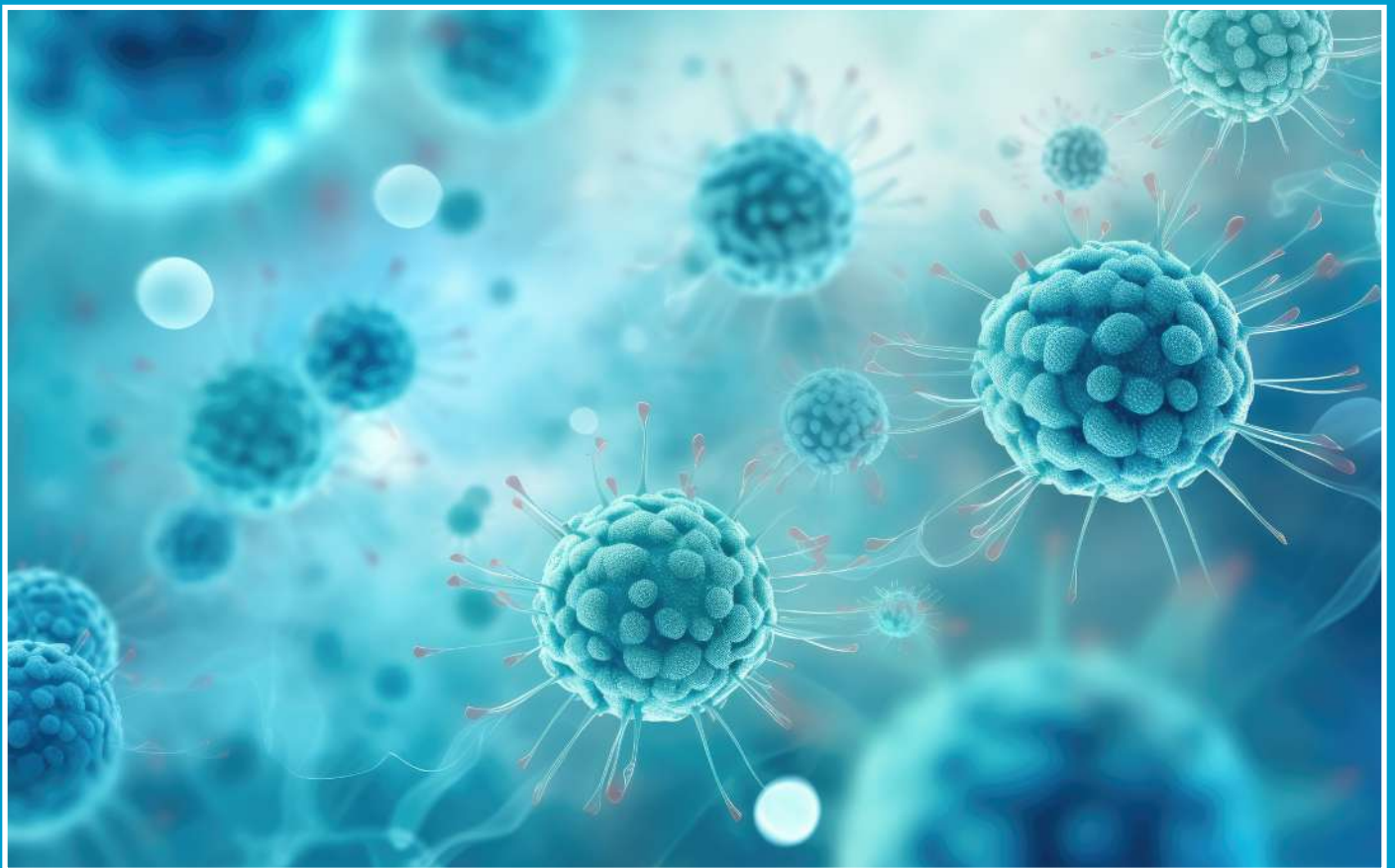


Tumor-Agnostic Therapies: Challenges in Evidence, Access, and Generalizability



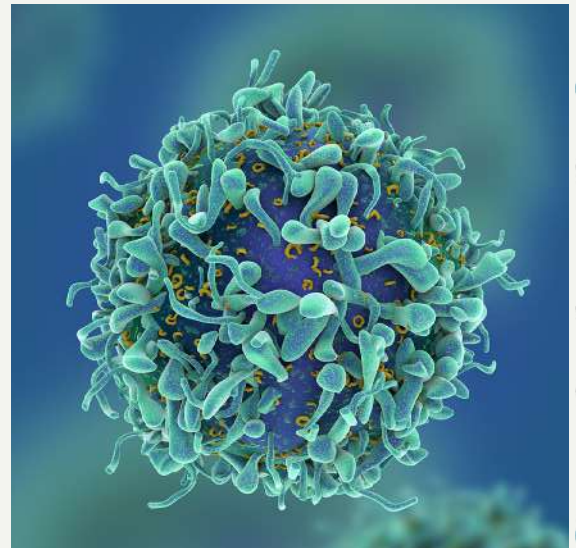
Tumor-Agnostic Therapies: Challenges in Evidence, Access, and Generalizability

Tumor-agnostic therapies have come to symbolize the precision medicine ideal: identify a genomic driver, target it effectively, and treat patients based on biology, not tumor origin. Regulators have shown selective openness to this logic, granting conditional or accelerated approvals in specific cases—such as larotrectinib (for NTRK fusions) and pembrolizumab (for MSI-H tumors)—based on compelling molecular rationale and early signals of efficacy. These approvals reflect emerging but still limited acceptance, often accompanied by postmarketing requirements or limited to high-need populations.

But translating that promise into practice has proven more complex. While regulators may accept objective response rates from small, pooled cohorts as evidence of benefit, HTA bodies and national payers may hesitate. They ask whether a mutation behaves consistently across histologies, whether clinical outcomes are durable, and whether the trial population reflects the patients who will actually receive the therapy.

What looks like precision at the molecular level can blur quickly at the clinical and economic level, especially when:

- Trial cohorts are heterogeneous and underpowered.
- Response rates don't correlate with survival or quality-of-life.
- Or the mutation in question produces variable effects across tumor types.



These challenges arise largely from the rarity of eligible populations, which limits the feasibility of generating large-scale data or conducting randomized trials—not from a lack of underlying efficacy. In some cases, later-phase trials have confirmed utility and supported broader access. Until then, early approvals based on compelling biology may be viewed by HTA bodies as incomplete without additional evidence of durability, comparability, or real-world relevance.

Regulatory Momentum Without Convergence

Tumor-agnostic therapies targeting genomic alterations such as NTRK fusions and MSI-high status have gained regulatory momentum over the past decade. A shift toward mechanism-based targeting is increasingly evident, even as regulatory expectations remain uneven. Some therapies targeting RET rearrangements (e.g., selpercatinib) have received approvals in multiple tumor types but not pan-tumor labels, often because their development programs were structured around histology-specific studies. In cases like MSI-high colorectal cancer, separate trials were feasible due to higher prevalence, while other tumor types with the same biomarker lacked the population size for dedicated studies. These patterns reflect both scientific rationale and pragmatic trial design, shaped by feasibility as much as biology.

The FDA has prioritized strong biological rationale and response outcomes in high-need populations, particularly for tumor-agnostic indications. Early checkpoint inhibitors and TRK-targeted agents exemplify this approach, having secured broad labels (often via the Accelerated Approval pathway) based on non-randomized trials and high response rates in biomarker-defined populations.

In contrast, the EMA has taken a more cautious stance, seeking broader confirmatory data and applying restrictions when generalizability is uncertain. One example is entrectinib, which received FDA approval in 2019 but was granted only conditional approval in Europe, reflecting concerns about long-term durability and cross-tumor consistency.

Other agencies, including Japan's PMDA and Health Canada, have adopted intermediate approaches, weighing both genomic rationale and disease-specific context. These approvals were not formally labeled as conditional but were accompanied by expectations for additional evidence generation post-authorization.

Efforts like parallel scientific advice and ICH guidance are helping to bridge gaps. But differences persist in how regulators assess data robustness, comparator expectations, and the level of evidence needed to support pan-cancer claims.

This creates a strategic challenge for developers: optimize for early approval in a single region or build a more universally persuasive case? Often the answer lies in parallel strategies, requiring early planning and recognition that novelty alone won't carry approvals everywhere.

Generalizability and the Limits of Mechanistic Logic



Tumor-agnostic therapies are based on a straightforward hypothesis: if a genomic alteration drives cancer, then inhibiting that driver should yield benefit regardless of tumor origin. In practice, biology is rarely that clean.

The same mutation may behave differently depending on tumor context. NTRK fusions, for example, are strong drivers in secretory breast cancer and infantile fibrosarcoma, but less so in colorectal or lung cancer, where co-mutations or tissue environment may diminish response.

Even when responses occur, their durability and relevance to real-world outcomes can vary. Tumor burden, prior treatments, and disease trajectory influence how meaningful a molecular response becomes in clinical terms.

These biological and clinical differences lead regulators and HTA bodies to seek more granular data. Increasingly, they request tumor-specific subgroup analyses to understand where benefit truly lies, even within a tumor-agnostic trial.

This introduces difficult design choices:

- Should trials be powered to detect effects in individual tumor types?
- Can sponsors justify extrapolation when natural histories differ widely?
- At what point does biological plausibility fall short without context-specific validation?

The EMA has responded with conditional marketing authorizations that require postmarketing data disaggregated by histology. European HTA bodies such as NICE and HAS similarly treat tumor-agnostic labels as provisional in practice, requiring additional data to assess clinical value and cost-effectiveness by tumor type. While such therapies may be formally approved, access and reimbursement in Europe are often contingent on further validation, underscoring that biological plausibility alone rarely guarantees broad acceptance.

While mechanistic rationale can support the case for tumor-agnostic use, generalizability is rarely absolute.

The same biomarker may behave differently across tumor types, influenced by tissue context or co-mutations that alter response. Where pathophysiology is well understood, and where scientific rationale rules out known resistance mechanisms, targeted therapies may be justifiably extrapolated, even in the absence of large, tumor-specific trials. But this requires more than assertion. Developers must carefully present where generalization is supported, and where it is not, to bring regulators along with the science rather than pushing against evidentiary norms. The line between promise and overreach remains delicate and it must be walked with transparency, rigor, and respect for both feasibility and uncertainty.

Statistical and Operational Realities

Tumor-agnostic trials must overcome two major constraints: rarity of the alteration and diversity of the affected population.

To capture enough patients, sponsors have leaned on basket trials; single protocols enrolling across multiple tumor types with a shared biomarker. These studies offer efficiencies but also introduce trade-offs:

- Small histology subgroups limit power for tumor-level conclusions.
- Single-arm designs leave HTA bodies without comparators.
- Statistical pooling can obscure differential effects across tumors.

Efforts to address these challenges include Bayesian borrowing and hierarchical models. While promising, these methods require transparency and alignment with both regulators and payers.

Operational hurdles compound the challenge. Identifying patients requires broad genomic screening, which remains uneven across health systems. Trial participation may be hampered by referral delays, limited sites, or competing studies.

Unless these constraints are anticipated in program design, sponsors risk producing data that is approvable but not actionable, especially in systems where reimbursement depends on tumor-specific value.

The Translation to Value

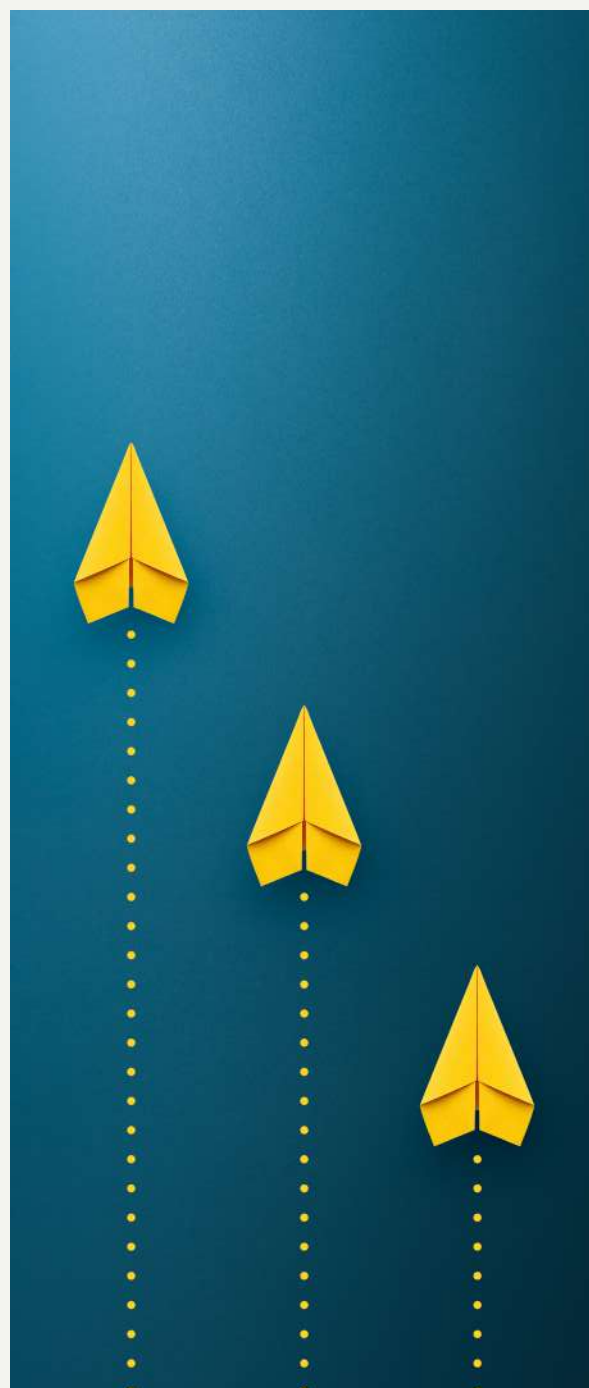
For tumor-agnostic therapies, regulatory approval is often only the first hurdle. HTA assessments introduce a different lens: does the therapy deliver value, in context, compared to available alternatives?

HTA bodies raise consistent concerns:

- Evidence from small, pooled populations lacks internal comparability.
- Absence of randomized data limits price justification.
- Basket trials blur which tumors drive the observed benefit.

Moreover, reimbursement frameworks are not designed for pan-cancer pricing. Should the price reflect outcomes in the best-performing tumor type, the least, or some average? How should countries handle access in tumors with effective standard treatments?

The common theme: a tumor-agnostic approval does not equal a tumor-agnostic value proposition. Sponsors must go beyond biological plausibility to demonstrate meaningful, context-sensitive benefit.



Strategic Imperatives for Developers

Effective development in this space depends on pairing scientific ambition with a clear, context-aware evidence strategy. Key imperatives include:

Anchor mechanism in disease context. Even when the target is agnostic, the tumor isn't. Design trials with tumor-specific cohorts or stratified analyses to support interpretation by histology.

Plan for value, not just efficacy. Include endpoints relevant to HTA: duration of benefit, symptom impact, and healthcare resource use.

Invest early in statistical planning. Use adaptive designs and pre-specified subgroup analyses. Make pooling assumptions transparent and justifiable.

Use basket trials strategically. They are valuable for signal detection but often insufficient alone. Plan for follow-up studies to confirm or expand findings.

Align global messaging. Ensure consistency across jurisdictions. Divergent narratives between regulatory and reimbursement filings can slow both approval and access.

Conclusion

Tumor-agnostic development holds significant scientific promise, but its success hinges on a disciplined evidence strategy. Sponsors must anticipate where mechanistic logic may falter in the face of clinical, operational, or reimbursement scrutiny.

By planning for heterogeneity, building robust statistical frameworks, and aligning value arguments across stakeholders, developers can increase the chances that approvals translate into access and access into impact.

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