PEER REVIEWED

Advancing Precision Medicine in Oncology:

Companion Diagnostic Devices and IRB Best Practices for Identification and Regulatory Assessment

Precision medicine has transformed the landscape of cancer treatment by shifting from histology-based to biomarker-driven therapies and enabling targeted interventions within molecularly defined patient populations. This paradigm shift has incorporated adaptive clinical trial designs and companion diagnostic (CDx) devices for participant selection, treatment assignment and response monitoring. However, CDx devices present distinct regulatory and ethical challenges. Institutional Review Boards (IRBs) are pivotal in systematically identifying CDx utilisation within clinical protocols, evaluating device-associated risks and ensuring adherence to regulatory compliance, ultimately safeguarding the rights and welfare of trial participants.

Cancer treatment has traditionally been guided by tumour site, histology, stage and prior therapy. While still important, these factors no longer fully define therapeutic opportunities. Precision medicine has transformed oncology by shifting treatment decisions toward biomarker-driven approaches that use tumour-specific molecular features such as genomic alterations, protein expression, immune signatures and resistance mechanisms to determine eligibility, guide treatment and monitor response. Precision oncology relies on two linked systems: clinical trials that evaluate targeted therapies in molecularly defined populations and diagnostic technologies that identify those populations accurately and reproducibly. This article examines companion diagnostic devices in precision oncology and presents a practical Institutional Review Board (IRB) framework for biomarker-guided oncology trials. The framework will help reviewers identify companion diagnostic use, assess regulatory status, evaluate participant risk, strengthen informed consent and document review determinations.

Limitations of Traditional Clinical Trial Designs

Traditional oncology trials generally evaluate a single investigational product in a single disease population using fixed eligibility criteria, fixed randomisation, a prespecified sample size and a stable statistical analysis plan. The traditional trial design is familiar, interpretable and relatively straightforward for investigators, participants, regulators and IRBs. However, it is often inefficient in precision oncology. Patients with the same histologic diagnosis may have distinct molecular drivers, whereas patients with different tumour types may share the same actionable alteration. Broad histology-based enrolment can dilute treatment effects, increase the likelihood of negative trials and expose participants to interventions from which they are unlikely to benefit. Traditional designs also provide limited flexibility once a protocol is underway. Adding a promising arm, discontinuing an ineffective arm, modifying biomarker-defined eligibility, or responding to an evolving standard of care often requires substantial amendments or an entirely new trial. These constraints may delay development, increase cost and slow participant access to effective therapies.[5] Such limitations have contributed to the growth of biomarker-guided designs that align trial architecture more closely with tumour molecular biology.

Biomarker-Guided Adaptive Platform Study Designs for Precision Oncology

Biomarker-guided study designs use molecular, immunologic, pathologic, or other biologic characteristics to define eligibility, stratify participants, enrich for likely responders, assign treatment, or guide response assessment. These designs may rely on single-gene assays, immunohistochemistry, fluorescence in situ hybridisation, polymerase chain reaction testing, next-generation sequencing, circulating tumour DNA analysis, or composite algorithms.[6] A biomarker-guided trial is only as reliable as the diagnostic strategy that identifies its target population.[7,8]

Precision oncology has accelerated the use of biomarker-guided adaptive platform designs, including umbrella and basket trials. These designs are often conducted under master protocols, which provide a single overarching infrastructure for evaluating multiple therapies, sub-studies, biomarkers, or disease populations. When appropriately designed and governed, master protocols can reduce redundancy, improve operational efficiency and generate evidence more rapidly than multiple independent trials. However, their success depends heavily on accurate and reliable biomarker testing. Table 1 summarises key differences between traditional histology-based trial designs and adaptive platform trial designs.[11,12]

Companion Diagnostic Devices (CDx) as the Backbone of Precision Oncology

Companion diagnostic devices occupy a central place in this evolving landscape of precision oncology. As per the FDA, a companion diagnostic is a medical device, often an in vitro diagnostic, that provides information essential for the safe and effective use of a corresponding drug or biological product.[13]

Companion diagnostics may also include certain imaging devices when they are necessary to guide the appropriate use of a therapeutic product. 'Essential,' means that use of the diagnostic device is required in the labelling of the drug or biological product to support patient selection, dosing, monitoring, or other clinically important decisions.

Clinical Uses of Companion Diagnostic Devices

- **Patient Identification:** Determine which patients are most likely to benefit from a specific therapeutic product.
- **Risk Mitigation:** Identify patients at increased risk of serious treatment-related side effects from a specific therapeutic product.
- **Treatment Response Monitoring:** Track treatment response to inform adjustments that may improve safety or effectiveness.

In precision oncology, companion diagnostics include immunohistochemistry assays, polymerase chain reaction tests, fluorescence in situ hybridisation assays, next-generation sequencing panels, liquid biopsy platforms and, in selected contexts, imaging tools. The FDA maintains a public list of cleared or approved companion diagnostic devices, including in vitro diagnostics and imaging tools; the list is periodically updated and should be consulted when evaluating the regulatory status of a specific device. As of July 2026, there are 226 FDA-cleared or approved CDx devices, including 219 for oncology indications and seven for non-oncology indications (Figure 1). Oncology represents a substantial portion of this landscape, with companion diagnostics used in non-small cell

Feature	Traditional Histology-Based Trial Design	Adaptive Platform Trial Design
Primary Organising Principle	Single tumour type, histology, stage and line of therapy.	Master protocol organised around disease area, biomarker-defined subgroups, multiple agents, or evolving therapeutic questions.
Study Structure	Usually, one drug or regimen tested against placebo, standard of care, or another comparator in a fixed design.	Multiple arms or sub-studies may operate concurrently; arms may be added, modified, expanded, or closed over time.
Patient Selection	Eligibility is often based on histology and clinical factors, with biomarkers sometimes used as secondary or exploratory variables.	Eligibility and treatment assignment frequently depend on molecular profiling, biomarker testing, or adaptive enrichment of biomarker-defined populations.
Flexibility	Limited flexibility once the protocol is finalised; major changes usually require substantial amendments or new trials.	High flexibility when adaptations are prospectively planned, statistically justified and implemented through predefined decision rules.
Efficiency	Can be slower and resource-intensive because each question often requires a separate protocol, trial infrastructure and control group.	Can improve efficiency by sharing infrastructure, screening procedures, control arms, data systems and oversight processes across multiple questions.
Advantages	Straightforward design, simpler consent, clearer statistical interpretation, familiar IRB review pathways, and strong suitability for confirmatory trials.	Accelerates evaluation of multiple therapies, supports biomarker-driven matching, may reduce participant exposure to ineffective arms and can respond to emerging evidence.
Disadvantages	May be inefficient for rare biomarkers, may enroll biologically heterogeneous populations, may miss tissue-agnostic signals, and may delay development when separate trials are needed.	Requires complex statistical planning, operational coordination, amendment management, data monitoring and clear IRB review of evolving biomarker-based eligibility and treatment-assignment criteria.

Table 1. Comparison of traditional histology-based oncology trial designs and adaptive platform trial designs

lung cancer, breast cancer, colorectal cancer, melanoma, prostate cancer, gynecologic malignancies, gastric cancer and hematologic malignancies. Common biomarkers include EGFR, ERBB2/HER2, KRAS, NRAS, BRAF, PD-L1, BRCA1/2, ALK, MSI/MMR, PIK3CA/AKT/PTEN, RET and IDH1.[14]

IRB Best Practices for Identifying Companion Diagnostics and Assessing Regulatory Status

Identification of companion diagnostic use should begin with systematic protocol review. IRBs should determine whether any diagnostic, biomarker, molecular, genomic, imaging or laboratory test affects eligibility, stratification, treatment assignment, safety monitoring, dose modification, response assessment, or discontinuation. Table 2 provides a practical review framework for oncology protocols that involve companion diagnostic or biomarker-based decision-making.

Regulatory Assessment

Companion diagnostic review intersects with FDA device and human-subject-protection regulations, including 21 CFR Part 812 for investigational device exemptions, 21 CFR Part 56 for IRB review, 21 CFR Part 50 for informed consent, and 21 CFR Part 809 for in vitro diagnostic labeling. Significant-risk device (21 CFR 812.3(m)) studies require FDA IDE approval and IRB approval before initiation. Nonsignificant-risk device investigations may proceed under abbreviated IDE requirements (21 CFR 812.2(b)) when the IRB agrees with the sponsor's determination and the applicable regulatory conditions are satisfied. This distinction is important because the IRB may accept a nonsignificant-risk determination, but FDA retains authority to determine that a study is significant risk and requires an approved IDE.

Key review questions include whether investigational test results could cause participants to forgo or delay effective treatment, expose them to risks beyond standard care or control therapy, reduce

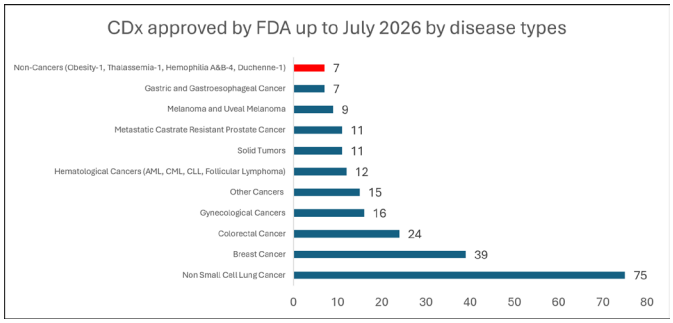


Figure 1 showing Companion Diagnostic devices (CDx) approved by FDA up to July 2026 by disease type.

the safety or efficacy of treatment if incorrect, or require invasive specimen collection outside of standard care.[22,23,24] Procedural risk should be distinguished from decisional risk: a blood draw or archival tissue review may be physically low risk, while the resulting diagnostic decision may carry substantial clinical consequences.

Recommendations for Sponsors and Investigators

Sponsors and investigators can support efficient IRB review by clearly identifying companion diagnostic devices in the protocol, protocol-support documents and consent materials. The protocol should describe the test, regulatory status, intended use, specimen requirements, result-reporting process and clinical impact. Sponsors should provide a study-specific device-risk determination and justify whether the diagnostic use is legally marketed and on-label, IDE-exempt approved device, non-significant risk, significant risk, or already reviewed by FDA. Consent forms should clearly explain diagnostic uncertainty, including whether the test is approved for the proposed use, whether it affects enrolment or treatment, whether confirmatory testing is required, whether results will be returned and how indeterminate or failed results will be handled. Clear communication reduces therapeutic misconception and supports meaningful informed consent.

Oncology CDx Review Question	Where to Look in the Protocol	IRB Reviewer Focus
Is a tumour biomarker required for eligibility?	Inclusion/exclusion criteria; disease-specific eligibility; molecular testing requirements.	Confirm whether enrolment depends on a specific oncology biomarker, such as EGFR, ALK, ROS1, BRAF, HER2, BRCA, IDH1/2, KRAS, NTRK, MSI-H/dMMR, TMB, or PD-L1 expression.
Is the CDx essential for safe and effective use of the investigational or approved oncology therapy?	Study rationale; investigational product section; prescribing information references; treatment algorithm.	Determine whether the test identifies participants most likely to benefit, those at increased risk, or those requiring monitoring or treatment selection based on biomarker status.
Is testing used to assign treatment, cohort, arm, or dose?	Study design; cohort definitions; randomisation; stratification; dose-escalation or expansion cohort criteria.	Assess whether the CDx result determines treatment arm, tumour-agnostic cohort placement, molecularly defined subgroup, or eligibility for targeted therapy or immunotherapy.
What specimen type and collection method are required?	Screening procedures; biopsy requirements; laboratory manual; schedule of assessments.	Evaluate whether testing uses archival tumour tissue, fresh biopsy, blood-based circulating tumour DNA, bone marrow, or other samples and whether any invasive biopsy risks are justified and clearly described.
Is the assay analytically and clinically appropriate for the oncology use case?	Device description; assay methodology; biomarker testing plan; central/local laboratory information.	Review whether the assay platform, such as IHC, FISH, PCR, NGS, liquid biopsy, or imaging-based testing, is appropriate for the cancer type, biomarker, specimen type and treatment-selection purpose.
What is the regulatory status of the CDx?	Device section; FDA approval/clearance information; IDE documentation; sponsor device-risk rationale.	Identify whether the CDx is FDA-approved/cleared for the specific oncology indication and drug, used under broader oncology group labelling, investigational, or subject to IDE significant risk/non-significant risk considerations.
Are false-positive, false-negative, and test-failure risks addressed?	Risks section; limitations of testing; retesting plan; treatment-decision algorithm; Informed consent.	Ensure the protocol and informed consent form explains how inaccurate, indeterminate, insufficient-tissue, or failed test results may affect eligibility, treatment access, delay in therapy, or assignment to an inappropriate treatment.
Are participant protections for genetic and tumor-profiling information adequate?	Informed consent; confidentiality section; genomic data-sharing plan; optional future-use biospecimen language	Confirm that participants are informed about the purpose of testing, privacy protections, return or non-return of results, incidental or germline findings when applicable, data sharing, and future use of biospecimens.
Is the consent clear about investigational oncology treatment implications?	Informed consent; eligibility language; alternative treatment section	Verify that the consent explains how biomarker results may affect study eligibility, access to targeted therapy or immunotherapy, potential exclusion from the study, and available alternatives if the biomarker requirement is not met.

Table 2. IRB reviews framework for identifying companion diagnostic use in oncology protocols

Future Directions and Conclusion

Precision oncology will continue to advance through genomic profiling, liquid biopsy, artificial intelligence, adaptive trial designs and biomarker-driven strategies that improve patient matching to targeted therapies. Companion diagnostic devices will remain central to this model by supporting patient selection, treatment monitoring, resistance detection and real-time therapeutic decision-making; however, they also introduce regulatory and ethical complexity because diagnostic results may determine study eligibility, access to treatment, exposure to toxicity, or delays in standard care. IRBs should therefore evaluate diagnostic validity, clinical utility, decisional and procedural risk, informed consent, data privacy, equitable access and the regulatory status of the CDx. By maintaining scientifically informed, participant-centered review and clearly documenting regulatory determinations, IRBs can support responsible innovation in precision oncology while preserving participant safety, rights, welfare and scientific integrity.

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