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MULTI-OMICS TARGET DISCOVERY AFTER DATA INTEGRATION: AN UMBRELLA REVIEW OF CAUSAL EVIDENCE, REPRODUCIBILITY, AND TRANSLATIONAL READINESS

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ABSTRACT

Multi-omics integration is increasingly used to prioritize therapeutic targets by combining genomic, transcriptomic, proteomic, metabolomic, and related molecular evidence. Yet the accumulation of data layers does not necessarily produce stronger target claims. Reviews differ substantially in their definitions of integration, evidentiary standards, causal assumptions, validation requirements, and interpretation of translational readiness. This umbrella review evaluates how review-level evidence supports multi-omics target discovery and where conclusions remain constrained by methodological heterogeneity, overlapping primary studies, population underrepresentation, technical variability, and insufficient experimental confirmation. Eligible reviews and supporting methodological sources were organized through a review-of-reviews framework that distinguishes substantive evidence synthesis from reporting guidance and selected translational anchors. Review quality, search transparency, primary-study overlap, consistency, modality-specific contributions, causal inference, perturbational validation, reproducibility, diversity, druggability, and safety were treated as separate but connected dimensions. The synthesis indicates that genomic evidence can strengthen causal prioritization under explicit assumptions; transcriptomic and single-cell evidence can localize disease-relevant cellular contexts; proteomic evidence can support mechanism and target engagement; and metabolomic evidence can reveal phenotype-proximal pathway consequences. Integration becomes scientifically persuasive only when disagreement among modalities remains visible and when causal, perturbational, and cross-cohort validation are added. The principal contribution is a proposed target-evidence pyramid that separates association, contextual localization, causal support, experimental confirmation, reproducibility, and conditional translational readiness. The framework is an organizing synthesis rather than a validated scoring system. Its interpretation remains limited by incomplete review reporting, heterogeneous evidence structures, shared primary studies, and uneven availability of independent validation. Multi-omics integration should therefore be treated as a mechanism for evidence coordination, not as an automatic indication of pharmaceutical readiness.

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Introduction

Disease-relevant molecular variation is distributed across several biological layers. Genomic measurements can identify inherited or acquired variation, transcriptomic profiles can characterize expression states, proteomic assays can reveal abundance and interaction changes, and metabolomic measurements can capture downstream biochemical consequences. These layers provide complementary information, but their integration remains analytically and biologically heterogeneous because they differ in scale, temporal responsiveness, tissue specificity, measurement error, and proximity to phenotype [1-3].

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Consequently, the presence of several omics modalities in one analysis does not by itself establish coherent evidence for a therapeutic target. Integration can reveal convergence, but it can also combine incompatible contexts, propagate technical artefacts, or conceal disagreement behind a composite score.

Target-discovery platforms use omics evidence for substantially different purposes, including candidate generation, disease-mechanism reconstruction, cell-type localization, causal prioritization, target-engagement assessment, safety prediction, and therapeutic stratification. These purposes carry different evidentiary burdens. Omics-enabled target platforms therefore differ not only in computational architecture but also in the type of evidence produced, the biological context represented, and the validation required before a target hypothesis can influence a pharmaceutical decision [4]. An association between a molecular feature and disease may support prioritization, whereas evidence of causal direction, functional dependency, pharmacological tractability, acceptable safety, or clinical usefulness requires additional designs. Treating these levels as interchangeable encourages an unjustified progression from statistical signal to therapeutic claim.

The expanding review literature creates a second evidentiary problem. Reviews of genomics, single-cell analysis, proteomics, metabolomics, causal genetics, functional screening, machine learning, and translational development frequently examine different slices of the same target-discovery landscape. Their conclusions may depend on overlapping primary studies, dissimilar disease contexts, distinct definitions of validation, or selective emphasis on successful applications. Counting the number of reviews that repeat a conclusion can therefore exaggerate confidence when those reviews rely on the same underlying experiments or databases. Conversely, apparent disagreement may reflect differences in modality, tissue, population, intervention, or development stage rather than a direct contradiction. A review-of-reviews design is needed to identify what the available reviews collectively establish, which conclusions remain conditional, and where overlap prevents an inference of independent replication.

This umbrella review evaluates multi-omics target discovery after data integration through the linked domains of review eligibility, methodological quality, primary-study overlap, modality-specific evidence, causal inference, perturbational validation, reproducibility, cohort diversity, and translational readiness. Molecular stratification and biomarker-rich discovery may improve biological understanding and patient classification, but they do not alone establish therapeutic success [5]. The review therefore distinguishes demonstrated analytical capability from biological plausibility, causal support, experimental confirmation, prospective decision utility, and pharmaceutical readiness. Its original contribution is a proposed evidence-escalation interpretation in which integrated omics generates or refines target hypotheses, while stronger claims require independent causal, functional, reproducibility, tractability, and safety evidence. This interpretation is intended to organize review-level findings and their boundaries; it is not presented as an empirically validated target-scoring system.

Umbrella-Review Protocol and Review-Level Eligibility Criteria

The umbrella question was defined before synthesis to prevent the evidence base from expanding according to whichever technologies reported the most favorable results. An overview question should specify the relevant population or biological context, the phenomenon being evaluated, the eligible review designs, and the decision the overview is intended to inform [6]. Here, the population and context comprise human disease biology and pharmaceutical target discovery, while the phenomenon is the use of genomic, transcriptomic, proteomic, metabolomic, and integrated evidence to identify or strengthen target hypotheses. The intended decision is not whether a particular target should enter development, but whether review-level evidence supports a given class of target claim and what additional validation would be required. The principal eligible evidence therefore consists of reviews that synthesize target-relevant omics, causal, perturbational, reproducibility, diversity, or translational evidence. Methodological guidelines and selected integrative studies serve as supporting anchors rather than additional review-level votes.

Eligibility was based on evidentiary function rather than on the label attached to an article. Systematic reviews, scoping reviews, methods primers, state-of-field reviews, and sufficiently analytical narrative reviews could contribute when they described their evidence base, separated empirical findings from interpretation, and supported a planned review question. Overview methods should be selected explicitly in relation to the question and the structure of the available evidence [7]. Accordingly, systematic reviews were eligible for domain-based critical appraisal, whereas narrative reviews and perspectives were interpreted through descriptive criteria such as search transparency, evidence-selection logic, claim specificity, acknowledgement of conflicting findings, and disclosure of limitations. Narrow benchmark reports, articles mentioning multi-omics only incidentally, and sources that equated predictive performance with target validation were outside the substantive synthesis. Primary studies were not treated as independent review-level confirmation even when retained to contextualize druggability or translational interpretation.

The unit of synthesis was the review conclusion linked to its underlying primary-study set, not the number of publications expressing that conclusion. This distinction is essential because several reviews may reuse the same cohorts, public datasets, perturbation screens, target databases, or landmark experiments. Review conclusions were therefore interpreted according to methodological quality, comprehensiveness, recency, contextual fit, and independence of the underlying evidence. A pre-specified overview framework is also required to make eligibility, methods, synthesis decisions, and reporting boundaries visible [8]. Within this framework, consistency was categorized as convergent, conditionally convergent, mixed, divergent, or not assessable. Translational readiness was treated as a multidimensional interpretation involving causal support, functional confirmation, independent reproducibility, cohort diversity, druggability, safety, and decision relevance rather than as a direct

output of data integration. **Table 1** organizes the evidence, constructs, and interpretation boundaries needed to develop umbrella-review protocol and review-level eligibility criteria within the article's central argument.

Table 1. Evidence domains, core questions, scientific requirements, and interpretation boundaries for Umbrella-review protocol and review-level eligibility criteria

Evidence domain	Eligible evidence or method	Reported capability or claim	Strength of support	Reproducibility or bias concern	Unresolved gap
Review-question framing	Pre-specified overview question defining biological context, evidence type, review design, and intended decision	Prevents technology-led or outcome-led expansion of the review scope	Foundational methodological support	Broad questions can combine incompatible diseases, modalities, and development stages	No universal formulation captures every target-discovery context
Substantive review-level evidence	Systematic, scoping, state-of-field, methods-oriented, or analytical narrative reviews addressing target-relevant evidence	Synthesizes modality-specific capabilities, limitations, and validation practices	Conditional on review transparency and methodological fit	Reviews may selectively emphasize successful applications or omit negative evidence	Search and appraisal methods are not consistently reported across review types
Supporting methodological evidence	Reporting guidelines, appraisal tools, overlap methods, and evidence-synthesis guidance	Supports transparent conduct and defensible interpretation of an umbrella review	Strong for methodological organization, not for target validity	Reporting completeness can be mistaken for substantive evidentiary strength	Methodological guidance requires adaptation to heterogeneous omics evidence
Review-quality appraisal	Domain-based appraisal for systematic reviews and descriptive appraisal for other designs	Identifies weaknesses that can affect confidence in review conclusions	Design-dependent	A single score can conceal critical weaknesses or create false comparability between unlike designs	Quality domains specific to computational target-discovery reviews remain underdeveloped
Primary-study overlap	Review-by-primary-study citation matrix and corrected covered area when study lists are sufficiently complete	Distinguishes repeated reporting from independent evidentiary convergence	Strong when primary-study lists are recoverable	Hidden dataset reuse and incomplete study lists can leave overlap underestimated	Overlap cannot always be quantified reliably across databases, secondary analyses, and reused cohorts
Consistency and readiness interpretation	Contextual comparison of conclusions across modality, disease, population, validation setting, and development stage	Identifies convergent, conditional, mixed, divergent, or unassessable findings	Conditional synthesis support	Agreement may arise from shared evidence, while disagreement may arise from incomparable contexts	No validated universal scale links review agreement directly to pharmaceutical readiness

Search, Quality Assessment, Overlap Analysis, and Evidence Extraction

The search and selection logic was organized around linked concept blocks rather than a single broad multi-omics term. These blocks covered review methodology; genomic, transcriptomic, proteomic, metabolomic, and integrated target evidence; causal inference; perturbational validation; reproducibility; population diversity; cross-study consistency; druggability; safety; and translational interpretation. Search, eligibility, extraction, and synthesis procedures should be reported transparently enough for readers to understand how evidence entered the review and how conclusions were constructed [9]. Eligibility decisions were therefore tied to predefined review questions and specific manuscript claims. Evidence extraction recorded article aim and review type, application context, omics modality, integration method, claimed capability, causal design, validation setting, population representation, reproducibility considerations, translational interpretation, availability of underlying study lists, and reported limitations. Categories absent from a source were treated as not clearly reported rather than inferred from disciplinary convention.

Quality assessment was matched to article design. Eligible systematic reviews were appraised through critical methodological domains, including protocol specification, search adequacy, study selection, data extraction, risk-of-bias assessment, synthesis appropriateness, explanation of heterogeneity, and consideration of publication bias where applicable. Systematic reviews should be judged through critical domains rather than reduced to a single undifferentiated numerical score [10]. A review with an extensive search but an inappropriate synthesis can therefore be less dependable for a particular claim than a narrower review with explicit eligibility and careful interpretation. Narrative reviews, primers, perspectives, consensus guidance, and

primary translational anchors were not assigned artificial systematic-review scores. They were assessed descriptively for transparency, balance, evidence traceability, conflict acknowledgement, applicability, and separation of demonstrated findings from proposed interpretation. Quality appraisal informed the weight and wording of synthesis claims but did not automatically exclude a source whose limited design was appropriate for a narrowly defined conceptual contribution.

Overlap analysis was conducted conceptually at the level of underlying primary evidence because overviews frequently report incompletely how overlapping, discordant, or otherwise problematic evidence has been handled [11]. Where reviews provided sufficiently complete study lists, a review-by-primary-study citation matrix was the preferred method for identifying shared evidence. Corrected covered area can summarize the degree of primary-study overlap when such citation matrices are available, but its interpretation depends on accurate identification of studies, cohorts, follow-up reports, and secondary analyses [12]. When study lists were incomplete, overlap was addressed through narrative sensitivity analysis, including examination of shared datasets, recurring cohorts, landmark perturbation studies, and reused target resources. Repeated conclusions from overlapping reviews were not counted as independent confirmation. Discordance was traced to eligibility criteria, disease context, omics layer, population composition, analytical assumptions, validation model, and evidence maturity. Consistency was then graded only after these dependencies were considered. Transparent overview reporting should disclose eligibility, appraisal, overlap, synthesis, and certainty procedures so that readers can distinguish evidentiary convergence from repeated interpretation of the same primary material [13].

Genomic, Transcriptomic, Proteomic, Metabolomic, and Integrated Target Evidence

Genetic association data and single-cell RNA sequencing contribute different but complementary forms of target evidence: the former can support prioritization under assumption-dependent causal and pharmacological interpretation, whereas the latter can localize target-relevant cell states while remaining constrained by sampling, annotation, and model context [14, 15]. Genomic evidence is comparatively stable across time and can connect inherited variation to disease liability, but variant-to-gene assignment, linkage disequilibrium, tissue relevance, and population structure complicate target attribution. Transcriptomic evidence is more responsive to disease state and treatment context, yet expression change may reflect compensation, cellular composition, or downstream injury rather than a therapeutically actionable cause. Their convergence is therefore informative only when locus resolution and cellular localization point toward a compatible biological mechanism.

Proteomic evidence brings target discovery closer to molecular function by measuring protein abundance, modification, interaction, complex membership, and drug engagement. Mass-spectrometry-based proteomics can connect target hypotheses to selectivity, pathway response, and mechanism-of-action questions, although incomplete coverage, dynamic-range limitations, missingness, and platform-specific measurement remain important constraints [16]. A protein-level signal may strengthen a transcript-derived hypothesis when it is reproduced through an independent assay or observed after a relevant perturbation. It cannot, however, be assumed that altered protein abundance establishes functional necessity. Evidence of binding or engagement must likewise be separated from evidence that modulation produces the intended disease-relevant phenotype.

Metabolomics captures biochemical states that are often closer to the expressed phenotype than genomic or transcriptomic measurements. Metabolite profiles can reveal pathway disruption, systemic adaptation, substrate-product imbalance, and consequences of treatment, but they often provide limited unique gene-to-target specificity [17]. Diet, microbiome composition, medications, organ function, sample handling, and incomplete metabolite annotation can all influence the observed pattern. Metabolomic evidence is therefore most persuasive when used to test whether a proposed target mechanism produces a coherent biochemical consequence. A metabolite signature may support pathway plausibility or treatment response, but it does not independently identify which molecular node caused the change.

Integrated evidence should preserve these modality-specific meanings instead of compressing them into an opaque consensus score. Multi-omics and single-cell information can organize target hypotheses by linking genetic support, cellular context, molecular mechanism, and phenotype-proximal consequences, but causal and functional follow-up remain necessary [18]. Agreement across layers is strongest when measurements arise from compatible tissues, populations, disease stages, and perturbational conditions. Disagreement should not automatically be treated as analytical failure: it may reveal temporal separation, compensatory biology, cell-type restriction, or measurement limitations. The umbrella synthesis therefore interprets integration as structured evidence coordination. More modalities do not automatically produce a more valid target; credibility depends on provenance, contextual compatibility, independent support, and the visibility of uncertainty.

Causal Inference and Perturbational Validation across Reviews

Causal inference addresses whether modification of a molecular exposure is expected to alter a disease outcome rather than merely accompany it. Mendelian randomization can contribute to this question by using genetic variants as instrumental variables, but its interpretation depends on explicit assumptions concerning instrument relevance, confounding, exclusion restrictions, population structure, and sensitivity to pleiotropy [19]. Colocalization and fine-mapping evidence are often needed to reduce the risk that associations with an exposure and an outcome arise from different causal variants. Even when these conditions are reasonably supported, the inference concerns the genetically proxied exposure represented by the instrument; it is not an unrestricted claim about every pharmacological method of modifying the target.

Drug-target Mendelian randomization can strengthen human causal support by estimating the direction and potential consequences of target modulation, yet it cannot substitute for pharmacological validation [20]. Lifelong genetic variation may

differ from a treatment in dose, timing, reversibility, tissue distribution, developmental compensation, and molecular selectivity. A target may appear causally favorable while remaining inaccessible to an appropriate therapeutic modality, or an intervention may produce effects not anticipated by the genetic proxy. Genetic evidence should therefore be interpreted as one element of causal triangulation. Its value rises when instrument construction is biologically credible, results are robust to sensitivity analyses, and the inferred direction is compatible with independent molecular and experimental findings.

Perturbational evidence tests whether deliberate molecular intervention produces a measurable change. High-content CRISPR screening can connect gene perturbations to transcriptional, morphological, viability, differentiation, or other phenotypic responses, but the resulting evidence remains dependent on guide performance, phenotype selection, model-system relevance, and control of off-target effects [21]. Screens can distinguish functional dependency from passive association and can identify context-specific effects that are obscured in bulk observational data. Nevertheless, a strong screen phenotype in a cell line does not establish therapeutic efficacy. Replication across guides, perturbation modalities, cellular backgrounds, and disease-relevant models is needed before a hit can be interpreted as credible mechanistic confirmation.

Functional-genomics screens are most informative when initial hits are followed by orthogonal validation, rescue experiments, dose-sensitive perturbation, temporal analysis, and mechanistic characterization [22]. CRISPR-based perturbomics may further prioritize targets by linking genotype, molecular response, cellular state, and functional phenotype, provided that the observed effect is reproduced through independent assays and interpreted within the limitations of the model [23]. The proposed review interpretation therefore distinguishes three escalating claims: association indicates that a target is connected to disease; causal evidence suggests that modifying the relevant exposure may influence disease; and perturbational confirmation shows that deliberate intervention produces a compatible functional consequence in a specified system. None of these claims alone establishes druggability, safety, human efficacy, or routine development readiness.

Reproducibility, Cohort Diversity, and Cross-Study Consistency

Limited ancestral representation weakens the transportability and equity of human genetic target inference, whereas appropriately analyzed diverse-population studies can improve discovery, fine mapping, and discrimination among correlated candidate variants [24, 25]. Broad ancestry categories should not be treated as fixed biological mechanisms because genetic structure intersects with geography, environment, healthcare access, social conditions, and study design. Representation is therefore not merely a demographic reporting issue. It affects variant frequency, linkage patterns, instrument performance, molecular reference panels, imputation, calibration, and the relevance of target conclusions across populations. Diversity strengthens inference when accompanied by population-aware methods and sufficiently detailed biological and contextual interpretation.

Technical variation creates a separate threat to consistency. Batch effects can arise from sample collection, storage, reagent lots, sequencing runs, instrument settings, laboratory procedures, data processing, or changes in personnel and platforms. Uncontrolled variation can create apparent omics signals, obscure real biology, or alter relationships among modalities [26]. Correction is not automatically beneficial because biological variables may be confounded with technical structure, and aggressive adjustment can remove the disease signal under investigation. Cross-study comparison should therefore document preprocessing, quality control, normalization, feature filtering, missing-data handling, software versions, and the relationship between technical and biological covariates.

Replicability should be evaluated as an explicit property rather than inferred from analyses that appear nominally similar. Cancer-omics research illustrates that agreement can vary according to endpoint definition, feature construction, statistical method, data platform, cohort composition, and the criterion used to define replication [27]. Reanalysis of one shared dataset with several pipelines may assess computational sensitivity but does not constitute independent biological confirmation. Stronger evidence arises when a target signal survives changes in cohort, site, assay, pipeline, and analytical team while retaining compatible direction and biological interpretation. Failure to reproduce should be examined for contextual explanations rather than concealed by selective reporting.

Cross-study consistency is consequently a structured judgment about independence, comparability, and contextual coherence. Convergence is strongest when reviews draw on non-overlapping cohorts, compatible phenotypes, transparent pipelines, and external validation across populations and platforms. Conditional convergence applies when findings agree only within a particular tissue, disease stage, molecular subtype, or analytical definition. Mixed or divergent findings may indicate hidden heterogeneity, ancestry mismatch, batch structure, inadequate power, or model dependence. The umbrella review therefore does not grade confidence by the frequency with which a claim is repeated. It gives greater interpretive weight to methodological quality, independence of the underlying evidence, diversity of represented contexts, and direct testing of replicability.

Review-of-Reviews Synthesis of Translational Readiness

Human genetics can inform multiple stages from target discovery to clinical development, but evidentiary strength varies across that chain [28]. A genetically supported target may have a stronger human-disease rationale than a target supported only by model systems, particularly when directionality, colocalization, and phenotypic consequences are coherent. This advantage remains conditional. Genetic evidence does not guarantee that an appropriate intervention can be created, delivered to the relevant tissue, dosed safely, or shown to improve a meaningful clinical outcome. Translational readiness must therefore be interpreted as a portfolio of mutually constraining evidence rather than as the final score from an integration algorithm.

Safety constitutes a distinct dimension of that portfolio. Human genetic evidence may help anticipate some consequences of prolonged target modulation, identify phenotypes associated with reduced or increased target function, and highlight possible on-target liabilities. It cannot replace experimental and clinical safety assessment because genetic proxies incompletely represent exposure magnitude, timing, developmental stage, off-target pharmacology, rare events, or modality-specific toxicities [29]. **Figure 1** presents the multi-omics target-evidence pyramid, showing how the article's key components and boundaries are connected within review-of-reviews synthesis of translational readiness.

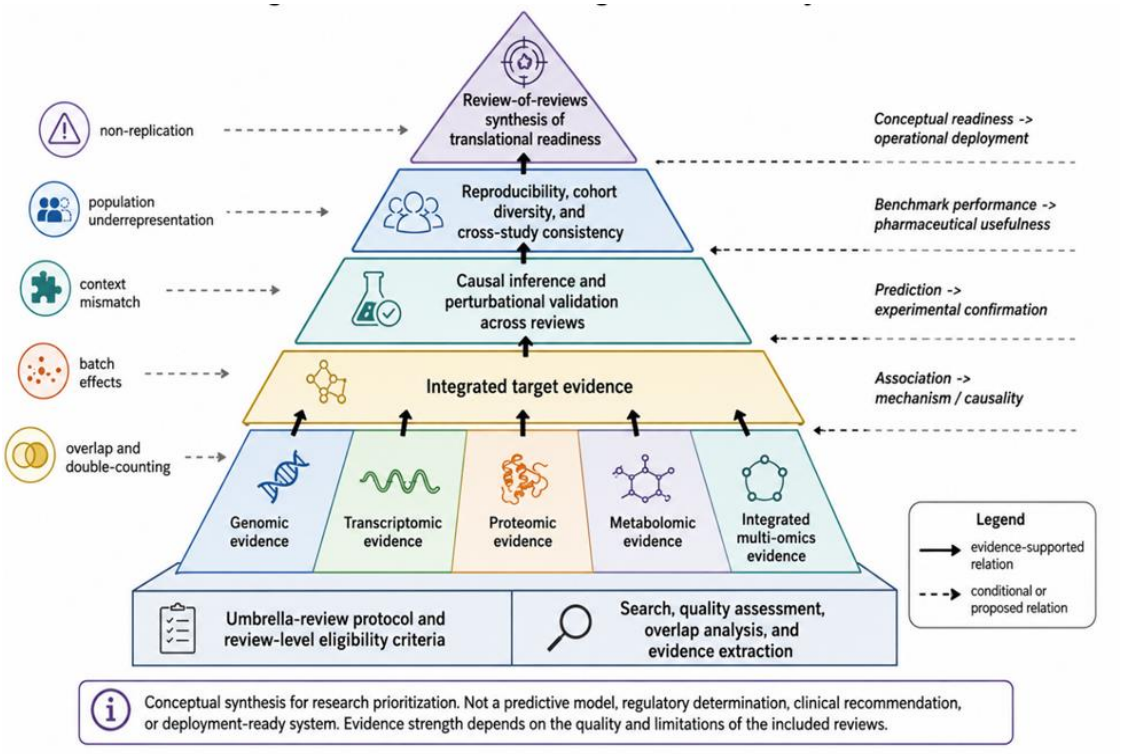

Figure 1. Multi-Omics Target-Evidence Pyramid

The figure is an original conceptual synthesis that organizes the article's central contribution across umbrella-review protocol and review-level eligibility criteria, search, quality assessment, overlap analysis, and evidence extraction, quality assessment, overlap analysis, evidence extraction, genomic, transcriptomic, proteomic, metabolomic, and integrated target evidence. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

The proposed pyramid is intentionally non-automatic. Its lower region contains modality-specific and integrated observations that can generate biologically grounded target hypotheses. Higher regions require causal support, perturbational confirmation, independent reproducibility, cohort diversity, and cross-context consistency. Computational and machine-learning performance becomes decision-relevant only when the data, validation design, and intended use are suitable [30]. A model may accurately reproduce labels derived from one dataset while exploiting technical structure, population composition, or information leakage. External validation reduces but does not eliminate this risk unless the external setting is sufficiently independent and representative of the proposed pharmaceutical use.

The pyramid's upper boundary separates target credibility from therapeutic readiness. Evidence for disease association, causal relevance, and functional consequence must be interpreted alongside druggability and development feasibility rather than association alone [31]. A credible target may lack a selective binding site, an effective delivery strategy, a suitable therapeutic modality, an acceptable safety margin, or a biomarker capable of demonstrating target engagement. Conversely, a technically tractable target may have weak disease-mechanism support. The review-of-reviews synthesis therefore grades readiness as conditional and target-specific. Omics integration can strengthen the evidentiary starting point, but progression requires an explicit portfolio addressing causality, mechanism, reproducibility, tractability, exposure, safety, and prospective decision utility.

Recommendations for Evidence-Strengthened Target Discovery

First, every integrated target claim should carry an evidence record that preserves provenance, context, and uncertainty. Responsible large-scale data research requires attention to bias, privacy, data-generating conditions, contextual interpretation, and communication of limitations [32]. For target discovery, this record should identify the disease definition, population, tissue, cell state, assay, preprocessing pipeline, integration method, missing-data strategy, model version, and origin of each supporting dataset. It should also distinguish observations derived from independent evidence from those produced through

reuse of the same cohort or reference resource. Such documentation would not validate a target, but it would make the basis of the claim inspectable and reduce false impressions of multimodal convergence.

Second, causal claims should be accompanied by transparent reporting of design assumptions and sensitivity analyses. Mendelian-randomization studies should specify instrument construction, exposure definition, outcome selection, population composition, analytical methods, tests of robustness, and the limits placed on interpretation [33]. Reporting should also explain whether the genetic proxy plausibly represents the direction, tissue, and biological function relevant to the proposed intervention. When causal methods disagree, the discrepancy should be retained and investigated rather than resolved by selecting the most favorable estimate. A target should advance on the basis of triangulation across independent designs, not because one method produces a nominally persuasive result.

Third, computational reproducibility should be treated as part of evidence quality. Data access conditions, code, software environments, parameter settings, randomization, model selection, evaluation procedures, and reporting should be sufficiently documented to permit reproduction or a defensible independent reimplementation [34]. Versioning is especially important when public databases, annotations, reference genomes, or pretrained models change over time. Reproducibility also requires clear separation of exploratory analyses from locked validation. A fully reproducible analysis may still be biased or biologically irrelevant, but an analysis that cannot be reconstructed provides an unstable basis for comparison, review-level synthesis, or pharmaceutical decision-making.

Fourth, benchmark design should be aligned with the intended scientific and development use. Representative data, fair comparator selection, robust metrics, transparent implementation, and disclosure of uncertainty are required for credible method benchmarking [35]. Random data partitioning may be inadequate when future use involves new cohorts, institutions, populations, disease subtypes, platforms, or target classes. Evaluation should therefore include context-relevant external validation, stress testing, ablation of dominant modalities, assessment of missing-data robustness, and examination of cross-modal disagreement. **Table 2** organizes the evidence, constructs, and interpretation boundaries needed to develop recommendations for evidence-strengthened target discovery within the article's central argument.

Table 2. Evaluation, implementation, and research priorities arising from Multi-Omics Target Discovery after Data Integration An Umbrella Review of Causal Evidence

Approach or application	Data and task context	Evaluation practice	Evidence maturity	Translational limitation	Review interpretation
Genomic target prioritization	Disease-associated variants, loci, molecular quantitative traits, and target-linked genetic proxies	Fine mapping, colocalization, sensitivity analyses, population-aware replication, and directionality assessment	Causality-supporting but assumption-dependent	Variant-to-gene ambiguity, pleiotropy, tissue mismatch, ancestry dependence, and pharmacological non-equivalence	May strengthen prioritization when independent genetic and biological evidence converge; does not alone validate a drug mechanism
Single-cell transcriptomic localization	Disease tissues, cellular states, treatment responses, and heterogeneous samples	Replication of cell states, annotation sensitivity, cross-cohort mapping, orthogonal localization, and perturbational follow-up	Context-localizing	Sampling bias, dissociation effects, annotation instability, temporal variation, and model transfer	Identifies where and under what cellular conditions a target may matter; expression specificity is not functional necessity
Proteomic mechanism and engagement analysis	Protein abundance, interactions, modifications, selectivity, and target engagement	Orthogonal assays, platform comparison, dose-response analysis, temporal profiling, and independent replication	Mechanistically informative	Coverage, dynamic range, missingness, isoform ambiguity, and assay-specific effects	Can strengthen mechanism and engagement claims when replicated; abundance or binding alone is insufficient
Metabolomic pathway assessment	Biofluids, tissues, cellular systems, physiological states, and treatment consequences	Preanalytical control, pathway coherence, independent validation, temporal analysis, and integration with upstream evidence	Phenotype-proximal	Diet, microbiome, medication, organ function, annotation ambiguity, and low target specificity	Supports pathway consequence and systemic coherence but rarely establishes unique target identity
Integrated multi-omics prioritization	Heterogeneous molecular layers, networks, latent factors, and	External validation, modality ablation, provenance	Hypothesis-prioritization	Scale imbalance, leakage, dominant modalities, incompatible contexts,	Integration is useful when modality-specific evidence and discordance remain

	evidence-fusion models	tracking, missing-data stress testing, and disagreement analysis		and opaque composite scores	visible; additional modalities do not automatically increase validity
Causal and perturbational triangulation	Genetic instruments, CRISPR perturbations, functional screens, cellular phenotypes, and disease models	Assumption testing, orthogonal perturbations, rescue experiments, temporal and dose-sensitive designs, and cross-model replication	Causal-supporting to experimentally confirmatory	Genetic and experimental interventions may not reproduce partial, reversible, tissue-specific pharmacology	Stronger than association when independent causal and experimental designs agree; still requires pharmacological equivalence testing
Reproducibility and transportability assessment	Independent cohorts, laboratories, platforms, populations, and analytical environments	Locked external validation, batch diagnostics, versioned pipelines, reproducible environments, and population-aware evaluation	Readiness-enabling	Hidden dataset overlap, technical confounding, underrepresentation, and inconsistent phenotype definitions	Required before broad target claims; repetition on shared data is not independent confirmation
Translational-readiness evaluation	Target selection, tractability, engagement, exposure, safety, developability, and decision consequences	Stage-appropriate experimental validation, modality feasibility, safety assessment, and prospective decision-impact evaluation	Conditional and target-specific	No omics or computational layer resolves efficacy, safety, delivery, or comparative benefit alone	Readiness should be judged as an evidence portfolio; the proposed categories are organizing concepts rather than validated development gates

Conclusion

This umbrella review proposes that multi-omics target discovery should be evaluated as an escalation of evidence rather than as a competition among integration algorithms or a count of supporting modalities. Genomic, transcriptomic, proteomic, and metabolomic evidence contribute distinct forms of information whose value depends on biological context, measurement quality, independence, and the claim being made. Integration can coordinate these contributions and expose convergence, but it can also obscure disagreement and propagate shared bias. Stronger target credibility requires explicit causal assumptions, perturbational confirmation, independent reproducibility, diverse and context-matched cohorts, and transparent computational practice. Translational readiness requires further evidence concerning tractability, exposure, safety, development feasibility, and prospective decision value. The proposed target-evidence pyramid and associated recommendations are conceptual organizing devices, not validated scoring systems or operational approval criteria. Their principal purpose is to prevent association, prediction, mechanism, experimental confirmation, and pharmaceutical readiness from being treated as interchangeable conclusions. Multi-omics integration may improve target prioritization, but its scientific value ultimately depends on whether the resulting evidence remains traceable, reproducible, causally defensible, experimentally testable, and appropriately bounded.

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References

1. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18(1):83. doi:10.1186/s13059-017-1215-1
2. Karczewski KJ, Snyder MP. Integrative omics for health and disease. Nat Rev Genet. 2018;19(5):299-310. doi:10.1038/nrg.2018.4

3. Wörheide MA, Krumsiek J, Kastenmüller G, Arnold M. Multi-omics integration in biomedical research - a metabolomics-centric review. Anal Chim Acta. 2021;1141:144-62. doi:10.1016/j.aca.2020.10.038
4. Paananen J, Fortino V. An omics perspective on drug target discovery platforms. Brief Bioinform. 2020;21(6):1937-53. doi:10.1093/bib/bbz122
5. Dugger SA, Platt A, Goldstein DB. Drug development in the era of precision medicine. Nat Rev Drug Discov. 2018;17(3):183-96. doi:10.1038/nrd.2017.226
6. Hunt H, Pollock A, Campbell P, Estcourt L, Brunton G. An introduction to overviews of reviews: Planning a relevant research question and objective for an overview. Syst Rev. 2018;7(1):39. doi:10.1186/s13643-018-0695-8
7. Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: Implications from five exemplar overviews. Syst Rev. 2017;6(1):145. doi:10.1186/s13643-017-0534-3
8. Pollock M, Fernandes RM, Pieper D, Tricco AC, Gates M, Gates A, et al. Preferred Reporting Items for Overviews of Reviews (PRIOR): A protocol for development of a reporting guideline for overviews of reviews of healthcare interventions. Syst Rev. 2019;8(1):335. doi:10.1186/s13643-019-1252-9
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372. doi:10.1136/bmj.n71
10. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358. doi:10.1136/bmj.j4008
11. Lunny C, Brennan SE, Reid J, McDonald S, McKenzie JE. Overviews of reviews incompletely report methods for handling overlapping, discordant, and problematic data. J Clin Epidemiol. 2020;118:69-85. doi:10.1016/j.jclinepi.2019.09.025
12. Hennessy EA, Johnson BT. Examining overlap of included studies in meta-reviews: Guidance for using the corrected covered area index. Res Synth Methods. 2020;11(1):134-45. doi:10.1002/jrsm.1390
13. Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: Development of the PRIOR statement. BMJ. 2022;378. doi:10.1136/bmj-2022-070849
14. 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
15. Van de Sande B, Lee JS, Mutasa-Gottgens E, Naughton B, Bacon W, Manning J, et al. Applications of single-cell RNA sequencing in drug discovery and development. Nat Rev Drug Discov. 2023;22(6):496-520. doi:10.1038/s41573-023-00688-4
16. Meissner F, Geddes-McAlister J, Mann M, Bantscheff M. The emerging role of mass spectrometry-based proteomics in drug discovery. Nat Rev Drug Discov. 2022;21(9):637-54. doi:10.1038/s41573-022-00409-3
17. Wishart DS. Metabolomics for investigating physiological and pathophysiological processes. Physiol Rev. 2019;99(4):1819-75. doi:10.1152/physrev.00035.2018
18. Loscalzo J. Multi-omics and single-cell omics: New tools in drug target discovery. Arterioscler Thromb Vasc Biol. 2024;44(4):759-62. doi:10.1161/ATVBAHA.124.320686
19. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, et al. Mendelian randomization. Nat Rev Methods Primers. 2022;2(1):6. doi:10.1038/s43586-021-00092-5
20. Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, et al. Genetic drug target validation using Mendelian randomisation. Nat Commun. 2020;11(1):3255. doi:10.1038/s41467-020-16969-0
21. Bock C, Datlinger P, Chardon F, Coelho MA, Dong MB, Lawson KA, et al. High-content CRISPR screening. Nat Rev Methods Primers. 2022;2(1):8. doi:10.1038/s43586-021-00093-4
22. Przybyla L, Gilbert LA. A new era in functional genomics screens. Nat Rev Genet. 2022;23(2):89-103. doi:10.1038/s41576-021-00409-w
23. Park BS, Lee M, Kim J, Kim T. Perturbomics: CRISPR-Cas screening-based functional genomics approach for drug target discovery. Exp Mol Med. 2025;57(7):1443-54. doi:10.1038/s12276-025-01487-0
24. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. Cell. 2019;177(1):26-31. doi:10.1016/j.cell.2019.02.048
25. Peterson RE, Kuchenbaecker K, Walters RK, Chen CY, Popejoy AB, Periyasamy S, et al. Genome-wide association studies in ancestrally diverse populations: Opportunities, methods, pitfalls, and recommendations. Cell. 2019;179(3):589-603. doi:10.1016/j.cell.2019.08.051
26. Yu Y, Mai Y, Zheng Y, Shi L. Assessing and mitigating batch effects in large-scale omics studies. Genome Biol. 2024;25(1):254. doi:10.1186/s13059-024-03401-9
27. Wang J, Liang H, Zhang Q, Ma S. Replicability in cancer omics data analysis: Measures and empirical explorations. Brief Bioinform. 2022;23(5). doi:10.1093/bib/bbac304
28. Trajanoska K, Bhérer C, Taliun D, Zhou S, Richards JB, Mooser V. From target discovery to clinical drug development with human genetics. Nature. 2023;620(7975):737-45. doi:10.1038/s41586-023-06388-8
29. Carss KJ, Deaton AM, Del Rio-Espinola A, Diogo D, Fielden M, Kulkarni DA, et al. Using human genetics to improve safety assessment of therapeutics. Nat Rev Drug Discov. 2023;22(2):145-62. doi:10.1038/s41573-022-00561-w

30. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-77. doi:10.1038/s41573-019-0024-5
31. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, et al. The druggable genome and support for target identification and validation in drug development. Sci Transl Med. 2017;9(383). doi:10.1126/scitranslmed.aag1166
32. Zook M, Barocas S, Boyd D, Crawford K, Keller E, Gangadharan SP, et al. Ten simple rules for responsible big data research. PLoS Comput Biol. 2017;13(3). doi:10.1371/journal.pcbi.1005399
33. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: The STROBE-MR statement. JAMA. 2021;326(16):1614-21. doi:10.1001/jama.2021.18236
34. Heil BJ, Hoffman MM, Markowetz F, Lee SI, Greene CS, Hicks SC. Reproducibility standards for machine learning in the life sciences. Nat Methods. 2021;18(10):1132-5. doi:10.1038/s41592-021-01256-7
35. Weber LM, Saelens W, Cannoodt R, Soneson C, Hapfelmeier A, Gardner PP, et al. Essential guidelines for computational method benchmarking. Genome Biol. 2019;20(1):125. doi:10.1186/s13059-019-1738-8