# Integrative Multi-omics in Oncology: Bridging Molecular Complexity and Clinical Relevance

**Chaitali Dhande[1], Shiwani Kawade[2], Shlok Kadam[3], Aman Tiple[2,*]**

[1]*Asian International University, Manipur*

[2]*Institute of Biosciences and Technology, MGM University, Chh. Sambhajinagar India*

[3]*Dr. D. Y. Patil Institute of Management & Research, Pimpri, Pune, Maharashtra,*

**Corresponding author**: Aman Tiple
**Email**: amantiple97@gmail.com
**Doi**: **10.5281/zenodo.16603404**
**Received**: 25 June 2025
**Accepted**: 05 July 2025

**Abstract**:

is a global health concern since it is a multifactorial complex disease, and early detection and novel therapeutic options are necessary for more successful cancer treatment. Cancer affects the entire body and causes several alterations at the molecular level. Biological omics, which includes genomes, transcriptomics, proteomics, metabolomics, and radiomics, seeks to better understand cancer development at these several levels. This strategy shifts cancer research from analyzing single factors to investigating several factors simultaneously. The rapid advancement of omics technologies enables the easy collecting of multi-omics data, hence improving predictive, preventative, and customized treatment. In terms of cancer prognostic prediction, diagnostics, and prevention, as well as cancer therapy and drug responses, this study presented a complete and critical assessment of the systematic method for predictive, preventive, and personalized medicine (PPPM) for cancer. To improve the effectiveness of PPPM for cancer, this review paper looked at multidimensional data from several sources, as well as the use of computational approaches and multidisciplinary omics methodology. This review provided new viewpoints on how both individual and integrated -omics technologies are currently being employed. This review article discusses the methods, achievements, and clinically relevant outcomes of multi-omics technologies in cancer research, with a focus on the necessity and scientific validity of incorporating multi-omics into cancer research and clinically applicable outcomes.

**Keywords**: Multi-omics, Cancer, Omics Technologies, PPM, Clinical Relevance

**Introduction**:

According to the World Health Organization (WHO), cancer is the second biggest cause of death worldwide, accounting for nearly 10 million deaths in 2020. Low- and middle-income nations account for over 70% of all cancer fatalities [1]. The high-mortality cancer experiences a complex and multistep development, malignant cells acquired eight biological capabilities, including sustaining proliferative signalling, evading growth suppressors, resisting cell death, inducing angiogenesis, activating invasion and metastasis, enabling replicative immortality, reprogramming of energy metabolism, and evading immune destruction, which are considered the hallmarks of cancer [2]. The Human Genome Project, the coming scientific era of "omics" has revolutionised the study of cancer. "OMICS" technologies are distinguished by high-throughput interfaces that allow for unbiased investigation of the genome, epigenome, transcriptome, proteome, and metabolome. OMICS techniques are currently being used to study the sophisticated biological systems and discover the molecular signatures underlying the diverse cellular phenotypes [3]. Various OMICS techniques have been developed to

disentangle the complexity of biological systems at different levels (e.g., DNA, RNA, and protein). Omics technologies have a broad range of applications in both basic research and therapeutic cancer treatment. Based on next-generation sequencing (NGS), genomics and transcriptomics provide a deeper knowledge of the structure of the cancer genome and find differentially expressed genes that cause and perpetuate carcinogenesis [4]. Multidimensional -omics data that is thoroughly described in individuals through computer analysis utilizing bioinformatics methodologies allows for the identification of pharmacological targets and the most effective treatments. Genomics investigates genome structure and function using DNA sequencing and genetic polymorphism analysis. When compared to analyses using only one type of data, a systemic genomic approach using next-generation sequencing (NGS) technology can reveal genotype-phenotype relationships. More crucially, genome profiling has the potential to identify diverse molecular subtypes and stratify individuals, which is critical for precisely individualized treatment. High performance liquid chromatography, mass spectrometry, enzyme linked immunosorbent assay, and nuclear magnetic resonance technologies are frequently employed in the development of new biomarkers and therapeutic targets from the cancer proteome and metabolome [5]. These biomarkers, which include predictive biomarkers for therapy stratification, diagnostic biomarkers for early detection, and prognostic biomarkers for estimating patient clinical outcomes, are critical for tumor prediction and prevention. At the same time, important molecules in the tumor pathway and network, such as proteins and metabolites, can be identified as potential targets for targeted therapy. Currently, several kinase inhibitors are being employed in targeted therapy for a variety of cancers with promising clinical results. Radiomics is the link between medical imaging and personalised medicine. Quantitative study of imaging features offers not only the tumor phenotype but also the underlying genetic information, extending imaging analysis from qualitative to quantitative and revealing clinical significance that the naked eye cannot detect. Changes in the amounts of DNA, RNA, protein, metabolite, and medical imaging created an array of dysfunctionally mutually connected molecular networks, making cancer a complex systems biology disease [6].

Any one study at a level is insufficient to understand the complex etiology of cancer. The integration of multi-omics data is critical for understanding the molecular mechanism of cancer and identifying new biomarkers and therapeutic targets. As a result, cancer treatment is undergoing a drastic transition toward predictive, preventative, and personalized medicine (PPPM) [7]. This review paper discusses the methods, achievements, and clinically relevant outcomes of multi-omics technologies in cancer research, as well as the significance and scientific benefits of incorporating multi-omics into cancer research and clinically applicable outcomes.

**PPPM in Cancer Diagnosis and Treatment**

PPPM for cancer is a global concern. The concept of PPPM was introduced at the first European Association for Predictive, Preventive, and Personalized Medicine (EPMA) World Congress in 2011 [8], and global collaboration is helping to develop and execute innovative PPPM techniques. It entails employing a variety of unique, quick, sensitive, and particular technologies to develop optimal cancer treatment options for individual patients. PPPM trials seek to give a speedy, efficient, and accurate prediction of the best course of treatment for a patient. The difficulty of PPPM for cancer is to close the gap between researchers and doctors. Thus, efforts to determine the ideal PPPM for cancer patients will include determining the proper amount and timing of administration of the optimal drug for each particular patient. novel advanced breast cancer patient stratification and a novel paradigm of "pre-metastatic niches" were addressed for effective breast cancer care and pre-treatment prediction of chemoradiotherapy response was also detailed in rectal cancer in the context of PPPM [9].

PPPM is based on identifying and validating biological markers of cellular, biochemical, or molecular changes in tissues, cells, or fluids. Recent advances in -omics technologies have resulted in the study of numerous biological samples for cancer prognostic and diagnostic biomarkers (Fig 1). Biomarker discovery has helped to advance cancer research and drug development by identifying mechanisms of cancer progression, improving individual and group risk assessments, establishing therapeutic responses, and reducing bias in cancer risk factor measurements. Biobanks or biorepositories collect and store biological samples, as well as clinical, pathological, and medical history data. Well-regulated population- and disease-based biobanks comprising a variety of biological materials are a useful resource for both cohort studies and disease investigations. Such studies seek to

develop unique and reliable PPPM methodologies for disease treatment, prediction, and diagnosis, as well as patient response monitoring.

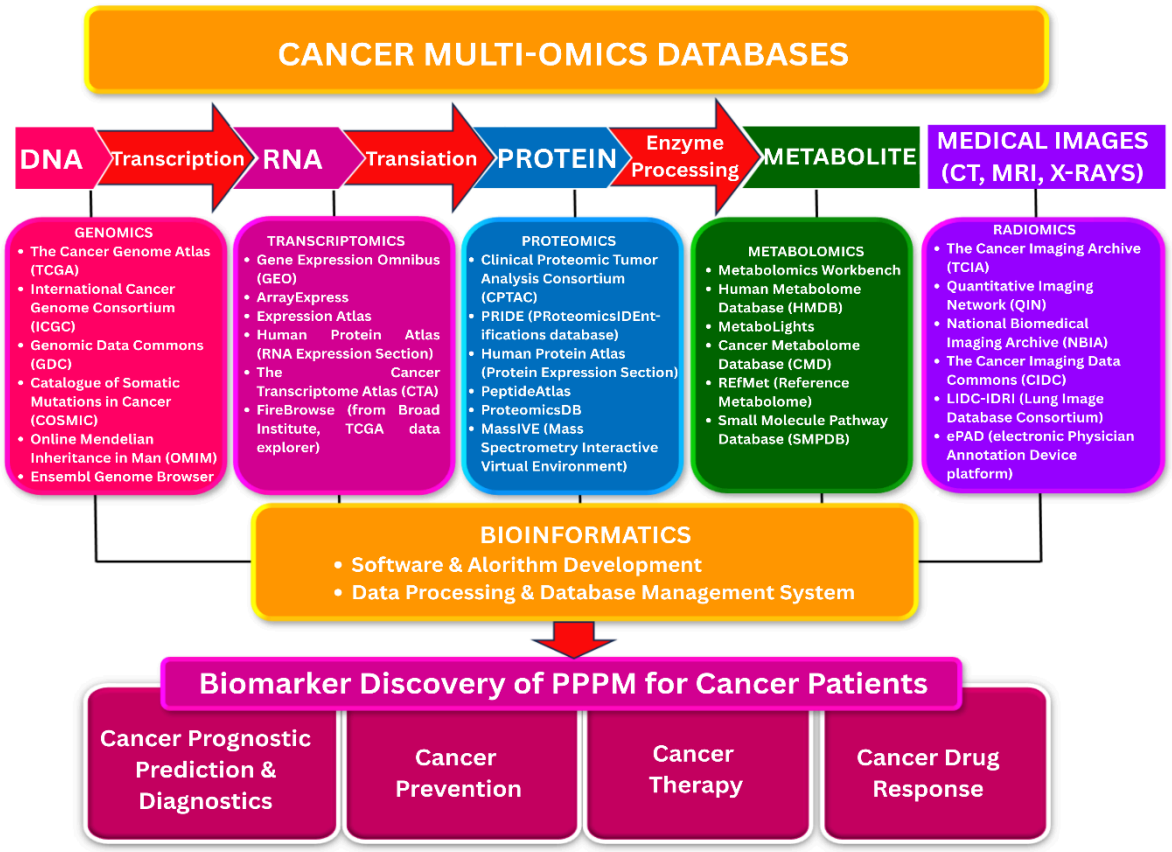


Fig 1. Multi-omics application in Cancer Treatment and Diagnosis

Tumor tissue, which is readily available via surgical specimens or biopsies, is a valuable resource for biomarker development. Fresh, frozen, and formalin-fixed paraffin-embedded (FFPE) tissues have yielded useful information for clinical diagnosis and treatment using genomes, transcriptomics, proteomics, and metabolomics methods. NGS-based genomics and mass spectrometry-based proteomics have been used on FFPE clinical specimens. Tissue biopsy allows for direct analysis, however there are still obstacles owing to sample inaccuracy, such as surgical complications, tumor propagation, false negative results, and invasiveness. Blood-based biomarker assays are suitable for population-wide or risk group-based screening programs because they may be repeated at shorter intervals and are less invasive to patients. DNA, RNA, proteins, and metabolites are common biomarker discovery samples, although platelet RNA, circulating tumor cells, and circulating tumor DNA (ctDNA) have also been employed to develop cancer diagnostics [10]. CtDNA has received a lot of attention in PPPM for cancer. Blood ctDNA is a promising, non-invasive biomarker for cancer. It has the advantage of being easily accessible and is utilized for cancer diagnosis, prognosis, and treatment guidance for patients with cancer of many histological kinds [11]. Studies on ctDNA detection are increasing because ctDNA can be detected and tracked using tumor-related genetic and epigenetic changes [12]. The clinical implications of monitoring ctDNA levels in patients with lung cancer and renal cell carcinoma have been documented.

In addition to digital PCR, targeted NGS technology was used for ctDNA profiling. Shu et al. discovered a unique mutation spectrum in lung cancer patients using ctDNA, demonstrating the viability of targeted NGS-based ctDNA mutation profiling to guide cancer therapy decisions [13]. Tumor tissue DNA and ctDNA-based NGS were utilized to evaluate the genetic changes in metastatic renal cell carcinoma patients. A sufficient volume of urine, containing few interfering variables and reflecting the individual's systemic health, can be collected in a non-invasive manner with a low number of interfering molecules. However, urine biomarker concentrations can be impacted by the patient's hydration status as well as sample collection,

processing, storage, and measurement methods, resulting in uneven sample management in clinical research. Other physiological fluids, such as sperm, faeces, saliva, sputum, perspiration, cerebrospinal fluid, and tears, are emerging as accessible, non-invasive biomarker discovery tools in PPPM. Omics experiments on saliva have identified potential biomarkers for oral squamous cell carcinoma [14]. Tear fluid included biomarkers associated with eye diseases [15]. Stool has also been studied for colorectal cancer screening, including the faecal occult blood test (FOBT) and the faecal immunochemical test (FIT) [16].

Molecular markers of several forms of cancer have been studied to improve individual patient prognosis and diagnostic stratification. These markers are used to anticipate undesirable medication effects and/or treatment responses caused by metabolic or excretion dysregulation as a result of molecular changes. Although these are potential biomarkers of disease status, biomarker-directed individualized therapy is limited to a small number of patients due to the rarity of predictive biomarkers and the absence of response predictive biomarkers for the majority of first-line anticancer therapies. However, technological advancements will improve prognostic classification and enable testing of drug sensitivity and therapy responses in cancer patients.

Several PPPM indicators that supplement standard biomarkers have been studied. Recent research has identified a novel biomarker, prostate cancer antigen 3 (PCA3) [17], and produced the prostate health index, the OPKO 4K score and a prostate cancer genomic classifier for cancer outcome prediction [18]. In addition to biochemical biomarkers, multiparametric magnetic resonance imaging or prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and computed tomography (CT) show potential for prostate cancer treatment Oncotype DX is a molecular classifier used in breast cancer management [19]. Several predictive PPPM biomarkers for lung cancer have been identified, including actinin-4 protein, which is used in adjuvant treatment for resected lung adenocarcinoma [20]. The clinical value of recently discovered prognostic, diagnostic, and predictive molecular biomarkers in mature B-cell neoplasms was studied, and the controlled nutritional status score is now utilized as a prognosis marker for gastric cancer patients after curative resection [21]. Screening programs for PPPM have detected individuals with a genetic predisposition to cancer at an early stage, allowing for timely provision of suitable prophylactic or treatment. Molecular changes that lead to carcinogenesis, such as mutations of BRCA1/2 [22] and hMSH2 [23] in breast and colorectal cancer, are being studied to determine cancer risk. The ultimate goal of PPPM is to provide cancer treatment that is tailored to the unique characteristics of each patient. Efforts to improve the quality and management of medical services have centred on patient demands, expert viewpoints, and novel procedures. Acute myeloid leukemia (AML) treatment was improved by monitoring the response and employing residual disease diagnostics to guide therapeutic decisions. Efforts are being made to improve the identification of low levels of AML and create clinically relevant minimal residual disease (MRD) thresholds in order to improve AML treatment [24]. PPPM uses molecular diagnostic testing, such as DNA sequencing, to determine the etiology of cancer. NGS technology have been developed to use genetic mutation profiles to select patients and guide treatment decisions.

**Genomics**

Since 1914, researchers discovered that aberrant chromosomal distribution during cancer cell division may play a role in malignancy [25]. In-depth examinations of chromosomes found the Philadelphia chromosome, which occurred from a translocation between chromosomes 9 and 22 in chronic myelogenous leukemia (CML) cells [26]. Following the foundational finding of a single point mutation of HRAS that was responsible for the activation of an oncogene in T24 human bladder cancer cells in 1982 [27], further oncogenes such as EGFR, RAS, PI3K, and ERK were identified. These findings encourage scientists to learn more about tumors caused by the accumulation of genomic changes such as base substitutions, minor insertions and deletions, chromosomal rearrangements, copy number variations, and microbial infections [28]. Less than three years after the completion of the Human Genome Projects, the National Institutes of Health formally initiated the pilot stage of an endeavor to establish a comprehensive library of cancer-related genetic alterations in 2006, known as the Cancer Genome Atlas (TCGA) [29]. Furthermore, the International Cancer Genome Consortium (ICGC) and the Cancer Genome Project of the United Kingdom have the similar goal of identifying all genetic variants that are strongly related with cancer. Cancer genomics is inextricably linked to advances in DNA sequencing

technologies. From first-generation sequencing to next-generation sequencing, DNA sequencing technology has advanced at a rapid pace.

Sanger sequencing, which relies on DNA polymerase's selective incorporation of chain-terminating dideoxynucleosides during in vitro DNA replication, has previously been the most used approach. Sanger sequencing, with long read lengths (up to ~1000 bp) and high per-base "raw" accuracies as high as 99.999% [30], produced several significant feats, including the completion of the Human Genome Project. Its downsides include high cost and low throughput. The quest for completely new methods that provide fast, low-cost, and accurate genome information fueled the development of next-generation sequencing (NGS) technology. The second- and third-generation technologies are known as NGS. Several commercially available platforms, including Roche/454, Illumina/Solixa, Life/APG, and Helicos BioSciences, all use cyclic array sequencing, which is defined as the sequencing of a dense array of DNA features through iterative cycles of enzymatic manipulation and imaging-based data collection [31]. Second-generation sequencing has several advantages over Sanger sequencing, including increased speed and throughput at a lower cost, quicker gene library building, a higher degree of parallelism, and more economical reagent use. Shorter read lengths, ranging from 32 to 330 bp on average, make genome matching and assembly difficult [32]. In terms of raw accuracy, the NGS platforms are at least ten times less precise than Sanger sequencing. The third generation of sequencing technology, such as PacBio RS and Oxford Nanopore sequencing, is being developed to address the shortcomings of the second generation, with a fundamental feature of single molecule sequencing but no requirement for any PCR process, which effectively avoids PCR bias caused by system error, improves read length, and maintains the advantages of high-throughput and low cost of the second-generation technology.

The use of high-speed and high-throughput NGS technologies significantly improves cancer genome analysis and reveals the entire repertoire of mutated cancer genes, which not only can be used to guide the discovery of new targeted drugs, but also has a massive impact on cancer biology and accelerates PPPM strategies in cancer. Gene fusions caused by chromosome translocations play a significant role in the early stages of carcinogenesis, as evidenced by the identification of gene fusions in all cancers [33]. Functionally recurring gene fusions provide for more exact clinical-related subclassifications of cancers than traditional morphological classifications, accelerating the development of specialized targeted therapies. Previously, due to a lack of systematic methodologies, this type of genetic aberration was viewed as a key mechanism in haematological and soft-tissue cancers.

In recent years, with the application of NGS, novel recurrent chromosomal rearrangements have been discovered in many kinds of solid tumors, such as TMPRSS2-ETS fusion oncogenes in prostate cancer (Pca) [34], EML4-ALK fusion oncogenes in non-small cell lung cancer (NSCLC) [35], ETV6-NTRK3 fusion oncogenes in secretory breast cancer [36], BRAF and RAF1 fusion oncogenes in melanoma [37], BRAF gene fusions in pilocytic astrocytomas, pancreatic In July 2017, the Tumor Fusion Gene Data Portal published information on 33 tumor types and 20731 fusion genes. Kinase and transcription factors are ubiquitous fusion genes that play essential roles in carcinogenesis and metastasis, providing insight into PPPM practice in cancer [38]. EGFR mutants were the most common genetic mutation seen in NSCLC, and patients with EGFR mutants were typically treated with an EGFR kinase inhibitor. In recent years, new recurring fusion oncogenes EML4-ALK and FGFR3-TACC3 have been discovered in NSCLC [39]. These genetic defects have different tumorigenic pathways than EGFR mutations. The former responds to ALK tyrosine kinase inhibitors such as crizotinib, whereas the latter responds to FGFR kinase inhibitors such as BGJ398 [40]. These discoveries add to the genotyping diagnosis of NSCLC and will benefit particular categories of patients, potentially enabling tailored medical therapy.

**Transcriptomics**

The genetic central rule demonstrates that genetic information is transmitted from DNA to protein via RNA (mRNA) with perfect regulation. The mRNA serves as a "bridge" in the process of biological information transfer from DNA to protein. The primary goals of transcriptomics are to catalog all transcript species, identify gene transcriptional organization, and measure each transcript's expression level during development and under various situations. Methods for studying the transcriptome have been developed, including hybridization and

sequence-based approaches. The former is based on nucleic acid hybridization, which typically involves incubating fluorescently labelled cDNA derived from reverse transcription of various mRNAs with microarrays containing genes of interest, followed by digitalization with a specialized scanner and image analysis. The information obtained includes the gene name, clone identifier, and intensity values. Tiling microarrays, adapted from normal gene expression microarrays, are now made up of oligonucleotide probes that span an organism's whole genome, providing a more unbiased picture of transcriptional processes inside a genome [41]. Sequence-based techniques determine cDNA sequence without relying on probes. The Sanger sequencing technique was initially used to detect the sequences of cDNA or EST libraries; however, it is rather expensive, has low throughput, and provides no quantitative information. Following that, tag-based methods were developed to overcome those limitations, including serial analysis of gene expression (SAGE), cap analysis of gene expression (CAGE), and massively parallel signature sequencing (MPSS), which can provide high throughput and precise gene expression levels but are still based on Sanger sequencing technology, resulting in an analysis of only a portion of the transcripts and isoform differentiation. The birth and development of NGS has resulted in a new technology, RNA-seq, for mapping and measuring the transcriptome using high-throughput DNA sequencing.

Alternative splicing of precursor messenger RNA from a single gene which produces multiple Different functional messenger RNAs pand the associated proteins generated from the same gene [42]. Splicing abnormalities are a prevalent feature of cancer, seen in all types of cancer hallmarks. Abnormal splicing can produce aberrant protein variants that serve a variety of roles, including transcription factors, cell signal transducers, and extracellular matrix components [43]. The changed gene products usually indicate an active engagement in malignancy. RNA-seq can detect RNA splicing events more directly and easily than typical gene expression microarrays, making it a powerful tool for identifying cancer-related alternative splicing, which could be a diagnostic or prognostic marker and potential tailored therapeutic target. In NSCLC research, a comprehensive investigation of prognosis-related alternative mRNA splicing using RNA-seq data revealed a substantial number of alternative splicing events associated with NSCLC prognosis. Furthermore, prognostic models based on alternative splicing events were developed for risk categorization and demonstrated outstanding performance. RNA-seq also enables quantitative analysis of alternative splicing. The insulin receptor isoform A (IR-A) and insulin receptor isoform B (IR-B) exist as a result of alternative splicing [44]. Another study employed bioinformatics tools to evaluate RNA-seq data from both isoforms and discovered that lower IR-B levels and higher IR-A/IR-B mRNA ratios were associated with a slower epithelial-mesenchymal transition and a longer survival period. Furthermore, this behavior has been observed in 18 other forms of cancer, implying that this ratio could be used to predict prognosis and measure therapy response [45]. Several EMT-associated alternative splicing events have been identified in breast cancer, and the majority of these alternative splicings are regulated by one or more members of splicing factor classes such as PBFOX and ESRP, which may provide new diagnostic and prognostic markers as well as personalized treatment targets for breast cancer [46]. Compared to the analysis of DNA sequencing-based structural variations, transcriptomics can provide an analysis of DNA functional characteristics at the RNA level, allowing researchers to link gene structural features to their functions and more easily determine the cause of physiological or pathological conditions. RNA-seq has proven to be a valuable method for discovering novel gene fusions in cancer transcriptomes. Oncogenic gene fusions were discovered systematically in primary colon cancer using IIumina RNA-seq, with a relevant gene fusion occurring in 2.5% of all specimens; of these, USP9X-ERAS formed by Chromothripsis was considered highly oncogenic, capable of activating AKT signalling [47].

Analysis of Ovarian Cancer RNA-seq data combined with a unique computational method for fusion discovery defuse provides the first gene fusion discovery for ovarian cancer, potentially contributing to the study of tumor initiation, progression, and treatment [48]. MicroRNAs (ncRNAs) are small non-coding RNAs (~22 nucleotides) that regulate gene expression by binding to particular mRNA sites and inducing translational inhibition. RNA-seq is a great technique for identifying unannotated ncRNA species. The extensive expression of miRNA-1323 and its specific connection in tumors developing from a cirrhotic background were observed in hepatocellular carcinomas (HCCs) [49], and overexpression of miRNA-1323 in cirrhotic-HCCs was associated with poorer disease-free and overall survival of patients.

**Proteomics**

Proteins are the effectors of DNAs in a biological system, and the expression levels of all proteins in a proteome would undoubtedly offer the most significant phenotypic properties of that system [50]. The purpose of proteomics is to quantify information flow through protein pathways and networks in order to better understand the function of proteins in a cell or organism. variances in a proteome are easier to measure than variances in the genome and transcriptome. The proteome, a crucial component of a phenome, is the end performer of genomic activities; much information in a proteome is observable, including amino acid sequence, splicing, copy number, post-translational modifications (PTMs), variations, spatial conformation, and spatial re-distribution. In the recent decade, numerous proteomics research has focused on protein profiling and protein expression changes that are associated with diverse circumstances. Protein preparation, separation, and identification are common steps in proteomics methods. Protein separation is used to minimize the complexity of a proteome sample, and it mostly involves gel- and liquid chromatography (LC) methods. The gel methods are one-dimensional gel electrophoresis (1DGE), two-dimensional gel electrophoresis (2DGE), and two-dimensional difference in gel electrophoresis (2D-DIGE).

If variants of a specific protein or kind of PTM are to be discovered, the corresponding antibody must be employed in conjunction with those gel methods. The LC methods as proteomic separation techniques are widely employed in the field of modern proteomics, primarily 2DLC and multi-dimensional LC (MDLC), and stable isotope labelling combined with 2DLC can measure the component of a proteome. Furthermore, several LC approaches in conjunction with MS are being developed to identify protein variations and species [51]. MS-based proteomics employs both top-down and bottom-up techniques. Top-down proteomics may detect and quantify unique proteoforms by feeding intact complete proteins directly into MS, which can provide specific properties of each type of proteoform together with more precise and rich biological information [52]. Bottom-up proteomics begins with enzyme digestion of protein components, followed by LC fractionation and MS-identification, which can detect and quantify differentially expressed proteins as well as PTMs [53].

The discovery of novel tumor biomarkers is a prominent topic in cancer research, particularly with high-throughput MS-based proteomics. For example, glycosylated proteins accounted for 50% of the secretory proteome, and aberrant glycosylation has been linked to cancer growth [54]. Because glycosylated proteins account for more than half of all confirmed cancer biomarkers, MS-based glycoproteomics has the potential to identify novel cancer biomarkers by analyzing thousands of glycosylated proteins qualitatively and quantitatively. Thus, glycoproteomics has been widely used in cancer research. A quantitative proteomics investigation of fucosylated glycoproteins in small cell lung cancer (SCLC) patients [55] discovered a significant decrease in PON1 protein expression in SCLC patient sera, but a large increase in PON1 fucosylation. The altered fucosylated glycan patterns and PON1 levels were investigated as possible diagnostic and prognostic indicators for SCLC. Another MS-based glycoproteomics showed significantly higher fucosylated haptoglobin (HP) with three α-2, 6-linked sialic acids in blood of each subtype of lung tumors compared to controls [56]. This unique Hp glycan found in serum may act as a diagnostic glycobiomarker for lung cancer. Personalized cancer treatment necessitates continuous monitoring of all aberrant molecular processes and their interactions. MS-based proteomics and route network analysis technologies have proven critical to expediting tailored treatment.

**Metabolomics**

Metabolism is an essential component of life. Studies have revealed that the physiological condition of cells and tissues is determined by both the cell's regulatory systems and the status of intermediate metabolism [57]. Metabolites are tiny compounds (<1 KDa) produced by metabolism. These metabolic profiles are linked to completely biological processes as beginning, intermediate, or end products, and they provide information on the complicated connections between genes and their environment in a given circumstance [58]. Metabolome-wide association can reveal the etiology caused by the complex interaction of genes, environment, and lifestyles in the general population [59]. Metabolomics entails identifying biochemical and molecular characteristics of the metabolome, characterizing interactions among different metabolites or between metabolites and genetic/environmental factors, and evaluating biochemical mechanisms related to a given condition, such as different pathophysiologic processes [60].

Two of the most common spectroscopic techniques employed in metabolomics are NMR spectroscopy and chromatography combined with MS. NMR provides the identification of structures for unknown metabolites and has the ability to non-constructively analyze materials, eliminating the need to separate and elaborately prepare samples, which can then be analyzed with other platforms [61]. Furthermore, using isotope labelling, NMR provides a window into the dynamic alterations of metabolite synthesis and metabolic pathways, which might be utilized to monitor metabolite disturbance before and after intervention treatment [62]. Chromatographic methods have been used to separate complicated mixtures of metabolites, hence improving analysis and identification. Metabolic profiling has been quantified using both GC and GC-MS approaches, however GC-MS is mostly employed for volatile chemicals [63].

LC-MS has substantially increased the capabilities of MS-based metabolomics since it is more sensitive than 1HNMR and can identify and quantify hundreds of metabolites in a single extract [64]. NMR is less sensitive than MS by up to 100 times, and the apparatus is pricey. LC-MS is highly sensitive; however, samples must be separated and prepared, which may alter metabolite structure and make analysis more challenging. None of them can adequately identify and quantify the vast spectrum of metabolites in cells with appropriate sensitivity and precision. An integrated method combining these methods is required to improve the accuracy and efficiency of metabolite identification and to advance the field of metabolomics. Cancer is engaged in a variety of metabolic processes. Metabolites are the result of gene-environment interactions. Metabolites, unlike genes and proteins, are more closely related to the organism's phenotype.

Metabolomics has been utilized to identify noninvasive diagnostic biomarkers for lung cancer, which has a high incidence and fatality rate. An unbiased LC-MS analysis of the metabolic profiling of urines from 469 lung cancer patients and 536 controls [65] revealed creatine riboside and N-acetylneuraminic acid (NANA) as powerful urinary clinical metabolomic biomarkers for putative diagnosis and prognosis, which was further confirmed in an independent population of 80 patients and 78 controls. Sweat metabolomics has also been utilized to identify non-invasive biomarkers for cancer diagnosis and prognosis. LC-MS analysis of the metabolome of lung cancers relative to normal smokers identified trisaccharide phosphate as an individual metabolite biomarker to discriminate lung cancer from controls with specificity of 80% and sensitivity of 72.7% [66], and a panel of five metabolites (trihexose, tetrahexose, suberic acid, monoglyceride MG (22:2), and nonanedioic acid) significantly improved specificity (80%) and sensitivity (79%). Furthermore, a sputum metabolomics investigation [67] of 34 lung cancer patients and 33 healthy controls discovered that ganglioside GM1 may be a valid biomarker and demonstrated that the sputum metabolomics method may be used to screen the high-risk population of lung cancer. Cancer research has always focused on increasing efficiency and reducing side effects in cancer therapy, which is consistent with the goal of precision medicine, which is to use advanced multi-omics testing to customize a personalized medical treatment based on their specific biomarker profiling. Cancer genomic profiling is now widely utilized to guide cancer precision treatment and has yielded some results. Genomic profiling is a valuable tool for predicting what will happen in tumors, whereas metabolomics can provide information about what has happened and is happening in cancer.

Metabolomics has the ability to measure the sum of all these genotypic, environmental, and physiological effects, making it a very promising method for using metabolomics to predict and assess responses to anticancer treatments in cancer research. Metabolic profiles can also be used to predict the response of individual patients to a class of treatments. With the widespread use of metabolomics technology in cancer research, the term "oncometabolites" has been coined and characterized as endogenous metabolites and their accumulation that initiates or sustains cancer growth and metastasis [68]. Several oncometabolites have been found, including 2-hydroxyglutarate and glucose in gliomas and acute myeloid leukemia [69], fumarate in papillary kidney cancer [70], asparagine in ovarian cancer [71], and lactate in breast cancer [72]. These oncometabolites are leading to the discovery of new pharmacological targets and therapies.

**Radiomics**

CT, PET/CT, and MRI are critical medical imaging modalities for tumor diagnosis and prognosis. In general, medical images are viewed as photographs. Physicians visually interpreted these "pictures" and drew qualitative and preliminary quantitative conclusions about tumors, such as tumor location, internal heterogeneity, overall

and marginal morphology of the lesion, relationship with surrounding tissues, rough diameter measurements, tumor volume, CT and PET/CT values, MRI signal height, and other values. This type of information is critical for tumor diagnosis, but it does not accurately reflect a tumor's morphological and behavioral intricacies, and it provides limited benefits in determining therapy sensitivity and prognosis [73]. Medical imaging analysis and recognition technology has advanced fast, allowing for the extraction and quantitative analysis of all information and spawning a new discipline radiomics. Radiomics, which is based on computer-aided diagnosis and detection systems, is described as the high-throughput extraction and conversion of quantitative features from medical imaging into mineable data and their subsequent analysis within clinical decision support systems [74]. Because medical imaging is commonly utilized in clinical decision-making, radiomics, which extends imaging analysis from qualitative to quantitative and identifies clinical relevance that cannot be seen with the naked eye, may have a clinical impact on cancer research.

Radiomics, like other omics, has the potential to play an analogous role in cancer PPPM. Comprehensive quantitative information on tumor phenotypes can be obtained by analyzing radiomics-based features. Furthermore, novel non-invasive imaging biomarkers for predicting therapy response and outcomes could be developed. PET/CT imaging research in NSCLC found that aberrant texture, as defined by coarseness, contrast, and busyness, is linked with nonresponse to chemoradiotherapy and a worse prognosis [75]. Another study analyzed 635 CT-derived imaging features, including intensity, shape, texture, Laplacian of Gaussian, and wavelet filters, and discovered that 35 and 12 features were associated with distant metastases and survival, respectively [76]. Haralick texture analysis of prostate MRI can detect tumor lesions and differentiate Pca with varying Gleson scores [77]. Another research of T2-weighted MRI-derived textural features found that these features compensated considerably for Gleason score and could discriminate Gleason score 3+4 from 4+3 tumors with good sensitivity to pathological differences [78]. Furthermore, radiomics could be utilized to predict radiotherapy-related adverse effects and guide individualized radiotherapy treatment. Furthermore, radiomics has distinctive properties. In the age of precision medicine, tumor genotyping is a critical foundation for tailored treatment.

Due to tumor heterogeneity, genomic profiling acquired from clinical biopsy is insufficient to reflect the true genetic status of the tumor. Simultaneously, not all cancer patients can have a biopsy, which can result in catastrophic problems. In contrast, practically every cancer patient has radiologic pictures, and radiomics can objectively and precisely offer specific quantitative aspects of intra- and intertumoral heterogeneity in a non-invasive way. Based on the idea that genotypic variation accounts for a fraction of radiomic feature variance, a novel multidisciplinary radiogenomics mining of radiomic data to find correlations with genomic patterns has been developed. Radiogenomics enables a more in-depth understanding of tumor biology, captures inherent tumor heterogeneity, and may give diagnostic and prognostic imaging biomarkers to guide precisely personalized treatment.

## Conclusion

Multi-omics technologies have ushered in a new era in oncology, providing researchers and clinicians with unprecedented insights into the molecular intricacies of cancer. By integrating genomics, transcriptomics, proteomics, metabolomics and radiomics scientists can unravel the mysteries of cancer heterogeneity, enabling personalized diagnosis and treatment strategies. As these technologies continue to advance, the future of oncology holds the promise of more effective, targeted and personalized therapies, bringing hope to millions of cancer patients worldwide.

## References

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.

2. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The next generation. *Cell*, *144*(5), 646–674.

3. Hasin, Y., Seldin, M., & Lusis, A. (2017). Multi-omics approaches to disease. *Genome Biology*, *18*(1). https://doi.org/10.1186/s13059-017-1215-1

4. Cibulskis, K., Lawrence, M. S., Carter, S. L., Sivachenko, A., Jaffe, D., Sougnez, C., Gabriel, S., Meyerson, M., Lander, E. S., & Getz, G. (2013). Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat Biotechnol.*, *31*(3), 213–219.

5. Zhang, H., & Chan, D. W. (2007). Cancer biomarker discovery in plasma using a tissue-targeted proteomic approach. *Cancer Epidemiol Biomark Prev.*, *16*(10), 1915–1917.

6. Tian, Q., Price, N. D., & Hood, L. (2011). Systems cancer medicine: towards realization of predictive, preventive, personalized and participatory (P4) medicine. *J Intern Med.*, *271*(2), 111–121.

7. Grech, G., Zhan, X., Yoo, B. C., Bubnov, R., Hagan, S., Danesi, R., Vittadini, G., & Desiderio, D. M. (2015). EPMA position paper in cancer: current overview and future perspectives. *EPMA J*, *6*(1).

8. Golubnitschaja, O., & Costigliola, V. (2012). General Report & Recommendations in Predictive, Preventive and Personalised Medicine 2012: White Paper of the European Association for Predictive, Preventive and Personalised Medicine. *EPMA J*, *3*(1).

9. Yoo, B. C., & Yeo, S. (2017). Clinical utility of pretreatment prediction of chemoradiotherapy response in rectal cancer: a review. *EPMA J*, *8*(1), 61–67.

10. Bielčiková, Z., Jakabová, A., Pinkas, M., Zemanová, M., Kološtová, K., & Bobek, V. (2017). Circulating tumor cells: what we know, what do we want to know about them and are they ready to be used in clinics?. *Am. J. Transl. Res.*, *9*(6), 2807–2823.

11. Schrump D. S. (2017). Circulating tumor DNA: Solid data from liquid biopsies. *The , J. Thorac. Cardiovasc. Surg., 154*(3), 1132–1133.

12. Han, X., Wang, J., & Sun, Y. (2017). Circulating Tumor DNA as Biomarkers for Cancer Detection. *Genomics, Proteomics Bioinformatics*, *15*(2), 59–72.

13. Shu, Y., Wu, X., Tong, X., Wang, X., Chang, Z., Mao, Y., Chen, X., Sun, J., Wang, Z., Hong, Z., Zhu, L., Zhu, C., Chen, J., Liang, Y., Shao, H., & Shao, Y. W. (2017). Circulating Tumor DNA Mutation Profiling by Targeted Next Generation Sequencing Provides Guidance for Personalized Treatments in Multiple Cancer Types. *Sci Rep*, *7*(1), 583.

14. Ohshima, M., Sugahara, K., Kasahara, K., & Katakura, A. (2017). Metabolomic analysis of the saliva of Japanese patients with oral squamous cell carcinoma. *Oncol Rep.*, *37*(5), 2727–2734.

15. Hagan, S., Martin, E., & Enríquez-de-Salamanca, A. (2016). Tear fluid biomarkers in ocular and systemic disease: potential use for predictive, preventive and personalised medicine. *EPMA J*, *7*(1), 15.

16. Iannone, A., Losurdo, G., Pricci, M., Girardi, B., Massaro, A., Principi, M., Barone, M., Ierardi, E., & Di Leo, A. (2016). Stool Investigations for Colorectal Cancer Screening: From Occult Blood Test to DNA Analysis. *J. Gastrointest. Cancer*, *47*(2), 143–151.

17. Wang, T., Qu, X., Jiang, J., Gao, P., Zhao, D., Lian, X., & Li, X. (2017). Diagnostic significance of urinary long non-coding PCA3 RNA in prostate cancer. *Oncotarget*, *8*(35), 58577–58586.

18. Den, R. B., Yousefi, K., Trabulsi, E. J., Abdollah, F., Choeurng, V., Feng, F. Y., Dicker, A. P., Lallas, C. D., Gomella, L. G., Davicioni, E., & Karnes, R. J. (2015). Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. *J Clin Oncol*, *33*(8), 944–951.

19. Rakha, E. A., Reis-Filho, J. S., Baehner, F., Dabbs, D. J., Decker, T., Eusebi, V., Fox, S. B., Ichihara, S., Jacquemier, J., Lakhani, S. R., Palacios, J., Richardson, A. L., Schnitt, S. J., Schmitt, F. C., Tan, P. H., Tse, G. M., Badve, S., & Ellis, I. O. (2010). Breast cancer prognostic classification in the molecular era: the role of histological grade.
*Breast Cancer Res*, *12*(4), 207.

20. Shiraishi, H., Fujiwara, Y., Kakuya, T., Tsuta, K., Motoi, N., Miura, N., Watabe, Y., Watanabe, S. I., Noro, R., Nagashima, K., Huang, W., Yamada, T., Asamura, H., Ohe, Y., & Honda, K. (2017). Actinin-4 protein overexpression as a predictive biomarker in adjuvant chemotherapy for resected lung adenocarcinoma. *Biomarkers Med*, *11*(9), 721–731.

21. Kuroda, D., Sawayama, H., Kurashige, J., Iwatsuki, M., Eto, T., Tokunaga, R., Kitano, Y., Yamamura, K., Ouchi, M., Nakamura, K., Baba, Y., Sakamoto, Y., Yamashita, Y., Yoshida, N., Chikamoto, A., & Baba, H. (2018). Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. *Gastric cancer*, *21*(2), 204–212.

22. Maleva, I., Madjunkova, S., Bozhinovski, G., Smickova, E., Kondov, G., Spiroski, Z., Arsovski, A., & Plaseska-Karanfilska, D. (2012). Genetic variation of the brca1 and brca2 genes in macedonian patients. *Balkan J Med Genet*, *15*(Suppl), 81–85.

23. Germini, D., Gehrke, F., Lira, D., Alves, B., Azzalis, L., Perez, M., Fonseca, F., & Waisberg, J. (2016). HMSH2 and HMSH6 gene expression profiles in colorectal adenocarcinoma in patients up to 50 years of age. *Biomed Pharmacother.*, *83*, 602–606.

24. Tomlinson, B., & Lazarus, H. M. (2017). Enhancing acute myeloid leukemia therapy - monitoring response using residual disease testing as a guide to therapeutic decision-making. *Expert. Rev. Hematol.*, *10*(6), 563–574.

25. Calkins, G. N. (1914). Zur Frage der Entstehung maligner Tumoren . By Th. Boveri. Jena, Gustav Fischer. 1914. 64 pages. *Science*, *40*(1041), 857–859.

26. Rowley, J. D. (1973). A New Consistent Chromosomal Abnormality in Chronic Myelogenous Leukaemia identified by Quinacrine Fluorescence and Giemsa Staining. *Nature*, *243*(5405), 290–293.

27. Reddy, E. P., Reynolds, R. K., Santos, E., & Barbacid, M. (1982). A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. *Nature*, 300(5888), 149–152.

28. Meyerson, M., Gabriel, S., & Getz, G. (2010). Advances in understanding cancer genomes through second-generation sequencing. *Nat Rev Genet. 11*(10), 685–696.

29. Collins, F. S., & Barker, A. D. (2007). Mapping the cancer genome. Pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies. Sci Am., 296(3), 50–57.

30. Shendure, J., Ji, H. (2008). Next-generation DNA sequencing. *Nat Biotechnol* 26, 1135–1145.

31. Morozova, O., & Marra, M. A. (2008). Applications of next-generation sequencing technologies in functional genomics. *Genomics*, *92*(5), 255–264.

32. Mitelman, F., Johansson, B., & Mertens, F. (2007). The impact of translocations and gene fusions on cancer causation. *Nat Rev Cancer.*, *7*(4), 233–245.

33. Tomlins, S. A., Rhodes, D. R., Perner, S., Dhanasekaran, S. M., Mehra, R., Sun, X. W., Varambally, S., Cao, X., Tchinda, J., Kuefer, R., Lee, C., Montie, J. E., Shah, R. B., Pienta, K. J., Rubin, M. A., & Chinnaiyan, A. M. (2005). Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science (New York, N.Y.)*, *310*(5748), 644–648.

34. Soda, M., Choi, Y. L., Enomoto, M., Takada, S., Yamashita, Y., Ishikawa, S., Fujiwara, S., Watanabe, H., Kurashina, K., Hatanaka, H., Bando, M., Ohno, S., Ishikawa, Y., Aburatani, H., Niki, T., Sohara, Y., Sugiyama, Y., & Mano, H. (2007). Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*, *448*(7153), 561–566.

35. Tognon, C., Knezevich, S. R., Huntsman, D., Roskelley, C. D., Melnyk, N., Mathers, J. A., Becker, L., Carneiro, F., MacPherson, N., Horsman, D., Poremba, C., & Sorensen, P. H. (2002). Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer cell*, *2*(5), 367–376.

36. Palanisamy, N., Ateeq, B., Kalyana-Sundaram, S., Pflueger, D., Ramnarayanan, K., Shankar, S., Han, B., Cao, Q., Cao, X., Suleman, K., Kumar-Sinha, C., Dhanasekaran, S. M., Chen, Y. B., Esgueva, R., Banerjee, S., LaFargue, C. J., Siddiqui, J., Demichelis, F., Moeller, P., Bismar, T. A., … Chinnaiyan, A. M. (2010). Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat Med.*, *16*(7), 793–798.

37. Ross, J. S., Wang, K., Chmielecki, J., Gay, L., Johnson, A., Chudnovsky, J., Yelensky, R., Lipson, D., Ali, S. M., Elvin, J. A., Vergilio, J. A., Roels, S., Miller, V. A., Nakamura, B. N., Gray, A., Wong, M. K., & Stephens, P. J. (2016). The distribution of BRAF gene fusions in solid tumors and response to targeted therapy. *Int J Cancer., 138*(4), 881–890.

38. Kumar-Sinha, C., Kalyana-Sundaram, S., & Chinnaiyan, A. M. (2015). Landscape of gene fusions in epithelial cancers: seq and ye shall find. *Genome Med.*, *7*, 129.

39. Tognon, C., Garnett, M., Kenward, E., Kay, R., Morrison, K., & Sorensen, P. H. (2001). The chimeric protein tyrosine kinase ETV6-NTRK3 requires both Ras-Erk1/2 and PI3-kinase-Akt signaling for fibroblast transformation. *Cancer Res*, *61*(24), 8909–8916.

40. Capelletti, M., Dodge, M. E., Ercan, D., Hammerman, P. S., Park, S. I., Kim, J., Sasaki, H., Jablons, D. M., Lipson, D., Young, L., Stephens, P. J., Miller, V. A., Lindeman, N. I., Munir, K. J., Richards, W. G., & Jänne, P. A. (2014). Identification of recurrent FGFR3-TACC3 fusion oncogenes from lung adenocarcinoma. *Clin Cancer Res.*, *20*(24), 6551–6558.

41. Yazaki, J., Gregory, B. D., & Ecker, J. R. (2007). Mapping the genome landscape using tiling array technology. *Curr Opin Plant Biol*, *10*(5), 534–542.

42. Nilsen, T. W., & Graveley, B. R. (2010). Expansion of the eukaryotic proteome by alternative splicing. *Nature*, *463*(7280), 457–463.

43. Liu, S., & Cheng, C. (2013). Alternative RNA splicing and cancer. *Wiley Interdiscip Rev RNA*, *4*(5), 547–566.

44. Venables J. P. (2004). Aberrant and alternative splicing in cancer. *Cancer Res.*, *64*(21), 7647–7654.

45. Frasca, F., Pandini, G., Scalia, P., Sciacca, L., Mineo, R., Costantino, A., Goldfine, I. D., Belfiore, A., & Vigneri, R. (1999). Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. *Mol Cell Biol.*, *19*(5), 3278–3288.

46. Jiang, L., Zhu, W., Streicher, K., Morehouse, C., Brohawn, P., Ge, X., Dong, Z., Yin, X., Zhu, G., Gu, Y., Ranade, K., Higgs, B. W., Yao, Y., & Huang, J. (2014). Increased IR-A/IR-B ratio in non-small cell lung cancers associates with lower epithelial-mesenchymal transition signature and longer survival in squamous cell lung carcinoma. *BMC cancer*, *14*, 131.

47. Shapiro, I. M., Cheng, A. W., Flytzanis, N. C., Balsamo, M., Condeelis, J. S., Oktay, M. H., Burge, C. B., & Gertler, F. B. (2011). An EMT-driven alternative splicing program occurs in human breast cancer and modulates cellular phenotype. PLoS Genet, 7(8), e1002218.

48. Kloosterman, W. P., Coebergh van den Braak, R. R. J., Pieterse, M., van Roosmalen, M. J., Sieuwerts, A. M., Stangl, C., Brunekreef, R., Lalmahomed, Z. S., Ooft, S., van Galen, A., Smid, M., Lefebvre, A., Zwartkruis, F., Martens, J. W. M., Foekens, J. A., Biermann, K., Koudijs, M. J., Ijzermans, J. N. M., & Voest, E. E. (2017). A Systematic Analysis of Oncogenic Gene Fusions in Primary Colon Cancer. *Cancer Res.*, *77*(14), 3814–3822.

49. McPherson, A., Hormozdiari, F., Zayed, A., Giuliany, R., Ha, G., Sun, M. G., Griffith, M., Heravi Moussavi, A., Senz, J., Melnyk, N., Pacheco, M., Marra, M. A., Hirst, M., Nielsen, T. O., Sahinalp, S. C., Huntsman, D., & Shah, S. P. (2011). deFuse: an algorithm for gene fusion discovery in tumor RNA-Seq data. *PLoS computational biology*, *7*(5), e1001138.

50. Law, P. T., Qin, H., Ching, A. K., Lai, K. P., Co, N. N., He, M., Lung, R. W., Chan, A. W., Chan, T. F., & Wong, N. (2013). Deep sequencing of small RNA transcriptome reveals novel non-coding RNAs in hepatocellular carcinoma. *J Hepatol.*, *58*(6), 1165–1173.

51. Cox, J., & Mann, M. (2007). Is proteomics the new genomics?. *Cell*, *130*(3), 395–398.

52. Tran, J. C., & Doucette, A. A. (2009). Multiplexed size separation of intact proteins in solution phase for mass spectrometry. *Anal Chem.*, *81*(15), 6201–6209.

53. Durbin, K. R., Fornelli, L., Fellers, R. T., Doubleday, P. F., Narita, M., & Kelleher, N. L. (2016). Quantitation and Identification of Thousands of Human Proteoforms below 30 kDa. *J Proteome Res.*, *15*(3), 976–982.

54. Aebersold, R., & Mann, M. (2003). Mass spectrometry-based proteomics. *Nature*, *422*(6928), 198–207.

55. Hägglund, P., Bunkenborg, J., Elortza, F., Jensen, O. N., & Roepstorff, P. (2004). A new strategy for identification of N-glycosylated proteins and unambiguous assignment of their glycosylation sites using HILIC enrichment and partial deglycosylation. *J Proteome Res.*, *3*(3), 556–566.

56. Ahn, J. M., Sung, H. J., Yoon, Y. H., Kim, B. G., Yang, W. S., Lee, C., Park, H. M., Kim, B. J., Kim, B. G., Lee, S. Y., An, H. J., & Cho, J. Y. (2014). Integrated glycoproteomics demonstrates fucosylated serum paraoxonase 1 alterations in small cell lung cancer. *Mol Cell Proteomics*, 13(1), 30–48.

57. Tsai, H. Y., Boonyapranai, K., Sriyam, S., Yu, C. J., Wu, S. W., Khoo, K. H., Phutrakul, S., & Chen, S. T. (2011). Glycoproteomics analysis to identify a glycoform on haptoglobin associated with lung cancer. *Proteomics*, *11*(11), 2162–2170.

58. McKnight S. L. (2010). On getting there from here. *Science.*, *330*(6009), 1338–1339.

59. Mirsaeidi, M., Banoei, M. M., Winston, B. W., & Schraufnagel, D. E. (2015). Metabolomics: Applications and Promise in Mycobacterial Disease. *Ann Am Thorac Soc.*, *12*(9), 1278–1287.

60. Holmes, E., Loo, R. L., Stamler, J., Bictash, M., Yap, I. K., Chan, Q., Ebbels, T., De Iorio, M., Brown, I. J., Veselkov, K. A., Daviglus, M. L., Kesteloot, H., Ueshima, H., Zhao, L., Nicholson, J. K., & Elliott, P. (2008). Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature*, *453*(7193), 396–400.

61. Tebani, A., Abily-Donval, L., Afonso, C., Marret, S., & Bekri, S. (2016). Clinical Metabolomics: The New Metabolic Window for Inborn Errors of Metabolism Investigations in the Post-Genomic Era. *Int J Mol Sci.*, *17*(7), 1167.

62. Giskeødegård, G. F., Cao, M. D., & Bathen, T. F. (2015). High-resolution magic-angle-spinning NMR spectroscopy of intact tissue. *Methods Mol Biol.*, *1277*, 37–50.

63. Barding, G. A., Jr, Salditos, R., & Larive, C. K. (2012). Quantitative NMR for bioanalysis and metabolomics. *Anal Bioanal Chem.*, *404*(4), 1165–1179.

64. Pan, Z., & Raftery, D. (2007). Comparing and combining NMR spectroscopy and mass spectrometry in metabolomics. *Anal Bioanal Chem.*, *387*(2), 525–527.

65. Fernie, A. R., Trethewey, R. N., Krotzky, A. J., & Willmitzer, L. (2004). Metabolite profiling: from diagnostics to systems biology. *Nat Rev Mol Cell Biol.*, *5*(9), 763–769.

66. Mathé, E. A., Patterson, A. D., Haznadar, M., Manna, S. K., Krausz, K. W., Bowman, E. D., Shields, P. G., Idle, J. R., Smith, P. B., Anami, K., Kazandjian, D. G., Hatzakis, E., Gonzalez, F. J., & Harris, C. C. (2014). Noninvasive urinary metabolomic profiling identifies diagnostic and prognostic markers in lung cancer. *Cancer Res.*, *74*(12), 3259–3270.

67. Calderón-Santiago, M., Priego-Capote, F., Turck, N., Robin, X., Jurado-Gámez, B., Sanchez, J. C., & Luque de Castro, M. D. (2015). Human sweat metabolomics for lung cancer screening. . *Anal Bioanal Chem.*, *407*(18), 5381–5392.

68. Cameron, S. J., Lewis, K. E., Beckmann, M., Allison, G. G., Ghosal, R., Lewis, P. D., & Mur, L. A. (2016). The metabolomic detection of lung cancer biomarkers in sputum. *Lung Cancer 94*, 88–95.

69. Wishart D. S. (2016). Emerging applications of metabolomics in drug discovery and precision medicine. *Nat Rev Drug Discov.*, *15*(7), 473–484.

70. Abbas, S., Lugthart, S., Kavelaars, F. G., Schelen, A., Koenders, J. E., Zeilemaker, A., van Putten, W. J., Rijneveld, A. W., Löwenberg, B., & Valk, P. J. (2010). Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. *Blood*, *116*(12), 2122–2126.

71. Tomlinson, I. P., Alam, N. A., Rowan, A. J., Barclay, E., Jaeger, E. E., Kelsell, D., Leigh, I., Gorman, P., Lamlum, H., Rahman, S., Roylance, R. R., Olpin, S., Bevan, S., Barker, K., Hearle, N., Houlston, R. S., Kiuru, M., Lehtonen, R., Karhu, A., Vilkki, S., … Multiple Leiomyoma Consortium (2002). Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet.*, *30*(4), 406–410.

72. Lorenzi, P. L., Reinhold, W. C., Rudelius, M., Gunsior, M., Shankavaram, U., Bussey, K. J., Scherf, U., Eichler, G. S., Martin, S. E., Chin, K., Gray, J. W., Kohn, E. C., Horak, I. D., Von Hoff, D. D., Raffeld, M., Goldsmith, P. K., Caplen, N. J., & Weinstein, J. N. (2006). Asparagine synthetase as a causal, predictive biomarker for L-asparaginase activity in ovarian cancer cells. *Mol Cancer Ther*, *5*(11), 2613–2623.

73. Hirschhaeuser, F., Sattler, U. G., & Mueller-Klieser, W. (2011). Lactate: a metabolic key player in cancer. *Cancer Res*, *71*(22), 6921–6925.

74. Kumar, V., Gu, Y., Basu, S., Berglund, A., Eschrich, S. A., Schabath, M. B., Forster, K., Aerts, H. J., Dekker, A., Fenstermacher, D., Goldgof, D. B., Hall, L. O., Lambin, P., Balagurunathan, Y., Gatenby, R. A., & Gillies, R. J. (2012). Radiomics: the process and the challenges. *Magn Reson Imaging.*, *30*(9), 1234–1248

75. Lambin, P., Leijenaar, R. T. H., Deist, T. M., Peerlings, J., de Jong, E. E. C., van Timmeren, J., Sanduleanu, S., Larue, R. T. H. M., Even, A. J. G., Jochems, A., van Wijk, Y., Woodruff, H., van Soest, J., Lustberg, T., Roelofs, E., van Elmpt, W., Dekker, A., Mottaghy, F. M., Wildberger, J. E., & Walsh, S. (2017). Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol.*, *14*(12), 749–762.

76. Cook, G. J., Yip, C., Siddique, M., Goh, V., Chicklore, S., Roy, A., Marsden, P., Ahmad, S., & Landau, D. (2013). Are pretreatment 18F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy?. *J Nucl Med*, *54*(1), 19–26.

77. Coroller, T. P., Grossmann, P., Hou, Y., Rios Velazquez, E., Leijenaar, R. T., Hermann, G., Lambin, P., Haibe-Kains, B., Mak, R. H., & Aerts, H. J. (2015). CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol.*, *114*(3), 345–350.

78. Wibmer, A., Hricak, H., Gondo, T., Matsumoto, K., Veeraraghavan, H., Fehr, D., Zheng, J., Goldman, D., Moskowitz, C., Fine, S. W., Reuter, V. E., Eastham, J., Sala, E., & Vargas, H. A. (2015). Haralick texture analysis of prostate MRI: utility for differentiating non-cancerous prostate from prostate cancer and differentiating prostate cancers with different Gleason scores. *Eur Radiol.*, *25*(10), 2840–2850.