Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

From Multi-Omics Association to Therapeutically Actionable Targets: A Causal Reasoning Framework for Artificial Intelligence–Enabled Bioinformatics across Molecular Networks, Tissue Contexts, and Disease Heterogeneity

Clara Novak[1]*, Ahmed El-Sayed[2], Hana Kim[3], Peter Nagy[4]

1. ***Department of Bioinformatics and Multi-Omics Integration, Vienna University of Economics and Business, Vienna, Austria.***
2. ***Department of Computational Biology and Causal Inference, American University in Cairo, Cairo, Egypt.***
3. ***Department of Genomic Medicine and AI-Based Target Discovery, Seoul National University, Seoul, South Korea.***
4. ***Department of Pharmaceutical Bioinformatics and Systems Pharmacology, Corvinus University of Budapest, Budapest, Hungary.***

ARTICLE INFO

Received:
18 May 2026
Received in revised form:
12 September 2026
Accepted:
14 September 2026
Available online:
28 October 2026

Keywords: Multi-omics integration, Causal inference, Artificial intelligence, Therapeutic target identification, Molecular networks, Disease heterogeneity

ABSTRACT

Multi-omics and artificial intelligence can rank genes, proteins, pathways and molecular states with increasing resolution, yet therapeutic target selection requires a stronger inference than statistical association or predictive relevance. This article develops a causal-reasoning framework for deciding when an omics-supported target claim is sufficiently credible to inform therapeutic progression. The analysis separates five questions that are frequently collapsed: whether the disease-associated signal is assigned to the correct causal gene or molecular entity; whether perturbing that entity is likely to change the disease process in the intended direction; how network structure modifies the consequence of perturbation; whether the mechanism is active in the relevant tissue, cell state and disease stage; and whether disease heterogeneity restricts benefit or introduces harm in particular subgroups. The framework treats actionability as a context-bounded intervention claim rather than a property conferred by cross-omics concordance, network centrality, feature importance or model performance. Evidence can therefore move a target forward, hold it in an exploratory state, restrict it to a conditional domain, or move it backward when counterevidence emerges. The central implication is that multi-omics becomes therapeutically informative only when association is converted into a defensible, revisable account of causal mechanism, intervention direction and context-specific consequence.

*This is an **open-access** article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, and build upon the work non commercially.*

To Cite This Article: Novak C, El-Sayed A, Kim H, Nagy P. From Multi-Omics Association to Therapeutically Actionable Targets: A Causal Reasoning Framework for Artificial Intelligence– Enabled Bioinformatics across Molecular Networks, Tissue Contexts, and Disease Heterogeneity. Pharmacophore. 2026;17(5):54-62. https://doi.org/10.51847/L4h0RW5WCR

Introduction

The current generation of drug-discovery bioinformatics can integrate genomic, transcriptomic, epigenomic, proteomic, metabolomic and phenotypic signals at scales that were previously impractical. Artificial intelligence expands this capacity by learning joint representations, detecting cross-modal structure and prioritizing targets or pathways across heterogeneous data sources [1]. Network-based approaches add relational information by embedding genes, proteins and disease phenotypes within interaction or similarity structures rather than treating each molecular feature as independent [2]. Yet the expansion of integration methods has also widened the distance between what can be detected computationally and what can be justified therapeutically, because data-driven concordance remains sensitive to missingness, dimensionality, cohort composition, measurement platform and analytic design [3].

Human genetics partly narrows this gap. Across drug-development portfolios, stronger genetic support for a target–disease relationship is associated with improved aggregate clinical success, particularly when the evidence more confidently identifies

Corresponding Author: Clara Novak; Department of Bioinformatics and Multi-Omics Integration, Vienna University of Economics and Business, Vienna, Austria. E-mail: clara.novak@wu.ac.at.

the causal gene and mechanism [4]. However, this enrichment is probabilistic rather than deterministic. Clinical translation remains disease dependent, and even sophisticated AI–omics applications can change meaning when the relevant biology, tissue architecture, phenotype definition or treatment context differs [5]. A target-selection argument therefore cannot stop at the claim that a molecular signal is reproducible or that a model predicts an outcome accurately. Computational evidence must be credible for its intended use, with explicit attention to verification, validation, reproducibility and uncertainty [6].

The core problem is consequently inferential rather than merely technical. Multi-omics can make a target hypothesis denser by attaching more layers of evidence, but density does not by itself establish that the nominated entity is the correct causal intervention point. Nor does a causal relationship automatically establish that the target is therapeutically actionable. Actionability additionally depends on the direction and degree of perturbation, the network consequences of intervention, the tissue and cell states in which the mechanism operates, the populations and disease states to which the claim applies, and whether the expected biological effect connects to a clinically relevant outcome.

This article addresses that gap through a causal-reasoning framework for AI-enabled bioinformatics. Its distinctive question is not how to identify associations more efficiently, nor how to advance an already nominated drug candidate. It asks what must be true before an association-supported molecular entity can be treated as a therapeutically actionable target, and what kinds of evidence should weaken, restrict or reverse that judgment. The analysis therefore proceeds from failures of association-level reasoning to causal and contextual requirements, before translating those requirements into a revisable target-actionability logic.

Why Multi-Omics Association Is Insufficient for Target Selection

Integrated multi-omics can strengthen target discovery because independent molecular layers may converge on a common gene, protein, pathway or disease process. Reviews of contemporary target-identification workflows show that integration can reveal relationships that are difficult to detect in single-omics analyses [7]. Large proteogenomic studies similarly demonstrate the scale at which genetic variation can be connected to circulating protein abundance and disease-related phenotypes [8]. Population resources such as the UK Biobank extend this logic across thousands of proteins and large participant cohorts [9]. These advances increase the number and richness of target hypotheses, but they do not resolve the central causal question: whether the measured association identifies a manipulable disease mechanism rather than a correlated marker, downstream consequence or context-specific proxy.

One source of uncertainty is locus-to-gene assignment. Disease-associated variants may influence genes at a distance, operate through enhancers, or participate in loci containing several candidate causal signals. Integrative prioritization that combines fine-mapping, colocalisation and functional annotation improves the probability that a GWAS signal is assigned to the biologically relevant gene [10]. Colocalisation itself must accommodate multiple causal variants when loci are complex; otherwise, a shared regional signal can be mistaken for a shared causal mechanism [11]. Functional enhancer maps further show that noncoding disease-associated variants can be connected to genes through cell-type-specific regulatory architecture rather than physical proximity alone [12]. These methods improve causal-gene inference, but none converts gene assignment directly into evidence that pharmacological intervention on the gene product will improve a clinically meaningful outcome.

Tissue context creates a second break in the inference chain. The GTEx atlas established that the genetic regulation of gene expression varies substantially across human tissues [13]. Large blood eQTL analyses add power for detecting cis- and trans-regulatory effects but also illustrate the dependence of measured expression relationships on cellular composition and the sampled compartment [14]. A target supported by blood, plasma or another accessible biospecimen may therefore be mechanistically irrelevant in the tissue where disease progression is determined, or the direction of its effect may differ across tissues. For target selection, tissue concordance should be treated as evidence about the domain in which a causal claim may hold, not as an optional annotation added after a target has already been declared actionable.

Network structure introduces a third limitation. Protein interaction maps provide a reference for how molecular entities are embedded in broader biological systems [15]. However, proteome-scale network studies also show that interaction architecture can be remodeled across cellular contexts [16]. This matters because network centrality and causal leverage are not equivalent. A highly connected protein may be buffered by redundancy, embedded in essential physiology or positioned so that perturbation produces broad adverse consequences. Conversely, a less central node may control a context-specific disease mechanism. The relevant question is therefore not whether a target occupies an important position in an abstract network, but what perturbing that target is expected to do in the particular network state associated with disease.

These distinctions also expose a common problem in integrated target-prioritization systems: evidence dimensions with different meanings can be collapsed into a composite rank. Platforms such as Open Targets explicitly bring together genetics, molecular evidence, tractability, safety and drug-related information because no single dimension is sufficient for target assessment [17]. That architecture is informative precisely because causal relevance, targetability and translational risk answer different questions. A genetic association may raise confidence that a target participates in disease biology; structural or pharmacological tractability concerns whether the target can be modulated; tissue expression constrains where the mechanism can operate; and safety evidence concerns the consequences of intervention beyond the desired disease pathway. A target should therefore not acquire actionability merely because several evidence layers point in the same direction.

The distinction can be stated operationally: association evidence identifies relationships that merit explanation, whereas actionability requires a justified intervention claim. The latter must specify the causal entity, the intended direction of perturbation, the network consequences expected to follow, the tissue or cell context in which the mechanism is relevant, and

the population or disease state in which the resulting effect is expected to be beneficial. Cross-omics agreement can strengthen confidence in one or more of these components, but it cannot substitute for components it does not measure.
Table 1 summarizes why multi-omics evidence can remain non-actionable across distinct inferential units.

Table 1. Why multi-omics evidence can remain non-actionable across distinct inferential units

Analytical unit	What association-level evidence can establish	Unresolved causal question	Context that can alter interpretation	Actionability consequence
Disease-associated locus	A reproducible relation between genetic variation and phenotype	Which molecular entity mediates the association?	Linkage disequilibrium, multiple causal variants, regulatory architecture	Keep target exploratory until locus-to-gene inference is defensible
Gene or transcript	Expression or regulatory association with disease	Would changing expression alter disease in the intended direction?	Tissue, cell composition, developmental or disease state	Restrict inference to the biological domain actually represented
Protein abundance	Association between protein level and phenotype or genetic variation	Is the protein causal, reactive or a circulating proxy?	Plasma versus disease tissue, secretion, clearance, systemic physiology	Require evidence that the measured compartment reflects the operative mechanism
Network position	Connectivity or pathway membership	Does perturbation produce beneficial causal leverage rather than compensation or toxicity?	Cell-specific interactome, redundancy, feedback, essential physiology	Do not convert centrality into therapeutic importance
Cross-omics concordance	Multiple modalities implicate the same molecular system	Are the modalities independent evidence for the same causal mechanism?	Shared confounding, correlated measurement, common downstream response	Treat concordance as support for prioritization, not as causal validation
AI-derived feature or representation	Predictive relevance within a model	Does the feature correspond to a manipulable biological mechanism?	Dataset shift, model architecture, latent representation, label definition	Require external causal and contextual validation before progression

Causal and Contextual Evidence for Therapeutic Actionability

Causal evidence strengthens target-selection claims only when the assumptions connecting genetic or molecular variation to intervention are made explicit. Human genetic data can guide drug discovery by informing target mechanism, expected direction of effect, relevant populations and potential on-target consequences [18]. Mendelian randomization formalizes part of this reasoning by using genetic variants as instruments for an exposure or target-related trait, but causal interpretation depends on instrument relevance, independence from confounding and the absence of alternative pathways from instrument to outcome [19]. Drug-target Mendelian randomization introduces additional complications because a genetic proxy is not identical to a pharmacological intervention: variants may alter a target throughout life, in multiple tissues, and by a smaller or qualitatively different mechanism than a drug [20]. Causal evidence should therefore upgrade target confidence only when the proxy is biologically interpretable and the sensitivity of the result to linkage, pleiotropy, tissue and scaling assumptions has been examined.

A second requirement is alignment between the inferred biological effect and the clinically relevant intervention consequence. Genetic inhibition of ANGPTL3 illustrates why changes in a molecular or biomarker phenotype should not be assumed to translate proportionally into all downstream clinical endpoints [21]. This type of discordance does not invalidate genetics as a target-discovery tool; it clarifies that causal evidence can be endpoint specific. Conversely, triangulation can materially strengthen a target hypothesis when genetically anchored proteomic and transcriptomic evidence, colocalisation and orthogonal biological information converge. Integrative analyses in chronic kidney disease show how such combinations can identify candidate targets with stronger support than any single modality provides [22]. The appropriate inference remains "strengthened candidacy," not clinical validation.

Disease heterogeneity changes the expected domain of actionability. Large multi-ancestry analyses of type 2 diabetes identify genetically distinct pathophysiological clusters associated with different biological processes and cell types [23]. A target that appears causal in an average case–control analysis may therefore be relevant to only a subset of patients, or may have different expected consequences across mechanistic subtypes. Heterogeneity should not be treated only as a nuisance that lowers statistical power. For target selection it is a boundary condition: an intervention claim should specify the population or disease state to which the causal mechanism plausibly applies.

Spatial and cellular context provide another layer of qualification. Spatial multi-omics can preserve tissue architecture while resolving molecular states and cell–cell relationships that are lost in bulk assays [24]. Contemporary integration approaches increasingly combine spatially indexed transcriptomic, proteomic, epigenomic and other modalities to describe local biological organization [25]. In liver, single-cell spatial multi-omics coupled with deep learning has been used to reconstruct enhancer-driven regulatory networks associated with zonation, demonstrating that regulatory relationships can depend on position and cell state [26]. Spatially resolved genomic and transcriptomic measurements likewise show that nuclear organization differs

across cell types [27]. These findings do not make spatial evidence intrinsically causal; instead, they establish that a causal claim can be mis-specified when the relevant molecular relationship is inferred outside the tissue, cell or subcellular context in which it operates.

Artificial intelligence adds analytical power but does not relax these causal requirements. Foundation models such as scGPT learn transferable representations from single-cell and multi-omic data and can support downstream tasks including integration and perturbation-related prediction [28]. Large-scale single-cell foundation models similarly demonstrate that broad pretraining can improve performance across several biological tasks [29]. Their value for target discovery lies in organizing high-dimensional evidence, generating hypotheses and identifying state-dependent patterns that can be tested. Model performance, however, remains evidence about prediction or representation unless connected to an independently supported mechanism. A feature that improves classification, a latent embedding that separates disease states, or a predicted perturbation response should therefore enter the target-evidence record as a model-derived claim with explicit validation requirements.

The evidence needed for therapeutic actionability is thus configurational rather than additive. Strong target support requires more than the accumulation of independent-looking signals. It requires a coherent relation among causal-gene assignment, perturbation direction, network consequence, disease-relevant tissue or cell localization, and the population or disease state in which benefit is expected. Evidence can also be asymmetric: a strong causal assignment may coexist with weak tissue relevance, or convincing tissue expression may coexist with an uncertain intervention direction. Drug-target Mendelian randomization can fail because of invalid proxies, while apparently favorable molecular effects can fail to align with the endpoint that matters clinically [20, 21]. These are not equivalent deficiencies and should not be repaired by simply adding more omics layers.

Table 2 summarizes evidence tests that strengthen or weaken target-actionability claims across causal and contextual levels.

Table 2. Evidence tests that strengthen or weaken target-actionability claims across causal and contextual levels

Evidence question	Configuration that strengthens the claim	Evidence that should downgrade the claim	Boundary that must remain explicit	Permitted target-selection inference
Is the correct causal entity identified?	Fine-mapped or colocalized signal aligned with functional gene-regulatory evidence	Ambiguous locus, competing genes, unresolved multiple signals	Locus and regulatory context	The nominated entity is a more credible causal candidate
Does perturbation act in the intended direction?	Concordant genetic, molecular or functional perturbation evidence with interpretable direction	Proxy with unclear biological effect, pleiotropy, direction discordance	Mechanism and dose/direction	Intervention direction is supported, not yet clinically validated
Does the biological effect reach a relevant endpoint?	Mechanistic change aligns with disease-relevant phenotype or validated downstream consequence	Biomarker change without corresponding endpoint support	Endpoint and surrogate validity	Causal biology is more likely to translate to therapeutic benefit
Is the mechanism active in the relevant tissue or cell state?	Disease-relevant localization with context-consistent regulation or perturbation	Evidence confined to an accessible but mechanistically distant compartment	Tissue, cell, spatial and disease state	Actionability can be restricted to a defined biological domain
What does network perturbation imply?	Context-specific interaction or pathway evidence supports beneficial leverage	Redundancy, compensatory routes, essential-network dependence or broad off-target consequence	Network state and cellular context	Target relevance is qualified by expected system response
Who is expected to benefit?	Causal mechanism is coherent within a defined disease subgroup or state	Mechanistic heterogeneity that changes target relevance	Population, ancestry, subtype, stage and treatment history	Actionability is conditional rather than population universal
What role can AI-derived evidence play?	Model-derived pattern is reproduced and connected to independent biological evidence	Benchmark-only performance, dataset shift or uninterpretable latent association	Dataset, task and intended use	AI can strengthen prioritization but cannot independently confer causality

A defensible target-actionability claim therefore has to survive movement across levels. The association must be assigned to a plausible causal molecular entity; the expected intervention must alter that entity in the relevant direction; network responses must not overturn the intended effect; the mechanism must operate in a disease-relevant tissue or cellular context; and heterogeneity must not make the claim invalid for the population being considered. AI-derived evidence can strengthen each step by improving representation, integration and prediction, but it remains subordinate to the causal and contextual question that the step is intended to answer. **Figure 1** summarizes this cross-level reasoning without treating any single evidence stream as sufficient.

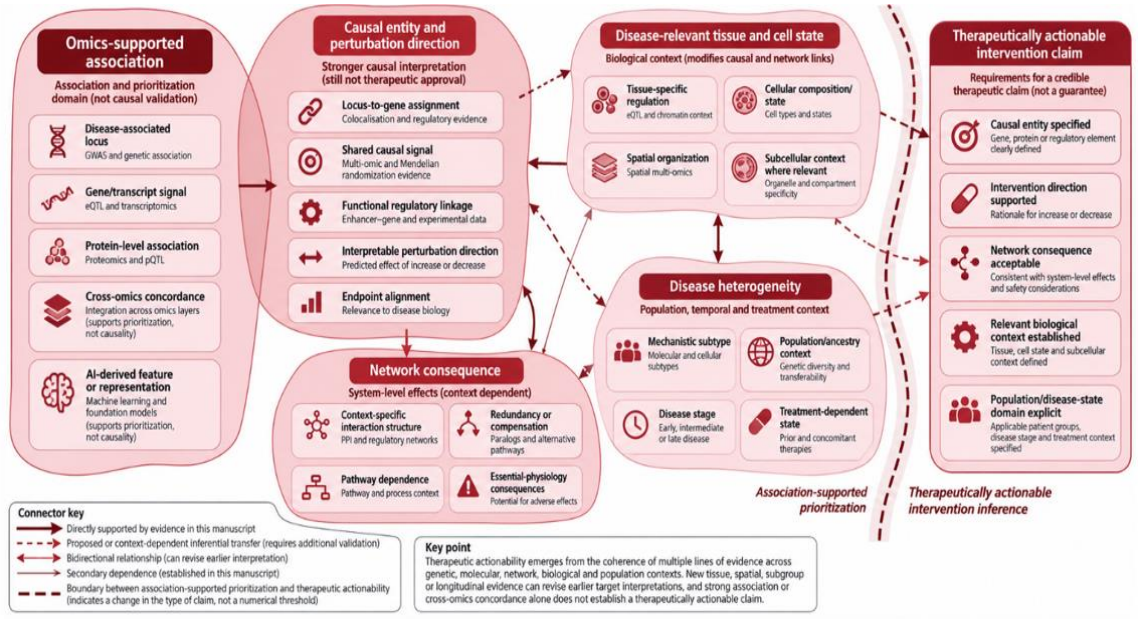


Figure 1. Cross-level conditions that determine whether an omics-supported target claim remains exploratory or becomes therapeutically actionable.

Proposed Target-Actionability Framework

Therapeutic actionability should be assigned to a target–intervention–context relationship, not to a gene or protein in isolation. The relevant unit of assessment comprises the nominated molecular entity, intended perturbation, disease-relevant biological compartment, expected network response, and population or disease state. These elements can change independently. Longitudinal single-cell multi-omics in complex-karyotype acute myeloid leukemia demonstrates that evolving subclones can exhibit distinct targetable phenotypes [30]. Single-cell systems pharmacology in B-cell acute lymphoblastic leukemia similarly shows that developmental state can shape drug sensitivity and combination-treatment opportunities [31]. A target supported under one cellular configuration may consequently become less relevant as disease composition changes.

The proposed framework distinguishes three evidence states: exploratory, conditionally actionable, and progression-ready. These are qualitative decision states, not experimentally validated categories, numerical scores, or substitutes for regulatory evaluation. Their purpose is to identify which inference is currently justified and which unresolved observation could materially change that inference.

An exploratory target has sufficient association or preliminary mechanistic evidence to justify further investigation, but at least one decisive component of therapeutic actionability remains unresolved. This may involve uncertain causal-gene assignment, ambiguous intervention direction, insufficient disease-tissue relevance, or an untested relationship between molecular perturbation and the clinically relevant phenotype.

A conditionally actionable target has credible causal support and a plausible beneficial intervention mechanism within a specified context. Its actionability remains restricted by disease subtype, tissue, cellular state, intervention modality, or an unresolved network consequence. Such a designation should state the applicable biological domain and the evidence needed before broader progression is justified.

A progression-ready target has a sufficiently coherent evidence configuration to justify the next defined translational investigation. This requires defensible causal assignment, interpretable intervention direction, disease-relevant contextual support, and a credible account of expected perturbation consequences. Progression-ready does not mean clinically effective, safe for human use, or suitable for unrestricted development. It means that the available evidence supports a particular next-stage investigation without a known unresolved contradiction that would undermine its central premise.

These states must remain revisable. Single-cell response models can contribute evidence about likely treatment response and resistance, but predictive performance does not independently establish the biological mechanism responsible for the predicted outcome [32]. Spatial profiling of immunotherapy resistance demonstrates that changing tumor-microenvironment organization can expose vulnerabilities or limitations that were not apparent in an initial molecular assessment [33]. Accordingly, new evidence should be capable of moving a target backward as well as forward.

The framework also distinguishes uncertainty from counterevidence. An unmeasured tissue effect creates an evidence gap; a reproducible finding that perturbation produces an adverse effect in the intended disease tissue challenges the intervention claim directly. Similarly, a conserved cellular label cannot guarantee equivalent therapeutic relevance across biological settings. Pan-cancer spatial multi-omics reveals both conserved cancer-associated fibroblast states and differences in their spatial organization [34]. Longitudinal analyses of CDK4/6 inhibitor resistance further demonstrate that treatment can produce distinct molecular trajectories rather than a single uniform resistance mechanism [35]. These findings justify context-specific reassessment rather than treating baseline target status as permanent.

The proposed decision states therefore depend on the configuration of evidence and the significance of its unresolved contradictions. **Table 3** distinguishes incomplete causal assignment, uncertainty about intervention direction, restricted biological applicability, emerging counterevidence, and sufficiently convergent support. These configurations require different next investigations and should not be collapsed into one aggregate confidence score.

Table 3. Proposed target-actionability states under distinct causal and contextual evidence configurations

Target-evidence configuration	Causal and intervention status	Network, tissue or heterogeneity constraint	Proposed decision state	Evidence needed to change the decision
Cross-omics convergence with unresolved gene assignment	Association supported; causal entity uncertain	Context may be inadequately represented	Exploratory	Discriminating locus-to-gene and functional evidence
Credible causal entity with ambiguous perturbation direction	Causal relevance supported; therapeutic mechanism unresolved	Potential opposing effects across compartments	Exploratory	Direction-specific perturbation and endpoint evidence
Causal mechanism restricted to a defined biological context	Intervention rationale supported within a bounded domain	Tissue, subtype or cellular-state dependence	Conditionally actionable	Validation within the intended indication and treatment context
Strong molecular evidence with unresolved network consequences	Target involvement supported; system response uncertain	Compensation, redundancy or essential physiology	Conditionally actionable	Context-relevant perturbation and safety characterization
Previously supported target with contradictory longitudinal evidence	Original mechanism challenged by evolving biology	Clonal selection, resistance or altered cellular neighborhoods	Reassess; potentially downgrade	Mechanistic investigation of the contradiction and revised applicability
Convergent causal, perturbational and contextual support	Intended intervention and relevant consequences sufficiently supported	Population and disease-state boundaries explicitly defined	Progression-ready for the next specified investigation	Prospective translational validation and continued safety assessment

Note: The decision states are original proposed synthesis. They are qualitative and do not constitute validated clinical classifications, quantitative thresholds, or predictions of drug-development success.

The central decision rule is that additional evidence changes target status only when it resolves a consequential uncertainty or alters the expected intervention outcome. Repeated measurements of the same association may improve precision without changing causal interpretation. Conversely, one well-supported observation of incompatible perturbation direction, clinically relevant endpoint discordance, or disease-state-specific resistance may substantially alter the decision.

Figure 2 represents this reversible decision logic. Its progression paths depend on the kind of evidence obtained, while reassessment pathways preserve the possibility that tissue-specific, network-level, or longitudinal findings invalidate an earlier actionability claim.

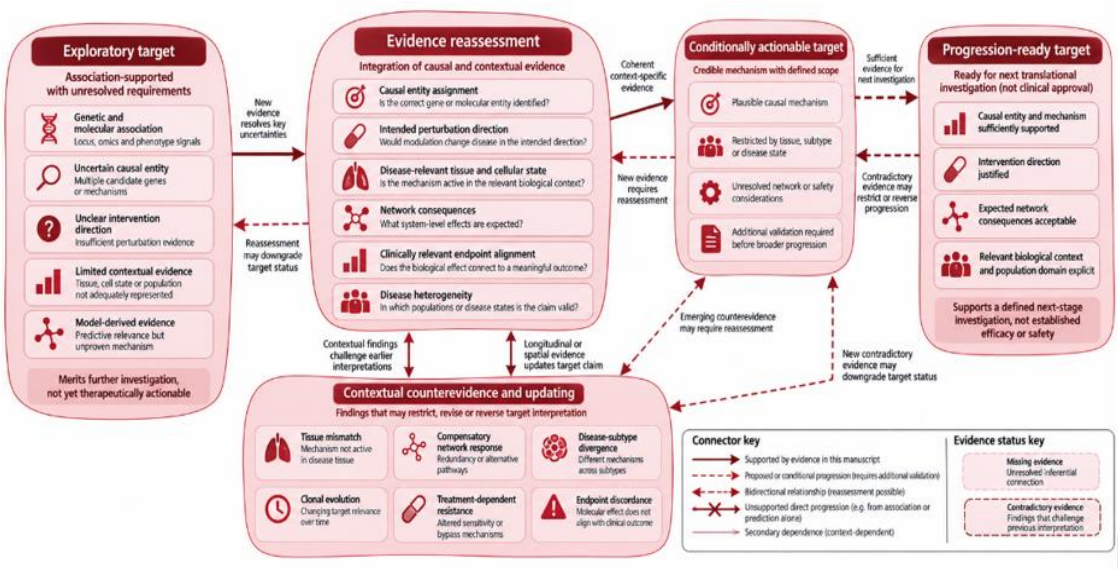


Figure 2. Reversible target-selection decisions under convergent and contradictory evidence.

Translational Implications and Research Priorities

The principal translational implication is that target progression should depend on the unresolved inference most capable of changing the intervention decision. Genetic evidence remains important because it is associated with greater aggregate success in historical drug-development analyses [36]. More recent work also indicates that the strength of this association depends on

confidence in the underlying causal gene and mechanism [4]. Neither finding licenses an individual target to progress automatically. Genetic support should instead help determine which causal questions deserve priority and whether the proposed intervention is consistent with the available human evidence.

This distinction has practical consequences for experimental planning. If locus-to-gene assignment remains ambiguous, additional association measurements are unlikely to resolve the central uncertainty unless they discriminate among candidate causal entities. If a target is genetically implicated but its therapeutic direction is uncertain, functional perturbation should establish whether inhibition, activation, or another mode of modulation produces the intended disease-relevant effect. If network consequences remain unresolved, experiments should examine compensation, pathway adaptation and potentially harmful effects in relevant cellular systems. The evidentiary gap should determine the experiment, rather than allowing the availability of a particular omics platform to determine the question.

Endpoint selection requires similar discipline. A molecular response can provide compelling evidence that an intervention engages a biological mechanism without establishing the expected clinical benefit. Findings concerning genetically proxied ANGPTL3 inhibition illustrate the importance of examining whether molecular and clinical endpoint evidence align [21]. Target validation should therefore identify the clinically relevant consequence that the proposed perturbation is expected to produce, distinguish it from intermediate biomarkers, and examine competing explanations when these outcomes diverge.

Disease heterogeneity should also be incorporated before a target is assigned broad therapeutic relevance. Genetic clustering in type 2 diabetes demonstrates that apparently unified disease categories may contain distinct pathophysiological processes [23]. A target-selection strategy should therefore specify whether its evidence concerns a general disease mechanism, a molecularly defined subgroup, or a particular disease stage. The absence of subgroup evidence should remain visible as an applicability limitation. A restricted but defensible actionability claim may be more useful for experimental planning than an unsupported population-wide assertion.

Artificial intelligence can improve the efficiency of this process by integrating evidence, representing complex cellular states, identifying candidate interactions and generating perturbation hypotheses. Nevertheless, its contribution should be judged according to the inferential question it addresses. Computational-model credibility requires fit-for-purpose verification, validation and uncertainty assessment [6]. Predictive accuracy may justify further investigation, but mechanistic interpretation requires evidence beyond the model's learned associations. Research should prioritize independent biological validation, evaluation under dataset and population shifts, and explicit comparison between model-generated mechanisms and plausible alternatives.

A particularly important priority is the integration of causal perturbation with spatially resolved and longitudinal evidence. Spatial multi-omics can characterize biological relationships within the tissue architecture in which disease operates [25]. However, an observed cellular neighborhood or molecular colocalization does not establish the consequences of intervention. Combining spatial characterization with appropriately designed perturbational experiments would help distinguish causal mechanisms from correlated tissue states. Longitudinal sampling would additionally allow investigators to determine whether a mechanism remains relevant after treatment or disease evolution.

The need for such updating is demonstrated by distinct molecular trajectories of resistance to CDK4/6 inhibition [35]. A baseline target assessment may cease to describe the operative disease mechanism after treatment selects alternative cellular states. Target-actionability records should consequently retain the conditions under which the original claim was established and identify which subsequent observations warrant reassessment. This approach is particularly relevant when a target is supported by molecular evidence obtained before exposure to the intended treatment.

The broader research agenda is to develop validation strategies that connect genetic causal inference, mechanistically interpretable perturbation, network consequence, tissue and cellular context, and longitudinal patient heterogeneity without assigning these different evidence types interchangeable meanings. Future work should test whether explicitly recording these distinctions improves the reproducibility and transparency of target-selection decisions. Such evaluation must compare decision consequences against appropriate alternatives rather than assume that a more elaborate evidence configuration is intrinsically superior.

The framework's proposed states are not substitutes for pharmacological characterization, exposure assessment, toxicology, clinical evaluation or regulatory review. They define what is currently justified about the target–intervention relationship and what uncertainty remains before the next investigation. A target is therapeutically actionable only within the intervention direction, tissue, indication, population and disease state supported by its evidence. As those conditions change, the claim must remain open to revision.

Conclusion

Multi-omics association becomes therapeutically informative when its molecular signals support a defensible causal intervention claim whose biological and clinical domain is explicit. Gene assignment, perturbation direction, network consequences, tissue relevance and disease heterogeneity answer different questions and cannot be replaced by greater data volume, cross-modal concordance or predictive performance. The proposed target-actionability framework translates these distinctions into revisable exploratory, conditionally actionable and progression-ready states. Its central contribution is the requirement that progression depend on resolving consequential uncertainty while contradictory evidence retains the power to restrict or reverse an earlier decision. Therapeutic actionability is therefore neither a permanent property of a molecular target

nor the inevitable outcome of increasingly sophisticated bioinformatics. It is a context-bounded judgment about what intervention is justified, for whom, under which biological conditions, and with what remaining uncertainty.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Liu Y, Zhu K, Peng W, Liu Z, Mao X. Multi-omics and artificial intelligence for precision drug discovery and potential clinical applications. Signal Transduct Target Ther. 2026;11(1):210. doi:10.1038/s41392-026-02631-6
2. Jiang W, Ye W, Tan X, Bao YJ. Network-based multi-omics integrative analysis methods in drug discovery: A systematic review. Bio Data Min. 2025;18(1):27. doi:10.1186/s13040-025-00442-z
3. Morabito A, De Simone G, Pastorelli R, Brunelli L, Ferrario M. Algorithms and tools for data-driven omics integration to achieve multilayer biological insights: A narrative review. J Transl Med. 2025;23(1):425. doi:10.1186/s12967-025-06446-x
4. Minikel EV, Painter JL, Dong CC, Nelson MR. Refining the impact of genetic evidence on clinical success. Nature. 2024;629(8012):624-9. doi:10.1038/s41586-024-07316-0
5. Ghosh S, Zhao X, Alim M, Brudno M, Bhat M. Artificial intelligence applied to 'omics data in liver disease: Towards a personalised approach for diagnosis, prognosis and treatment. Gut. 2025;74(2):295-311. doi:10.1136/gutjnl-2023-331740
6. Sauro HM, Agmon E, Blinov ML, Gennari JH, Hellerstein JL, Heydarabadipour A, et al. From FAIR to CURE: Guidelines for computational models of biological systems. NPJ Syst Biol Appl. 2026;12(1):77. doi:10.1038/s41540-026-00651-0
7. Du P, Fan R, Zhang N, Wu C, Zhang Y. Advances in integrated multi-omics analysis for drug-target identification. Biomolecules. 2024;14(6):692. doi:10.3390/biom14060692
8. Ferkingstad E, Sulem P, Atlason BA, Sveinbjornsson G, Magnusson MI, Styrmisdottir EL, et al. Large-scale integration of the plasma proteome with genetics and disease. Nat Genet. 2021;53(12):1712-21. doi:10.1038/s41588-021-00978-w
9. Sun BB, Chiou J, Traylor M, Benner C, Hsu YH, Richardson TG, et al. Plasma proteomic associations with genetics and health in the UK Biobank. Nature. 2023;622(7982):329-38. doi:10.1038/s41586-023-06592-6
10. Mountjoy E, Schmidt EM, Carmona M, Schwartzentruber J, Peat G, Miranda A, et al. An open approach to systematically prioritize causal variants and genes at all published human GWAS trait-associated loci. Nat Genet. 2021;53(11):1527-33. doi:10.1038/s41588-021-00945-5
11. Wallace C. A more accurate method for colocalisation analysis allowing for multiple causal variants. PLoS Genet. 2021;17(9):e1009440. doi:10.1371/journal.pgen.1009440
12. Nasser J, Bergman DT, Fulco CP, Guckelberger P, Doughty BR, Patwardhan TA, et al. Genome-wide enhancer maps link risk variants to disease genes. Nature. 2021;593(7858):238-43. doi:10.1038/s41586-021-03446-x
13. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020;369(6509):1318-30. doi:10.1126/science.aaz1776
14. Võsa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53(9):1300-10. doi:10.1038/s41588-021-00913-z
15. Luck K, Kim DK, Lambourne L, Spirohn K, Begg BE, Bian W, et al. A reference map of the human binary protein interactome. Nature. 2020;580(7803):402-8. doi:10.1038/s41586-020-2188-x
16. Huttlin EL, Bruckner RJ, Navarrete-Perea J, Cannon JR, Baltier K, Gebreab F, et al. Dual proteome-scale networks reveal cell-specific remodeling of the human interactome. Cell. 2021;184(11):3022-40.e28. doi:10.1016/j.cell.2021.04.011
17. Ochoa D, Hercules A, Carmona M, Suveges D, Baker J, Malangone C, et al. The next-generation Open Targets Platform: Reimagined, redesigned, rebuilt. Nucleic Acids Res. 2023;51(D1):D1353-9. doi:10.1093/nar/gkac1046
18. Burgess S, Mason AM, Grant AJ, Slob EAW, Gkatzionis A, Zuber V, et al. Using genetic association data to guide drug discovery and development: Review of methods and applications. Am J Hum Genet. 2023;110(2):195-214. doi:10.1016/j.ajhg.2022.12.017
19. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, et al. Mendelian randomization. Nat Rev Methods Primers. 2022;2:6. doi:10.1038/s43586-021-00092-5
20. Gill D, Dib MJ, Cronjé HT, Karhunen V, Woolf B, Gagnon E, et al. Common pitfalls in drug target Mendelian randomization and how to avoid them. BMC Med. 2024;22(1):473. doi:10.1186/s12916-024-03700-9
21. Gobeil É, Bourgault J, Mitchell PL, Houessou U, Gagnon E, Girard A, et al. Genetic inhibition of angiopoietin-like protein-3, lipids, and cardiometabolic risk. Eur Heart J. 2024;45(9):707-21. doi:10.1093/eurheartj/ehad845

22. Si S, Liu H, Xu L, Zhan S. Identification of novel therapeutic targets for chronic kidney disease and kidney function by integrating multi-omics proteome with transcriptome. Genome Med. 2024;16(1):84. doi:10.1186/s13073-024-01356-x
23. Suzuki K, Hatzikotoulas K, Southam L, Taylor HJ, Yin X, Lorenz KM, et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. Nature. 2024;627(8003):347-57. doi:10.1038/s41586-024-07019-6
24. Kiessling P, Kuppe C. Spatial multi-omics: Novel tools to study the complexity of cardiovascular diseases. Genome Med. 2024;16(1):14. doi:10.1186/s13073-024-01282-y
25. Liu X, Peng T, Xu M, Lin S, Hu B, Chu T, et al. Spatial multi-omics: Deciphering technological landscape of integration of multi-omics and its applications. J Hematol Oncol. 2024;17(1):72. doi:10.1186/s13045-024-01596-9
26. Bravo González-Blas C, Matetovici I, Hillen H, Taskiran II, Vandepoel R, Christiaens V, et al. Single-cell spatial multi-omics and deep learning dissect enhancer-driven gene regulatory networks in liver zonation. Nat Cell Biol. 2024;26(1):153-67. doi:10.1038/s41556-023-01316-4
27. Takei Y, Yang Y, White J, Goronzy IN, Yun J, Prasad M, et al. Spatial multi-omics reveals cell-type-specific nuclear compartments. Nature. 2025;641(8064):1037-47. doi:10.1038/s41586-025-08838-x
28. Cui H, Wang C, Maan H, Pang K, Luo F, Duan N, et al. scGPT: Toward building a foundation model for single-cell multi-omics using generative AI. Nat Methods. 2024;21(8):1470-80. doi:10.1038/s41592-024-02201-0
29. Hao M, Gong J, Zeng X, Liu C, Guo Y, Cheng X, et al. Large-scale foundation model on single-cell transcriptomics. Nat Methods. 2024;21(8):1481-91. doi:10.1038/s41592-024-02305-7
30. Leppä AM, Grimes K, Jeong H, Huang FY, Andrades A, Waclawiczek A, et al. Single-cell multiomics analysis reveals dynamic clonal evolution and targetable phenotypes in acute myeloid leukemia with complex karyotype. Nat Genet. 2024;56(12):2790-803. doi:10.1038/s41588-024-01999-x
31. Huang X, Li Y, Zhang J, Yan L, Zhao H, Ding L, et al. Single-cell systems pharmacology identifies development-driven drug response and combination therapy in B cell acute lymphoblastic leukemia. Cancer Cell. 2024;42(4):552-67.e6. doi:10.1016/j.ccell.2024.03.003
32. Sinha S, Vegesna R, Mukherjee S, Kammula AV, Dhruba SR, Wu W, et al. PERCEPTION predicts patient response and resistance to treatment using single-cell transcriptomics of their tumors. Nat Cancer. 2024;5(6):938-52. doi:10.1038/s43018-024-00756-7
33. Quek C, Pratapa A, Bai X, Al-Eryani G, Pires da Silva I, Mayer A, et al. Single-cell spatial multiomics reveals tumor microenvironment vulnerabilities in cancer resistance to immunotherapy. Cell Rep. 2024;43(7):114392. doi:10.1016/j.celrep.2024.114392
34. Liu Y, Sinjab A, Min J, Han G, Paradiso F, Zhang Y, et al. Conserved spatial subtypes and cellular neighborhoods of cancer-associated fibroblasts revealed by single-cell spatial multi-omics. Cancer Cell. 2025;43(5):905-24.e6. doi:10.1016/j.ccell.2025.03.004
35. Kan Z, Wen J, Bonato V, Webster J, Yang W, Ivanov V, et al. Real-world clinical multi-omics analyses reveal bifurcation of ER-independent and ER-dependent drug resistance to CDK4/6 inhibitors. Nat Commun. 2025;16(1):932. doi:10.1038/s41467-025-55914-x
36. King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 2019;15(12):e1008489. doi:10.1371/journal.pgen.1008489