CHAPTER 1

Introduction to Cancer and Precision Medicine

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1.1 Overview of Cancer Biology and Progression

1.1.1 Definition and General Features

Cancer comprises a heterogeneous set of diseases in which cells acquire the capacity for uncontrolled proliferation, local invasion, and, often, distant metastasis [1, 2]. In normal tissues, proliferation, differentiation, and programmed cell death are coordinated by cell intrinsic programs and external cues such as growth factors, contact inhibition, DNA damage checkpoints, senescence, and apoptosis [3]. Malignant transformation reflects the progressive failure of these safeguards.

The resulting neoplasms are highly diverse. Hundreds of histopathological entities have been described, each shaped by its cell of origin, tissue context, immune surveillance, and environmental exposures [4, 5]. Two complementary views help organize this complexity. First, cancer as a genomic disease: tumors accumulate "driver" alterations such as mutations, copy-number changes, structural rearrangements, and epigenetic reprogramming that confer a selective growth advantage [6, 7]. Second, cancer as an evolving ecosystem: malignant cells interact with stromal and immune cells and co-adapt under selection pressures imposed by the tumor microenvironment (TME) and by therapy [8, 9]. Both perspectives underpin modern diagnostics and precision therapeutics.

1.1.2 Tumor Microenvironment (TME) and Heterogeneity

TME comprises not only cancer cells but also cancer-associated fibroblasts (CAFs), endothelial cells, and a diverse immune infiltrate, including T and B cells, NK cells, dendritic cells, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) [10, 11]. These populations communicate through cytokines, chemokines, growth factors, and danger signals.

This cross talk influences almost every aspect of tumor behavior. CAFs remodel extracellular matrix and secrete pro-angiogenic factors; TAMs and MDSCs often adopt immunosuppressive phenotypes that support angiogenesis and metastasis; regulatory T cells dampen effector responses; and disorganized vasculature creates hypoxic, acidic niches that foster the selection of more aggressive clones [10–12]. Conversely, effective antigen presentation by dendritic cells and sustained cytotoxic T-cell infiltration can restrain tumor growth and predict response to immune checkpoint blockade [12, 13].

Intratumor heterogeneity arises from the interplay between genetic diversification and microenvironmental selection. Different regions of the same tumor, or different metastases in one patient, may harbor distinct subclonal mutations and immune landscapes. This heterogeneity underlies variable responses and is a major challenge for precision oncology.

1.1.3 Hallmarks of Cancer and Key Mechanistic Pathways

The "hallmarks of cancer" framework proposed by Hanahan and Weinberg summarizes the functional capabilities that malignant cells acquire despite their diversity [14, 15]. In the original formulation, six core hallmarks were described. Cancer cells sustain proliferative signaling by producing autocrine growth factors, overexpressing receptors, or activating downstream cascades such as RAS-RAF-MEK-ERK and PI3K-AKT-mTOR, thereby uncoupling proliferation from normal environmental cues [14, 16]. They evade growth suppressors by inactivating tumor suppressors such as RB1 and TP53 or disrupting antiproliferative signaling pathways, abrogating cell-cycle checkpoints [17].

Malignant cells resist cell death, for example, through overexpression of anti-apoptotic BCL-2 family proteins or inactivation of pro-apoptotic mediators such as BAX or BIM, enabling survival under genotoxic or oncogenic stress [14, 18]. They enable replicative immortality by reactivating telomerase (hTERT) or engaging alternative lengthening of telomeres (ALT), circumventing telomere-driven senescence [19]. To grow beyond a few millimeters, tumors induce angiogenesis, often via upregulation of VEGF and related factors, creating abnormal vasculature that supports growth yet imposes hypoxic stress [14, 20]. Finally, they activate invasion and metastasis through epithelial-mesenchymal transition (EMT), matrix metalloproteinase-mediated matrix degradation, altered adhesion, and cytoskeletal remodeling [14, 21].

An updated framework added two additional hallmarks and highlighted two "enabling" characteristics [15]. Tumors reprogram cellular energetics, favoring aerobic glycolysis (the Warburg effect), enhanced glutaminolysis, and increased lipid synthesis to support biomass accumulation and redox homeostasis [22, 23]. They also avoid immune destruction by downregulating antigen presentation, expressing inhibitory ligands such as PD-L1,

secreting immunosuppressive cytokines, and recruiting Tregs and MDSCs to build a tolerogenic microenvironment [24, 25].

These capabilities rest on genome instability and mutation, which accelerate the emergence of driver alterations and subclonal diversity, allowing tumors to explore different adaptive solutions under microenvironmental and therapeutic pressures. The other enabling characteristic of cancer is tumor-promoting inflammation, which provides growth and survival signals, pro-angiogenic mediators, and reactive oxygen species that foster genetic damage and immune evasion [2]. Together, the hallmarks and enabling traits provide a conceptual map of malignant phenotypes and align with recurrently perturbed pathways, including mitogenic signaling, cell-cycle and apoptotic control, telomere maintenance, angiogenesis, invasion, metabolism, and immune regulation.

Crucially, this framework also shaped the evolution of precision medicine. By structuring complexity into recurring capabilities such as proliferative signaling, angiogenesis, immune escape, and metabolic rewiring, it highlighted specific targets (e.g., epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), BCL-2, PD-1/PD-L1, and PARP) and corresponding biomarkers that could be exploited therapeutically [14, 16].

1.1.4 Summary

Cancer is best understood as a dynamic, evolving ecosystem driven by genomic and epigenomic alterations, shaped by microenvironmental interactions, and sculpted by host immunity and therapy. This complexity helps explain why uniform treatment strategies often fail and why precision medicine, diagnosing the actionable biology of each patient's tumor and adapting therapy over time has become central to modern oncology.

The hallmarks of cancer provide a unifying scaffold linking genotype, pathway dysregulation, and clinical phenotype. They enabled a shift from "one-size-fits-all" cytotoxic regimens to rational, pathway-directed interventions and still underpin patient-specific drug selection, companion diagnostics, and biomarker-enriched trial designs that shape how precision oncology is conceived and implemented.

1.2 Historical Advancements in Cancer Diagnosis and Treatment

1.2.1 The Formative Era: Clinical Recognition, Histopathology, Surgery, and Early Systemic Therapy

For much of medical history, cancer was recognized by visible or palpable masses, ulcerating lesions, or progressive cachexia, rather than by precise tissue diagnosis. Autopsies and gross pathology helped distinguish tumors from infection or degeneration, but systematic

classification only became possible with the rise of microscopic pathology in the nineteenth century, particularly through Virchow's work linking cellular morphology to disease. The introduction of formalin fixation, paraffin embedding, and routine hematoxylin–eosin staining in the late nineteenth and early twentieth centuries allowed reproducible recognition of malignant patterns and laid the foundation for histologic classifications and staging systems [26].

Treatment advances followed diagnostic capability. Improvements in anesthesia, antisepsis, and technique made surgery the first reliable curative option for localized solid tumors. The discovery of X-rays and the rapid adoption of radiation therapy provided a nonsurgical modality for locoregional control [27]. By the mid-twentieth century, cytotoxic chemotherapy added systemic options that could cure selected hematologic malignancies and germ cell tumors when combined with local therapies [28]. Yet diagnosis remained largely morphologic and anatomical; cancers were still defined by where they arose and how they looked, rather than by their molecular drivers.

1.2.2 Histopathology as the Foundation of Tissue-based Diagnosis

Histopathology has been the bedrock of cancer diagnosis for more than a century. Early descriptions focused on broad categories (carcinoma vs. sarcoma), degree of differentiation, and invasion beyond the basement membrane. Over time, refinements in processing, staining, and classification made histopathology a powerful predictive and prognostic tool.

Special stains added functional context, and grading and staging systems including Broders', Nottingham, and tumor-node-metastasis (TNM) linked microscopic features to outcome. The introduction of immunohistochemistry (IHC) in the latter half of the twentieth century allowed the detection of specific proteins in formalin-fixed tissue. Initially used to clarify lineage, IHC soon became central to diagnostic subtyping and therapeutic stratification. In breast cancer, for example, expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) helps identify candidates for endocrine and HER2-targeted therapies [29, 30].

Today, histopathology is a biomarker-rich platform integrating morphology, protein expression, and in situ nucleic acid detection. Even in the genomic era, most molecular tests still depend on the pathologist's assessment of tumor content and quality, making histopathology indispensable to precision oncology.

1.2.3 Chromosomal and Molecular Diagnostics

Direct evidence that cancer is a genomic disease came from chromosomal and cytogenetic analysis. The Philadelphia chromosome in chronic myeloid leukemia, a recurrent t(9,22) translocation generating the BCR::ABL1 fusion gene, showed that specific chromosomal lesions could define distinct cancer subtypes [31]. Karyotyping and later

fluorescence in situ hybridization (FISH) revealed recurrent abnormalities in leukemias, lymphomas, and some solid tumors, enabling finer classification and risk stratification [31, 32].

In parallel, molecular pathology emerged with polymerase chain reaction (PCR), Sanger sequencing, and eventually real-time PCR and gene-expression profiling. These methods allowed sensitive detection of minimal residual disease (MRD) (e.g., BCR::ABL1 fusion transcripts), identification of point mutations and indels in oncogenes and tumor suppressors (e.g., KRAS proto-oncogene, GTPase (KRAS), EGFR, and BRAF), and measurement of expression signatures associated with prognosis or treatment response.

Breast cancer provided early examples of companion diagnostics, where ER/PR and HER2 assays directly influenced systemic therapy [29, 30]. In chronic myeloid leukemia (CML), BCR::ABL1 testing evolved from a diagnostic marker to a therapeutic target once imatinib became available, establishing the modern template: a defined molecular lesion, a matched targeted drug, and a sensitive assay to monitor disease burden [31, 33]. Diagnosis began to ask not only "where is the tumor and what does it look like?" but also "what lesions drive it and can they be targeted?"

1.2.4 Imaging-Based Diagnostics and Serum Biomarkers

Imaging has been essential for detecting lesions, defining anatomical extent, staging, and assessing response. The historical trajectory runs from plain radiography, through ultrasound, to cross-sectional and functional imaging [27, 34]. X-rays revealed lung and bone lesions; mammography became a diagnostic and then a screening tool for breast cancer. Ultrasound offered a radiation-free method for evaluating soft tissue and abdominal organs and for guiding procedures.

The advent of computed tomography (CT) in the 1970s enabled cross-sectional imaging of the whole body, improving detection of deep tumors, nodal disease, and visceral metastases and allowing more precise surgical and radiotherapy planning. Magnetic resonance imaging (MRI) added superior soft-tissue contrast and multiplanar capability without ionizing radiation, particularly valuable for brain, spine, pelvis, and musculoskeletal tumors.

Nuclear medicine, especially positron emission tomography (PET) with tracers such as ^{18}F-FDG, added a metabolic dimension [34]. PET/CT and PET/MRI integrate anatomical and functional information, improving sensitivity and specificity for nodal and distant metastases and providing early indicators of treatment response. In parallel, serum tumor markers such as PSA, AFP, CA-125, and CEA offered simple, repeatable assays for surveillance and, in some settings, early detection or MRD assessment [35].

Refinement of staging systems, notably TNM, incorporated imaging findings and standardized prognosis and clinical trial design. Over time, the field has moved from single-analyte markers to multi-parametric and multi-omic signatures, but the historical progression from plain films to CT/MRI to PET, and from crude markers to more specific biomarkers, has been central to making diagnosis earlier, more accurate and more tightly coupled to therapy.

1.2.5 Cytotoxic Chemotherapy and Radiotherapy

The first effective anticancer drugs appeared in the mid-twentieth century, often through serendipity. Nitrogen mustards, developed as chemical weapons, were found to cause profound lymphoid and myeloid suppression, prompting their use in lymphoma; antifolates such as aminopterin induced remissions in childhood leukemia. Early chemotherapy was empirical and toxic, but the concept of combination chemotherapy, using drugs with different mechanisms and nonoverlapping resistance, transformed diseases such as Hodgkin's lymphoma and childhood acute lymphoblastic leukemia from uniformly fatal to frequently curable [28].

In parallel, radiation therapy evolved from orthovoltage X-rays and radium applicators with rudimentary dosimetry to megavoltage cobalt units and linear accelerators, CT-based planning, three-dimensional conformal techniques, intensity-modulated and image-guided radiotherapy, and stereotactic approaches. These advances allowed better tumor coverage, sparing of normal tissues, and in selected settings, organ-preserving curative treatment.

Chemotherapy and radiotherapy became integrated as concurrent chemoradiation in several locally advanced cancers (e.g., head and neck, cervix, rectum, and lung) [28]. Historically, these modalities showed that systemic and local treatments could cure disseminated or locally advanced disease, setting benchmarks that later targeted and immune therapies would be measured against.

1.2.6 Endocrine Therapy and Early Targeted Treatment

Endocrine manipulation provided some of the earliest rationally targeted cancer therapies. Clinical observations that oophorectomy or adrenalectomy could induce regression of some breast cancers and that orchiectomy could palliate prostate cancer suggested hormone dependence [26]. This led to modern endocrine therapy: selective estrogen-receptor modulators, aromatase inhibitors, and ovarian suppression in ER/PR-positive breast cancer, and androgen-deprivation and androgen-receptor targeted agents in prostate cancer [29, 30].

Endocrine therapy demonstrated that tumors can be addicted to specific signaling pathways and that simple, robust biomarker assays (ER/PR IHC) can guide treatment with favorable toxicity compared to nonspecific cytotoxic drugs [36]. It is often regarded as the first major "targeted" systemic therapy.

1.2.7 Molecular Targeted Therapies and Oncogene Addiction

Molecular targeted therapies are built directly on chromosomal and molecular diagnostics. Imatinib in CML, by inhibiting the BCR::ABL1 tyrosine kinase, achieved deep, durable remissions with comparatively mild toxicity and validated the concept of oncogene addiction in humans [33]. In solid tumors, trastuzumab for HER2-overexpressing breast cancer was another landmark, solidifying the triad of a defined lesion (HER2 amplification), a companion diagnostic (HER2 testing), and a matched agent (trastuzumab) [30, 37].

Subsequent decades saw approval of multiple inhibitors targeting EGFR, ALK, ROS1, BRAF, MEK, BTK, PI3K, and others [32, 33, 37]. More recently, tumor-agnostic approvals for NTRK fusions, RET alterations, and BRAF V600E in selected contexts have further shifted thinking from "what organ?" to "what alteration?" [38]. At the same time, experience with targeted therapy highlighted the inevitability of acquired resistance via secondary on-target mutations, bypass pathway activation, or phenotypic shifts [39, 40], prompting iterative molecular testing and the diagnostic–therapeutic feedback loops that are now core to precision oncology.

1.2.8 Immunotherapy

Immunotherapy's trajectory spans crude early attempts (Coley's toxins), systemic cytokines (high-dose IL-2 and interferon-α), and, more recently, mechanistically informed interventions [41]. The modern era began with recognition of immune checkpoints such as CTLA-4 and PD-1/PD-L1 and with antibodies that block these inhibitory receptors and restore antitumor immunity. Checkpoint inhibitors have produced durable remissions in melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, Hodgkin's lymphoma, and other cancers and are now standard therapies [24, 42, 43].

Adoptive cell therapies, particularly CAR-T cells targeting CD19 and other antigens, have achieved high response rates in refractory B-cell malignancies [44]. These advances re-emphasized the role of host biology and the TME. Biomarkers such as PD-L1 expression, MSI-H/dMMR status, and tumor mutational burden now inform the use of checkpoint blockade and have led to tumor-agnostic approvals based on immune phenotype rather than tissue of origin [24, 38].

1.2.9 Summary

Over the past century, cancer diagnosis and treatment have evolved from purely clinical recognition and gross pathology to highly refined, multilayered approaches. Histopathology established the foundation for classifying tumors, linking microscopic features to prognosis, and guiding surgery and radiotherapy. Chromosomal and molecular diagnostics then revealed cancer as a genomic disease, with recurrent lesions such as BCR::ABL1 and HER2 providing the first clear examples of companion diagnostics and matched targeted drugs. In parallel, imaging progressed from plain radiographs to CT, MRI, and PET, while serum and tissue biomarkers added quantitative tools for staging, surveillance, and MRD assessment.

On the therapeutic side, cytotoxic chemotherapy and radiotherapy demonstrated that systemic and local treatments could cure even advanced disease, whereas endocrine therapy offered an early model of biologically targeted intervention. More recent decades have seen the rise of kinase inhibitors and immune checkpoint blockade, followed by cell-based therapies, all of which rely on increasingly sophisticated molecular and immune profiling. Taken together, these historical advances transformed oncology from organ- and morphology-based practice to one in which diagnosis and therapy are progressively

intertwined, laying the groundwork for the fully integrated precision medicine paradigms discussed in subsequent sections.

1.3 The Evolution of Precision Medicine in Oncology

1.3.1 Definitions, Conceptual Foundations, and Scope

Precision medicine aims to replace "one-size-fits-all" therapies with approaches grounded in the specific biology and context of each patient, tailoring prevention, diagnosis, treatment, and surveillance to molecular profile, clinical phenotype, and environment [45]. Precision oncology applies this idea to cancer, using tumor and host features to select therapies most likely to benefit a given individual and to avoid those unlikely to help or likely to cause harm [46].

Initially, precision oncology was often equated with tumor genomics. Its scope now extends from single-gene tests to broad next-generation sequencing (NGS) panels and genome-wide assays [47, 48]; from DNA alone to multi-omic profiles (epigenome, transcriptome, proteome, metabolome, and microenvironment) [45]; from static snapshots to longitudinal profiling with liquid biopsy, serial imaging, and functional readouts [49, 50]; and from purely biological parameters to integration of clinical trajectories and real-world data in health systems [51]. Rather than a specific technology, precision oncology is best viewed as an organizing framework for using detailed biological information to guide individual decisions and improve population-level outcomes.

1.3.2 Milestones and Tumor-Agnostic Thinking

Key milestones include early targeted therapies (imatinib and trastuzumab) that showed molecular lesions can trump tissue of origin for some decisions [33, 37]; the cancer genome characterization era, which catalogued recurrent drivers and pathways across tumor types [48]; and the shift from single-gene assays to routine targeted NGS panels that detect multiple classes of alteration in one test [47]. These developments supported the rise of companion diagnostics, where defined test results (EGFR mutations, ALK fusions, PD-L1 expression, and MSI-H) became prerequisites for prescribing specific drugs [32, 47, 52].

A further conceptual leap came with tumor-agnostic approvals. Checkpoint inhibitors for MSI-H/dMMR tumors and TRK inhibitors for NTRK fusions, followed by drugs for RET alterations and BRAF V600E in selected contexts, were approved irrespective of tissue of origin, provided that the molecular criterion was met [32, 38, 53]. Regulation and practice thus began to shift from organ-centric to biology-centric models.

As data volumes and complexity rose, many centers established molecular tumor boards (MTBs) to interpret sequencing reports, prioritize targets, adjudicate variants of uncertain significance, and match patients to trials [54]. Together, mass genomics, routine

NGS, companion diagnostics, tumor-agnostic approvals, and MTBs mark the transition from isolated targeted therapies to a coherent precision oncology ecosystem.

1.3.3 Enabling Technologies and AI-Enabled Integration of Multimodal Diagnostic Data

Implementation of precision oncology depends on technologies that generate, analyze, and integrate diverse data streams. NGS and RNA-seq underpin detection of actionable alterations, fusions, and expression signatures [47, 48]. Single-cell and spatial transcriptomics, though currently research tools, highlight how intratumor heterogeneity and immune niches may eventually be captured in clinically relevant assays [55].

Liquid biopsy with circulating tumor DNA (ctDNA) offers a minimally invasive view of tumor genomics, allowing non-tissue genotyping, real-time monitoring of clonal dynamics, and the detection of MRD and molecular relapse before radiographic changes [49, 50]. Digital pathology and AI turn whole-slide images into quantitative data; machine-learning approaches can infer mutation status, immune phenotypes, and prognostic features and help standardize scoring of markers such as PD-L1 or tumor-infiltrating lymphocytes [56]. More broadly, AI is becoming a cross-cutting enabler, learning relationships across pathology, radiomics, genomics, laboratory data, and longitudinal electronic records to support variant interpretation, risk prediction, treatment recommendation, and trial matching [51, 57, 58]. These systems are best seen as decision-support tools, whose safe deployment requires transparent validation, unbiased monitoring, and integration into multidisciplinary workflows such as MTBs.

Integrated clinical-genomic platforms and data commons combine genomic results, imaging, and structured clinical data to support individual decisions and continuous learning [59]. Such resources help identify rare responders, new resistance mechanisms, and patterns of actionability. Together, these technologies are transforming diagnostics from discrete, siloed tests into a connected, longitudinal view of each patient's disease.

1.3.4 Precision Therapeutics

The therapeutic arm of precision oncology now encompasses multiple modalities. Molecularly targeted agents against kinases and pathways such as EGFR, ALK, ROS1, RET, BRAF, MEK, BTK, and PI3K depend on detecting the relevant alteration and understanding resistance patterns so that second- and third-generation inhibitors can be synthesized rationally; basket trials enroll patients based on shared molecular features rather than tumor site [57].

Monoclonal antibodies and antibody–drug conjugates (ADCs) targeting HER2, EGFR, VEGF, and other proteins deliver targeted blockade or cytotoxic payloads; the emergence of HER2-low breast cancer responsive to trastuzumab deruxtecan illustrates how refined biomarker thresholds can expand eligible populations [30, 37, 58]. Similarly, checkpoint inhibitor-based immunotherapies and adoptive cell therapies such as CAR-T cells are increasingly deployed using immune-informed biomarkers such as PD-L1 expression, MSI-H/dMMR, and tumor mutational burden [38, 42, 44]. Synthetic lethality, exemplified

by PARP inhibitors in BRCA1/2-mutant and HR-deficient cancers, extends precision concepts to DNA repair networks [60]. Theranostics such as PSMA-targeted PET ligands paired with ^{177}Lu-PSMA-617 in prostate cancer blur diagnostic and therapeutic boundaries [53]. Adaptive and evolutionary informed strategies use real-time biomarkers to modulate therapy with the aim of slowing resistance [52, 61].

Collectively, precision therapeutics have moved beyond simple genotype–drug pairs to multimodal strategies guided by integrated tumor and host biology.

1.3.5 Implementation Challenges, Evidence Generation, and Equity

Despite scientific progress, precision oncology faces practical barriers. Intratumor heterogeneity and temporal evolution under therapy mean that single biopsies may miss relevant clones; combining tissue and liquid biopsies and, in selected cases, repeat sampling can mitigate but not eliminate this [62]. NGS panels frequently detect variants of uncertain significance, requiring expert frameworks, functional data, and clinico-genomic correlations to assign pathogenicity and actionability [59, 63].

Many molecular subsets are rare, challenging traditional trial designs. Basket, umbrella, and platform trials have been developed, but only a subset of alterations currently have level 1–2 evidence for a specific therapy, and extrapolation or off-label use remains common [57, 64].

Access is uneven: comprehensive testing, advanced imaging, and targeted or immune therapies are expensive and require infrastructure that may be limited outside major centers and high-income settings [64]. At the same time, precision oncology generates large volumes of sensitive data, raising issues of privacy, consent, and interoperability, even as data sharing is essential for learning health systems [59]. These challenges highlight that precision oncology is not only a molecular problem but also one of systems design, implementation science, and health policy.

1.3.6 Summary

Precision oncology has evolved from a narrow focus on single-gene–drug pairs to a broad framework that uses multilayered biological and clinical information to guide care. Its conceptual core is simple: match the right patient to the right intervention at the right time. But implementing this requires coordinated advances in genomics, imaging, pathology, bioinformatics, and data science. Large-scale cancer genome projects, the routine use of NGS panels, and the development of companion diagnostics and tumor-agnostic approvals have shifted practice from organ-centered to biology-centered decision-making, with MTBs acting as a critical interface between complex reports and real-world treatment choices.

On the therapeutic side, precision oncology now spans kinase inhibitors, monoclonal antibodies and ADCs, checkpoint inhibitors, cellular therapies, and theranostic radionuclide

approaches, increasingly deployed in rational combinations and adaptive regimens. Enabling technologies such as liquid biopsy, single-cell and spatial profiling, digital pathology, and AI-driven analytics are transforming diagnostics from isolated tests into an integrated, longitudinal view of each patient's disease. At the same time, challenges in variant interpretation, evidence generation, cost, infrastructure, and equity underscore that precision oncology is as much a problem of systems design and policy as of molecular biology.

1.4 Importance of Integrating Diagnostics with Therapeutic Strategies

1.4.1 From "Test Then Treat" to a Diagnostic–Therapeutic Continuum

Classically, cancer care followed a linear path: make a diagnosis, deliver a standard regimen, and reassess months later by imaging. Contemporary practice increasingly adopts a diagnostic–therapeutic continuum, in which testing and treatment are tightly interwoven [49, 65].

Baseline diagnosis like histology, immunophenotype, and molecular profiling guides initial therapy selection. Once treatment begins, on-treatment monitoring with imaging, laboratory markers, and ctDNA provides early readouts of biological response. At progression or relapse, repeat tissue or liquid biopsy is used to map resistance mechanisms and inform next-line therapy [65–67]. This diagnostic–therapeutic continuum is summarized in Figure 1.1, which links baseline profiling, biomarker-guided treatment, early response assessment, MRD surveillance, and resistance mapping into a single closed feedback loop.

1.4.2 How Diagnostics Shape Treatment Selection

Modern guidelines embed biomarkers in treatment algorithms. In many tumors, systemic therapy decisions now depend on specific molecular or immune features rather than histology and stage alone. Examples include kinase alterations and PD-L1 in lung cancer; ER/PR, HER2, PIK3CA, and BRCA1/2/HRD in breast cancer; BRAF in melanoma; and MSI-H/dMMR, tumor mutational burden, and PD-L1 across multiple tumor types [38, 43].

Testing can be tissue-based, plasma-based, or both, depending on feasibility and urgency. Proper identification of relevant alterations can transform prognosis; for instance, EGFR TKIs in EGFR-mutant NSCLC or HER2-targeted therapy in HER2-positive and HER2-low breast cancer [32, 58]. Conversely, not testing or misclassifying biomarker status risks exposing patients to ineffective or unnecessarily toxic regimens.

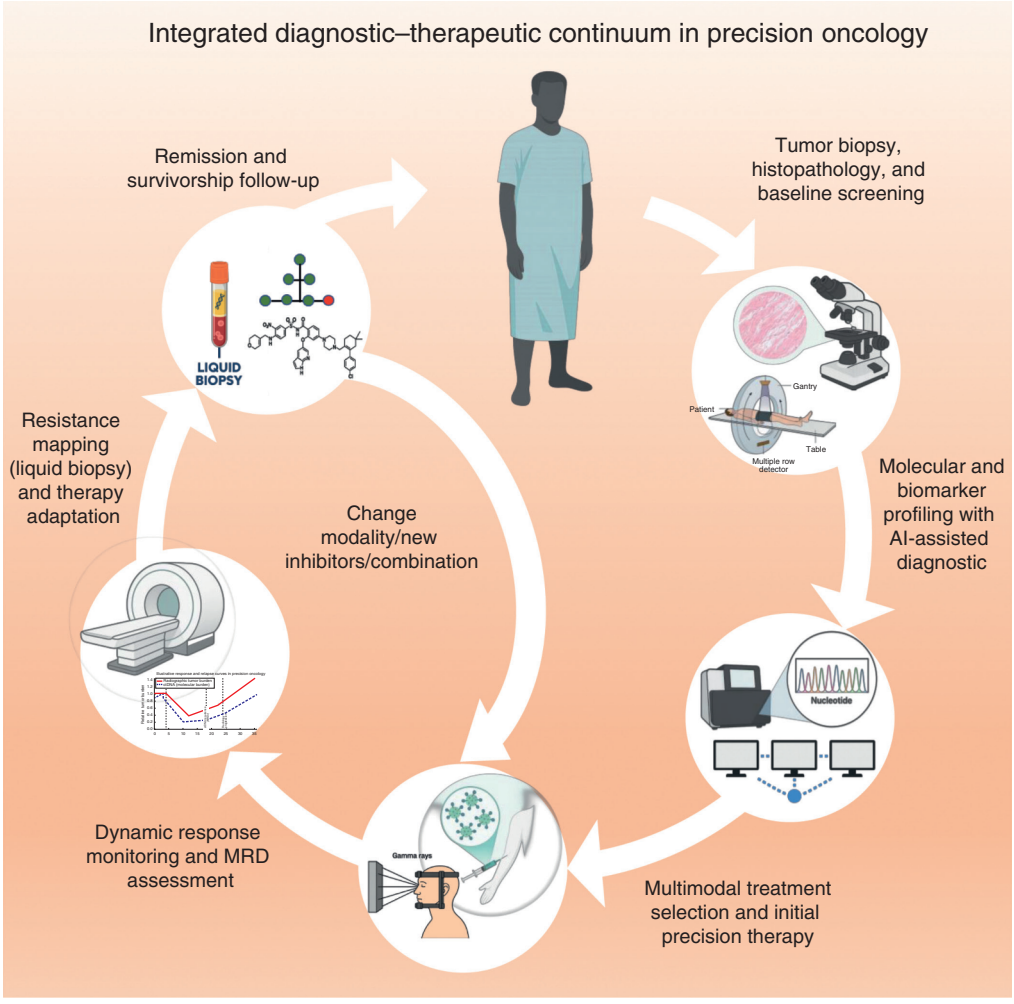

FIGURE 1.1 Integrated diagnostic–therapeutic continuum in precision oncology. The patient journey is represented as a dynamic loop in which diagnostics and therapy are tightly interwoven. Initial tumor biopsy, histopathology, and baseline imaging feed into molecular and biomarker profiling by NGS, increasingly supported by AI-assisted interpretation of complex datasets. These results guide multimodal treatment selection and initiation of precision therapy. During treatment, dynamic response monitoring with imaging, blood-based biomarkers, and minimal residual disease (MRD) assays provides early feedback on biological effect. At progression or molecular relapse, resistance mapping through repeat tissue biopsy or liquid biopsy identifies new driver events or escape pathways, enabling therapy adaptation with new agents, combinations, or modalities. When disease is effectively controlled, patients may enter remission and long-term survivorship follow-up, with ongoing surveillance poised to feed back into the cycle if relapse occurs.

1.4.3 Monitoring Response, Minimal Residual Disease, and Relapse

Diagnostics continue to matter after therapy starts. ctDNA kinetics often change before radiographic response, with rapid clearance under targeted therapy or immunotherapy correlating with deeper and more durable responses, while persistent or rising ctDNA can herald resistance [65]. In curative-intent settings, tumor-informed MRD assays detect very low levels of residual disease after surgery or chemoradiation, long before recurrence is visible on imaging [50, 66].

These tools enable risk-adapted strategies: MRD-negative patients may be candidates for de-escalation or shorter adjuvant therapy, while MRD-positive patients may benefit from treatment intensification, closer surveillance, or early trial enrollment [65, 66]. Monitoring thus becomes actionable, influencing the duration, intensity, and sequencing of therapy.

1.4.4 Resistance Biology and Rational Adaptation

Even optimally chosen therapies eventually encounter resistance, via on-target mutations (e.g., EGFR T790M and C797S), bypass pathway activation (e.g., MET and ERBB2), lineage plasticity (e.g., small-cell transformation in EGFR-mutant NSCLC), or microenvironment-mediated protection [39, 40, 68]. Serial ctDNA profiling is well-suited for capturing this evolving landscape in a minimally invasive manner, often revealing multiple resistance alterations across metastatic sites [50, 65]. Depending on the pattern, clinicians may switch to next-generation inhibitors designed to overcome specific on-target mutations; add agents targeting bypass pathways (e.g., combining MET and EGFR inhibition when MET amplification emerges); or pivot from targeted therapy to immunotherapy or chemotherapy.

In parallel, adaptive dosing and sequential combinations seek to slow resistance by modulating selective pressure rather than maintaining a constant maximal dose [68, 69]. Here again, integration of diagnostics with evolutionary thinking allows a more nuanced and biologically informed approach to sequencing therapy.

1.4.5 Operationalizing Integration

Genuine diagnostic–therapeutic integration requires organized systems of care rather than tests alone [63, 64]. Key elements include multidisciplinary teams (MTBs and disease-site groups), standardized pre-analytic handling and validated assays, structured reports that link findings to levels of actionability, decision-support tools that map variants to evidence and trials, and turnaround times aligned with clinical decision windows.

Equity-focused strategies such as reflex testing pathways, centralized diagnostic hubs, tele-MTBs, and context-appropriate gene panels are essential for bringing precision oncology to hospitals beyond large academic centers and high-income settings. Without

this kind of infrastructure, even the most advanced tests and treatments tend to remain patchy in their availability and are often underused in routine care.

1.4.6 Ethical, Regulatory, and Societal Considerations

Deep integration of diagnostics and therapy raises issues that extend beyond biology. Incidental and germline findings from tumor-normal sequencing require policies for disclosure, counselling, and cascade testing [70]. High-dimensional molecular and imaging data demand robust safeguards for privacy, data security, and consent for secondary use.

Regulatory frameworks must be flexible enough to accommodate companion diagnostics, adaptive trial designs, and real-time learning systems, while still safeguarding safety and efficacy and not unduly constraining innovation [57]. At the same time, the cost of testing and high-priced therapies risks amplifying financial toxicity and global inequities if not addressed through appropriate reimbursement and prioritization, particularly in low- and middle-income countries.

Ultimately, dynamically integrating diagnostics and therapeutics is not an optional refinement but the operating principle of modern oncology. The goal is a continuously learning system in which each patient's diagnostic profile and treatment course inform not only their own care but also the refinement of strategies for future patients.

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