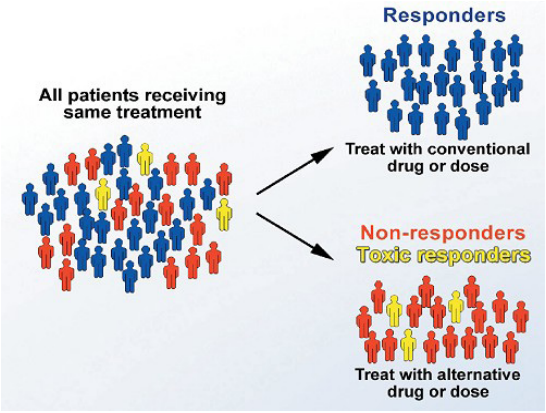

Figure 17: Predictive DNA testing in cancer practice.

Pharmacogenomic tests can be used to predict and to target medicines to good responders or to identify whether an individual has an increased risk of a specific adverse drug reaction from a particular medicine[159-161].

This scenario illustrates the fundamental idea behind PPM and PPO: coupling established clinical-pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic and therapeutic strategies precisely tailored to each patient's requirements. Recent design-inspired biotechnological advances have led to an explosion of cancer-relevant molecular information, with the potential for greatly advancing patient care[139,18,16].

In reality, PPO is an emerging approach for tumor treatment and prevention that takes into account inter- and intra-tumor variability in genes, tumor (immune) environment and lifestyle and morbidities of each person diagnosed with cancer (including pre-cancer person-at-risk). PPM-driven PPO-armed cancer therapy have the potential to tailor therapy towards the oncogenic drivers of the tumor and modulate the tumor immune environment. Furthermore, PPO aims to optimize tumor response, thereby taking into account the therapy-induced toxicities for each specific patient. In this way, optimized tumor response is combined with the preservation of organ function and, thus, quality of life. Moreover, this ensures better patient care in the end, which is, of course, what it aims for[72].

Approaches to PPM-guided areas of clinical oncology and cancer therapy can generally be categorized into biomarker-driven targeted diagnostic techniques, data integration methods and treatment modalities (Figure 18).

To understand the unique molecular make-up of each patient, biopsy samples are analyzed via different sequencing techniques, (including genetic, epigenetic, RNA and ncRNA sequencing) and through medical imaging/histological analysis. These techniques potentially reveal the different pharmacogenomic markers commonly altered in different cancer types, including but not limited to, KRAS, BRCA1/2, EGFR, HLA-B, ALK, PIK3CA, B-RAF, VHL, BCR-ABL1, PTEN, TP53. Additionally, different molecular patterns, biomarkers or integrated panels are also analyzed, serving as predictive or diagnostic signatures. These include, but are not limited to, dMMR (deficient DNA mis-match repair)/MSI-high (microsatellite instability-high), TMB (tumor mutation burden), RET (RE-arranged during Transfection) genetic fusion, NTRK (neurotrophic tyrosine receptor kinase gene) fusion, PD-1/PD-L1 (Programmed Cell Death Protein 1 and Programmed Cell Death Ligand 1), T-cell

or B-cell focused gene signature profile, PSA (prostate-specific antigen), GEP (T cell–inflamed gene expression profile), tumor imaging and histology. AI/ML is used for a myriad of functions such as sorting the markers, screening across real world data (RWD), generating prognostic models, risk prediction, selecting specific targets and testing drug combinations. Patient-derived data (based on tested samples and medical history) is curated and streamlined not only for specific clinical trial design, but also to record, statistically analyze and compare the results[162-165].

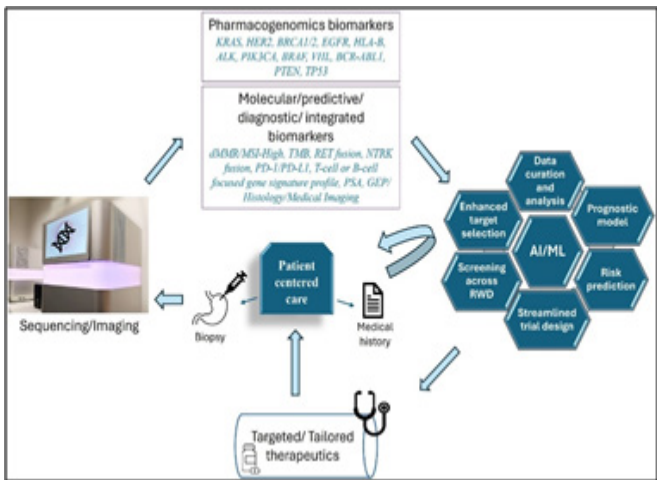

Figure 18: Patient centered personalized care for cancer treatment and PPM-guided cancer care.

Meanwhile, multi-OMICS screening for biomarkers, bioanalytic approaches and bioinformatics-assisted algorithms synthesize diverse transdisciplinary biological and clinical data to provide a comprehensive view of the cancer landscape. Beyond traditional OMICS techniques, the field is rapidly expanding into medical imaging techniques, which utilize large-scale digital archives for cancer diagnosis, integrating medical molecular imaging with genomics to deepen our understanding of cancer mechanisms and biomarker discovery. Treatment modalities include targeted therapies and immunotherapies, which tailor drug treatments according to the individual characteristics of each tumor[166,16].

Open-access databases could facilitate the above-mentioned, allowing cancer practitioners to contribute to and access data for bio analytics and more comprehensive studies, whilst requesting algorithms of the next-step generation, capable of handling the heterogeneity in multi-OMICS data, to provide a holistic but evidence-based and clinically valuable view of cancer.

One of the crucially valuable and innovation combinatorial (diagnostic-predictive-prognostic-therapeutic) areas of PPO - panels of upgraded tools (companion diagnostics and theragnostic as tests and medicines) used to identify specific biomarkers and profiled targets of a disease or disease susceptibility and aimed to lead us to the approach of PPO (162). In this context, evidence-based clinical guidelines increasingly include biomarker-driven OMICS profiling and recent evidence suggests that PPO can be delivered in a cost-effective way for health systems. Therefore, precision OMICS testing for cancer biomarkers supported by IT algorithms and tools, must be embedded into the clinical practice of PPO-guided care delivery going forward[20].

For instance, PPO-driven therapies, including tumor-infiltrating lymphocytes that are extracted from a patient's melanoma and eventually reinfused into the patient, as well as mRNA vaccines used to target neoantigens unique to a patient's tumor, show great promise. Improvements in accompanying imaging modalities have allowed for accurate staging of disease and assessment of treatment response. Continued growth in the role of molecular imaging in the evaluation of melanoma, including the incorporation of IT algorithms into image interpretation and use of radiolabeled tracers allowing for intricate imaging of the tumor immune microenvironment, is expected in the coming years[167].

Another trend in PPO is the development of personalized vaccines presenting multifaceted challenges. The potential of personalized vaccines to optimize responses and mitigate disease burden underscores the significance of ongoing research and collaboration in advancing PPM- and PPO-guided resources in immunization[168].

Moreover, PPO presents principally new opportunities for patients with cancer and pre-cancer persons-at-risk as well, whilst emerging as the tumor treatment and prevention that consider the cancer variability in terms of gene expression patterns, tumor specific (immune) microenvironment and patients' particular lifestyles and morbidities, covering huge Data Sets! As PPO introduces a Big Data analysis of PPO-guided OMICS approaches, there are still challenges in the translation of all these data into meaningful and equitable benefits to patients and health care. And thus, each patient presents its specific preferences, needs, tolerances and unique tumor vulnerabilities even when suffering from very similar diseases or course of treatment, which demands and highlight the im-portance of the PPO approach and the personalized cancer or pre-cancer care. In reality, it is time to recognize the possibility that advanced computer implementation could generate real-world data that expand our understanding of cancer, rapidly identify new treatments and create personalized drugs or immune therapies[27,72].

This perspective fosters the development of specialized treatments for each specific subtype of cancer, based on the measurement and manipulation of key patient OMICS data. And the field of systems biology, design-driven biotech and translational applications would thus aid in the development of diagnostic and therapeutic tools and medicines of the next step generation by analyzing data from preclinical and clinical studies. This approach is used to develop predictive and prognostic tools that replicate biological systems in order to characterize their behavior and response in the context of disease and drug development. This is particularly relevant to forthcoming cancer treatments, as a significant portion of oncology drugs in development are personalized medicines. PPM therapies that are currently being developed include cancer vaccines, mAbs and CAR T-cells[169].

4. Conclusion

Following the above-mentioned, we would stress that effective data management is becoming crucial to ensure the success of PPM-guided cancer research and oncology clinical practice. Moreover, the capacity to build relation-ships within the bioindustry is important, as it can help to foster collaborations and facilitate the development and implementation of new PPM-driven technologies in daily cancer practice. Beyond the fragmentation in fostering bridging connections, a recurring observation from multiple stakeholders is the fragmented nature of the relation-ship between research, healthcare, industry,

government and patients. There are multiple obstructions or lack of capacities, resulting in divides in the continuum from research to healthcare.

Pooling common resources across stakeholders is essential for advancing translational research in PPM-driven cancer practice. Bringing together bio designers, researchers, healthcare providers and other stakeholders, can leverage the collective expertise and resources to accelerate the development of new treatments and therapies. Meanwhile, a lack of medical guidelines has been identified by the majority of responders as the predominant barrier for adoption, indicating a need for supporting the implementation of PPO! Implementation of the latter, being paired and integrated in one and new entity, require a lot before the current model "physician-patient" could be gradually displaced by a new model "medical advisor-healthy person-at-risk". This is the reason for developing global scientific, clinical, social and educational projects in the area of PPM to elicit the content of the new branch.

PPM plays a central role in oncology, providing targeted solutions to complex challenges. By employing cutting-edge diagnostic, predictive and prognostic techniques, data analytics and treatment modalities aimed at revolutionizing cancer care - making it more tailored, effective and safer - PPM-driven approaches stand to revolutionize cancer treatment paradigm[16].

A major challenge in PPO lies in establishing the relationship between biological data, disease, design-driven biotech and clinical translation: how can we interpret "Big Data," referring to the greater collection of healthcare data across thousands of patients and pre-cancer persons-at-risk, involving the tracking of various medical indica-tors and biomarkers (primarily clinical and OMICS data). collected to make meaningful medical decisions? High-throughput data collection enables researchers, bio designers and bioengineers to screen tissues for thousands of molecular targets, effectively capturing the response of a complex system over time. Statistically interpreting trends from Big Data is a discipline unto itself and is necessary for predictive modeling and clinical decision sup-port[170-177,127,27,16].

Rare cancers pose unique challenges for patients and their physicians arising from a lack of information regarding the best therapeutic options. Physicians are increasingly using genetics to identify cancer patients or persons-at-risk at high risk for certain cancers to allow for pre-early detection or prophylactic interventions. Genomic analysis is used to inform prognosis and more accurately establish a diagnosis, as well as to expose therapeutic targets for which drugs are currently available and approved for personalized use[178-187].

PPO as the trend toward PPM in oncology continues, coordination of all health care stakeholders has become more important than ever. Oncologists, pathologists and payers must work with pharmaceutical, biotech and diagnostic companies to develop products, services and coverage policies that improve patient outcomes and, as we have begun to see, lower overall health care costs for institutions that put personalized regimens in place[188-196].

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