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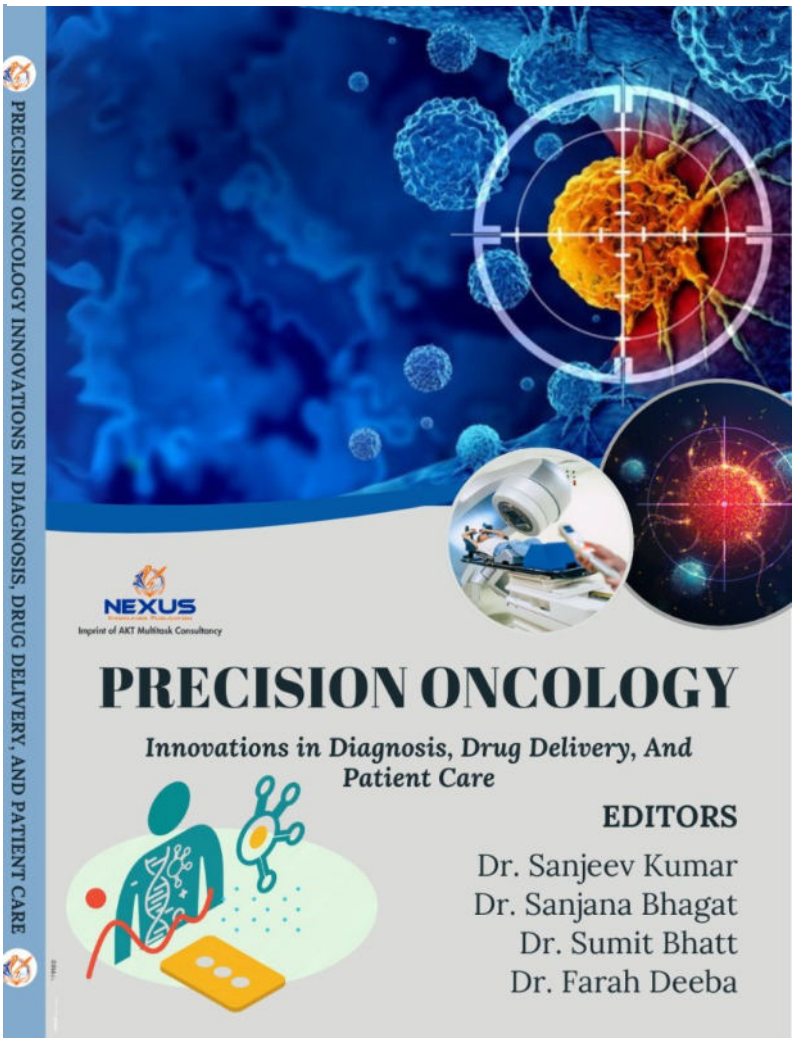
Precision Oncology: Innovations in Diagnosis, Drug Delivery, And Patient Care



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Chapter- 1

INTRODUCTION TO PRECISION ONCOLOGY

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Chapter 1…

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Precision oncology, or personalized or stratified oncology, is a paradigm shift of cancer therapy and understanding. In contrast to the traditional model of disease treatment, which was based on the tumor type, location, stage, and histological peculiarities as the main factors, precision oncology goes deeper into the molecular and genetic background of the disease. Transcriptomic, proteomic, immune signature, and other biomarkers analysis can give the clinician a detailed view of the unique biology that drives the tumor in each patient. Such a molecular-level understanding enables oncologists to determine targeted therapies, immunotherapies, and combination regimens that are most likely to be effective with a particular patient and avoid exposing them to treatment that would be ineffective or too toxic. It also transcends treatment into early detection, prevention and risk stratification which allows more active and personalized treatment of cancer.

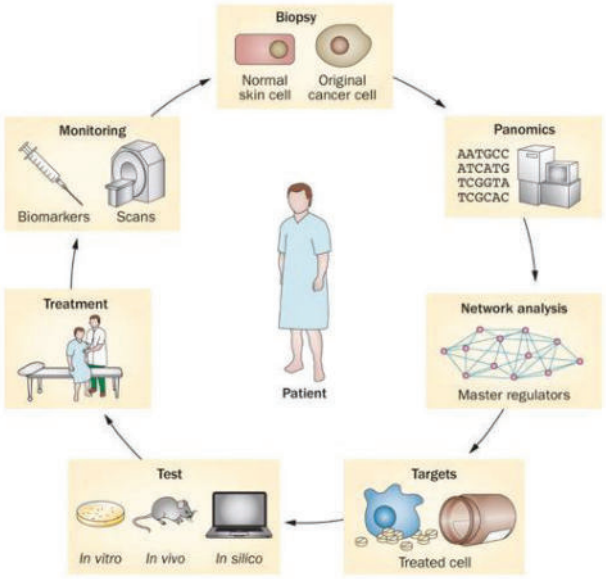

Figure 1: Precision oncology

Source: (https://www.nature.com/articles/nrclinonc.2013.244)

The general objective of precision oncology is to optimize therapeutic efficacy and patient survival and limit avoidable toxicity, side effects and financial burden. It is a holistic and patient-centered approach that considers medical decisions with reference to both biological markers and patient-specifics: overall health, co-morbidities, and personal preferences. The strategy improves life quality by lowering the exposure to untested interventions and increasing the response rate to individual therapies. Moreover, accuracy oncology is cost-effective because it focuses on procedures with a greater probability of success, and avoids wasteful

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spending on wide-spectrum treatment. With future developments in next-generation sequencing, big data analytics, and biomarker discovery, precision oncology is establishing itself as a foundation of contemporary cancer treatment and may offer a future in which cancer treatment is not only more scientifically accurate, but also more human and patient-centric.

1.1. HISTORICAL EVOLUTION: FROM TRADITIONAL TO PERSONALIZED MEDICINE

The history of oncology is marked by a gradual change towards highly personalized care as opposed to the generalized one. During the early-stage, treatment of cancer was depending on the location of the tumor, morphology and staging with surgery, radiation and cytotoxic chemotherapy as the main instruments. Effective in a few of the cases, these approaches were mean, non-selective, and did not always reflect the diversity of tumors. A discovery-based change came with the late 20 th century, with breakthroughs in molecular biology and high-throughput technologies revealing the genomic cancer nature. The discovery of oncogenes, tumor suppressor genes and molecular subtypes showed that tumors with common histology might be biologically different and formed the basis of precision oncology. Targeted treatments such as imatinib in chronic myeloid leukemia and trastuzumab in HER2-positive breast cancer, as well as biomarker-based diagnostics such as PCR, FISH, and next-generation sequencing, pointed to the possibility of matching therapies with a molecular profile of a tumor.

The development of immunotherapy became one of the principal ones, where checkpoint blockers (antiPD-1, PD-L1, and CTLA-4) re-initiate the immune system to combat cancer. This period broadened the use of biomarkers to PD-L1 expression, microsatellite instability, mismatch repair deficiency and tumor mutational burden, and the first histology-agnostic approvals, including pembrolizumab in MSI-high tumors. Multi-omic profiling, single-cell and spatial technologies, liquid biopsies, and adaptive clinical trial designs (basket, umbrella, and platform trials) are considered the drivers of precision oncology today. These advances do not only enhance our knowledge of tumor heterogeneity and resistance, but also increase the speed of drug development and more patients receiving targeted treatment. The specialty has therefore become a systems level, patient-centered model, with biology and not anatomy dictating cancer care.

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❖ **Early era — histology and empiricism**

The early years of oncology were characterized by the initiation of treatment based on the same pattern largely determined by anatomical location of the tumor (e.g., lung, breast, colon) and microscopic characteristics (histology). Pathology reports of tumor morphology, grading and staging were used by clinicians to decide on treatment. The most powerful tools were surgery, radiation therapy and cytotoxic chemotherapy and each one of them was meant to eliminate or reduce the size of a tumor by blindly attacking rapidly growing cells. Although these approaches helped to save more lives of numerous patients, they were commonly characterized by toxicities, inconsistent efficacy, and the lack of personalization, as they failed to consider the biological differences in tumors. Basically, the model was a mass-market model, which was rooted in empiricism more than in molecular knowledge.

❖ **Discovery-driven transition**

The shift of the paradigm started with radical developments in the late 20 th century. Ongcology was redefined by two related revolutions:

1. **Molecular biology and cancer genetics -**The identification of oncogenes (e.g., RAS, MYC), tumor suppressor genes (e.g., TP53, RB1), and cell signaling pathways out of control showed that cancer was not merely a disease of uncontrolled cell proliferation but a genomic disease that was caused by particular molecular changes.
2. **High-throughput technologies -**With the introduction of DNA sequencing, microarray-based methods of gene expression and protein profiling, researchers could now examine thousands of genes and proteins at once. This demonstrated molecular heterogeneity of cancer: a tumor that appeared the same under the microscope could appear biologically distinct, and could have they own weaknesses to therapy. This awareness formed the basis of the idea of molecular subtyping, and the ultimate personalization of therapies.

❖ **Targeted therapy and biomarkers**

Targeted therapies, drugs that disrupt specific molecule drivers necessary to tumor growth and survival, were developed in the late 20 th and early 21 st centuries. Landmark examples include:

- BCR-ABL BCR-ABL inhibitors (imatinib/Gleevec) in chronic myeloid leukemia that turned the once terminal disease into a manageable one.

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- HER2-targeted therapies (trastuzumab/Herceptin) in breast cancer with HER2-positive cancer, which enhanced patients' outcomes in a subset. These achievements highlighted the fact that the process of locating and addressing actionable changes could produce radically and lasting reactions.

Simultaneously, there were parallel developments in diagnostic methods (immunohistochemistry, fluorescence in situ hybridization [FISH], polymerase chain reaction [PCR], and subsequently targeted next-generation sequencing [NGS] panels) to enable clinicians to test tumors on a biomarker basis, and to be assured of giving therapies based on their molecular makeup.

❖ **Immunotherapy and biomarker expansion**

The second revolution was that of cancer immunotherapy particularly immune checkpoint inhibitors such as PD-1, PD-L1 and CTLA-4. These drugs did not affect tumor cells directly as targeted therapies would but instead restored the functioning of the immune system in the patient to recognize and destroy cancer. Their success brought in the necessity of new biomarkers other than the genetic mutations including:

- PD-L1 on tumor/immune cells.
- Instability of micro satellites (MSI-high) and lack of mismatch repair (dMMR).
- Tumor mutational burden (TMB), which is a measure of the general tumor genomic instability.
- Notably, a few immunotherapies received histology-agnostic approval, which implied that they could be used across the cancers based on their molecular characteristics, not the site of the tumor (e.g. MSI-high tumours with pembrolizumab). This was a huge leap in the development of a real personalized medicine.

The approval of pembrolizumab in MSI-high cancers of any anatomical origin was notably the first histology-agnostic approval- solidifying the transition of precision oncology to focus less on site and more on the mutations and mechanisms that drive oncogenesis.

❖ **Current era — multi-omics, liquid biopsy, and adaptive trials**

Precision oncology today is described as a combined, systems-level approach:

- Multi-omic profiling (genomics, transcriptomics, epigenomics, proteomics, metabolomics) offers a system-wide understanding of tumor biology, and can help better understand how resistance is formed and therapy vulnerable points.

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- Single-cell sequencing and spatial technologies enable the resolution of tumor heterogeneity and tumor microenvironment at a new level.
- Liquid biopsies with circulating tumor DNA (ctDNA) and circulating tumor cell analysis provide non-invasive means to follow the progression of the disease, identify small residual disease, and make real-time changes to treatment options.
- Adaptive clinical trial designs, including basket trials (testing a therapy in many different types of cancers with a shared biomarker), umbrella trials (testing many different therapies in a single type of cancer with different subgroups), and platform trials (flexible, evolving trial designs) have enabled faster drug development, and increased patient access to novel therapeutic options, particularly in response to rare genomic alterations.

It was notable that the pembrolizumab approval in MSI-high cancers of any anatomical origin became the first histology-agnostic approval -finalizing the history of precision oncology transitioning to site-independent treatment based on mutations and mechanisms.

1.2. CORE PRINCIPLES AND OBJECTIVES OF PRECISION ONCOLOGY

The premise of precision oncology is to provide highly personalized cancer treatment through detailing both biological and molecular characterization of the tumors. The genetic, transcriptomic and immunologic profiling of each patient cancer is performed to discover specific alterations which may be mutations, gene fusions or immune signatures. Such data facilitates the choice of biomarker-based therapies, whereby the most likely treatment regimen with maximum minimal toxicity is given to patients. Dynamical monitoring techniques, such as circulating tumor DNA and minimal residual disease methods, enable clinicians to monitor the tumor evolution in real time, thereby enabling prompt corrective changes in treatment plans and overall clinical results.

Key to precision oncology is combined, multidisciplinary decision-making, using molecular tumor boards, in which oncologists, geneticists, pathologists, and other experts discuss complex data to formulate clinically actionable treatment courses. Patient-centricity has been a fundamental goal and treatment is designed to meet the specific tastes, quality-of-life, and economic realities. The continuous creation of evidence via adaptive trials, real-world data registries and learning health systems is used to ensure that clinical knowledge continually changes in accordance with new knowledge. Collectively, these principles render precision

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oncology a dynamic, evidence-based and patient-centered paradigm, shifting cancer care away to a one-size-fits-all model, and instead to a precise, patient-centered model.

❖ ***Core principles***

Precision oncology aims to personalize cancer care by molecular profiling, biomarker-directed therapy, and dynamic monitoring with multidisciplinary decision-making, patient-centered care, and ongoing evidence generation through learning health systems.

- **Individualized biological characterization:** Precision oncology focuses on cancer molecular and genetic character, and not just histology or anatomical location. Tumors are profiled to reveal somatic mutations, gene fusions, copy-number changes, epigenetic modifications, expression signatures as well as immune microenvironment features. Such a personalized biological description enables clinicians to value the molecular fingerprint of each tumor and establish the basis of customized treatment.
- **Biomarker-based therapy choice:** Predictive biomarkers help clinicians to make the right drug choice on the right patient. Indicatively, EGFR mutations in lung cancer indicate predictable sensitivity to EGFR tyrosine kinase inhibitor, whereas ALK fusions indicate predictable benefit to ALK inhibitors. On the other hand, adverse biomarkers may prevent futile or toxic therapies. This concept optimizes the effectiveness of treatment in addition to minimizing unnecessary toxicity and expenditures.
- **Dynamic monitoring:** Precision oncology is not a single decision but a permanent journey. It is monitored by techniques like the circulating tumor DNA (ctDNA) assays, minimal residual disease (MRD), and serial imaging to determine tumor changes over time. Such dynamic monitoring would allow the early relapse to be detected, the emergent resistance mutations to be identified and the therapy adjusted promptly away from fixed treatment regimens towards the real-time personalization of treatments.
- **Multidisciplinary, integrated decision-making:** Molecular data is very complex and thus needs to be interpreted collaboratively. Molecular tumor boards (MTBs), which include oncologists, molecular pathologists, geneticists, bioinformaticians and pharmacists, are involved in the review of genomic reports, clinical setting and therapeutic options. Such boards make sure that the decisions are based on science, are relevant to clinical attributes, and are practical in the care environment of the patient.

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- **Patient-centricity and shared decision-making:** Beyond biology, the patient-centric approach to oncology is based on the personal values and treatment preferences of the patient, as well as socio-economic realities. Topics that are discussed are toxicity tolerance, quality-of-life priorities, drugs accessibility, and monetary costs. This will make treatment decisions not only biologically correct, but also in accordance with the principles of patient-centered care.
- **The evidence and learning health systems:** A lot of the genomic changes are infrequent and not widely covered by the randomized trials. Precision oncology is thus based on adaptive clinical trials, registries and real-world evidence platforms to enable ongoing creation of knowledge. Learning health systems allow clinicians to input de-identified patient data and enhance evidence-generation around rare variants and novel drug combinations, plus a feedback loop around improved clinical practice.

❖ ***Primary objectives***

Precision oncology enhances by improving outcomes by matching therapy to tumor biology, decreasing toxicity, enable early detection of relapse and overcome resistance, and add therapeutic options to rare subtypes and increase cost-efficiency by directing resource utilization.

- **Enhance efficacy through tumor biology matching therapy:** Personalized therapies have ensured that therapies are matched to unique molecular weaknesses of a tumor of a patient. Such a fit increases the efficacy of treatment, leading to an increase in response rates, progression-free survival, and the overall outcome in comparison with other, more traditional, non-targeted methods.
- **Reduce toxicity and overtreatment:** Precision oncology can save a patient the hassle of being subjected to ineffective therapies by determining which therapies have little or no likelihood of benefiting the patient. This will minimize the number of adverse effects, hospitalizations, and overall burden of treatment, increasing the quality of life of patients.
- **Earlier detection of relapse or recurrence (MRD monitoring):** Molecular monitoring, like monitoring minimal residual disease (MRD), can help identify relapse or progression before it manifests in an imaging-based observation. Timely intervention enables clinicians to modify the treatment in a timely manner, which may enhance the

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long-term results and even prevent the development of the full-scale disease development.

- **Prevent or overcome treatment resistance:** Clinical researchers can use insights into resistance mechanisms by secondary mutations, circumventing signaling pathways, and phenotypic plasticity to conduct therapies in a strategic manner or employ combination therapies. This preventive therapy has the power to stretch the length of treatment gain and postpone disease advancement.
- **Make rare molecular subtypes and histology-agnostic cases treatable:** Precision medicine has made available new targeted therapies to patients with unusual molecular alterations or histology-agnostic tumors, including tumors with NTRK fusions. This increases the scope of treatment among underserved patient groups in the past.
- **Cost-effectiveness:** Optimize the use of therapeutic resources: Precision oncology can help cut down painful spending on irrelevant treatments by directing therapeutic resources to interventions with the highest probability of success. The practice does not only improve patient outcomes but it promotes sustainable healthcare provision and use of clinical resources effectively.

❖ ***Typical clinical workflow***

Precision oncology is a step process, which involves collecting tumor or liquid biopsy samples, molecular testing and interpreting data supported by bioinformatics, which is followed by professional review of the tumor board. On this basis, patients are given customized therapies or trial alternatives, and continuing monitoring is done using imaging and biomarkers to make a dynamic adjustment to treatment.

1. **Sample & data acquisition:**

Precision oncology begins with the acquisition of high-quality biological material on which to run its analyses. In a traditional approach, this is done by means of tumor tissue biopsies, which allow direct access to cancer cells. Nevertheless, when insufficient tissues, inaccessible tissues, or repeated sampling is necessary, liquid biopsies- the analysis of the circulating tumor DNA (ctDNA) or circulating tumor cells (using blood plasma) are becoming more common. Also, the germline DNA samples (blood or saliva) can be provided when the hereditary cancer syndromes are suspected to separate between inherited and tumor-specific changes.

2. **Molecular testing:**

After samples are gathered, there are various molecular tests that can be used based on the clinical requirement and resources. This can be targeted next-generation sequencing (NGS) panels to measure actionable mutations; whole-exome or whole-genome sequencing to measure extensive genomic profiles; RNA sequencing to measure fusion detectors, expression patterns; immunohistochemistry (IHC) to measure protein expression (e.g., HER2, PD-L1); fluorescence in situ hybridization (FISH) to measure gene amplification or rearrangements; methylation profiling to measure epigenetic markers. This step produces an effective molecular dataset upon which precision treatment is based.

3. **Bioinformatic analysis & interpretation:**

The raw molecular information is subjected to sophisticated bioinformatics pipelines to determine genetic variations, structural rearrangements, and changes in expression as well as in epigenetics. Every change is marked with its pathogenic and therapeutic interest, and it is possible to distinguish between driver mutations, passenger mutations, and variants of uncertain interest. Analysis identifies actionable targets, prognoses sensitivity or resistance to particular therapies and produces a clinically interpretable report that oncologists can employ in decision-making.

4. **Molecular tumor board review:**

Due to the fact that the complexity of genomic data is often beyond the knowledge of individual clinicians, multidisciplinary molecular tumor boards (MTBs) are assembled. These are oncologists, molecular pathologists, geneticists, bioinformaticians, and pharmacists, with all of them consulting the genomic results and analysing them relative to the clinical history of the patient, the type of tumour, previous treatments and comorbidity. The agreement of the board makes sure that treatment recommendations are scientifically valid, clinical feasible, and in line with patient-specific requirements.

5. **Treatment selection & access:**

According to the recommendations of the MTB, patients are paired with specific-targeted therapies, immunotherapies, or applicable clinical trial opportunities. In the absence of approved options, off-label drug use can be an option provided that it is accompanied by molecular rationale and clinical evidence. Treatment may also imply a process of negotiating

regulatory approvals, insurance access, and pricing, and thus this step is an important interface point between science and the healthcare systems.

6. **Monitoring & adaptation:**

Precision oncology is not a static situation. Monitoring of treatment responses includes imaging studies, serum biomarker, and more recently, liquid biopsy assays that can follow ctDNA as a disease burden and resistance marker. Identifying minimal residual disease (MRD) or emerging resistance mutations at an early stage enables timely adjustment of treatment plans, including sequencing therapy, combination therapy, or trial alternative, such that treatment is adaptive and individualized over the course of the disease.

❖ ***Key practical concepts***

Limitations of clinical actionability of most variants, clonal heterogeneity within tumors, and resistance mechanisms are among the challenges that Precision oncology is facing. It also calls on the ability to differentiate between somatic and germline mutations that have consequences both in treatment and in hereditary risk management.

- **Actionability:** Not all genomic changes can be taken clinical action. Most of them are classified as variants of uncertain significance (VUS), which may only undergo additional research before they can be applied in treatment. The availability of therapies, the strengths of evidences, and approval status determine the clinical actionability.

- **Clonal heterogeneity:** Clonal heterogeneity is characterized by common occurrence of more than one subclone within a particular tumor with different genetic mutations. One biopsy might not reflect on this diversity resulting in incomplete molecular profiling. Efforts such as multi-region sampling or liquid biopsies are useful in overcoming this obstacle.

- **Cancers often resist in multiple ways (including, but not limited to):** secondary mutations of the target gene (e.g., T790M in EGFR), activation of bypass signaling pathway(s) (e.g., MET amplification), phenotypic changes (e.g., epithelial-to-mesenchymal transition), or immune evasion. Handling resistance involves sequential therapy, combination therapies that are rational and monitoring.

- **Germline vs somatic:** Precision oncology separates somatic mutations (only tumor cells have restricted sets of mutations) and germline mutations (inherited and found in

all cells). Germline discoveries, e.g. BRCA1/2 mutations, are information that has applications in hereditary cancer risk, family counseling and prevention measures, as well as determining treatment options (e.g., PARP inhibitors).

1.3. SCOPE ACROSS CANCER TYPES AND STAGES

Precision oncology is applicable to the whole range of cancer treatment, providing patient-centered interventions at all phases of the disease. Molecular profiling in early-stage cancers can inform adjuvant therapy with the aim to determine patients who may benefit most of the treatment after surgery. Further, the use of minimal residual disease (MRD)-centered approaches helps to identify microscopic disease that might persist after treatment and intervene at the earliest stage to minimize the probability of relapse. These methods do not only help in refining treatment selection but also reduce exposure to treatment that is not vital thus preventing toxicity and loss of quality life to patients.

In the locally advanced and metastatic cancers, precision oncology promotes the use of biomarker-guided combination therapy, which is created to ensure treatment efficacy and reduce adverse effects. In unusual, or hard-to-treat malignancies, molecular and immunologic profiling makes it possible to target therapies, immunotherapies, or participate in novel clinical trials previously unavailable. This population of patients with traditionally limited therapeutic options has better outcomes due to the combination of treatment with the unique genetic and immunological properties of tumors. All in all, precision oncology offers a dynamic model of individualized care, enhanced treatment response, and increased clinical opportunities in cancer types and stages.

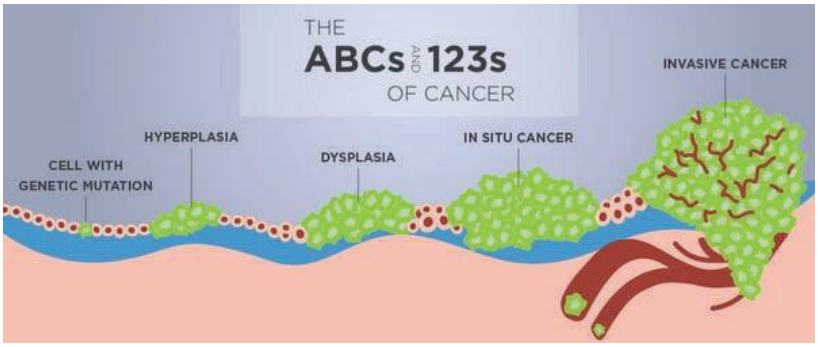

Figure 2: The ABCs and 123s of Cancer Stages

Sources: (https://www.lanermc.org/community/lane-health-blog/the-abcs-and-123s-of-cancer-stages)

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There is also a range of cancer types and patients where precision oncology can be applicable. Strategies are tailored to hematologic malignancies as opposed to solid tumors and to pediatric cancers, in which there are special considerations of genetic and developmental factors that determine the choice of therapy. In addition to treatment, precision oncology can be used in the prevention and risk stratification by performing germline tests and individualized screening programmes. The combination of molecular knowledge and aspects of the individual patient enables earlier interventions, more effective monitoring and more effective specific treatment approaches, thereby ensuring that cancer management is more accurate, proactive and personalized at all stages of the disease and in all its forms.

- ***Early-stage disease (curative intent)***

Oncology, Precision oncology in early-stage cancers, the aim is to cure, and precision oncology supports the refinement of perioperative and adjuvant approaches. The use of biomarker-guided escalation (including the addition of specific or immune-based treatment to high-risk patients) and de-escalation (preventing unnecessary treatment in the low-risk group) is increasingly embraced. E.g., in breast cancer, HER2 or hormone receptor status guides adjuvant therapy choice, and, in lung cancer, adjuvant EGFR inhibitors can be given to EGFR-mutated tumors following surgery. One of the significant emerging instruments is minimal residual disease (MRD) detection with ctDNA, which may identify microscopic disease post-operative or chemotherapy and subsequently customize the need, intensity, and period of adjuvant therapy.

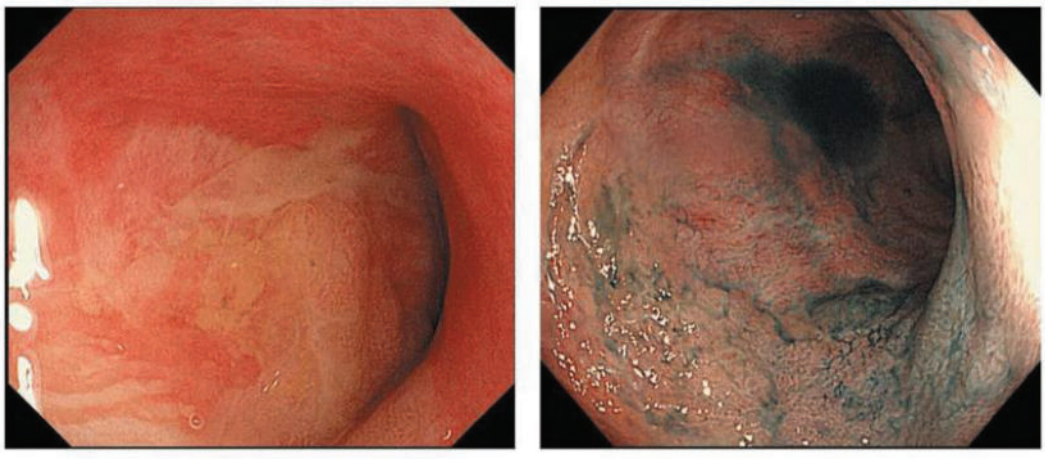

Figure 3: Early-Stage Cancers

Sources: (https://www.researchgate.net/figure/A-visible-lesion-that-remained-an-early-stage-cancer-after-36-months-Left-picture-IIa_fig3_304630008)

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- ***Locally advanced disease***

Precision oncology is used to inform combination strategies in cancers that are locally advanced but might be cured. Molecular profiling can support radio sensitization opportunities (e.g., repairing DNA repair pathways to boost the efficacy of radiotherapy) and allows the combination of targeted or immune agents with chemoradiation. In cancer types such as rectal or head-and-neck cancers, organ-specific biomarkers inform organ-preservation techniques and reduce morbidity with no harm to survival rates. Therefore, the decisions which are precision-guided moderate aggressive therapy and long-lasting functional outcomes.

- ***Metastatic disease (palliative/long-term control)***

Precision oncology has the most mature applications in advanced or metastatic cancers in which a treatment option is used to extend life and preserve quality of life. Targeted treatments (e.g., EGFR, ALK, ROS1 inhibitors in lung cancer; BRAF inhibitors in melanoma; PARP inhibitors in ovarian cancer) and immunotherapies (e.g., checkpoint inhibitors of PD-L1+ or MSI-high tumors) are being regularly paired with molecular changes. Notably, histology-agnostic approvals, including NTRK fusions or high levels of microsatellite instability have broadened the therapeutic potentials of patients with rare underlying genomic drivers, irrespective of the site of tumor origin.

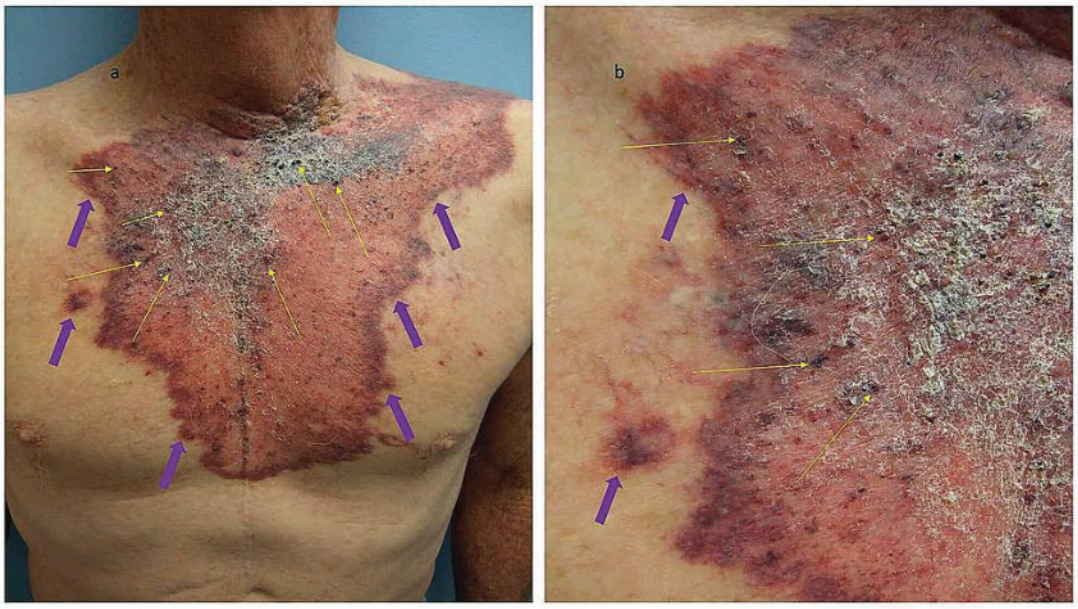

Figure 4: Metastatic Cancers

Source: (https://www.cureus.com/articles/49635-cutaneous-metastatic-cancer-carcinoma-hemorrhagiectoides-presenting-as-the-shield-sign#!/)

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- ***Hematologic malignancies vs solid tumors***

Hematologic malignancies are frequently associated with clear genetic drivers that render them highly susceptible to targeted therapies. As an example, in chronic myeloid leukemia (CML) BCR-ABL fusion protein can be blocked successfully by tyrosine kinase inhibitors, in acute myeloid leukemia (AML) FLT3 mutations can dictate the use of specific FLT3 inhibitors, and in some lymphomas, BTK dependency can be used to precisely block B-cell receptor signaling. The comparative genetic ease and accessibility of these cancers in the blood or bone marrow allow rapid application of molecular targeted interventions, which in most cases produce impressive clinical effects and better survival rates.

By contrast, solid tumours are more complex biologically in terms of space heterogeneity, tumor microenvironmental effects, and subclonal diversity within tumour lesions. These aspects are problematic to the process of recognizing and taking advantage of actionable molecular targets. However, precision oncology methods are finding greater application to solid tumors, with thorough profiling of diverse mutations, amplifications, or pathway dependencies that can be therapeutically exploited, possible via next-generation sequencing (NGS) and other molecular profiling techniques. Although approach to targeted strategies varies with the biology of tumors and accessibility to the tissues, the overall objective is the same: to pair the appropriate therapy with the individual molecular features of the patient, enhancing specificity of therapy, its effectiveness, and overall outcomes.

- ***Pediatric cancers***

In contrast to the situation with adult cancers, the burden of mutation and driver patterns in pediatric tumors vary dramatically. The number of somatic mutations is usually lower in pediatric cancers, however, these cancers can have highly specific genetic changes that propel tumor progression. Such examples are ALK mutations in neuroblastoma and fusion-driven events in other sarcomas, which can be addressed as actionable targets of therapy. Due to this unique molecular profile, accurate oncology in children needs to identify these essential changes with special attention to maximize the results and create a treatment choice. More sophisticated methods of sequencing and molecular profiling technologies are finding their way into pediatric oncology, with the ability to offer more personalized and precise treatment.

The application of precision oncology in pediatric clinical trials is increasingly possible, and programs such as the Pediatric MATCH trial indicate that it can be feasible to assign biomarker-guided therapies. Nevertheless, pediatric patients are vulnerable and require special

considerations because of the unique vulnerabilities. Targeted and immune-based therapies are of special interest in long-term toxicities, which may affect growth, development, and general quality of life. Decisions about treatment in children are thus a balance between the possible survival advantage and the risks of adverse effects and effective monitoring and long-term follow-up of treatment are key elements in pediatric precision oncology programs.

- ***Rare cancers & tumor-agnostic indications***

In the past, in most rare cancers patients have had scarce therapeutic options because of low trial enrolment and little commercial interest in drug development to treat these rare cancerous diseases. Traditional methods tended to produce an inferior result, which meant that these groups were under-served. The introduction of precision oncology has changed this situation to allow the use of molecularly guided treatment strategies even in low-incidence cancers. Basket trials, where patients are recruited on the basis of common molecular changes and not on tumor type, and platform studies have paved the way to assess targeted therapy in these hitherto neglected patient groups. These new trial designs enable the researchers to study the effectiveness of drugs on several types of cancer at once, speeding up the potential of effective treatment to patients with rare tumors.

Tumor-agnostic therapies are an example of the potential of molecularly driven oncology, whereby treatment choices are made based on unique genetic or molecular characteristics and not on the tissue of origin. Prominent examples are therapies that address NTRK fusion-positive tumors or microsatellite instability-high (MSI-H) tumors, which have shown clinical effect on a broad range of tumor types. The treatment of patients with rare or traditionally incurable cancers can provide new treatment opportunities through this technique because it is based on the molecular signature of the tumor and not its location. These approaches demonstrate the shift in oncology paradigm in which precision medicine can be used to provide increased applicability, individualized treatment, and potentially better patient outcomes because they were previously limited in treatment choices.

- ***Prevention and risk stratification***

Precision oncology is not used only in the treatment, but it is also pertinent in prevention and early cancer diagnosis. Germline genetic tests can be used to identify patients with inherited cancer predispositions, including BRCA1/2 mutation carriers or BRCA2 Lynch syndromes. Identifying these high-risk individuals means active intervention can be done such as increased surveillance, risk-reduction surgeries or chemoprevention, based on their unique genetic

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profile. These measures have the potential to be much more effective than cancer treatment; they can decrease morbidity and mortality by preventing cancer progression, which proves the preventative strength of precision oncology.

In addition to personal testing, the population-based risk stratification is becoming more informed by polygenic risk scores and molecular models that would help to better inform the intensity of screening and tailor the prevention measures. As an illustration, BRCA mutation carriers can experience earlier and more frequent breast imaging, and Lynch syndrome mutation carriers are on harder colonoscopy regimens. Such methods enable clinicians to use resources effectively and target preventive measures where they are most applicable as well as reduce unnecessary interventions to low risk groups. By so doing, precision medicine can not only expand its influence on treatment, but also on prevention, creating a care continuum that ensures the prevention of cancer, but at the same time maximizes patient outcomes.

1.4. GLOBAL TRENDS AND RESEARCH PRIORITIES

The use of state-of-the-art technologies, like multi-omics profiling, single-cell and spatial analyses, liquid biopsies, and artificial intelligence (AI) has grown to be the driving force in global trends in precision oncology. Such strategies allow clinicians and scientists to get an in-depth insight into tumor biology and personalize the treatment, as well as track tumor dynamics in real-time. The data sharing via the cloud also enhances the speed at which the knowledge is disseminated, leading to research collaboration across the borders of institutes and countries. The combination of these innovations aid in the discovery of novel resistance mechanisms, adaptive therapeutic approaches, and patient specific outcomes as treatments are customized to the molecular and cellular properties of individual tumors.

Simultaneously, the research priorities are changing to accommodate scientific and systemic issues in precision oncology. Newer clinical trial designs such as adaptive, combination therapy and N-of-1 studies are utilized in order to speed up drug testing and the strategies to treat patients in ways that are optimal. At the health system level, the focus is made on offering fair access to complex diagnostics and therapies, adjusting regulation systems to new trial designs, cost-effectiveness, clinical utility evaluation, and ethical implementation of interventions. All these priorities are intended to help bring technological improvements positively to the care of patients and reduce inequalities and capitalize on the effect of precision oncology globally.

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❖ Technological and Data Trends

The latest developments in multi-omics, spatial omics, liquid biopsies, AI, and cloud-based data sharing allow personalized and detailed tumor profiling, real-time monitoring, and predictive modeling, so innovations in the field will push towards more effective and personalized treatment of cancer.

- **Multi-omics and single-cell technologies:** Recent technological developments in genomics, transcriptomics, proteomics, metabolomics and epigenomics enable investigators to measure several layers of molecular information on tumors simultaneously. Single-cell sequencing offers a resolution to heterogeneity in tumors that has never been observed before, showing variability in gene expression, mutation patterns and cellular states even among tumor cells adjacent to one another. These differences are important to understand so that resistant subclones can be identified, disease progression can be predicted, and treatment can be individualized to each tumor ecosystem.
- **Spatial omics:** Spatial transcriptomics and proteomics provides a map of the physical positioning of cells in the tumor microenvironment. These methods will show cell cell interactions, immune infiltration patterns, and internal structure of tumors by retaining spatial context. Such understanding can be used to understand why certain areas of a tumor are sensitive to treatment and others are not, informing more efficient, targeted treatment.
- **Liquid biopsies:** Liquid biopsy technologies rely on circulating tumor DNA (ctDNA), exosomes, and circulating tumor cells (CTCs) to continuously monitor tumor dynamics with nonexploitative methods. They facilitate the early discovery of cancer, monitoring of minimal residual disease (MRD) post-surgery or therapy and discover novel resistance mutations. Liquid biopsies of serial sampling give a real time picture of the tumor evolution, and hence timely therapeutic corrections can be made.
- **AI and machine learning:** AI and machine learning (ML) are finding more and more applications to analyze varied extensive molecular data, predict phenotypes, model drug responses, and find patients who would respond better to specific clinical trials. These algorithms have the potential to combine genomic and clinical and imaging information to produce actionable insights more quickly than traditional approaches and thus accelerate precision oncology workflows.

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- **Cloud and federated data sharing:** Collaborative systems and cloud-based systems enable the sharing of big oncology datasets across institutions in a secure manner and maintain patient privacy. The federated learning methods can be used to create predictive models based on decentralized data without necessarily comingling sensitive data. The method improves the identification of rare biomarkers, cross-population validation of molecular signatures, and facilitated research reproducibility.

❖ **Clinica and Trial Design Trends**

The combination of therapies, innovative trial designs, including adaptive, platform, basket, umbrella, and N-of-1, allow both personalized and efficient testing of targeted strategies and treatments to overcome resistance in cancer.

- **Adaptive trials, platform trials, basket trials, and umbrella trials:** New trial designs are more effective in addressing targeted therapies. With adaptive trials, one is able to make adjustments based on initial findings. Platform trials are trials in which more than one treatment is tested on a common control group. Basket trials compare a single therapy in a wide range of tumor types with a common molecular feature, whereas umbrella trials compare more than one therapy in a tumor type stratified by sub-groups based on their molecular characteristics. Such designs speed up the process of identifying effective treatments and limit patient exposure to non-effective treatments.
- **Combination strategies: Immunotherapies:** Combinations of targeted agents, immunotherapies and epigenetic drugs are a major strategy to overcome primary and acquired resistance. The combinations are rationally dictated by a knowledge of molecular pathways, tumor heterogeneity, and immune evasion. The strategies are geared towards greater efficacy, increased response time and elimination of tumor adaptation.
- **n-of-1 and precision trial designs:** N-of-1 trials are conducted when the patient has a unique or rare molecular profile, and in this case, the treatment regimen is wholly personalized. Every patient is his or her own control, and it is possible to evaluate extremely individualized treatment options. These types of designs are becoming more and more applicable because molecular profiling is discovering patient-specific actionable mutations that are not reflected in larger populations.

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❖ Implementation and System-Level Priorities

The safe and sustainable adoption of precision oncology in the global arena requires equitable access, adjustment of regulations, cost-effectiveness, clinical utility, and ethical supervision to be ensured.

- **Equity and access:** Inequality in molecular testing and access to targeted therapies as well as engagement in clinical trials is still critical globally. There is a need to work towards equality in access to precision oncology particularly in low- and middle-income nations and underserved groups living in high-income areas.
- **Regulatory frameworks:** Regulators are adjusting to tumor-agnostic drug approvals, in which drugs are endorsed depending upon molecular markers, as opposed to tumor type. The standardization of companion diagnostics and agreement on testing criteria is a key to uniform patient selection and safe application of precision therapy.
- **Cost-effectiveness and reimbursement models:** Health systems and payers need evidence that precision-guided care is cost-effective to make a change and the outcomes of such care are better. Value-based reimbursement models, and cost-effectiveness studies are needed to support the broad application of molecular diagnostics and targeted therapies.
- **Clinical utility and outcomes:** Strong evidence supporting that molecularly directed interventions enhance survival, quality of life and use of healthcare resources is essential. Clinical outcomes combined with patient-reported outcomes and economic analysis as longitudinal studies provide information to inform clinical practice and policy decisions.
- **Ethical, legal and social concerns:** Precision oncology entails a number of ethical issues such as informed consent to genomic sequencing, data protection, handling of incidental germline findings, and resource priority. Resolving these concerns will guarantee the trust of the patients and fair use of new technologies.

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