Research Article

The Journal of Clinical Pathology (ISSN 2995-8598)

Personalized and Precision Medicine (PPM) as a Unique Healthcare Model through the View of Systems Biology, Design-inspired Translational Applications and Bioinformatics-driven Support to Secure the Human Healthcare: The Role of Clinical Pathology in the Era of PPM

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Received Date : March 02, 2024

Accepted Date : March 03, 2024

Published Date : April 03, 2024

Abbrevations

PPM - Personalized & Precision Medicine, CHD - coronary heart disease, CAD - coronary artery disease, SNPs - Single Nucleotide Polymorphisms, CVD - cardiovascular diseases, CDS - Clini-cal decision support, CTCs - circulating tumor cells, CSCs - cancer stem cells.

INTRODUCTION

Throughout its history, medicine and healthcare philosophy have paid special attention to already-diseased individuals, focusing on clinically manifested diseases (nosology) instead of one's health or so-called pre-illness conditions. The latter are left in the shade, while the former have been overlooked. This is a fact based on evidence. Therefore, clinical efficacy, chronicity, disability rates, and human longevity need to be drastically improved in the near future.

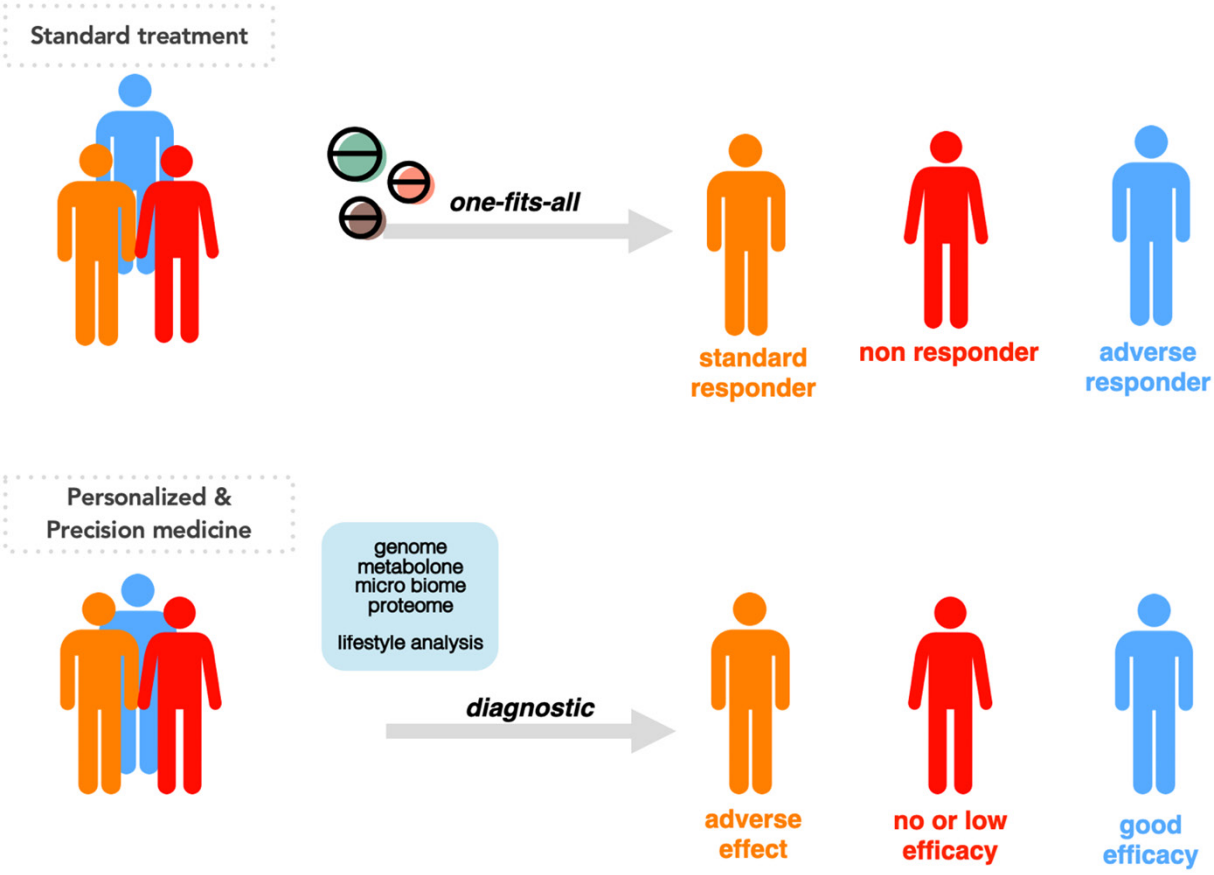
While analyzing and preselecting the basic determinants of health (Fig. 1).

Figure 1 : Core factors of health.

The Journal of Clinical Pathology (ISSN 2995-8598)

To be valuable for implementing and securing the effectiveness of the upgraded healthcare model in daily clinical practice, a group of recognized experts presented an evidence-based and well-documented assessment of global trends in medicine and healthcare develop-ment. They emphasized the exclusive value of Personalized & Precision Medicine (PPM), which is the next step in healthcare service delivery (Fig. 2). Precision medicine identifies differences between individuals, categorizing them based on environmental, biological, and psychosocial fac-tors. Personalized medicine uses these differences to implement preventions and treatments tai-lored to each individual. This approach alters the current treatment model, shifting focus towards identifying potential drug targets, real-time monitoring of patients' health, effective early detec-tion of disease, identification of genes causing diseases, phenotypic and genetic heterogeneity, and also altering the role of doctors.

Figure 2 : Next-step model of healthcare services



PPM refers to tailoring diagnostics or therapeutics to individual patients based on their unique genetic and physiological characteristics. Personalized medicine takes into account these differences and provides tailored preventions/treatments. Precision medicine identifies variations in environmental, biological, and psychological factors among individuals and develops tailored treatment strategies.

PPM is one of the most promising approaches for tackling diseases that have so far elud-ed effective treatments. An example of personalized care is using biomarkers and targets to bet-ter define disease subtypes, prognosis, or inform therapy decisions. Regarding cancer, PPM often means considering how changes in genes or proteins within a person's cancer cells could affect their care, including their treatment options.

Precision medicine has the potential to further personalize care in the future. To achieve further improvements in health care, progress in all of these areas needs to continue. This is true not only for OMICS-based PPM, but also for other aspects of health care [1, 2].

PPM as a model of healthcare services for the next generation is the application of science and art, illustrating the use of different tools from the model at population, community and indi-vidual levels. It has its roots in traditional medicine and has passed on to stratified medicine, and finally gave rise to PPM. It exerts reliable control over morbidity, mortality, disabling rates, as well as optimizing the cost and effectiveness of treatment for patients and at-risk persons. This strategy provides a real opportunity for preventive, prophylactic, therapeutic, and rehabilitative measures, whose personalization can have a significant positive impact on demographics. Person-alized treatment is therefore becoming a core goal of the medical field,

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and PPM in particular. In this context, each decision-maker values the impact of their decision to use PPM resources on their own budget and well-being. However, this may not necessarily be optimal for society as a whole, as the resources may not be used efficiently. PPM has achieved remarkable success in the treat-ment of chronic conditions, their prevention and prophylaxis, in particular cancer. Pathologists occupy an unusual position on this front. As both canonical researchers and clinicians, they want to contribute to medical advancements and ensure that patients and those at risk receive optimal treatment.

As representatives of clinical decision-making and therefore hospitals and specialties, ex-perts in PPM-focused pathology want to collaborate effectively to provide the necessary diag-nostic tissues for oncology patients' care. Many of these experts have serious concerns about cur-rent informed consent processes and standard tissue handling practices during clinical trials and translational studies.

Biomarkers & Targets through the View of Systems Biology, Translational applica-tions, OMICS technologies and PPM-dictated clinical approach towards decision making

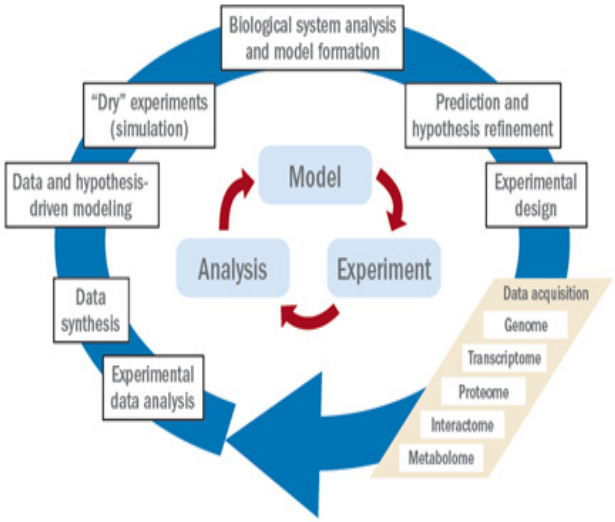
Systems biology

As the reader may sense, PPM is the grand challenge in forecasting, predicting, and pre-venting, rooted in a large and new science generated by the advances of systems biology and translational medicine. Translational biomedical research and applications will focus on "bench to bedside and back" research. In biomedical research, systems biology provides a holistic perspec-tive by assembling components at various levels - organism, tissue, or cell - rather than dissecting them individually, as seen in traditional reductionist biology approaches. This approach involves a thorough quantitative examination of how all elements within a biological system interact dy-namically over time. Interdisciplinary teams equipped with the necessary technologies and com-putational tools conduct this analysis in order to unravel the complex workings of biological sys-tems. In this model, biology determines what new technologies and computational methods should be developed. Once these tools are developed, they open up new avenues in biology for research. Thus, biotechnology drives technological innovation and computation, which in turn revolutionizes biology.

Systems biology focuses on the systematic study of complex interactions within biologi-cal systems, utilizing high-throughput genomic technologies, such as transcriptomics, proteomics, and metabolomics. In order to achieve the challenging goal of unraveling the complexities of bio-logical systems holistically, systems biology necessitates bridging the divide between various non-biological fields, such as information technology, mathematics, physics, and chemometrics.

Systems biology employs mathematical models to analyze extensive data sets and simu-late system behavior, enabling integrative analysis of diverse types of data, thereby providing novel insights into complex biological phenomena. (Fig. 3) [3,4].

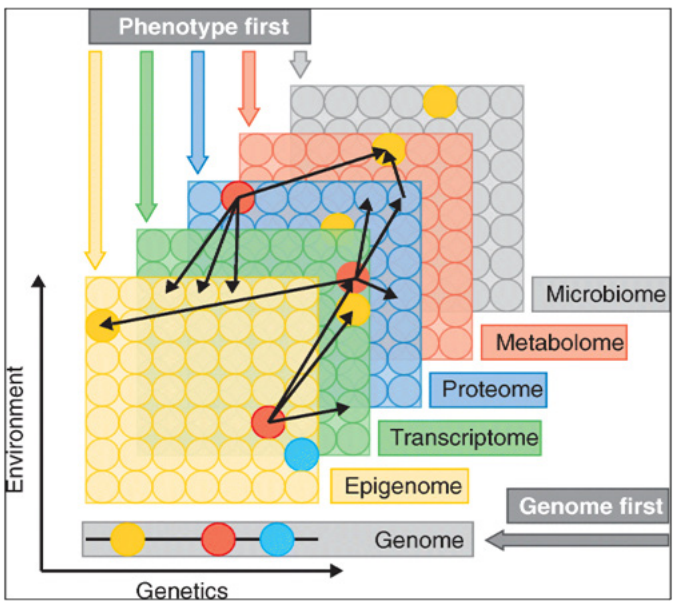
Figure 3 : Model of systems biology [5]



Genomics

To really understand the benefits of PPM, we need to understand the various fields of translational design applications that provide tools to exploit PPM. These include OMICS-related tools. Specifically, they are integrated into the OMICS portfolio (Fig. 4).

Figure 4 : The parts of OMICS-portfolio [6].



PPM encompasses the concept and the intent of finding the uniqueness in each pa-tient's physiology and pathology to

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tailor treatment and prevention plans to suit each in-dividual's condition for optimal results. This concept was made possible by dramatic in-creases in the capability for analyzing the tremendous amounts of medical data that mod-ern medicine almost routinely accumulates about each patient.

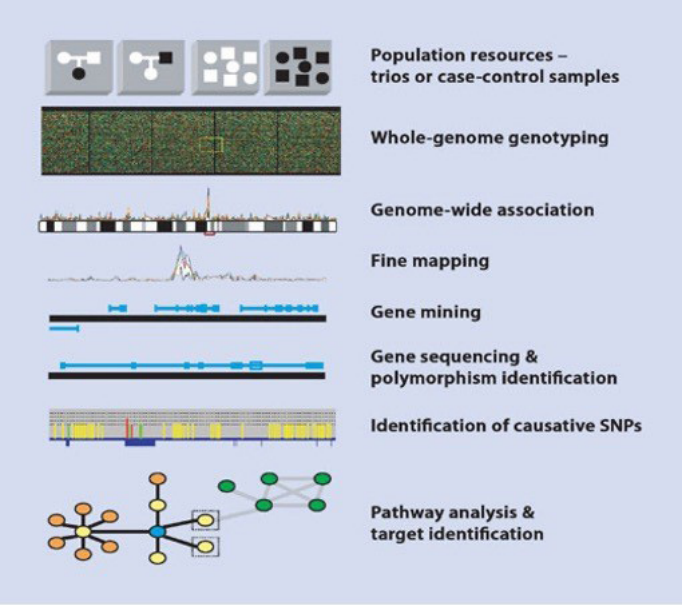
To taste a genuine smell of PPM, we would have to exploit and practice PPM and PPM-driving OMICS-technologies, and genomics tools, in particular. So, genomics is considered to be:

(i) a source of the unique (genomic) biomarkers;

(ii) a panel of the molecular tools to probe genome for its quality (Fig. 5);

(iii) and be used to get genomic landscape tested and profiled for predictive and prognostic biomarkers to assess and to manage the individualized (genome-dictated) risks.

Figure 5 : Multiplex genomic technologies-from tools to diagnosis and therapies [7].



Understanding the structure of the genome is an essential step in understanding its func-tion, both in health and disease. Advances in techniques for studying the genome's structure have gone hand in hand with developments in technology used to carry out these studies, with conse-quent reductions in time and cost. This has led to rapid progress and improvement in high throughput techniques, which range from traditional real time PCR to more complex systems such as next generation sequencing or mass spectrometry. These techniques give an opportunity for accurate and comprehensive analysis of structural and functional relationships, involving var-ious fields of omics research. Genome fine mapping, a technique used to generate genome map scaffolds, has now been combined with long-read sequencing.

The focus of genome technology has rapidly shifted to whole genome genotyping and next-generation genome sequencing techniques, which are derived from conventional laboratory genetic methods such as microscopic cytogenetics, fluorescent in situ hybridization, and South-ern blotting. These techniques involve single-stranded conformation and many other methods [8-10].

Genetic risk, determined by our genes, influences our susceptibility to various diseases. Identifying genes associated with increased disease risk is crucial for personalized healthcare. For example, everyone has a risk of developing cancer, but the individual risk varies. Specific genetic risks include:

1. Hereditary cancer risk: cancer can arise from the gradual accumulation of genetic changes over time. Individuals inherit genetic variants that accelerate this process and increase their risk of cancer. Variations in multiple genes predispose individuals to different types of can-cer, including both common and rare cancers;

2.Hereditary cardiovascular disease risk: cardiovascular conditions include a range of heart and blood vessel conditions. Although hereditary cardiovascular disorders are less com-mon, identifying genetic predispositions can help assess risk and provide lifestyle recommenda-tions, in addition to other risk factors like diet and smoking.

3. Risk of hereditary metabolic disorders: hereditary metabolic disorders are caused by genetic defects that disrupt metabolism. Some variations may manifest in early life, while others may remain latent for several years until symptoms appear. Assessing the genetic variations asso-ciated with these disorders helps clinicians anticipate and manage possible complications.

The use of genomics has been firmly established in clinical practice, leading to innova-tions across a wide range of fields, such as genetic screening, diagnosis of rare diseases, and mo-lecularly guided therapeutic choice. With the advancement of single-cell technology, we are quickly discovering how genomic data at the cellular level can be used to comprehend disease pathology and mechanisms. Single-cell technologies based on both DNA and RNA have the po-tential to enhance existing clinical applications and create new applications for genomics within clinical practice [11].

The use of genomic techniques has already demonstrated clear value in the diagnosis of diseases, with treatment tailored specifically to individual patients. Personalized & precision pa-thology demands PPM. The need to integrate the flood of new molecular data with surgical pa-thology and digital pathology, as well as the full range of pathology data into the digital medical record, has never been greater [12].

Among a scope of genomic testing procedures, the dominant one are:

i) diagnostic testing to identify or rule out a specific genetic or chromosomal condition; the results of a diagnostic test can influence a person's choices about health care and

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the man-agement of the disorder;

ii) predictive and pre-symptomatic testing can be helpful to people who have a family mem-ber with a genetic disorder or pre-cancer conditions, but who have no features of the dis-order themselves at the time of testing; or can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer.

iii) carrier testing to identify people who carry one copy of a gene mutation that, when pre-sent in two copies, causes a genetic disorder; this type of testing is offered to individuals who have a hidden (latent) viral gene pre-integrated into the human genome or to people in certain ethnic groups with an increased risk of specific genetic conditions;

iv) newborn testing is to identify genetic disorders that can be treated early in life and other disorders including monogenic and orphan diseases;

v) prenatal testing to detect changes in a fetus's genes or chromosomes before birth to secure the national biosafety;

vi) preimplantation testing (also called preimplantation genetic diagnosis is a specialized technique that can reduce the risk of having a child with a particular genetic or chromo-somal disorder. It is used to detect genetic changes in embryos that were created using ART such as in-vitro fertilization;

vii) 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 reac-tion from a particular medicine.

The landscape of genetic testing has changed considerably with the emergence of direct-to-consumer genetic testing).

Prediction of Coronary Heart Disease

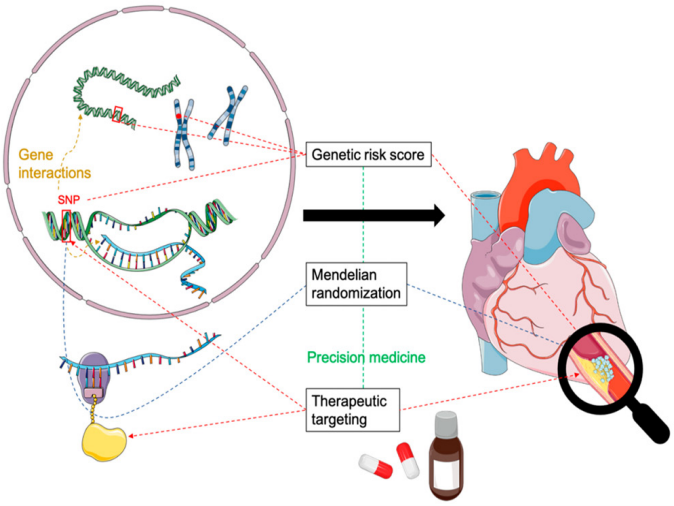
The latter and aforementioned genomic testing aims to create genetic risk prediction tools for a wide variety of common diseases, including heart failure, to prevent it and thus maintain national health stability. The conventional risk factor approach to primary prevention excludes many patients who could benefit from preventive therapies. A global risk approach allows for more accurate risk estimates to guide clinical primary prevention efforts. The global risk of coro-nary heart disease (CHD) is the calculation of the absolute risk of having a coronary heart disease event within a specified period. Patients who are aware of their risk level are more likely to start risk-reducing therapies. The Genetic risk score for coronary artery disease (CAD) enhances the ability to predict CHD.

It is unclear whether:

i) the use of a CAD genetic risk score is superior to the measurement of coronary ar-tery calcification (CAC) for CHD risk assessment and

ii) the CHD risk assessment using a CAD genetic risk score differs between men and women. A high genetic risk score defined by five Single Nucleotide Polymorphisms (SNPs) is associated with a 57% increased risk of CHD. Given the prevalence of CHD, identifying 4% of the population who are at greater risk could have a significant impact on public health (Fig.6) [13-16].

Figure 6 : Single nucleotide polymorphisms (SNPs) are associated with an increased risk of coronary heart disease (CHD) [17].



Polygenic Risk Score to improve Prediction of Coronary Heart Disease

There are several established predictive biomarkers that determine how a combined poly-genic risk score for CHD (CHD-associated biomarkers) can further improve the genetic predic-tion of CHD. DNA-based tests assessing genetic predisposition to CHD need to provide infor-mation beyond conventional risk factors currently used in risk algorithms, such as the Framing-ham Risk Score, to be clinically valuable. A polygenic risk score based on a large number of single nucleo-tide polymorphisms (SNPs) and genomic profiling, improves CHD risk prediction by encoding different trajectories of lifetime risk that are not captured by traditional clinical risk scores. Given the complex characteristics, advancement, and inherent genetic composition of cardiovascular diseases (CVD), personalized interventions are considered vital. The appropriate utilization of information technology (IT) methodologies can yield new insights into CVDs and enable im-proved personalized treatments through predictive analyses and deep phenotyping.The identified OMICS - related biomarkers served as potential indicators for early detection of CVDs. Through their effective deployment, the newly developed predictive engines provide a valuable tool for identifying individuals with cardiovascular disease (CVD) by evaluating their biomarkers pro-files. Predicting CHD risk with genetic biomarkers seeks to answer three key questions

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in as-sessing an individual's risk of CHD:

(i) how should risk be assessed?

(ii) which biomarkers should be incorporated into risk assessment?

(iii) can genetic information improve risk prediction? [18-21]

So, having access to genomic information is becoming increasingly important as physi-cians progressively incorporate genomics into clinical practice.

The scope of aims and objectives attributed to the testing mentioned above is rather broad. It includes whole genome sequencing of individual (pre-selected) genes in order to identi-fy specific mutations, and thus diagnostic and predictive risks. This is followed by targeted exo-me sequencing in order to find mutations for inherited cancer and orphan disorders, and finally transcriptome sequencing.

Computational pathology

Traditional pathology approaches have played an integral role in the delivery of diagnosis, the assessment of gene and protein expression, and the classification of disease. Technological advances and increased focus on PPM (precision pathology medicine) have recently paved the way for the development of digital pathology–based approaches for quantitative pathologic as-sessments. These include whole slide imaging and artificial intelligence (AI)-based solutions. This allows us to explore and extract information that goes beyond human visual perception.

Data processing and machine learning have become fundamental catalysts for the ad-vancement of medicine, a trend that has been observed in various domains, including pathology and laboratory medicine. The integration of scientific research through clinical informatics, which includes genomics, proteomics, bioinformatics, and biostatistics, into clinical practice brings in-novative approaches to patient care. The establishment of the entire computational pathology industry requires far-reaching changes to the three essential components that connect patients and doctors: local labs, scan cen-ters, and central cloud hubs / portals for data processing and retrieval. Computational pathology, made possible by the integration of information and advanced digital communication networks, has the potential to enhance clinical workflow efficiency, increase diagnostic precision, and ulti-mately facilitate the development of personalized diagnoses and treatment strategies for patients.

Clinical information from electronic health records, OMICS data from molecular patholo-gy, whole slide images from digital pathology, and results from clinical labs aggregated into la-boratory information system to create "algorithm 1" for diagnosis. The incorporation of updated disease-related data during follow-up is used to refine the existing dataset and develop "algo-rithm 2" over time, with the aim of enhancing patient care. In the field of immuno-oncology, the use of these methods in drug development and translation research has created invaluable oppor-tunities to uncover complex pathophysiology and identify new biomarkers and drug targets. With a growing number of treatment options available for each disease, practitioners face the challenge of selecting the most suitable treatment for each patient. The increasing use of AI-based methods significantly expands our understanding of tumor microenvironments, with digi-tal methods for patient stratification and selection of diagnostic tests supporting the identifica-tion of the optimal treatment regime based on patient profiles [22-23].

Clinical decision support

Clinical decision support (CDS) has the potential to bridge the gap between vision and implementation of precision medicine. This is guided by genetic data, which CDS enhances clini-cians' ability to make complex decisions. CDS integrates into electronic health records and other clinical processes, revolutionizing the management of chronic diseases. Personalized care is pro-vided across various treatment pathways, reducing medical errors and improving clinical effi-ciency.

As CDS becomes integrated into healthcare delivery systems, patient outcomes are im-proved. Evidence-based decision making at the point of care ensures optimal treatment plans tai-lored to each patient's genetic profile. [24].

Patient outcomes should not simply be measured by increasing survival or improving the quality of life. Rather, attention should be paid to enhancing clinical decision-making, minimiz-ing the risk of unnecessary therapy or adverse events through rapid learning and adaptation. This will allow for precision medicine to become a reality for all patients, leading to improved out-comes and a more efficient healthcare system. It is essential to continue developing molecular technologies and risk prediction algo-rithms to ensure the effectiveness of personalized medicine. The integration of data from various sources can be beneficial in predicting and tailoring treatments, leading to more individualized measures for patients. These tailored approaches can result in better outcomes, fewer adverse events, and cost-effective utilization of healthcare resources.

To achieve the implementation of the PPM concept, it is necessary to create a fundamen-tally new strategy based on the recognition of biomarkers, and thus the targets, in order to secure the great future of PPM and the development of drugs driven by PPM. Therefore, to secure ther-apeutic targeting, which is crucially important for the latter while implementing the key resources related to PPM into clinical practice, there is a strong need to develop a fundamentally new ap-proach based on biomarker-driven targeting aimed at recognizing

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biomarkers long before an ill-ness clinically manifests itself, including risk-enrichment stages (induction), subclinical stages, and clinical stages.

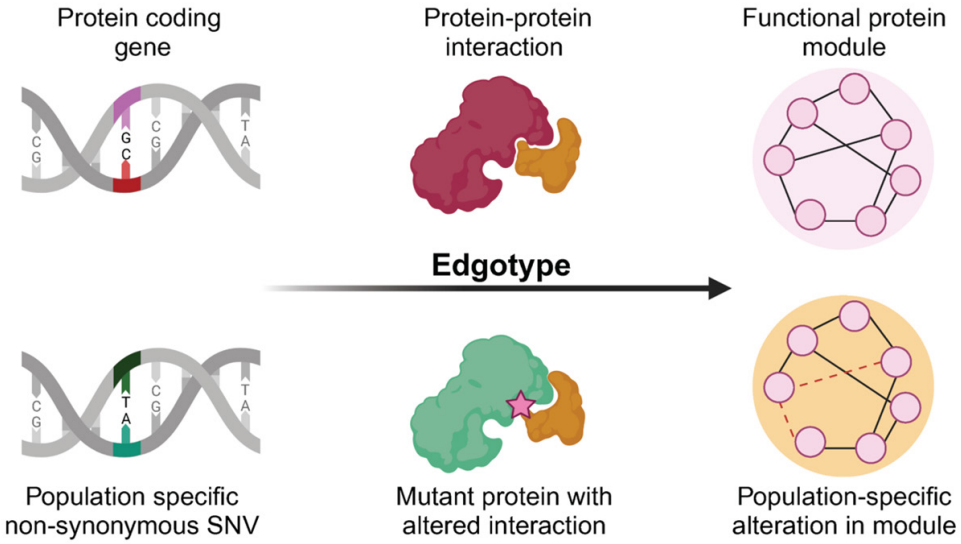
Molecular pathway maps indicate the involvement of multiple molecular mechanisms. Se-lected biomarker candidates that are reported to be associated with disease progression have been identified for specific molecular processes and stages of disease, including risk factors, screening, and diagnosis. The prognosis covers the induction stage, latency (sub-clinical or pre-disease), and clinical manifestations. [25-26].

Network-driven Pathology

The role of the pathologist in the future is to aid doctors in promptly diagnosing diseases at an early stage, thus facilitating optimal treatment plans. The use of advanced technology, driv-en by biomarkers for diagnosis and monitoring, is set to create comprehensive digital profiles of patients' samples integrating their genotype, phenotype, diagnosis, treatment, and outcome at a molecular level. Moving from using single biomarkers, known as "signatures," is a key approach to improving specificity.

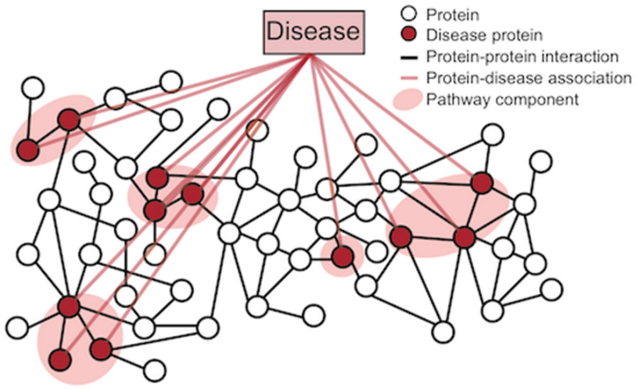
Gene-gene and protein-protein interactions are central to understanding biological pro-cesses, providing a unique approach to effective intervention. Each cell contains a protein interac-tion network (interactome), where connections between and within proteins provide insights into the cellular state. Perturbations in specific protein interactions highlight the effects of mutations in interacting proteins on the dynamics of the human interactome, revealing insights into disease mechanisms. (Fig. 7).

Figure 7 : Dynamics of Human Interactome Caused by Population-Specific Mutations [27].



Disease pathways, defined as sets of proteins associated with a given disease, play a piv-otal role in understanding disease pathology, diagnosis, prognosis, and treatment. Computational methods that utilize protein-protein interaction networks aid in pathway discovery by utilizing known disease-associated proteins as starting points (Fig. 8).

Figure 8 : Disease pathways in the wider network [28].



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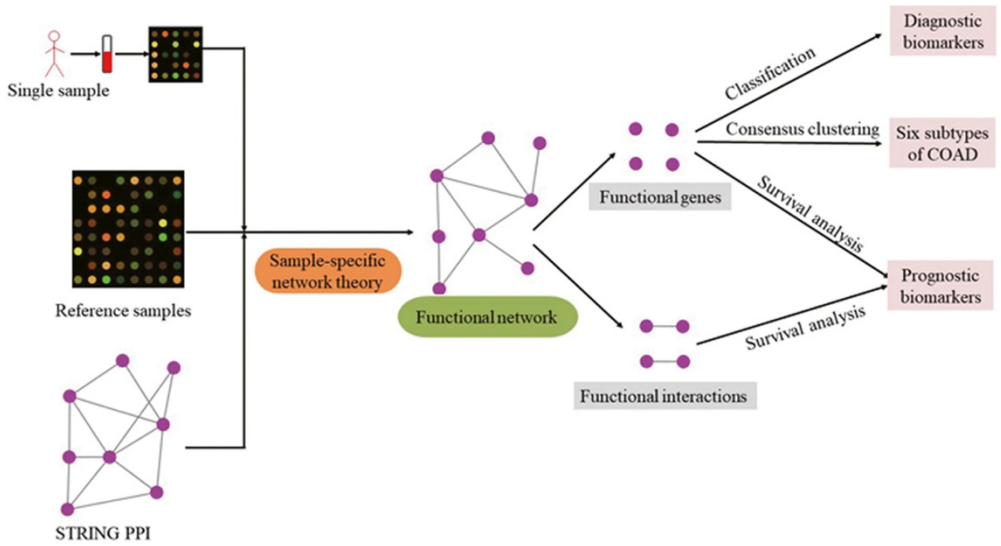
However, network connectivity alone is not sufficient for pathway discovery, and it ne-cessitates the exploration of higher-order network structures in order to distinguish between normal and pathological states. Due to the complexity of human diseases, network medicine pro-vides a comprehensive approach to decipher the molecular mechanisms and relationships between seemingly distinct phenotypes. By using network-based biomarkers, it is possible to illuminate the complexity of disease and identify disease modules and pathways, which can also help delin-eate molecular relationships among various phenotypes (Fig. 9).

Figure 9 : Sample-specific network method dentification of biomarkers for colon ade-nocarcinoma [29].



Pathologists play a crucial role in molecular diagnosis and therapeutic decision-making by bridging between morphology, clinical context, mutation status, and therapeutic implications. With the advent of precision medicine, genetic abnormalities have become emphasized, guiding the identification of novel biomarkers and druggable targets based on tissue or cytological sam-ples. Network approaches have revolutionized biomarker discovery by providing insights into pathway mapping and the development of disease-specific markers. Network-based biomarkers play a pivotal role in predicting disease-causing genes, identifying disease-related subnetworks, classifying diseases, modelling diseases, and screening for drug targets. All these activities ulti-mately improve patient outcomes and the quality of life.

Clinical bioinformatics integrates clinical measurements with tissue-generated bioinfor-matics, facilitating the translation of biomarkers into clinical pathology applications. Advances in this field are essential for identifying disease genes, elucidating the biological significance of dis-ease-associated mutations, and identifying drug targets within pathological models of complex diseases [30]. Network-driven pathology is an emerging field of research that focuses on molecu-lar and genetic interactions, as well as disease network biomarkers and therapeutic target discov-ery. This field integrates large-scale biomedical data with network medicine to create a frame-work for building meaningful models and achieving impactful results at the network level. This advancement in preventive medicine and healthcare has great potential to revolutionize precision medicine.

The Role of PPM-driven Pathology in the Era of Personalized (Precision) Medicine (PPM)

Recent advances in systems biology have greatly impacted the field of pathology, trans-forming it from a morphology-based to a molecular-based science and introducing specialized algorithms that can be applied in daily clinical practice [31]. Pathology is a central specialty in PPM, with pathologists playing a crucial role in implementing resources driven by PPM at the heart of decision making for therapeutic choices. The improved methodology of omics testing has made molecular pathology the cornerstone of personalized medicine healthcare services and overall clinical practice (Fig.10A,B).

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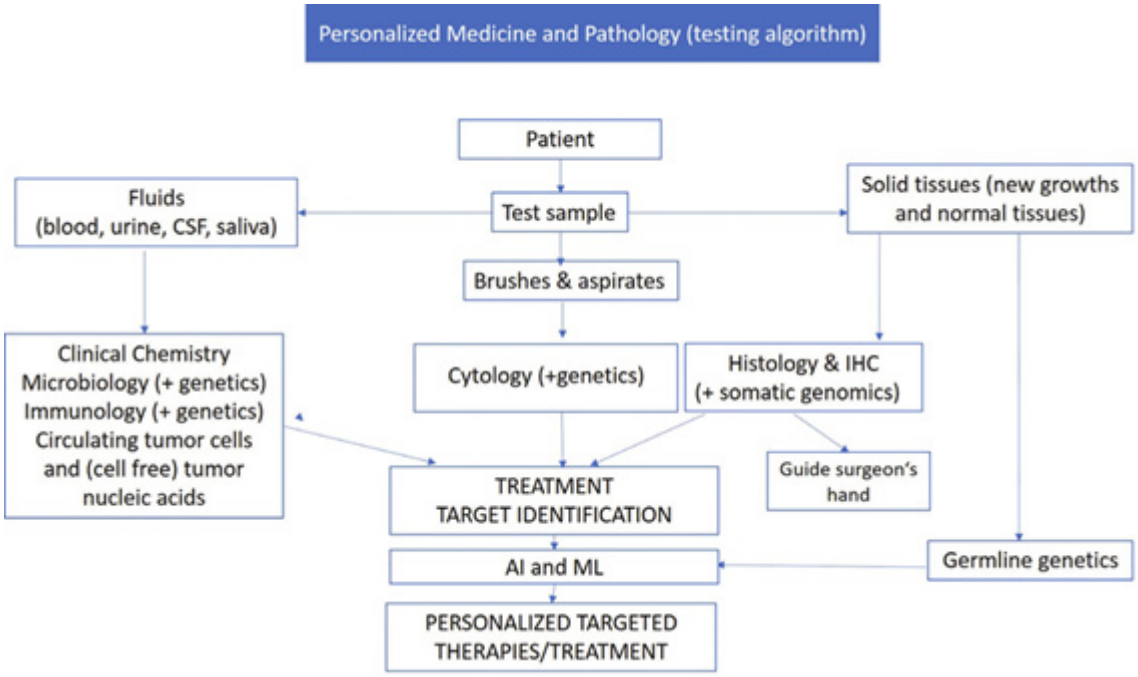
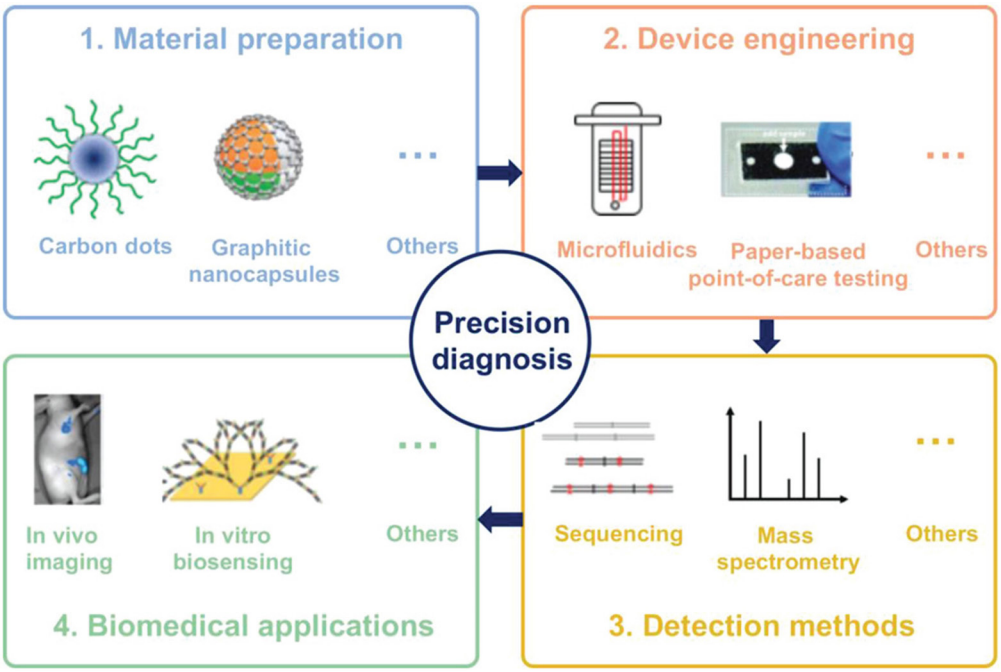
Figure - 10A,B : A proposed algorithm for the pathology role in PPM (left, A)[32] and a con-cept of precision diagnosis (right, B) [33]





State-of-the-art approaches in molecular pathology emphasize the increasing importance of pathology in personalized medicine (Fig. 10A). The practice of diagnostic pathology has sig-nificantly changed in recent years due to advances in molecular diagnostics and targeted treat-ment. Molecular pathology is now an essential component of personalized medicine, leading to the development of novel biomarkers that can aid in predicting the effectiveness of treatment and improving patient outcomes. Nevertheless, many of these markers require further refinement and standardization prior to widespread adoption in clinical practice (Fig. 10B), Therefore, they have become fundamental not only for informing about tumor diagnosis and prognosis but also for making therapeutic decisions in everyday practice. The introduction of next-generation se-quencing technologies and the increasing number of large-scale molecular profiling programs worldwide has revolutionized the field of precision medicine. With the increasing availability of comprehensive genomic analysis in both clinical and research settings, healthcare providers face a complex task of interpreting and translating the results. Various omics-based analyses of human diseases and premorbid conditions are integrated into diagnostic algorithms and decision-making processes. There is an increasing need for

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an accurate pathologic diagnosis of chronic diseases, as PPM-guided therapy requires a precise biomarker assessment. Digital image analysis promises to improve the accuracy and volume of morphological evaluation. For example, it can facilitate the early (subclinical) detection of cancer and precancer by providing more accurate information. In recent years, advances in our understanding of cancer biology have led to the development of new diagnostic techniques such as serum markers, liquid biopsy, and molecular diagnosis, as well as improvements in imaging technology. Bioinformatic techniques, especially deep learning, are accelerating the pace of computational pathology. The integration of information technology into clinical care is set to be a major focus for healthcare in the coming decade. Precision pathology is expected to play a central role in this transition. The core principle of precision pathology is to maximize therapeutic benefit for patients by using genomic and molecular data. It includes:

(i) evolving pathology from a paraclinical discipline to a medical field integral to clin-ical practice and overall clinical services;

(ii) playing a critical role in preventive, diagnostic, and therapeutic care, as well as fol-low-up;

(iii) being the future of tissue pathology in an era of PPM-guided oncology;

(iv) helping pathologists evolve to futureproof their profession.

The enormous development of precision pathology research has raised great expectations regarding its impact on personalized medicine (PPM). This aims to tailor medical practice to indi-viduals based on the use of omics tests and the identification of various biomarkers related to omics. The development of targeted therapies also plays a role.

The vast majority of tissue-based assays used in clinical practice are practiced globally, in-cluding translational research that is designed to translate research into practice, and clinical trials that are an integral part of diagnostic processes. However, integrating these approaches and re-sources poses a significant challenge in the future. This necessitates collaboration between clini-cians, pathologists, bioengineers, and biotechnologists. Although "next-generation pathologists" have been developed, continued education efforts are required to fully implement this shift in molecular pathology practice and make it a leading field in PPM. This requires highly trained mo-lecular pathologists who are skilled in pre-analytical processes, such as pathological areas like tu-mor nodes, microdissection to enrich tumor cells, methodological analyses, and interpretation of re-sults. The in-depth study of molecular changes in patients allows for an optimized molecular di-agnosis and the selection of candidates for novel treatments that target specific molecular altera-tions. These patients benefit from an upgraded, multidisciplinary approach and educational pro-grams.

OMICS Integration in Pathology

Recent advances in systems biology and innovations in translational applications have significantly impacted the field of pathology, shifting it from a morphology-based to a molecu-lar-based discipline. Molecular diagnostics, particularly genomic testing methodologies, have be-come pivotal in PPM, marking a departure from treatment decisions solely relying on histopatho-logical diagnoses.

Incorporating various genomic analyses of chronic disorders and cancers into diagnostic algorithms has become commonplace. Pathologists play a crucial role in the development and im-plementation of these molecular tests, ensuring accurate sample processing and morphological control to derive biomarkers and identify druggable targets. These are essential for translating scientific progress into tangible benefits for patients in the age of personalized medicine.

A major challenge in personalized medicine is establishing the relationship between bio-logical data, subclinical and clinical pathology, disease and clinical translation. This includes in-terpreting "Big Data," which refers to the extensive collection of healthcare data from thousands of patients and individuals at risk. It also involves tracking various biomarkers, mainly consisting of clinical and omics data. High-throughput data collection allows pathologists and practitioners to screen tissues for thousands of molecular targets, effectively capturing the response of com-plex systems over time. The statistical interpretation of trends from big data is a specialized dis-cipline necessary for predictive modeling and clinical decision support. This approach is used to develop predictive and prognostic tools that mimic biological systems, characterizing their behav-ior and response in the context of disease and drug development [34,35]. The aforementioned approach offers a genuine opportunity for secure diagnostic, predictive, and prognostic manipula-tions, along with preventive, prophylactic, and therapeutic measures. Personalized interventions could significantly influence clinical outcomes and demographics. By integrating OMICS, trans-lational, and clinical research, mathematical modeling, and bioinformatics algorithms into PPM practices, it is crucial to develop valuable biomarkers and tests to identify differential signatures between healthy individuals, patients, and disease subtypes. Advances in OMICS technologies and computational capabilities are leading to multidimensional deep phenotyping and precision healthcare approaches. Diseases can be classified using various methods, such as molecular and clinical classifications, alongside data from OMICS, environmental, and social factors. Precision medicine aims to integrate this data to achieve an accurate classification through large-scale anal-ysis and artificial intelligence [36-40].

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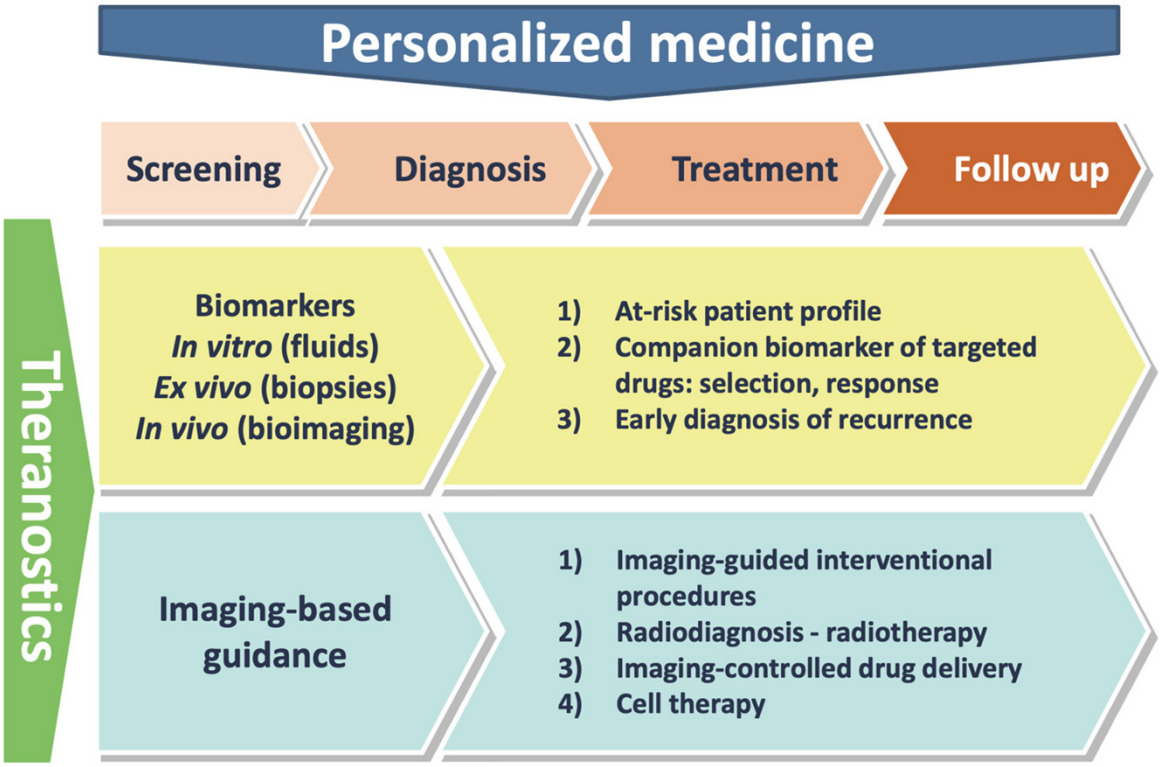
Advancements in Theranostics

It is true that the future of PPM hinges on the development of valid biomarker-based tests and targets, whilst molecular (targeted) therapy demonstrates remarkable response rates, making advances in reducing cancer mortality [41]. And thus the quality and outcomes of patient care can improve through the use of predictive and prognostic biomarker tests, integrating diag-nostic, predictive and therapeutic tools, e.g., companion diagnostics (CDx) and theranostics tests (Fig.11).

For example, companion diagnostics & theranostics - is a new field of PPM which combines spe-cific targeted therapy based on specific targeted diagnostic tests.

Figure 11: Theranostics as a primary model of PPM [42].



The potential success of PPM depends, in part, on the availability of a targeted medica-tion paired with a companion diagnostic. This diagnostic tool is designed to accurately determine whether a patient is likely to respond positively to a specific treatment or to monitor the effec-tiveness of treatment in real time

The Theranostics paradigm involves the use of nanoscience to combine diagnostic and therapeutic applications into a single agent, enabling the delivery of drugs, imaging, and monitor-ing of treatment response. Single chemical entities developed for Theranostic use simultaneously deliver therapy and diagnosis, having been successfully applied in oncology. It is now being ex-plored for use in autoimmune diseases, where its potential has caught the attention of industry and academia.

Theranostics, also known as Rx/Dx, represents a collaborative approach to the concurrent development of molecular diagnostic tests and targeted therapies. This goal is to provide tailored treatment based on the specific disease subtypes and genetic profiles of patients, improving the efficacy and safety of medications while streamlining the drug development process.Integrating the selection of drugs based on the results of personalized diagnostic tests has been considered one of the leading targeted therapy strategies in oncology by many experts. Co-development of theranostics is viewed as the ultimate goal for personalized and precision medicine [42-45].

Unveiling Subclinical and Predictive Cancer Risks

Another two unique examples that illustrate subclinical and predictive cancer risks are pre-cancer stem cells and circulating tumor cells (CTCs). As shown in (Figs. 29A,B), biomarkers are valuable tools that can accurately identify patients at high risk, improve diagnostic precision, and develop personalized follow-up plans. They can also aid in evaluating a patient's response to tar-geted therapies or immunotherapy and predicting prognosis.

Cancer stem cells, the focus of current research efforts to eradicate cancer, are capable of promoting metastasis and surviving

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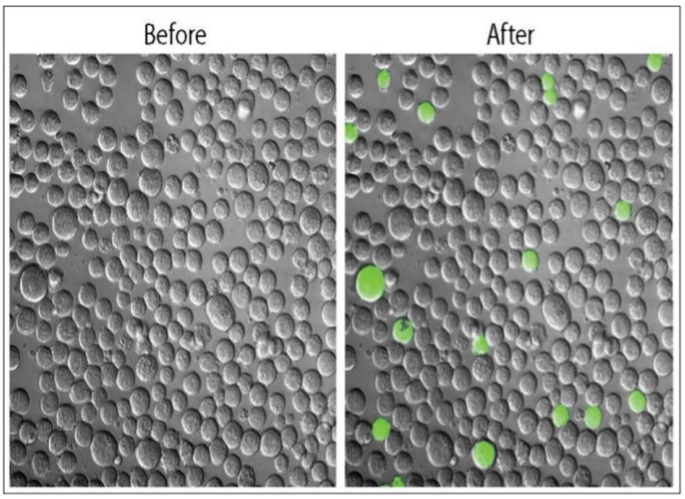
cytotoxic treatments due to their unique properties. Stem cell-based treatments provide specific tools for precise treatment, allowing clinicians to customize therapy based on a patient's unique needs. Variations in the tumor microenvironment can signifi-cantly contribute to cancer progression and resistance to treatment. resistance [46]. Therefore, the interaction between cancer stem cells (CSCs) and the immune system has become the focus of extensive research, with the aim of developing effective therapeutic strategies that target CSCs' ability to evade the immune response through immunoediting [47-52]. A key component of can-cer is a specialized subpopulation of highly aggressive tumor cells known as CSCs. These cells are located at the top of the tumor hierarchy, possessing the ability to self-renew and generate non-CSC/differentiated progeny. CSCs exhibit plasticity and can undergo functional alterations in response to environmental cues within the tumor microenvironment. This plasticity contributes to the diversity and complexity of the CSC population [42-50,53,54].

The clinical significance of CSC biomarkers is evident, as their expression has been linked to poor patient outcomes in numerous studies. CSCs possess inherent resistance to many conven-tional therapies, including anoikis (cell death in response to loss of adhesion), immune evasion, and tumor dormancy. These features can lead to tumor recurrence and metastasis. CSCs originate from either adult stem cells or differentiated cells at the onset of tumorigenesis. Due to their im-portance, several biomarkers have been identified that characterize cancer stem cells (CSC) and correlate with diagnosis, treatment, and prognosis. However, CSCs also exhibit high plasticity, which allows them to change their phenotypic and functional characteristics in response to chem-otherapy, radiotherapy, and the presence of senescent tumor cells that alter the tumor microenvi-ronment.

The significance of CSCs in tumor biology and cancer treatment lies in their ability to maintain a quiescent state, proliferate slowly, self-renew indefinitely, differentiate, and undergo transdifferentiation processes such as epithelial-to-mesenchymal transition and mesenchymal-to-epithelial transition, among other capabilities.

Their ability to detach from the primary tumor, migrate, extravasate, invade, and complete all necessary steps in the metastatic cascade highlights their importance in metastasis formation. CSC populations play a significant role in tumor growth and metastasis, as well as resistance to cancer therapy. In contrast to circulating tumor cells, CSCs provide tumor DNA, RNA, and pro-tein information that can be utilized in diagnosis, prognosis, and treatment planning (Fig. 12) [42-47,50,53,54].

Figure 12 : Visualize cancer stem cells (green) [55].



CTCs are crucial for metastasis, and their analysis in liquid biopsy samples is valuable for real-time monitoring of therapy and predicting prognosis. Characterization of CTCs has the po-tential to lead to the development of new treatment strategies for preventing metastasis and maintaining a stable disease status.

Liquid biopsy, along with CTC assays, is becoming an increasingly important tool for mo-lecular profiling of cancerous tissues, enabling precision medicine and personalized treatment ap-proaches. Liquid biopsy is a valuable tool that has had a significant impact on various aspects of cancer management. It contributes to early detection and treatment of metastatic disease that is resistant to conventional therapies [56 - 58]. The analysis of biomarkers is essential for chronic disease patients and cancer patients as well as for pre-cancerous individuals who are at risk dur-ing the pre and post treatment periods. This analysis helps to identify different types of cells that have the potential for disease progression or relapse after treatment.

Molecular pathology has become crucial not only for diagnosis and prognosis prediction, but also for therapeutic decision-making in clinical practice. With the advent of next-generation sequencing technologies and the proliferation of large-scale molecular profiling initiatives in insti-tutions worldwide, personalized medicine and pathology have been revolutionized [31]. Cancer is a leading cause of death worldwide. With limited treatment options available for advanced or metastatic cases, the prognosis is poor. Although morphological classifications, which are widely used, are useful for making decisions during endoscopic and surgical procedures, they are not enough to guide personalized treatments for each patient.

Understanding the genetic alterations underlying cancer development is becoming in-creasingly important. This can help identify potential biomarkers and target therapies for person-alized medicine. On the one hand, this aids in the

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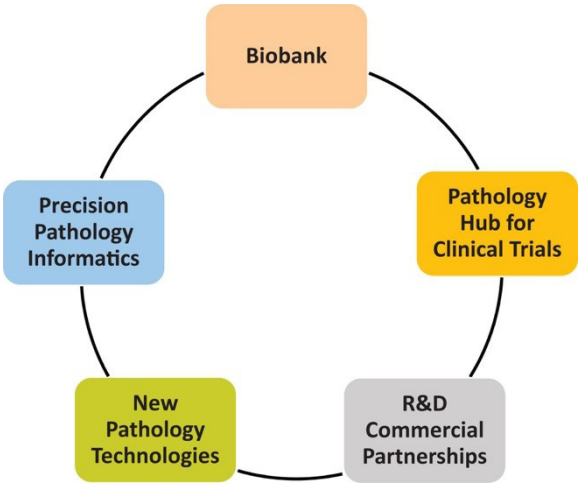
development of targeted treatments based on biomarkers. On the other hand, recognizing cancer as a heterogeneous disease with different growth patterns and subtypes allows for the identification of targetable genetic alterations that can be applied in personalized care. The role of pathology has expanded beyond its traditional function of confirming diagnoses, and now encompasses the prediction of molecular alterations, prognosis, and the behavior of diseases [59,60].

Molecular Diagnostics and Biobanking

Newer molecular diagnostic techniques and an enhanced understanding of chronic condi-tions and cancer etiology have identified multiple potential targets for novel therapeutic agents in development, ushering in a new era of precision medicine. However, there remains a need for more reliable, diagnostic, prognostic, and predictive tests, due to low treatment response rates and widespread resistance to current targeted therapies. For example, genomic testing has be-come a cornerstone of precision medicine, as decisions regarding biomarker-guided targeted therapies are no longer solely based on histopathological findings or Big Data sets from biorepos-itories (Fig.13).

Figure 13 : Biobank-related OMICS- and IT-technologies through the View of R&D Commercial Partnership [61].



The development of biomedical science requires the creation of biological material collections that allow for the search and discovery of biomarkers for pathological conditions, the identifica-tion of new therapeutic targets, and the validation of these findings in samples from patients and healthy people. Over the past decade, the importance and need for biobanks has increased con-siderably. Large national and international biorepositories have replaced small collections of bio-logical samples. Biobanks are an important component of personalized medicine and strongly support scientific progress in the stratification of populations and biomarker discovery and vali-dation, due to advances in personalized medicine. They are an essential tool for drug discovery and development. Biobank play an important role throughout the process of patient care, preven-tion, prediction, follow-up and therapy monitoring, and optimization. Biobanks are specific in that they take a multidisciplinary approach to human health, combining biological and medical methods as well as bioinformatics, computing and modeling techniques. Their importance has increased over the last decade, from small samples to large national and international collections. The samples collected are population-based or related to specific diseases, and can come from diverse individuals. Navigator is a network that develops an open imaging biobank to collect and preserve a large amount of standardized multimodal imaging datasets, including image data, as well as patient-related information and omics-related relevant data extracted from regional health services using a privacy-preserving approach [62,63]. Pathologists, working in collaboration with molecular biologists, can provide the molecular information necessary for a complete diagnosis. They become the final certifiers of a complex diagnostic process, as they are medical profession-als skilled at integrating morphological and molecular data into a report. This report includes a diagnosis and predictive biomarkers that allow clinicians to choose the most appropriate thera-peutic procedure for each individual patient, such as chemotherapy, immunotherapy, or gene therapy. Through innovative tools and collaboration with new professionals, pathologists play a guiding role in cancer care, allowing for a comprehensive characterization of tumors that directly influ-ences therapeutic decisions and guides pharmaceutical and diagnostic developments in clinical practice [64]. However, challenges such as data integration and interpretation need to be ad-dressed in order for personalized medicine to remain accessible and effective. Data processing and machine learning have become crucial in advancing personalized medicine, and pathology and laboratory medicine are no exception. The incorporation of designed applications through clinical informatics and biostatistics into clinical practice unlocks innovative approaches to pa-tient care. Computational pathology is a burgeoning specialty in pathology that promises a more integrated solution to whole slide images and multi-omics data. In this context, the establishment of a comprehensive industry for computational pathology requires significant changes to three essential elements linking patients and doctors: local laboratories, scan centers, and central cloud hubs/portals for data processing and storage. Computational pathology, enabled by information integration and advanced communication networks, has the potential to enhance clinical work-flow efficiency, improve diagnostic accuracy, and ultimately lead to personalized diagnosis and treatment planning for patients [65]. With the rapid development of digital, molecular, and com-putational pathology, pathology

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has increasingly become involved in many different specialties. For instance, common disease subtypes and variations of benign and malignant tumors should be included in the training and validation process to ensure the feasibility of everyday practice. Computational pathology, through the use of digital technology and statistical algorithms, will continue to improve the clinical workflow and collaboration between pathologists and other members of the team. The increased infrastructure of the network, as well as the increased computing power and broad integration of information, have created new opportunities for computa-tional pathology and collaboration. This means that data sharing, cloud-based storage and analy-sis, and better patient care are all possible through this marriage between bioinformatics and pa-thology.Because bioinformaticians can use computational approaches to interpret complex data from omics-driven assays and screens, all in order to develop IT algorithms that can identify mo-lecular signatures of disease types and predict responses to targeted therapies, and practicing molecular pathologists also require familiarity with databases, PPM is increasingly integrated into routine clinical practice for managing chronic conditions. Key areas where PPM can inform fu-ture health education initiatives include biomarker-based clinical decision support and literacy targeting for the general public, as well as an understanding of how tests, profiles, and treatments are applied to patients and individuals at risk of developing a condition, and the implementation of PPM technologies has also contributed to laboratory accreditation efforts. Pathologists rou-tinely oversee laboratories that offer a wide range of tests, including FDA-cleared assays in vitro diagnostics (diagnostic tests performed outside a patient's body), and laboratory-developed tests (tests developed and used only in a laboratory).They are responsible for ensuring compliance with the Clinical Laboratory Improvement Amendments and College of American Pathologists' accreditation standards, as well as compliance with other relevant accreditation programs. When laboratories decide to adopt or expand their test platforms, they often turn to pathologists to choose technologies that match their needs, workflow, and cost and reimbursement requirements.

We are entering a time of rapid change in translational medicine with personalized treat-ments based on detailed molecular information about a patient's condition. This shift toward in-dividualized healthcare requires a new approach to standardized healthcare that accounts for the unique needs and characteristics of each person. This is why we are working on global scientific, clinical, societal, and educational initiatives in the field of PPM to create content for this new area.

CONCLUSION

In this context, PPM strongly demands PPM-driven pathology. The need to integrate a flood of new molecular data with surgical pathology and digital pathology, as well as all the pa-thology data in electronic medical records, is never greater. Pathologists are the final validators of a complex diagnostic process. They are medical professionals with the skills necessary to inte-grate morphological and molecular information into reports, including diagnoses and predictive biomarkers.

This integrated information allows clinicians to select the best therapeutic approach for each patient or person at risk. Pathologists play a crucial role in developing and implementing molecular and genetic tests, as well as communicating their results and significance to clinicians. PPM (pathology practice management) represents a transformative approach to healthcare that shifts from a one-size-fits-all approach to an individualized one tailored to patients and those at risk, revolutionizing disease diagnosis, treatment, and prognosis in areas such as cancer, infec-tious diseases, autoimmune disorders, neurodegenerative diseases, and rare conditions. With the advancement of technology, PPM's reach in pathology is likely to expand, leading to increased accuracy in diagnosis and better treatment outcomes for patients, alongside enhanced patient care.

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