

Tissue-agnostic cancer therapies: promise, reality, and the path forward

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Tissue-agnostic cancer therapies promise to revolutionize oncology by targeting molecular drivers. Sledge et al.'s study of nearly 300,000 tumors found 21.5% with tissue-agnostic indications. Despite nine FDA approvals, real-world implementation challenges persist. Progress depends on universal genomic testing, an oncogenomic-savvy workforce, innovative trials, updated regulations, and real-world evidence to maximize potential.

The oncology landscape has undergone a remarkable transformation with the emergence of tissue-agnostic therapeutic approaches¹. At its core, the concept—treating cancer based on molecular drivers rather than tissue of origin—is both conceptually simple and clinically transformative. Pembrolizumab made history in 2017 as the first tissue-agnostic therapy receiving accelerated approval for MSI-H/dMMR solid tumors in both adults and children. By 2023, it received full approval based on data from 504 patients with over 30 cancer types. The FDA has now approved nine tissue-agnostic therapies across three categories: targeted therapies (*NTRK*-fusions, *BRAFV600E*-mutations, *RET*-fusions), immunotherapies (MSI-H/dMMR, TMB ≥ 10 mutations/megabase), and an antibody-drug conjugate for HER2-positive tumors (immunohistochemistry 3+ expression)¹. These tissue-agnostic and in some cases age-agnostic treatments offer critical alternatives for patients with advanced solid tumors carrying specific biomarkers—providing an option when standard approaches fail². For many patients, especially those with rare or refractory cancers, these therapies offer a promising alternative where few exist. As these approvals were based on single-arm non-randomized studies with limited patient numbers, real-world data and evidence become essential to fully comprehend their clinical impact.

Sledge et al. have conducted an extensive real-world analysis of nearly 300,000 molecularly profiled tumors, uncovering significant potential insights into tissue-agnostic therapies³. Their findings revealed that 21.5% of these tumors possess at least one tissue-agnostic indication, while 5.4% lack any cancer-specific indication³. The prevalence of tissue-agnostic indications varies widely across different tumor types, with frequencies ranging from 0% to 87%, depending on the tissue type³. Although drawn from a single source, this study provides valuable real-world insights into these novel therapies' implementation. The team deserves commendation for compiling comprehensive data that effectively demonstrates the practical impact of these approvals.

The implementation challenge- finding the needle in the haystack and threading it

The analysis reveals a concerning trend: only about one-third of eligible patients with rare tumor-agnostic indications, such as *NTRK* fusions, are receiving the appropriate therapy—a significant treatment gap that demands attention. Currently, there are three approved drugs (Larotrectinib, Entrectinib, and Repotrectinib) for treating *NTRK* fusion-positive cancers. These drugs are not only highly effective, with impressive response rates, but they are also generally better tolerated than traditional chemotherapies. Despite these advantages, their adoption in real-world settings remains disappointingly low. As a field, we face a challenge. Despite advances in comprehensive NGS to enable the detection of rare, actionable mutations, a critical gap remains: ensuring that patients are matched to appropriate targeted therapies in a timely manner. In essence, we fail to “thread the needle” (Fig. 1). Notably, even in lung cancer—the poster-child of precision oncology with ten biomarker-driven therapies—the adoption rate for molecular testing and matching in community practice hovers at around 50%, although increasing⁴. If this is the state in the US, the situation is likely exacerbated in many geographic regions that do not have these approvals or access to these drugs. This implementation gap highlights systemic challenges: our healthcare systems, regulatory frameworks, and medical education remain structured around traditional organ-based classifications, while modern precision oncology has shifted towards molecular profiling⁵. This disconnect results in unequal access to effective treatments for patients with similar molecular profiles but different cancer “types”⁵.

Reality check: the promise and complexity

Unfortunately, the real-world application of tissue-agnostic therapies is far more complex than the term suggests. The notion that targeting a specific mutation yields uniform results across tumor lineages oversimplifies cancer's molecular complexity. Treatment response varies dramatically, particularly with TMB-High and MSI-High/MMRd cancers³. Cancer cells employ multiple redundant pathways and adaptive mechanisms that vary by tissue context and treatment history. Effective treatment requires combination therapies addressing multiple oncogenic mechanisms through complementary approaches⁶. The story of BRAF inhibitors serves as an excellent illustration of the complexities involved in tissue-agnostic therapies. In basket trials conducted across multiple tumor types, all showed favorable responses except for colorectal cancer^{7,8}. Further investigation revealed that EGFR activation was an inherent resistance mechanism in these tumors. By incorporating EGFR inhibition, this resistance was successfully addressed⁹. However, does this negate BRAF as a tissue-agnostic target? Indeed, BRAFV600 *IS* a tissue-agnostic target, and in the case of colorectal cancer, it simply necessitates the addition of EGFR inhibition to achieve effective results.

Tumor-agnostic Precision Oncology: Finding vs. Threading the Needle

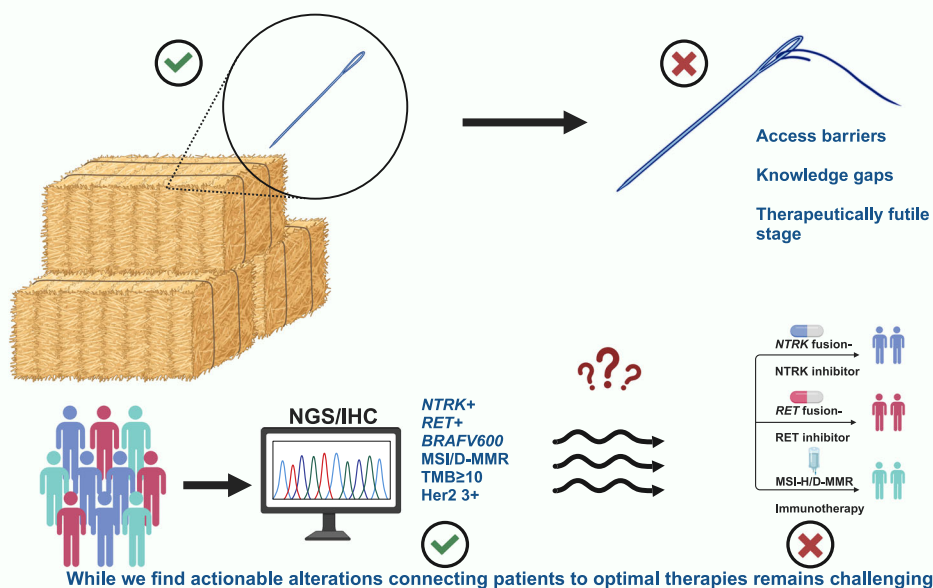


Fig. 1 | Tumor-agnostic precision oncology: finding vs threading the needle. This figure illustrates the dual challenges in tumor-agnostic precision oncology. On one hand, we have achieved significant advances in identifying actionable alterations across various cancer types, akin to “finding the needle” in a haystack. Key tissue-agnostic targets include BRAF, NTRK, RET, MSI-H/D-MMR, TMB-H, and Her2+. These targets represent pivotal biomarkers that can guide therapy selection. On the other hand, the “threading the needle” analogy highlights the current

challenges in aligning these identified alterations with optimal therapeutic strategies, ensuring that patients receive the most effective treatments tailored to their unique genetic profiles. This figure underscores the importance of bridging the gap between genomic insights and clinical application to enhance patient outcomes in the era of precision medicine. Created in BioRender. Subbiah, V. (2025) <https://BioRender.com/h6x60hb>.

Most tissue-agnostic approvals are currently limited to the relapsed/refractory setting, effectively positioning these therapies as alternatives to hospice care or best supportive care. While we’ve seen dramatic responses in terminal patients, expecting this universally when the disease is too advanced is unrealistic. Given the greater efficacy of targeted therapies in earlier treatment lines, future regulatory strategies should consider both line-agnostic and tissue-agnostic approvals to optimize patient outcomes. We need to profile and treat these cases early. Early treatment has already shown 100% complete responses in D-MMR-MSI-H cancers¹⁰.

Rethinking our approach

A recent commentary in *Nature* argues that classifying cancers by organ of origin is increasingly outdated and harmful to patients, denying them access to life-saving therapies⁵. The article proposes a shift toward molecular-based classification, which would better reflect current scientific understanding. While some regulatory progress has occurred—such as the FDA’s approval of tissue-agnostic drugs—a broader transformation is needed. ESMO’s framework for tumor-agnostic therapies represents a promising step forward¹¹. Their proposed ETAC-S criteria and taxonomy classifying therapies as “tumor-agnostic,” “tumor-modulated,” or “tumor-restricted” acknowledges the complex interplay between molecular drivers and tumor-specific biology¹¹. This provides an opportunity to screen early in drug development for tissue-agnostic therapies.

The approval of a tissue-agnostic therapy should be the starting point—not the endpoint—of research into a specific target across various diseases³. Real-world treatment of larger patient populations provides invaluable insights into how therapies perform across tumor types. Understanding patterns of non-response is critical: is it due to late-stage intervention, prior therapies, or inherent resistance mechanisms in particular tumor types? Potentially unidentified resistant tumors should drive further research rather than hinder therapy approval. HER2 exemplifies this evolution perfectly. Even after decades of HER2-targeted treatments, we continue uncovering new insights. The pursuit of perfection should not impede progress or restrict patient access to potentially beneficial therapies. Broad biomarker-based approval allows real-world access while encouraging ongoing research.

Why these approvals matter

Despite implementation challenges, the analysis shows that tissue-agnostic approvals are crucial for several reasons³. Firstly, they have spurred the adoption of essential genomic sequencing technologies, as evidenced by the molecular profiling of 300,000 tumors in real-world settings with over 21% of patients having a tissue-agnostic indication³. Secondly, these approvals provide access to potentially life-saving therapies for patients with rare cancers who would otherwise have very limited treatment options—for example, patients with *BRAFV600*-positive salivary gland cancers or ameloblastomas, who will

Table 1 | Innovative trial designs for Tissue-Agnostic Drug Development

Trial Design	Key Features	Patient Benefits	Statistical Approaches	Regulatory Considerations	Examples
Basket Trials	Evaluate single therapy across multiple tumor types with shared biomarker organized by molecular alteration rather than tumor origin.	Access to targeted therapies regardless of tumor type. Benefits patients with rare cancers	Bayesian methods to borrow information across cohorts. Simon two-stage designs for early futility assessment	Potential for tumor-agnostic approvals. May require smaller sample sizes for rare molecular subgroups	ROAR basket study, LIBRETTO-001, ARROW, NCI-MATCH, ASCO-TAPUR
Umbrella Trials	Test multiple targeted therapies within single cancer type. Stratification by molecular subgroups	Multiple treatment options within single protocol	Multi-arm multi-stage designs. Adaptive randomization	May support multiple simultaneous submissions. Provides comparative data within cancer type	LUNG-MAP, Myelo-MATCH
Platform Trials	Perpetual trial infrastructure. Therapies enter/exit based on ongoing results	Continuous access to emerging therapies	Response-adaptive randomization	Complex regulatory oversight. Supports iterative label expansion	STAMPEDE trial
Real-World Evidence Integration	Concurrent real-world data collection. External control arms. Registry-based trial components.	More representative patient populations	Propensity score methods. Synthetic control comparisons	Supports label expansion. Complements traditional efficacy data	SPECTA European collaborative platform

never have dedicated trials, rely on pan-cancer approvals for treatment access. Thirdly, the significant magnitude and durability of responses observed from these approvals mean they can be life-saving for a subset of patients with otherwise lethal malignancies. Fourthly, these approvals have validated biomarkers, such as TMB-H, as clinically actionable targets in real-world practice across various tumor types¹². Fifth, real-world data support extending tissue-agnostic approvals to tumor types not initially included in clinical trials, demonstrating similar benefits in non-trial tumor types. Finally, real-world data generated from these approvals can facilitate the extension to other members of the same drug class, thereby accelerating patient access to effective therapies across multiple indications—for example, nivolumab, which shows similar benefits to pembrolizumab in TMB-High and MSI-High/MMRd cancers. Moreover, the findings underscore the importance of educating oncologists about tissue-agnostic indications and the potential benefits of real-world data analyses in informing treatment decisions.

The path forward

To realize the full potential of tissue-agnostic therapies, we need:

1. **Universal genomic testing** that includes both somatic and germline analysis for all cancer patients at diagnosis, not just after standard therapies fail¹³.
2. **An oncogenomic-savvy workforce** equipped to interpret complex molecular data and match patients to appropriate targeted therapies¹⁴.
3. **Innovative trial designs** that capture the heterogeneity of responses across tumor types while providing access to promising therapies¹⁵. Many tissue-agnostic trials have employed basket and umbrella study designs, as well as pooled analyses from various studies, as outlined (Table 1). By embracing innovative endpoints, such as tissue-agnostic response rates, and utilizing real-world evidence (RWE), these trials possess the potential to effectively identify signals across a diverse range of cancers. This strategy may facilitate earlier access to potentially life-saving treatments through expanded access programs and conditional approvals based on surrogate endpoints. Additionally, trials should be adaptive, incorporating agents in combination based

on specific resistance mechanisms identified in particular tumor types. For example, the VE-Basket trial was amended to include cetuximab alongside the BRAF inhibitor after observing a lack of response in patients with BRAF V600+ colorectal cancer receiving BRAF inhibitor monotherapy. This decision was informed by emerging pre-clinical data that identified EGFR as an innate resistance mechanism in BRAF V600 colorectal cancer⁷.

4. **Regulatory frameworks and seamless global integration of tissue-agnostics** that recognize/accommodate the molecular basis of cancer alongside traditional classifications and approvals based on single arm studies for universal patient access.
5. **Real-world evidence generation** to continuously refine our understanding of how these therapies perform in diverse patient populations^{3,15}.

Conclusion

Cancer is fundamentally a genetic disease. The tissue-agnostic approach represents our journey toward truly personalized oncology, with its greatest value in expanding precision medicine access for patients with rare cancers and molecular alterations. As we advance, we must integrate scientific innovation with clinical pragmatism—embracing complexity while pursuing precision. Oncology is undergoing a seismic shift, with the future becoming molecular, not anatomical. This represents more than an academic distinction—it represents a fundamental reimagining of how we understand and treat cancer. AI methods are poised to identify more tissue-agnostic targets, and by focusing on cancer's genetic drivers while respecting tissue-specific biology, we can move toward a more precise, effective, and compassionate approach—personalizing treatment one patient, one tumor, and one molecular profile at a time.

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