Precision Oncology: Targeting Genomic Alterations and Cancer Signaling with Integrative Multi-Omics, Deep Learning and Network Biology in Medical Oncology

Manish Kumar[1]

[1]Affiliation not available

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Abstract

Cancer is a complex genetic disease involving uncontrolled cell growth and proliferation, and necessitates effective targeting of dysregulated cellular pathways underlying cancer progression. Multiple genetic and epigenetic alterations characterize tumor progression and define hallmarks of cancer. It may result in dysregulation of growth factors, regulatory proteins, cell adhesion molecules, and molecules of immune system driven by alterations in the expression profile of tumor suppressor genes and oncogenes that may vary among different cancer types. Importantly, patients with the same cancer type respond differently to available cancer treatments, likely due to tumor-specific DNA, RNA, and proteins, indicating the need for patient-specific treatment options. Precision oncology has evolved as a form of cancer therapy that is focused on genetic and molecular profiling of tumors to identify specific molecular alterations involved in carcinogenesis for tailored individualized cancer treatment. Advances in high-throughput technologies, that include next-generation sequencing, have enabled gene expression profiling, providing detailed molecular characterization of various tumors. Moreover, the application of multiomic technologies, including genomics, proteomics, metabolomics, and single-cell multiomics, constitutes a novel approach for the identification and quantification of a comprehensive set of biological molecules to study how they translate into cellular functions and tissue pathologies. Integration and analysis of various multiomic sequencing data are crucial in this regard, as they can reveal critical molecular changes, such as cancer-driving mutations, post-translational modifications, gene fusions, amplifications, and alterations in signaling networks within tumors. Furthermore, the role of computational techniques such as artificial intelligence and deep learning, in analyzing complex data and identifying patterns of disease development for better outcomes is now well established in precision medicine. Additionally, AI-powered multi-omics and network biology have been harnessed to integrate and analyze biological data through networks, which may prove crucial in solving key problems facing precision oncology. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of cutting-edge developments in tools and techniques associated with it, and try to assess its scope and importance in achieving the intended goals over time.

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Manish Kumar
School of Bio Sciences & Technology
Vellore Institute of Technology, Vellore, Tamil Nadu, India

Email: kmanish125@yahoo.com, kmanish.bt125@gmail.com
ORCID: https://orcid.org/0000-0002-6021-7063

CORRESPONDENCE
1.
C/O. Sri M. Narayan Swami
7/1A,1st Street, Bhavani Nagar
Katpadi P.O. Dharapadavedu,
Vellore- 632007, Tamil Nadu, India

2.
S/O. Nityanand Prasad
ME-010-0017, Dhruvneeti Colony
Near Samarpan Hospital, Rajneeti Road
Madhopur, P.0. Basudeopur
Munger- 811202, Bihar, India

Abstract: Cancer is a complex genetic disease involving uncontrolled cell growth and proliferation, and necessitates effective targeting of dysregulated cellular pathways underlying cancer progression. Multiple genetic and epigenetic alterations characterize tumor progression and define hallmarks of cancer. It may result in dysregulation of growth factors, regulatory proteins, cell adhesion molecules, and molecules of immune system driven by alterations in the expression profile of tumor suppressor genes and oncogenes that may vary among different cancer types. Importantly, patients with the same cancer type respond differently to available cancer treatments, likely due to tumor-specific DNA, RNA, and proteins, indicating the need for patient-specific treatment options. Precision oncology has evolved as a form of cancer therapy that is focused on genetic and molecular profiling of tumors to identify specific molecular alterations involved in carcinogenesis for tailored individualized cancer treatment. Advances in high-throughput technologies, that include next-generation sequencing, have enabled gene expression profiling, providing detailed molecular characterization of various tumors. Moreover, the application of multiomic technologies, including genomics, proteomics, metabolomics, and single-cell multiomics, constitutes a novel approach for the identification and quantification of a comprehensive set of biological molecules to study how they translate into cellular functions and tissue pathologies. Integration and analysis of various multiomic sequencing data are crucial in this regard, as they can reveal critical molecular changes, such as cancer-driving mutations, post-translational modifications, gene fusions, amplifications, and alterations in signaling networks within tumors. Furthermore, the role of computational techniques such as artificial intelligence and deep learning, in analyzing complex data and identifying patterns of disease development for better outcomes is now well established in precision medicine. Additionally, AI-powered multi-omics and network biology have been harnessed to integrate and analyze biological data through networks, which may prove crucial in solving key problems facing precision oncology. This article aims to briefly explain the foundations and frontiers of precision oncology in the context of cutting-edge developments in tools and techniques associated with it, and try to assess its scope and importance in achieving the intended goals over time.

Keywords: Cancer Genomics; Multiomics; Deep Learning; Network Biology; Single Cell Sequencing; Targeted Therapy; Immunotherapy; Cancer Stem Cells

GRAPHICAL ABSTRACT

Is it cancer, what is the cancer type?

What is the condition and stage of this cancer?

What is the survival rate for this type of cancer?

What are the factors likely to be involved in the disease progression?

Which driver mutations visibly reprogram the signaling pathways of the tumor cells?

What is the level of tissue heterogeneity and how does it relate to the mutations involved?

What are the likely treatment options? What should clearly work for this cancer?

What can be the appropriate drug combination and dose the patient must receive to recover?

How would the cancer respond to this treatment in terms of effectiveness, toxicity and relapse?

Is the patient at higher risk and how well the precision medication will work?

1. Introduction

Cancer is a deadly disease that causes one in six deaths worldwide and has significant physical, psychological, and economic repercussions for those affected. It remains the second leading cause of hospital death after heart disease, and most of these deaths could be prevented through early diagnosis and improved prevention and treatment strategies. Therefore, there is a clear need to develop effective cancer diagnostic techniques,

efficacious treatments, and a better understanding of the socioeconomic factors that influence cancer incidence, prevalence, and mortality worldwide [1,2].

Tumor is an abnormal mass of tissue that appears due to unregulated growth in the division of cells, which successfully prevents senescence. A tumor is benign until it is limited to its original position and becomes malignant or cancerous when it is capable of growing and metastasizing to other parts of the body. Rigorous research in the past few decades, supported by advances in cell and molecular biology, has led scientists to clearly understand that genetic changes associated with cancer incidence cause the disease to grow and spread to other parts of the body. Cancer is initiated as a result of uncontrolled cell division and proliferation, leading to tumor formation, which results in metastasis involving the dissemination of cancer cells from the original or primary tumor through the circulation of blood or lymph, and invasion to other normal tissues and organs to form secondary tumors at distant locations in the body, which is actually responsible for about 90% of cancer-related deaths reported globally. Cell proliferation requires a balanced rate of cell growth and division to maintain an increase in cell numbers for growth and development, maintenance of tissue homoeostasis and wound healing. The fundamental abnormality leading to cancer development is unwanted cell proliferation due to an absence of balance between cell division and cell loss through cell death and differentiation. Cell division relies on cell cycle regulation, which generally involves extracellular growth-regulatory signals as well as internal signaling proteins that monitor the genetic integrity of the cell to ascertain that cellular development progresses well in time. It depends on progression through distinct phases of the cell cycle and is regulated by several cyclin-dependent kinases (CDKs) that act in association with their cyclin partners. Alterations in the overall expression pattern of cyclins cause the cellular process to go awry and proliferate rapidly, resulting in tumor formation. Most of the related events accompanying tumor formation and cancer progression, such as cell differentiation, apoptosis, angiogenesis, invasion and metastasis, are guided similarly by alterations in the expression patterns of regulatory portions owing to changes (mutations) in the genes of interest, and the factors that cause these changes often tend to provoke cancer development [3,4]. Genetic mutations can be inherited or acquired mutations that appear later in life. Acquired mutations are of somatic origin, are much more common and cause most cancers. As the somatic mutation theory (SMT) is evidence-based, and it has become the dominant theory in cancer research.

In fact, cancer is a multistep process involving the initiation and progression of random mutations in certain key genes, such as oncogenes or tumor suppressor genes, which lead to the manifestation of cancer. Every single gene in the body is most likely to have undergone deleterious changes or mutations in its DNA sequence on a number of occasions in the cell’s lifetime, while the repair mechanism in place would restrict noticeable changes. In this way, the generation of cancer must be conclusively linked to sustained gene mutations caused by either external agents called mutagens, which often lead to the appearance of different somatic variants, or certain critical changes that might have been inherited in the body. Importantly, a single mutation will not be enough to transform a normal

cell into a cancer cell, as it would require a number of changes to accumulate in the cells in due course for cancer development to occur. For example, mutations in the most pronounced cancer-causing genes, such as *RAS* (derived from rat sarcomavirus) or *MYC* (derived from myelocytoma, a cancer of the myelocytes), may not lead to unchecked proliferation until changes in repressor genes, such as *RB* and *TP53* that encode components of protective mechanisms have not occurred simultaneously. Thus, multiple genetic changes are typically required for the development of cancer, so it must be seen as an evolutionary process involving both genetic changes and selection [5]. Multiple rate-limiting steps can work against the development of cancer, with persistent changes accelerating the process. Thus, most cancers are thought to be derived from a single abnormal cell or a small group of cells with a few deleterious gene mutations followed by the accumulation of additional changes in some of their descendants, allowing them to outgrow others in number and resulting in tumorous growth in the body. Moreover, cancer can also be driven by epigenetic changes that alter the gene expression pattern of cells without accompanying alterations in the DNA sequence of the cell [6]. Some physical modifications in the chromatin structure that are capable of influencing the pattern of gene expression are often led by DNA methylation, histone modifications, and miRNA-based alterations inside the cell. Epigenetic regulation of DNA and RNA usually controls how genes are turned on or off and thus plays important roles in maintaining normal cell behavior, whose deregulation causes alterations in gene expression patterns to potentially influence tumorigenesis. These changes are frequently accompanied by sustained exposure of the affected cells to several stressful external stimuli presented by certain environmental factors and/or lifestyle-related changes that may involve nutrition, toxicants, alcohol, etc. Although epigenetic changes do not alter the sequence of DNA, the process might cause point mutations and disable DNA repair mechanisms frequently involved in cancer development. Traditionally, epigenetic and genetic changes have been seen as two separate mechanisms that independently participate in carcinogenesis, which may not be the only possible mechanism involved in cancer development. Recent studies from whole-exome sequencing (WES), the technique for sequencing all of the protein-coding regions of genes in a genome, for thousands of human cancers have revealed the presence of many inactivating mutations in genes that can potentially disrupt DNA methylation patterns, histone modifications, and nucleosome positioning and hence control the epigenome to contribute to cancer progression. Thus, both the genome and epigenome can regulate the progression of cancer through associated mutations. Therefore, interference between the two is highly anticipated and can be exploited to provide new possibilities for cancer treatment [7].

Further, the tumor microenvironment (TME) is an integral part of tumors and plays a central role at all stages of cancer progression. Importantly, the activation and remodeling of stromal cells at the origin of cancer development precedes the formation of metastases. Each organ has a unique microenvironment where resident stromal cells are considered essential for tissue integrity and repair. Stromal cells refer to connective tissue cells that are heterogeneous in nature and surround parenchymal cells, which typically define the primary

function of an organ. Stromal cells mainly consist of fibroblasts, macrophages, self-renewing and multipotent mesenchymal stromal cells also known as mesenchymal stem cells (MSCs), immune cells, endothelial cells, and components of basement membrane. These cells are thought to be sentinels of tissue integrity as many of the cells in the stroma possess tumor-suppressing capabilities, but their transition to being dysfunctional modulator of angiogenesis and metastasis is common to cancer progression [8]. The tumor stroma may secrete growth factors, cytokines, and extracellular matrix proteins and many other regulatory proteins that are thought to promote cell growth, survival, and migration to promote metastatic spread of cancer cells. Therefore, better understanding of the complexity of interactions of stromal cells with cancer cells and other components of the TME seems necessary to design effective therapeutic options to prevent metastatic development and diseases relapse. Many oncogenes and tumor suppressor genes may exhibit mutations and epigenetic modifications closely linked to the critical regulation of the tumor microenvironment and may lead to the manifestation of cancer [9].

Cancer ultimately remains a selective multistep process triggered by mutations leading to the activation of specific oncogenic pathways with the concurrent inactivation of tumor suppressor genes that act as sentinels to control unwanted cell growth and proliferation. Scientists have been trying to analyze the totality of cancer-causing gene mutations, which are regarded as the “mutational landscape” of different types of cancer, and to target them effectively for cancer cure. As a matter of fact, most of these biochemical processes are conserved in model organisms, such as the free-living transparent nematode Caenorhabditis elegans and the fruit fly Drosophila melanogaster, along with other large animal models, and are widely used for ease of genetic manipulation to study the complex biology of cancer. Somatic cell mutations, called somatic structural variants (SVs), have been shown to account for more than half of all cancer-causing mutations. These variants or mutations differ from the hereditary or germline variants that have passed from parents to offspring and become incorporated into the DNA of every cell in the body. For example, Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary disease caused by mutations in the TP53 tumor suppressor gene located on chromosome 17p13, that predisposes carriers to a risk of up to 90% of developing cancer [10]. On the contrary, the SVs can be observed in transformed cells and in their daughter cells, which may continue to grow because of errors in DNA copying and their repair mechanisms during cell division, thereby altering the genomic structure, which becomes more numerous with time. Although somatic SVs play crucial roles in cancer development, relatively little is known about their mode of action in cancer development. Methods to detect and identify the functional effects of these SVs are sure to enable researchers to understand the molecular consequences of individual somatic mutations in cancer. The findings related to mutation-specific molecular alterations could be used to develop therapies that target mutated cells, opening great possibilities in cancer therapy [11].

The most important aspect of cancer biology is that all cellular behaviors turn out to be a manifestation of underlying cellular physiology and biochemistry that are ultimately guided

by the enzymes whose timely availability is controlled by genes. Enzymes catalyze specific reactions within compartments of the cell to maintain a balanced state of being. Cancer-based genomic studies highlight the many ways in which enzyme activities can be altered to contribute to cancer development due to certain genetic changes. Importantly, kinetic parameters associated with enzymatic activities are tangibly altered to influence cancer initiation and progression. Therefore, enzyme-based studies of cancer cells can provide critical insight into the molecular and biochemical mechanisms of cancer progression and help determine the effectiveness of anticancer agents. mechanisms of treatment resistance and disease relapse [12]. Additionally, changes in the tumor microenvironment (TME) can also affect enzyme activity and exaggerate cancer development. Enzymes specifically linked to the regulation of key cellular behaviors such as cell proliferation, death and differentiation may have a direct influence on cancer development, but some enzymes required for many other activities may also be involved in the incidences of cancer due to their crucial role in maintaining tissue homeostasis. For example, monoamine oxidase A (MAOA) is a mitochondrial enzyme found in animal tissues to catalyze the breakdown of biogenic monoamines, and is commonly known for the regulation of neurotransmitters such as dopamine, adrenaline, and serotonin. As cells of the nervous system and immune system have many common surface receptors, secretory molecules, they may share many common cellular pathways crucial to health and disease. Evidence suggests that MAOA is involved in other diseases, including cancer, cardiovascular disease, and diabetes, in addition to its role in neurobiology. MAOA can inhibit the activities of different types of tumor-associated immune cells, such as T cells and macrophages, and has been implicated in the regulation of anti-tumor immune responses. MAOA inhibitors are being studied for their potential in combination therapy to improve the effectiveness of cancer immunotherapy. [13].

Moreover, epidemiological studies have consistently shown that environmental factors or lifestyle changes involving mutagenic agents are the primary culprits. Thus, it is necessary not only to associate genetic mutations with different cancers but also to work on the mechanism of action of mutagens by focusing on enzymes that invariably mediate oncogenic transformations. For example, overexpression of the enzyme ribonucleotide reductase (RnR), which catalyzes the formation of deoxyribonucleotides from ribonucleotides necessary for cell division, is implicated in many forms of cancer, and the genes encoding the components of the enzyme are often mutated, leading to hyperactivity of the enzyme. However, there are instances indicating that cytoplasmic material rather than the karyoplast is mainly responsible for cellular transformation, which might be better explained as a consequence of certain external influences, including epigenetic modulations, than purely genetic changes [14]. RnR active site inhibitors have been developed to biophysically deactivate the enzymes, when necessary, with positive outcomes.

Furthermore, most of the human genome consists of noncoding regions, and studies on variations in the noncoding regions of cancer cells reveal additional mechanisms underlying cancer progression. For example, changes in noncoding regions such as point

mutations and complex genomic rearrangements can disrupt or create transcription factor-binding sites or even affect noncoding RNA loci, leaving options for unwanted changes in the gene expression pattern of the cell. Cancer whole-genome sequencing (WGS) remains the most comprehensive method for identifying variants in noncoding regions, as targeted approaches such as WES may miss certain variants residing outside coding regions. Pieces of evidence suggest that oncogenesis typically involves interplay between germline and somatic variants, and different modes of action of noncoding variants could further potentiate these developments. Thus, a systematic approach to unravel the roles of the noncoding genome in cancer progression should help improve cancer diagnosis and therapy [15].

2. Cancer Genomics and the Emergence of Precision Oncology

Changes in vulnerable genes involved in cell growth, proliferation, death, or differentiation appear to be essential for all changes in cell behavior and remain the most fundamental feature of all cancers; thus, cancer must be considered a genetic disease to be treated accordingly for better outcomes. Over the years, technological advances in the field of molecular biology have been exploited to unravel genomic changes to fully understand the pathogenesis of human cancer. The range of cancer-causing mutations is known to be very large, and the mutational landscape differs from one another depending on the type of cancer; even people suffering from the same cancer type are found to have considerably different mutation patterns. Moreover, it has long been known that every patient responds differently to particular treatments despite having the same type and stage of cancer. These observations have been compelling and led researchers to adopt a precision medicine approach to cancer therapy, necessitating the study of the genetic features of vulnerable individuals for a patient-specific treatment regimen towards the most effective treatment of cancer. Since the nineteenth century, biometricians have been interested in decoding the relationship between genetics and diseases and attempting to understand the roles of "constitutional" and "environmental factors" in the distribution of diseases. Werner Kalow's 1962 textbook 'Pharmacogenetics' published on the issue of heredity and the response to drugs, emphasizing the importance of relating the response of therapeutic drugs to their biochemistry and the role of genetics and evolution in shaping individual-level differences. Advances in genetic engineering and the consequent understanding of clinically relevant genetic variations over the years have revolutionized how a range of diseases can be diagnosed and treated in the clinic, exploiting the genetic peculiarities of individuals, and the idea needs to be adequately applied to cancer research for better outcomes [16]. Accordingly, in recent decades, precision oncology has emerged as a field of cancer research that takes into account the genetic specificities of individuals for efficient cancer treatment. The term precision oncology has been coined for specific clinical oncology practices that rely upon genomic profiling of individual tumors for complete molecular characterization of transformed cells and tissues to identify and target specific molecular

alterations for efficient cancer therapy [17,18]. Thus, precision oncology aims to achieve perfectly planned cancer therapy by designing a custom-tailored treatment regimen for vulnerable individuals by identifying their unique needs for the best possible results. Importantly, the effectiveness of precision oncology has been tested through progressive clinical trials on different tumor types, and recent precision oncology trials supported by National Cancer Institute (NCI) and others agencies, such as the NCI- MATCH, also known as MATCH (Molecular Analysis for Therapy Choice), the NCI- MPACT (Molecular Profiling-based Assignment of Cancer Therapy), the ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial), the TAPUR (Targeted Agent and Profiling Utilization Registry), and the DRUP, (Drug Rediscovery Protocol) have significantly helped shift the focus from cancer treatment on type and origin to target cancer-specific genetic mutations for a cure [19]. The discovery and approval of imatinib as the first signal transduction inhibitor (STI), for the treatment of chronic myeloid leukemia in 2002 virtually marked the beginning of precision oncology approach to cancer therapy. Trastuzumab, a monoclonal antibody, is a groundbreaking targeted therapy agent in oncology which is critical for treating cancers such as breast and gastric cancers that overexpress the HER2 proteins on cancer cells. Trastuzumab has recently completed 25th anniversary of its approval by the FDA and its impact has been huge on targeted therapy practice and precision oncology. The clinical use of precision oncology, which began about 25 years ago, has significantly improved the effectiveness of cancer treatment and is on the verge of becoming integrated into routine clinical practices [20].

The emergence of next-generation sequencing (NGS) in 2005, has proven to be hugely important in this direction, as this technology can be efficiently used to determine the order of nucleotides in entire genomes or selected regions of DNA or RNA to study genetic variation associated with different biological processes or diseases. NGS, also known as high-throughput sequencing or massive parallel sequencing, enables rapid and accurate sequencing of a great many different nucleotide strands at the same time, instead of one at a time as with traditional method of sequencing, and thus it has revolutionized biological research allowing scientists to study the genetic structure of biological systems at a level never tried before. Rapid progress in the development of NGS-based technologies for genomics, transcriptomics, and epigenomics over the years have provided many valuable insights into the genetic mechanisms underlying cancer development. NGS can swiftly reveal the nature of genes and proteins thought to be associated with cancer, and the application of a few such evolving molecular techniques to the study of cancer has also provided cancer biomarkers over the years that have led to new advances in tumor diagnosis, prognosis, and treatment, which have proven to be immensely helpful in advancing precision oncology [21]. Cancer biomarkers refer to a variety of biomolecules, including transcription factors, cell surface receptors, metabolites, circulating tumor DNA/RNA, and secreted proteins produced by tissues as a result of cancer development. The identification of biomarkers is important from a diagnostic, prognostic and therapeutic point of view, and must take advantage of increasing progress in our understanding of the

molecular pathways of cancer development. Definitive biomarkers can reveal disease prognosis, the chances of recurrence, and survival and predict the likely response to specific treatments and can therefore play a critical role in the development of anticancer agents. Many diagnostic and prognostic biomarkers can also be used as potential therapeutic targets. There are many reliable prognostic, diagnostic and therapeutic markers recognized for cancer, and some are highly effective targets for cancer therapy [22,23].

3. Signaling Pathway Deregulation and Targeted Cancer Therapeutics

Cancer growth and progression are dependent on complex interactions between tumor cells, surrounding stromal cells and the ECM present in the TME. However, the root cause underlying cancer progression remains genetic and epigenetic alterations linked to the regulation of cell growth and proliferation, cell adhesion, immune suppression, cell death, differentiation, and overall genomic stability of the affected cells, leading them to grow and proliferate uncontrollably beyond barriers [24,25]. It is ultimately driven by dysregulated molecular mechanisms involving tumor suppressor genes, oncogenes, growth factors, cell adhesion molecules, and molecules of the immune system, such as cytokines and chemokines, that may vary among different cancer types and stages. The cell signaling network, as the foremost system of communication between cells and their surroundings that involves a variety of chemical and mechanical signals and networks of intracellular proteins to constitute different molecular signaling pathways, is worth considering here, as all the essentials of cellular behaviors, such as cell growth and proliferation, cell polarity, cell metabolism, differentiation, survival, and migration, can be guided by the components of these pathways working in a collaborative manner inside the cell. A signaling pathway, in general, constitutes a cascade or chain of proteins that communicates signals from extracellular signaling molecules or other external stimuli, through the receptor on the cell surface to target genes in the nucleus of the cell and results in the expression of certain proteins that produce some changes in cell behavior, such as cell division and differentiation. Together, different signaling pathways maintain internal circuitry inside cells guided by external stimuli such as growth factors and cytokines, enabling them to sense whether their state of attachment to the ECM and other cells is appropriate, and if different growth factors, hormones, and cytokines guide them to proliferate or differentiate, they can move, stay put for now, or commit to cell death by apoptosis or autophagy [26]. Almost all gene modifications can be related to one or more of these signaling pathways that are deregulated in the affected cells to acquire hallmark properties of cancer. Cancer cell signaling typically involves altered expression of the components of the signaling network, which include many secreted protein receptors, growth factors and cytokines, protein kinases, phosphatases, different cytoplasmic proteins, and transcription factors, leading individual cells to respond to genomic changes with appropriate physiological behaviors. Cell division is regulated mainly by a group of extracellular growth factors that signal that

resting cells divide by exploiting their intrinsic regulatory processes. Cytokines signal immune cells to mount coordinated attacks on invading bacteria and viruses and play essential roles in cancer prevention. Thus, signals propagated by growth factors and cytokines can simply tell individual cells to divide or not under particular conditions whose alterations could lead to the pathophysiology of cancer.

The earliest information regarding the relationship between cancer and growth factors came from the observation that normal cells in culture often require serum for proliferation, whereas cancer cells have a much lower requirement for serum. Serum is known for providing growth factors, among other ingredients needed for the overall regulation of the cell cycle. The other indication revealed that gene mutations found in cancer cells cause changes in cell behaviors very similar to those related to the activities of growth factors and their receptors. Oncogenic mutations disrupt the cellular circuits that control cell adhesion and signaling, enabling cells that carry them to overproliferate and invade other tissues in an uncontrolled fashion. Many of these mutations have been directly linked to growth factors and their receptor proteins, which are involved in tumor growth, angiogenesis, invasion, and metastasis [27,28]. Importantly, one type of cell membrane receptor can mediate many different downstream intracellular pathways, and one pathway can also be activated by several upstream surface receptors, revealing common signaling components in multiple signaling pathways. For example, RTKs, such as EGFR, IGFR, PDGFR, FGFR, VEGFR, HGFR, or GPCR, can activate the mitogen-activated protein kinase (MAPK) cascade, whereas widely studied RTKs, such as the EGFR/HER family of receptors, can initiate different signaling pathways, including the MAPK, phosphoinositide-3-kinase (PI3K), and mammalian target of rapamycin (mTOR) pathways, which are commonly involved in the regulation of cell growth, proliferation, differentiation, and survival. This feature of the signaling process evidently presents the option for crosstalk between components of different signaling pathways at different stages of the cellular process. A molecule participating in crosstalk can affect the activation of alternate signaling pathways, and receptors can also have an altered ability to bind to ligands, which can swiftly lead to cancer manifestation. As generally observed, most cell signaling pathways contribute to the development of cancer, and very few cancer types arise from the deregulation of a single pathway. Breast cancer can arise from elevated expression of the estrogen receptor (ER), EGFR/HER, or IGFR, but in many cases, molecules and intermediates of multiple signaling pathways can be interactively involved in this process. In this way, many signaling molecules affecting cancer cells together could be considered to create elaborate integrated circuits within the cell, derived from the usual signaling circuits that operate in normal cells. The transformed intracellular circuit can be divided into distinct subcircuits specializing in specific cellular activities to promote hallmark features of cancer (Fig. 1) [29].

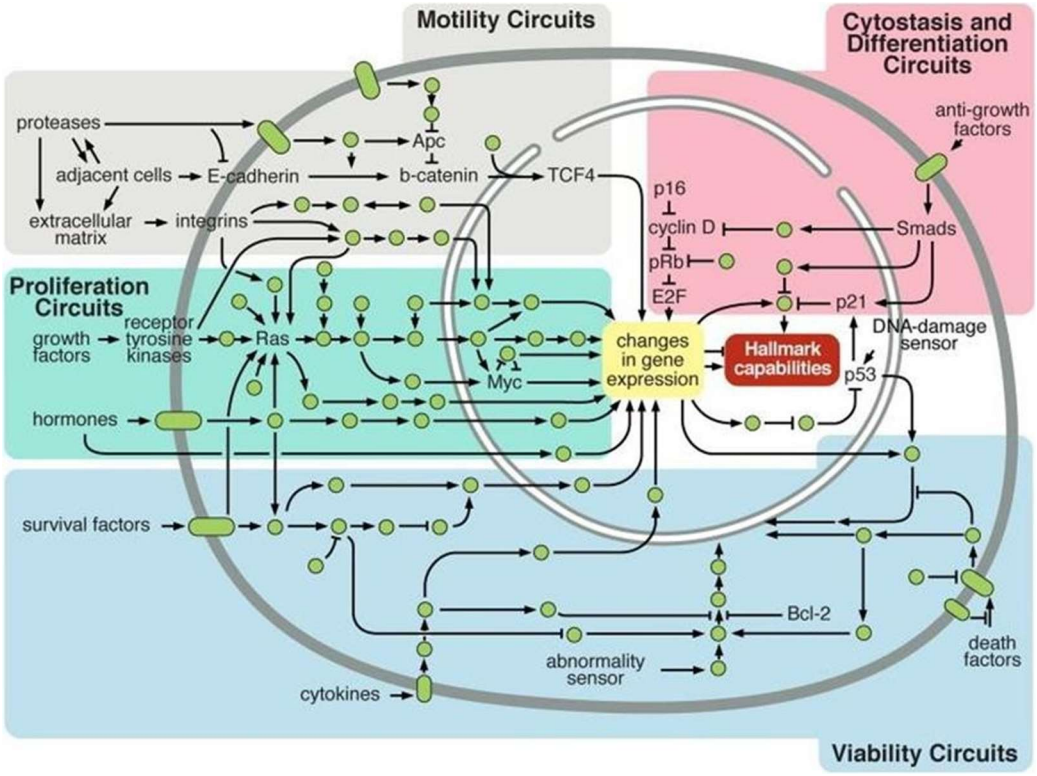

Figure 1. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell. An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment. (Hanahan and Wienberg [29]. With permission from Elsevier)

Signal transduction pathways that lead to tumor growth, cancer cell migration, metastasis, and drug resistance are often complex processes, as cancer cells typically develop abnormalities in multiple signaling pathways or rely on crosstalk between different pathways and some redundant pathways for the maintenance of growth and survival. As cancer progression involves alterations in signaling pathways due to mutations in relevant genes, it is worth considering that therapeutic intervention that takes into account the biology of the affected cells can pave the way for very effective cancer treatment [30,31]. Importantly, in clinical practice, targeting a single intermediate or pathway results in considerable recovery, possibly because it impedes the synergistic signaling process of disease progression.

Targeted cancer therapy is the form of cancer therapeutic that targets specific genes and proteins involved in cancer cell reprogramming, signaling molecules, and other molecules in the tumor microenvironment that contribute to cancer development. This contrasts with the single-target approach employed in chemotherapy to primarily target and kill actively dividing cancer cells with serious side effects; thus, the emergence of targeted

drug therapy can be seen as a natural outcome of decades of studies on the molecular reprogramming of affected cells in different cancers. Some notable breakthroughs have been made in certain cancers, as a renewed understanding of the signaling pathways underlying cancer development has led to the development of specific molecular targeted drugs in past decades. For example, tamoxifen is a wonder drug in medical oncology approved by the FDA in 1977 for the management of estrogen receptor-positive (ER-positive or ER+) breast cancer and can be used to treat all stages of breast cancer and as adjuvant treatment to alleviate the after-effects of surgery and radiotherapy. Studies have long supported the role of hormones, particularly estrogen, in the pathogenesis of breast cancer. Tamoxifen is essentially a hormone therapy drug that acts as an estrogen receptor antagonist to minimize the growth of breast cancer cells. It is among the first discovered to selectively target cancer cells with far fewer side effects and has successfully saved lives for decades and revolutionized the field of targeted cancer therapies (32, 33). This form of cancer therapy can be thoroughly optimized by means of precision oncology, which enables the use of genomic profiling of patient samples for insights into the mutational changes underlying pathway alterations responsible for cancer initiation and progression. Thus, precision oncology-based treatment strategies pledge the diagnosis and prognosis of cancer via the use of specific molecular-level information about a patient's tumor to treat the illness with selective targeting of affected cells with the desired results. In this way, this method can also be considered as a perfect theranostic approach for cancer treatment. The term ‘theranostic’ literally means a combination of diagnosis and therapeutics and refers to the pairing of diagnostic methods such as the proteogenomic approach to biomarker discovery, with appropriate therapeutic interventions for effective management of the disease. Theranostics focuses on patient-centered care and thus provides a transition from conventional to personalized medicine for targeted, efficient and safe pharmacotherapy relevantly applicable in precision oncology [34].

The anticancer drugs employed in targeted therapy are designed mainly to target selected molecules directly involved in cancer cell signaling or those in the tumor microenvironment essentially required for tumor growth and cancer manifestation [35]. They are broadly classified as monoclonal antibodies (mAbs) or small-molecule drugs. Small-molecule drugs are designed to directly approach the cell membrane and interact with targets inside the cell and usually inhibit the enzymatic activity of target proteins such as the proteasome complex, cyclin-dependent kinases and a variety of signaling proteins. Kinase family proteins, such as tyrosine kinases, Rho kinases, Bruton tyrosine kinases, ABL kinases, and NAK kinases, play essential roles in modulating signaling pathways associated with cancer progression and therefore constitute valuable sources of biological targets against cancers (Table 1). A type of targeted therapy, called tumor-agnostic therapy, uses drugs and other substances to target cancer-specific genetic changes or markers to treat the problem without requiring a focus on the cancer type or where the disease may have started in the body.

Table 1. List of Protein Kinase Inhibitors approved by FDA.
(NRY, nonreceptorprotein-tyrosinekinase; RTK, receptorprotein-tyrosinekinase; S/T,protein-serine/threoninekinase; T/Y, dual-specificityproteinkinase)

Protein kinase inhibitor	Approval year	Primary targets	Target kinase family	Indications
Abemaciclib	2017	CDK4/6	S/T	Breast cancer
Acalabrutinib	2017	BTK	NRY	Lymphoma
Afatinib	2013	ErbB1/2/4	RTK	Lungcancer
Alectinib	2015	ALK, RET	RTK	Lungcancer
Avapritinib	2020	PDGFR	RTK	Gastrointestinal Cancer
Axitinib	2012	VEGFR1/2/3	RTK	Kidney cancer
Binimetinib	2018	MEK1/2	T/Y	Melanoma
Bosutinib	2012	BCR-Abl	NRY	Leukemia
Brigatinib	2017	ALK	RTK	Lungcancer
Cabozantinib	2012	RET, VEGFR2	RTK	Thyroid, kidney, Hepatocellular cancer
Capmatinib hydrochloride	2020	c-MET	RTK	Lungcancer
Ceritinib	2014	ALK	RTK	Lungcancer
Cobimetinib	2015	MEK1/2	T/Y	Melanoma
Crizotinib	2011	ALK, ROS1	RTK	Lungcancer
Dabrafenib	2013	B-Raf	S/T	Melanoma, lung, thyroid Cancer
Dacomitinib	2018	EGFR	RTK	Lung cancer
Dasatinib	2006	BCR-Abl	NRY	Leukemia
Encorafenib	2018	B-Raf	S/T	Melanoma, colorectal cancer
Entrectinib	2019	TRKA/B/C ROS1	RTK	Lungcancer; solid Tumors
Erdafitinib	2019	FGFR1/2/3/4	RTK	Urothelial carcinoma

Erlotinib hydrochloride	2004	EGFR	RTK	Lung, Pancreatic cancer
Everolimus	2009	FKBP12/mTOR	S/T	Breast, kidney cancer, Neuroendocrine tumors
Fedratinib	2019	JAK2	NRY	Myelofibrosis
Futibatinib	2022	FGFR2	RTK	Cholangio carcinomas
Gefitinib	2003	EGFR	RTK	Lungcancer
Gilteritinib	2018	Flt3	RTK	Leukemia
Ibrutinib	2013	BTK	NRY	Lymphoma
Imatinib mesylate	2001	BCR-Abl	NRY	Leukemia; Gastrointestinal
Infigratinib	2021	FGFRs	RTK	Cholangiocarcinoma
Lapatinib ditosylate	2007	ErbB1/2/HER2	RTK	Breast cancer
Larotrectinib	2018	TRKA/B/C	RTK	Solid tumors
Lenvatinib	2015	VEGFR, RET	RTK	Hepatocellular, endometrial, Thyroid, Kidney cancer
Lorlatinib	2018	ALK	RTK	Lungcancer
Midostaurin	2017	Flt3	RTK	Leukemia
Mobocertinib	2021	EGFR with exon 20 insertions	RTK	Lungcancer
Neratinib	2017	ErbB2/HER2	RTK	Breast cancer
Nilotinib	2007	BCR-Abl	NRY	Leukemia
Osimertinib	2015	EGFRT790M	RTK	Lungcancer
Pacritinib	2022	JAK2	RTK	Myelofibrosis
Palbociclib	2015	CDK4/6	S/T	Breast cancer
Pazopanib hydrochloride	2009	VEGFR1/2/3	RTK	Kidney cancer; soft Tissue sarcoma
Pemigatinib	2020	FGFR2	RTK	Cholangiocarcinoma

Pexidartinib	2019	CSF1R	RTK	Tenosynovial giant cell tumor
Pirtobrutinib	2023	BTK	NRY	Lymphoma
Ponatinib hydrochloride	2012	BCR-Abl	NRY	Leukemia
Pralsetinib	2020	RET	RTK	Lungcancer
Quizartinib	2023	FLT3/STK1	RTK	Leukemia
Regorafenib	2012	VEGFR1/2/3	RTK	Gastrointestinal, Colorectal, Hepatocellular cancer
Ribociclib	2017	CDK4/6	S/T	Breast cancer
Ripretinib	2020	KIT/PDGFR	RTK	Gastrointestinal cancer
Ruxolitinib phosphate	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis
Selpercatinib	2020	RET	RTK	Lung, thyroid cancer
Selumetinib	2020	MEK1/2	T/Y	Neurofibroma
Sorafenib tosylate	2005	VEGFR1/2/3	RTK	Thyroid, Kidney, Hepatocellular cancer
Sunitinib malate	2006	VEGFR2	RTK	Gastrointestinal, kidney, Pancreatic cancer
Temsirolimus	2007	FKBP12/mTOR	S/T	Kidney cancer
Tepotinib	2021	Met	RTK	Lung cancer
Tivozanib	2021	VEGFR2	RTK	Kidney cancer
Trametinib	2013	MEK1/2	T/Y	Melanoma
Trilaciclib	2021	CDK4/6	S/T	Lung cancer
Tucatinib	2020	ErbB2/HER2	RTK	Breast cancer
Vandetanib	2011	VEGFR2	RTK	Thyroid cancer
Vemurafenib	2011	B-Raf	S/T	Melanoma; histiocytic sarcoma
Zanubrutinib	2019	BTK	NRY	Lymphoma

Nevertheless, the constitutive activation of a molecular event that contributes to cancer development can be sustained by different mechanisms, and strategies to inhibit multiple targets or redundant pathways simultaneously with molecular-targeted agents could prove to be an even more effective way to treat cancer and overcome resistance in cancer therapy [36]. This approach has indeed been used with anticipated outcomes in some forms of cancer, indicating the need for more research in that direction. The challenge of identifying the genes and signaling molecules relevant to different cancer types by cutting-edge technologies remains an essential part of cancer research and is most likely to help vulnerable people receive precisely designed treatments for cancer [37,38].

4. Integration of Multiomics and Artificial Intelligence (AI) in Precision Oncology

Multiomics: High-throughput sequencing technologies, also known as next-generation sequencing (NGS), are comprehensive terms used to describe technologies that sequence DNA and RNA rapidly and cost-effectively. It has revolutionized the fields of genetics and molecular biology and aided in the study of biological sciences as never before [39]. Technologies using NGS have been developed that measure some characteristics of a whole family of cellular molecules, such as genes, proteins, or metabolites, and have been named by appending the term "-omics. Multiomics refers to the approach where datasets of different omics groups are combined during sample analysis to allow scientists to read the more complex and transient molecular changes that underpin the course of disease progression and response to treatment and to select the right drug target for the desired results [40]. It forms the basis of precision medicine in general and is at the core of the development of precision oncology. The breakthroughs in high-throughput technologies in recent years have led to the rapid accumulation of large-scale omics cancer data and brought an evolving concept of “big data” in cancer analysis, which requires considerable computational resources with the potential to bring new insights into critical problems. The combination of big data, bioinformatics, and artificial intelligence is thought to lead to notable advances in translational research in cancer [41,42].

Artificial intelligence: Artificial intelligence (AI) encompasses multiple technologies with the common aim of computationally simulating human intelligence to solve complex problems. It is based on the principle that human intelligence can be defined in a manner such that a machine can easily mimic and execute tasks from simpler to far more complex ones successfully [43]. Broadly referred to as computer programming, which is enabled to perform specific tasks, the term may be applied to any machine that displays traits

associated with human intelligence, such as learning and problem solving. In regular programming, data are processed with well-defined rules to obtain solutions, whereas AI relies on the learning process to devise rules for the efficient processing of data to yield smart results. AI and related technologies have increasingly been prevalent in finance, security, and society and are now being applied to healthcare [44]. It has been widely applied in precision medicine-based healthcare practices and has been found to be highly useful in medical oncology practice. Precision oncology considers the molecular composition of cancer patients for effective targeted therapies, and therefore requires leveraging in-depth knowledge bases on associations of molecular characteristics, cancer types and drugs for therapeutic decisions that can be made by integrating multiple specialized databases via AI techniques. Therefore, many artificial intelligence algorithms have been developed and applied in cancer research in recent years. An exact understanding of the structure of a protein remains the first step toward understanding all of its roles in cancer progression, and therapeutic drugs are also designed using structural information of the target proteins where AI-based techniques can be used for the solutions. Advances in NGS have led multiomics data on cancer to become available to researchers, providing them with opportunities to explore genetic risk and reveal underlying cancer mechanisms to help early diagnosis, the exact prognosis, and the discovery, design, and application of specific targeted drugs against cancer. Thus, integrating multiomics-based studies with artificial intelligence is necessary and is likely to serve the purpose involved adequately. With the help of large datasets from multiomics platforms, imaging techniques, and biomarkers found and mined by artificial intelligence algorithms, oncologists can diagnose cancer early at its onset and help direct treatment options for individualized cancer therapy for anticipated results. Thus, advances in AI present an opportunity to perfect methods of diagnosis and prognosis and develop strategies for personalized treatment using large datasets, and future developments in AI technologies are most likely to help many more problems in this direction be resolved swiftly. In this way, AI is thought to be the future of precision oncology for the prevention, detection, risk assessment, and treatment of cancer [45,46].

Machine learning: Machine learning (ML) is a branch of artificial intelligence that aims to develop computational systems with advanced analytical capabilities. It is concerned with the development of domain-specific programming algorithms with the ability to learn from data to solve a class of problems [47]. ML techniques have long been exploited for their applications in protein structure analysis. Successful image processing and natural language processing strategies with end–to–end approaches have been very encouraging for their application in healthcare. The most common and purposeful application of traditional ML techniques in healthcare appears to be in the area of precision medicine and is most suited for the data-driven identification of cancer states and the design of treatment options that are crucial to precision oncology-based cancer treatment [48].

Deep Learning: Deep learning (DL) is a sub-branch of ML that uses statistics and predictive modeling to extract patterns from large datasets to precisely predict a result. A variety of data, including electronic health records, imaging, multiomics-based reports, and sensor data have appeared in modern biomedical research which are complex, heterogeneous, and poorly defined and need to be mined efficiently to obtain correct results. To meet this goal, DL uses a machine learning program called artificial neural networks (ANNs) modeled on the human brain that forms a diverse family of computational models consisting of many deep data processing layers for automated feature extraction and pattern recognition in large datasets to address these problems efficiently. The human brain consists of neurons arranged together as a network of nerves processing several pieces of information received from many different sources to translate into a particular reflex action. In DL, the same concept of a network of neurons is imitated on a machine learning platform to emulate human understanding to obtain perfect solutions. The neurons are created artificially in a computer system, and the data processing layers work together to create an artificial neural network where the working of an artificial neuron could be considered similar to that of a neuron present in the brain. Thus, DL is designed to use a complex set of algorithms, enabling it to process unstructured data such as documents, images, and text to find efficient results [49].

The effective development of drugs for the treatment of cancer is a major problem in cancer research, and DL provides immense help to researchers in this regard. Changes in the genetic composition of tumors translate into structural changes in cellular subsystems that need to be integrated into drug design to predict therapeutic response and concurrently learn about the mechanism underlying a particular drug response. A proper understanding of the mechanism of drug action can lead researchers to understand the importance of different signaling pathways, including some new and uncommon pathways associated with tumors, to help develop novel drugs for the therapeutic targeting of diverse forms of cancer. Drug combinations targeting multiple pathways are thought to address the incidence of drug resistance in cancer therapy, and computational models could be used to find solutions. Occupation-oriented pharmacology is the dominant paradigm of drug discovery for the treatment of cancer. It relies on the use of inhibitors that occupy the functional binding site of a protein and can disrupt protein interactions and their functions. New advances in AI have enabled researchers to develop DL-based models to predict the response of tumor cells to synergistic drug combinations to be employed effectively in precision oncology [50]. Researchers continue to discover proteins that may be the key drivers of cancer and need a fuller understanding of the 3D shape, or structure, of these proteins to determine their exact functions in the cell.

A recent development of the DL system is AlphaFold, which has been successfully used to predict the structures of different proteins. It was discovered through critical assessment of structure prediction (CASP), a community-based protein structure modeling initiative to determine the 3D structure of proteins from the amino acid sequence, organized by the Protein Structure Prediction Center, which is sponsored by

the US National Institute of General Medical Sciences (NIH/NIGMS). CASP is a biannual competition in which a set of proteins whose structures have not yet been revealed are released, and participants attempt to resolve protein structures via experimental methods such as X-ray crystallography, and magnetic resonance nuclear (NMR) and cryo-electron methods. microscopy. Google's DeepMind participated in 2020 with its deep learning-based algorithm AlphaFold and excelled. AlphaFold 2 was introduced in 2021 as a new version of the system with much improved capabilities, which has revolutionized research by simplifying the accurate prediction of 3D structures of proteins. The tool has already determined the structures of approximately 200 million proteins from almost every known organism on the planet [51]. Recently, it has been further upgraded to AlphaFold 3, which can accurately predict protein–molecule complexes containing different subunits and other molecules, such as DNA and RNA. The new version, with enhanced predictive capabilities, is poised to enable researchers to perform advanced molecular modeling and simulation with much broader options for the determination of possible biochemical pathways and effective drug discovery [52]. This revolutionary development in DL will be of great use in understanding the roles of suspected proteins in cancer development and in anticancer drug design.

A newly developed DL system called PocketMiner is an efficient tool for predicting the locations of binding sites on proteins. Proteins exist in a state of dynamic equilibrium with their different conformational structures, including experimentally determined structures that may not have targetable pockets. PocketMiner uses graph neural networks to find hidden areas or pocket formations from a single protein and is thought to be 1,000 times faster than existing methods of finding binding sites on proteins. This technology has led researchers to understand that approximately half of the proteins that were previously considered undruggable might have cryptic pockets that could be targeted successfully by anticancer agents. The AI-based system has multiple uses in cancer management, such as the prediction of treatment response, estimation of survival analysis, risk estimation, and treatment planning, and is becoming the central approach in precision oncology [53].

5. The Cancer Genome Atlas (TCGA) Program is the Landmark in Cancer Genomics Research

The National Institutes of Health (NIH) has taken the lead role in cancer research and is the largest funder of cancer-based initiatives in the world. The National Cancer Institute (NCI), the leading cancer research enterprise, is part of NIH and is committed to exploiting basic cancer research for efficacious cancer therapies. In this context, the Cancer Genome Atlas (TCGA) Program is the landmark cancer genomics program supported by the NIH, which has contributed immensely to realizing the importance of genomics in cancer research and treatment in the last decade and has begun to change the way the disease has been treated in the clinic. It is a joint effort by the NCI and the

National Human Genome Research Institute (NHGRI), also a part of the NIH, that began working in 2006 and has brought together researchers from diverse disciplines and multiple institutions to work on the characterization and analysis of cancer at the molecular level for a complete picture of the genetic basis of human cancer [54,55]. Since the start, the TCGA network has profiled and analyzed a large number of human tumors to discover molecular aberrations at the DNA, RNA, protein and epigenetic levels and provided reliable diagnostic, prognostic and therapeutic markers for different types of cancer (Table 2).

Table 2. Examples of representative cancer biomarkers and their relationship to the hallmark properties of cancer (Hanahan and Wienberg [Ref. 29])

Hallmarks of Cancer	Signaling Pathways	Example of Biomarkers	Example of a Major Therapeutic Target
Sustaining proliferative signaling	EGFR/ HER IGFR PKC MAPK	Breast cancer: ER PR HER2 p95 HER2 IGF-1R/IRS-1 EREG (CRC) IRS1 (BC) IGF2 (CRC) PTEN (BC)	ER HER2
Activating invasion and metastasis	PKC MAPK EGFR/HER IGFR TGF-β	TGFα (CRC) TGFα / Amphiregulin (NSCLC)	EGFR
Evading Growth Suppressors	EGFR/HER MAPK	PTEN (BC)	EGFR
Resisting cell death	IGFR EGFR/HER	IGF2 (CRC) PTEN (BC)	EGFR
Inducing Angiogenesis	VEGF EGFR/HER Ras	VEGF EREG (CRC)	VEGFR
Enabling Replicative Immortality	B-catenin	Telomerase length	

BC: Breast Cancer, CRC Colorectal Carcinoma, NSCLC: Non-Small Cell Lung Carcinoma

Predicting the effects of mutations via in silico tools has become a frequently used approach, but these data cannot be analyzlysed by simply using traditional tools and techniques that have been available to scientists. Therefore, even more advanced computational methods would be needed to gain insights into the molecular and biochemical basis of the origin and evolution of cancer. To meet this goal, a cancer hallmark framework through modeling genome sequencing data has been proposed for the systematic identification of representative driver networks to convincingly predict cancer evolution and associated clinical phenotypes [58,59]. This approach is based on the consideration that possible observable combinations of those mutations must converge to a few hallmarks signaling pathways and associated networks responsible for cancer development. In this way, the proposed framework aims to analyze the available data to explain how different gene mutations in different patients have the same downstream effects on protein networks, ultimately leading to a common path of cancer progression and direct treatment planning accordingly. In this context, researchers funded by the NIH have separately completed a detailed genomic analysis of data available through the TCGA program known as the PanCancer Atlas, providing an independent view of the oncogenic processes that contribute to the development of human cancer [60,61]. By analyzing over tens of thousands of tumors from the most prevalent forms of cancer and focusing on how germline and somatic variants collaborate in cancer progression, the Pan-Cancer Atlas has provided the most comprehensive and in-depth understanding of how and why tumors frequently arise in humans [62,63]. The synchronized view of oncogenic processes based on PanCancer Atlas analyses aims to elucidate the possible consequences of genome alterations on the different signaling pathways involved with human cancers, also reflecting their influence on the tumor microenvironment and immune cell responses, to provide new insights into the development of new forms of targeted drugs and immunotherapies. Furthermore, the stemness features extracted from transcriptomic and epigenetic data from TCGA tumors also present novel biological and clinical insight for cancer stem cell-targeted therapies [64,65]. Thus, the PanCancer Atlas initiative appears to be a natural outcome of the TGCA program dedicated to comprehensive analysis of tumors on the basis of genomic studies to reveal alterations in signaling pathways, patterns of vulnerability and identify prospective targets for the development of precise drug treatments and effective combination therapies.

6. The Cancer Cell Mapping Initiative (CCMI) and Related Programs in Oncogenomics

Nevertheless, the presence of mutated genes is strongly correlated with cancer incidence, and TGCA-based programs have provided a large amount of data to analyze to clarify how disease begins and progresses, but very specific causative genes or a small set of genes for most cancers have not been confirmed after decades of genomic studies. Nobel laureate James D. Watson opined in Cancer World in 2013: "We can go ahead and

sequence every piece of DNA that has ever existed, but I do not think we will find the Achilles heel of cancer". Since genes and proteins, and associated signaling pathways affecting different cancer types and individual tumors vary considerably, a better understanding of the mechanism underlying these alterations is essential to identify vulnerabilities and discover precise therapeutic solutions. Predicting the effects of mutations via in silico tools has become a frequently used approach in cancer research, but these data cannot be analyzlysed by simply using traditional tools and techniques that have been available to scientists. Identifying and characterizing specific mutations that influence cancer development has been a challenging task, and many computational methods are therefore being tested and evaluated to mine existing data to successfully identify driver mutations. Although AI-based techniques have led to significant advances in protein structure prediction and even biomarker discovery, their utility in identifying driver mutations in oncogenesis remains underexplored. Therefore, even more advanced computational methods would be needed to gain insights into the molecular and biochemical basis of the origin and evolution of cancer. To meet this goal, a cancer hallmark framework through modeling genome sequencing data has been proposed for the systematic identification of representative driver networks to convincingly predict cancer evolution and associated clinical phenotypes [66]. This approach is based on the consideration that possible observable combinations of those mutations must converge to a few hallmarks signaling pathways and associated networks responsible for cancer development. Thus, the proposed framework has the task of analyzing the available data to explain how different genetic mutations in different patients have the same downstream effects on protein networks, ultimately leading to a common pathway of cancer progression and direct treatment planning accordingly [67]. In this context, the Cancer Cell Mapping Initiative (CCMI), originally founded in 2015 by researchers from the University of California, San Francisco, and the University of California, San Diego, has been a major development in cancer research dedicated to generating complete maps of major protein-based genetic interactions underlying cancer progression and attempting to develop computational methods using these maps to identify novel drug targets and patient cohorts with common outcomes. In fact, it is an application of network biology, a branch of systems biology that utilises mathematical models to represent, integrate and analyse biological data through networks allowing the study of the properties of a complex system based on interactions between its individual constituents. Finally, the CCMI is programmed to integrate computational methods and biological sciences to advance our understanding of the cellular functions underlying cancer progression and metastasis. It is based on the NeST (Nested Systems in Tumors) map, which relies on an integrated protein network created by combining interaction evidence from major data types, such as protein–protein interactions, mRNA coexpression, protein coexpression, sequence similarity, and genetic codependency. A multiscale molecular community detection method could be applied to the network to detect protein communities at different size resolutions. Smaller communities will overlap with each other and fall naturally within larger communities to produce a hierarchy of molecular systems for

affected cells. Finally, a statistical model called HiSig was developed as needed to determine some smaller protein systems as novel protein assemblies on which different mutations would ultimately converge during disease progression. The NeST map thus presented a total of 395 protein systems frequently involved in one or more types of cancer and therefore constitutes a resource on the cancer mechanisms for somatic mutations under consideration. The signaling pathways and associated protein complexes involved, as key steps in disease progression, may be attractive targets for precise cancer therapy. This initiative helped successfully determine how hundreds of genetic mutations involved in breast cancer and head and neck cancer affect the activity of certain proteins that ultimately lead to disease progression. Because a vast amount of sequence data from many different cancer types exist, efforts are being made to extract mechanistic insight from the available information via integrated computational and experimental strategies to help place these alterations in the context of the higher-order signaling mechanisms involved in cancer development [68]. Thus, CCMI appears to be a categorical advancement aimed at embarking on a new era of cancer research and treatment on the basis of the complete elucidation of the molecular networks underlying different cancers. This is the defined goal of the CCMI and is likely to create a resource that will be used for interpretation of the cancer genome, enabling the identification of key complexes and pathways to be studied in greater mechanistic detail to properly understand the biology underlying different cancers [69]. Furthermore, the Broad Institute of MIT and Harvard's Cancer Dependency Map (DepMap) initiative, an academic–industrial partnership program formally announced in 2019, is devoted to accelerating precision cancer medicine by creating a comprehensive map of tumor vulnerabilities and identifying key biomarkers of cancer. The DeepMap initiative is focused on screening thousands of cancer cell lines via the use of RNA interference (RNAi) and CRISPR-Cas9 loss-of-function gene-editing strategies to identify genes whose expression may be essential for cancer cell development. CRISPR-Cas9 gene editing is an efficient method for the genome modification of nearly all cell types. CRISPR editing and screening have emerged as powerful tools for investigating almost all aspects of cellular behaviors, which have greatly impacted our understanding of cancer biology and continue to contribute to new discoveries. A related project called the Cancer Cell Line Encyclopedia (CCLE) project was initiated as a collaboration between the Broad Institute and the Novartis Institutes for Biomedical Research in 2008 and aimed at large-scale genetic characterization of thousands of cancer cell lines to link characteristic genetic alterations with distinct pharmacologic vulnerabilities and to translate cell line integrative genomics into cancer patient stratification. By access to critical genomic data such as gene mutation, copy number variation, gene expression, and methylation profiles from the CCLE, scientists can now predict novel synthetic lethality and identify new molecular markers whose selective targeting can control cells that possess specific genetic mutations. In this way, the initiative has provided a rigorous foundation on which to study genetic variants and candidate targets, design anticancer agents and identify new marker-driven cancer diagnoses and therapies [70]. By all such means, the field of cancer genomics can be seen

as constantly evolving to help identify cancer-causing changes to gain a better understanding of the molecular basis of cancer growth, metastasis, and drug resistance and translate cancer research into new cancer therapeutics.

7. Single-cell Multiomics Reveals Tumor Heterogeneity

Tumor heterogeneity is a hallmark property of cancer development and broadly refers to the differences between tumors of the same type in different patients, the differences between a primary and a secondary tumor, and the differences in genomic and phenotypic profiles displayed by cells within a single tumor. Heterogeneity within a single tumor, referred to as genetic intratumoral heterogeneity (ITH), has been documented across most cancers as an outcome of genome instability and clonal evolution. Tumor heterogeneity appears to be a critical phenomenon in the history of individual cancers, as its translational significance may reflect tumor progression, disease recurrence, treatment response, and resistance. Recent investigations on drug resistance and tumor heterogeneity have confirmed the clonal organization of tumors as the underlying basis for drug resistance, thus indicating the need to fully understand the structure and dynamics of ITH to develop advanced treatment strategies for cancer [71,72]. Provided the cellular composition of a tumor is precisely known, the underlying mechanism of disease progression is understood, molecules and pathways involved in the process are identified, a far more specific therapeutic strategy could be devised to achieve the desired result. This is the stated goal of precision oncology, and the emergence of single-cell technologies for biological analysis has become crucial tool in this regard in recent years. Single-cell Technology can carry out single-cell measurements of a sample using single-cell multi-omics that are based on NGS techniques to provide a clear picture of tumor heterogeneity and reveal how structural changes in chromosomes can lead to the complex biological processes involved in carcinogenesis. This technology mainly aims to study the complexity of gene function, disease development, and therapeutic response at single cell resolution for efficient cancer treatment [73].

Single-cell multiomics now facilitates the simultaneous measurement of thousands of genes and proteins in thousands of ‘single’ cells from a single sample, allowing researchers to compare the genomes of individual cells to determine the mutational profile of the affected cells to better understand the molecular consequences of different variants present in the tumor. This form of study of the complexities of disease development, gene function, and therapeutic response at the single-cell level relies on single-cell DNA sequencing (scDNA-seq) technology, which analyzes DNA at the level of a single cell genomes to explore cellular genomic diversity. This approach contrasts with standard DNA sequencing, which homogenizes the DNA content of millions of cells to read the nucleotide sequence. [74]. Single-cell template strand sequencing (Strand-seq), is a special single-cell sequencing technology that enables independent and efficient analysis of the two parental DNA strands t

resolve homologous chromosomes that are similar in shape and structure but not identical within single cells, which is crucial for identifying somatic SVs, understanding genomic rearrangements and unmasking tissue heterogeneity [75]. Single-cell RNA sequencing (scRNA-seq) is a transcriptomic approach that leads to the detection and quantitaive analysis of messenger RNA (mRNA) molecules to gain insight into the expression profiles of individual cells [76]. It is a standard protocol for determining cellular states and phenotypes. For example, Drop-seq is a scRNA-seq based technology that rely on separating cells into nanoliter-sized aqueous droplets to enable biologists analyze genome-wide RNA expression in thousands of individual cells at a time and, is a very useful for innovative discoveries such as identifying specific cell types within a cell population. Moreover, single-cell sequencing can also be combined with CRISPR knockout screening, to exploit the efficiency and flexibility of CRISPR–Cas9 genome editing to enable large-scale studies regarding how genetic modifications can affect individual cell behaviors or gain insights into the specific molecular events in complex tissues. Combining CRISPR with single-cell RNA sequencing (scRNA-seq), such as single-cell CRISPR sequencing (scCRISPR-seq), have been a crucial development in cancer genomics [77]. Furthermore, combining the CRISPR–Cas system and single-cell techniques for studying gene functions with the concurrent use of single-cell resolution techniques, such as flow cytometry, microfluidics, manual cell picking, or micromanipulation, can be exploited in cancer research in many ways, including identifying novel drug targets, studying unknown mechanisms of action of drugs and designing treatment regimens [78].

The importance of epigenetic reprogramming in cancer is well understood, as evidenced by the fact that chromatin regulators are often mutated in affected cells, and widespread epigenetic changes throughout cancer genomes can be identified and linked to the activities of different known oncogenes and tumor suppressor genes. Abnormal epigenetic changes are usually influenced by aging, viruses, and dietary and environmental factors that frequently contribute to cancer development and drug resistance. The interrelationship between genetic and epigenetic changes needs to be further examined for the discovery of screening markers to optimize pathways of diagnosis and prognosis and to develop strategies for individualized cancer treatment [79]. For example, DNA methylation is known to be associated with cell differentiation, aging, and diseases, including cancer. A considerable amount of understanding exists regarding tissue-specific DNA methylation patterns, but much less information about person-specific DNA methylation causing cancer is available. Thus, the premise of single-cell epigenomics holds great possibilities for deciphering the cellular state and characterizing tumor heterogeneity, with an option for therapeutic interventions to pin specific mutations that have profound effects on epigenetic pathways. The inclusion of epigenetics in clinical practice would require identifying epigenetic signatures that mediate distinct phenotypical changes of clinical relevance, such as epithelial mesenchymal transition, dormancy, and quiescence or therapy resistance.

Single-cell sequencing technologies have largely been successful in helping scientists understand the cell types and features associated with tumors; however, the spatial context

of this development is essential to better understand how cells organize and communicate across tissues to fully unlock the repertoire of tumor heterogeneity. Therefore, a clear understanding of which cells are present, where they are situated in the tissue, their biomarker expression patterns, and how they organize and interact to influence the tissue microenvironment is needed. This is an essential part of spatial biology and adds another dimension to single-cell analysis to unmask tumor heterogeneity [80]. Spatial biology simply combines whole-slide imaging (WSI), commonly referred to as 'virtual microscopy', at single-cell resolution to visualize and quantify biomarker expression and reveal how cells interact and organize across the entire tissue landscape. This technique can support research for early biomarker discovery to late-stage translational research and therapy development [81]. The latest development in this area is spatial multi-omics, that involves spatial mono-omics such as, spatial genomics, transcriptomics, proteomics, epigenomics, metabolomics, etc. to explore the spatial arrangement of cells and their interactions in the native tissue environment. Cells interact with each other in the TME based on their genetic features which may be critical for understanding cancer progression and treatment resistance. In situ genome sequencing (IGS), and slide-DNA-seq are two established spatial genomics methods that allows deciphering genetic behaviors of individual cells in the natural tissue compartments. Spatially resolved transcriptomics (SRT), is a set of NGS based technologies for fast and accurate spatial mRNA profiling to be used to probe genome-wide mRNA expression within sections of a tissue sample. This is a widely used technique which has been immensely useful in understanding molecular processes driving the spatial organization of the tissue system, and has opened up new possibilities in cancer research [82]. Similarly, Mass spectrometry and imaging-based spatial methods have been developed for the study of proteins, including their expression levels, modifications, and interactions within the tissues. Spatial epigenomics involves studying modifications to the chromatin structure and DNA expression patterns leading to changes in cell functions without changes in the DNA sequence. It aims to get a complete picture of the epigenome by combining information on DNA methylation, histone modifications, and gene expression, and mainly rely on bioinformatics tools and techniques to uncover the mechanisms underlying epigenetic changes at the spatial level. Further, the integration of specific spatial omics can be crucial to enhanced understanding of the spatial-based heterogeneity in diseases progression. In this regard, spatially integrated multi-omics techniques have been developed, such as multi-omics in situ pairwise sequencing (MiP-seq), to enable researchers to simultaneously visualize and quantify multiplexed DNA, RNA, proteins, and other biomolecules down to the subcellular level and compare expression profiles of individual cells in situ. It is one of the ground breaking spatially integrated molecular profiling methods that exploits specific multiomics technologies, allowing researchers to measure all the gene activity in a tissue sample and assay the genetic information of single cells in the tissue context to better understand cellular functions and disease mechanisms [83]. The growing ability to demonstrate the role and function of distinct cell types present in the tissue has paved the way for a new understanding of the tissue-specific cellular pathways and

interactions that lead to cancer manifestation. Thus, molecular analysis of cancer cells on the basis of single-cell technologies aims to present an accurate picture of the most recent developments regarding changes in genes and proteins in a sample responsible for alterations in cellular processes, enabling a better understanding of the prognosis and pathways involved in the development of cancer [84] (Fig. 2).

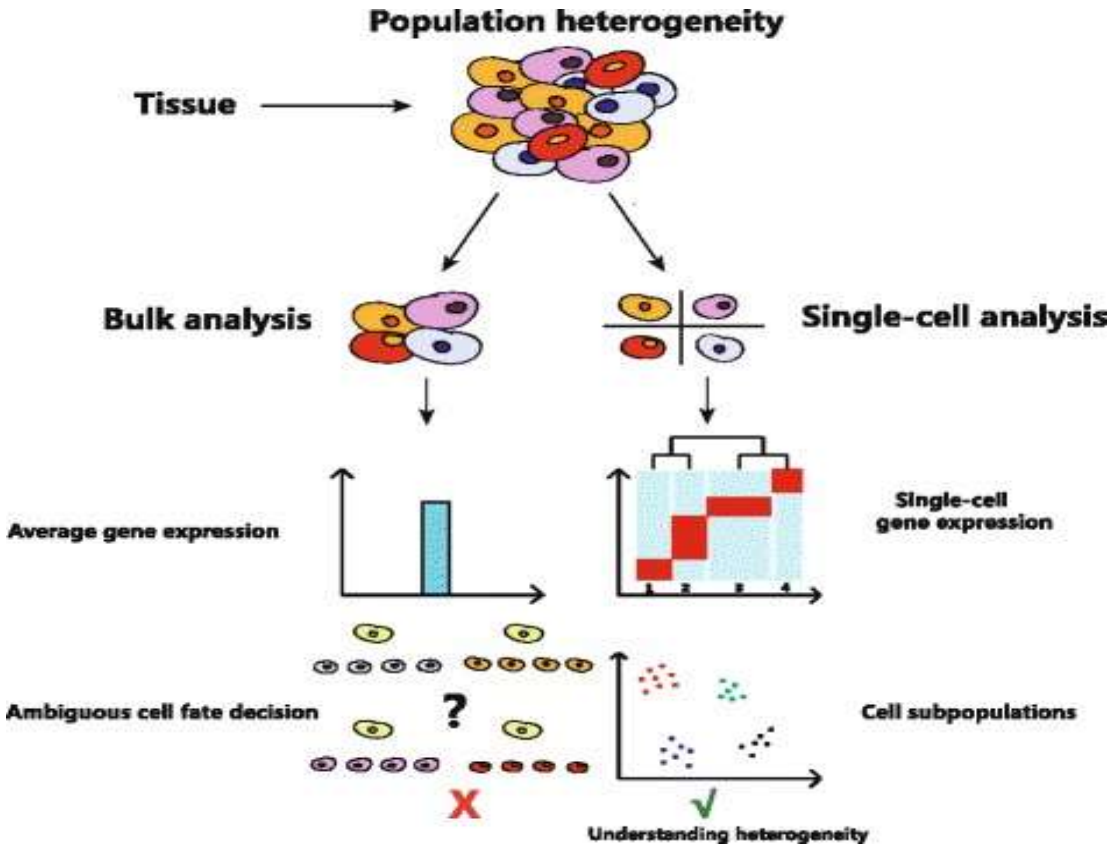

Figure. 2. Single Cell analysis reveals tissue heterogeneity.
Traditional studies on tissue samples mask heterogeneity between individual cells. To understand the heterogeneity of complex tissues, analysis performed on single-cell resolution could be used to unveil cell subpopulations and their gene expression patterns. (Fang Ye, Wentao Huang and Guoji Guo [84])

New advances in multiomics techniques powered by AI have enabled researchers to integrate genomic, transcriptomic, epigenomic, and other related data to gain the most accurate information on the activity state of individual genes and proteins to reveal novel cancer drivers and genetic vulnerabilities for prevention and cure [85]. The emerging field of single-cell technology thus provides unprecedented insight into the complex genetic and epigenetic heterogeneity within individual tumors for advanced precision oncology-based treatment and is likely to streamline future research directions.

8. Engineering Organoid Models for cancer research and Precision Oncology

Cancer is known for its complexity and tissue heterogeneity, factors that pose major challenges to its treatment. Chemotherapy and targeted therapies remain essential in cancer management, but the effectiveness of therapeutic interventions depends primarily on the selection of drugs tailored to the tumor type and/or patient cohort. Therefore, preclinical drug evaluation, followed by clinical trials, is a crucial step in the drug development process. Two-dimensional cell culture models are traditionally used to assess drug efficacy and resistance. Though highly efficient in terms of scalability and reproducibility, these models fail to accurately reproduce the complex architecture and biological dynamics of tumors in vivo. They suffer from an insufficient understanding of cell-cell and cell-matrix interactions, tumor heterogeneity, and an overly simplified tumor microenvironment that may not reflect the reality of individual tumors. Cellular heterogeneity and the diverse composition of the tumor microenvironment are key determinants of tumor progression, therapeutic response, and resistance mechanisms. Consequently, two-dimensional models have limited accuracy in predicting drug efficacy and contribute to the high failure rates observed during the clinical development of new drugs. Given the dynamic interactions between cancer cells, and surrounding stromal components, an ideal cancer model must accurately reproduce the histological patterns of tumor and its native microenvironment. Therefore, an urgent need appears for physiologically relevant in vitro platforms capable of accurately modeling tumour behaviors to improve translational outcomes. To address this problem, three-dimensional in vitro tumor models, tumor organoids, have been developed to reproduce controlled microenvironments to study tumor biology and predict drug responses. [86]Organoids are an advanced three-dimensional cell culture model that can be developed from pluripotent stem cells, organ progenitor cells, or adult stem cells that holds the key for understanding cellular processes in vivo, thus enabling elucidation of organ development dynamics, disease progression, and treatment efficacy. The goal remains to better assess therapeutic potential and dosage, thereby guiding treatment protocols prior to clinical trials [87].

Recent efforts have focused on patient-derived in vitro 3D models, tumor organoids, that replicate key features of cancer in vitro, such as angiogenesis, tissue heterogeneity, interactions with the tumor microenvironment, tumor cell invasion, and metastatic potential. Advances in organoid technologies, such as microfluidic platforms and 3D bioprinting technologies, have led to the creation of more relevant 3D biological models for cancer research. Recent advances in 3D bioprinting have enabled the creation of 3D organoids capable of replicating human tissues and microenvironments, as well as drug responses, in line with high-throughput screening results. [88]. Cancer cells derived from patients, combined with genetic material, ECM components, cytokines, and growth factors, can be used to create bioprinted tumor organoids. The autogenously 3D-printed bio-engineered tissue system uses a computer-aided design allowing the creation of multi-layered structures composed of different cell types and compatible biomaterials, enabling the recreation of specific histopathological architectural patterns and cellular arrangements of the tumor. The 3D organoid system thus represents a significant advancement over 2D culture systems mimicking the anatomical and physiological architecture as well as the microenvironment of tumors, capable of bridging the gap between in vitro research and clinical applications. These 3D cancer models represent an ideal platform for the early screening of potential drugs for effective personalized therapies [89,90].

9. Conclusion

Recent advances in cancer genomics, AI-based technologies and single-cell multiomics have made targeted therapy the accepted form of cancer treatment; however, a large amount of investment will be needed for future research, drug discovery, and diagnostics to fully unlock its potential and for its application in the management of cancer. The socioeconomic burden of cancer remains high, as the treatment options for most common cancers have been limited thus far, which is an indication for a renewed approach to expedite drug development to bring effective anticancer agents from the bench to the bedside in a cost-effective manner. The lack of understanding of the genetic heterogeneity of individual cancers has traditionally limited the search for efficacious agents for cancer treatment, and a wide range of possibly suitable agents from other disease areas has been missed. The use of molecular characterization of different cancer types through cancer genomics can help resolve drug-related issues to a reasonable extent by repurposing certain existing drugs as anticancer agents for a wide range of applications, and it will remain at the forefront of precision oncology. Furthermore, the move from tissue-based cancer-specific treatments to genome-based targeted treatments entails the reuse of anticancer drugs prescribed for one type of cancer to treat other cancer types as well. With the increasing understanding of cell signaling mechanisms and genetic alterations in carcinogenesis, considerable progress in cancer treatment may be realized in the near future. Continued research in this area holds the opportunity for improving cancer diagnosis, prevention, and treatment, thereby improving results. Considering that academia, industries, and civil society will work in tandem to cater to the contemporary needs of the system, it is hoped that a wide range of people with cancer will benefit from this new development in cancer research in the future to benefit the system as a whole.

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