



Review Article

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Why Translational Biomarkers Fail Between Preclinical Models and Early Human Studies

Peter Nilsson^{1*}, Eva Johansson¹, Lars Andersson²

¹Department of Translational Biomarkers and Preclinical Models, Faculty of Pharmacy, Karolinska Institute, Stockholm, Sweden.

²Department of Early Human Studies and Clinical Translation, Faculty of Pharmacy, Lund University, Lund, Sweden.

*Email: peter.nilsson@ki.se

ABSTRACT

Translational biomarkers are often expected to reduce uncertainty between preclinical experiments and early human development, yet many fail precisely at the point where they are asked to carry an inference across biological, analytical, pharmacological, or clinical boundaries. This review argues that biomarker failure is rarely a single event. A marker can be analytically robust but biologically nonrepresentative, transferable across assays but not across species or disease states, exposure-responsive without reflecting target-site pharmacology, or mechanistically proximal without informing a clinically meaningful endpoint. The central problem is therefore not biomarker presence or absence but whether each inferential link needed for a specific development decision remains valid. The review separates six recurrent failure classes: inadequate biological validity in the preclinical model, species or disease-context nontransferability, assay non-equivalence, exposure–biomarker discordance, tissue-compartment mismatch, and absence of decision-relevant endpoint linkage. It further distinguishes genuine biomarker failure from situations in which apparently discordant data are explained by temporal hysteresis, tissue retention, alternative context of use, or a correctly measured pharmacodynamic effect that is simply insufficient to produce clinical benefit. This boundary-based view supports a more disciplined strategy for early development: specify what a biomarker is intended to establish, identify the biological and measurement assumptions required for that inference, and falsify those assumptions before escalating confidence.

Keywords: Translational biomarkers, Target engagement, Pharmacokinetics–pharmacodynamics, Preclinical models, Assay transferability, Context of use

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INTRODUCTION

Biomarkers occupy a privileged position in translational drug development because they appear to convert biological uncertainty into something measurable. That promise is real, but it is incomplete. Portfolio-level experience indicates that clinical development productivity depends not simply on collecting more biomarker data but on using evidence to make disciplined, stage-appropriate decisions [1]. A biomarker can reduce uncertainty only when the inference built around it is itself valid. Mechanism-based pharmacokinetic–pharmacodynamic reasoning is valuable because it forces the development team to specify what biological process a marker represents, how drug exposure is expected to influence that process, and where important knowledge gaps remain [2]. Regulatory qualification experience adds a second constraint: biomarker credibility is inseparable from its stated context of use, evidentiary package, and analytical characteristics [3]. Mechanism-based biomarker

discovery likewise emphasizes that statistical association and mechanistic relevance are not interchangeable properties [4].

The practical consequence is that “biomarker failure” should not be used as a catch-all explanation for failed translation. A signal may be measured accurately yet represent a biology that is not conserved in humans. The same biology may be conserved while the assay measures a different molecular species, compartment, or temporal state. A drug may achieve systemic exposure and measurable target engagement while the downstream disease process remains unaffected. Conversely, a plasma exposure–response mismatch may reflect prolonged tissue residence rather than a false biomarker. The useful question is therefore not whether a biomarker worked, but which inferential claim it was supposed to support and which boundary that claim crossed.

Scope of the review

This review focuses on the preclinical-to-early-human interval, where biomarkers are used to support target validation, pharmacological bridging, dose selection, target engagement, pharmacodynamic interpretation, and early proof-of-concept decisions. It does not treat data quality, biological validity, mechanism, and clinical utility as equivalent. Data standardization is necessary for comparability across platforms and studies, but interoperability cannot by itself establish that two measurements carry the same biological meaning [5]. Similarly, causal-inference methods clarify why observed biomarker–outcome associations should not automatically be interpreted as mechanistic effects; causal claims remain conditional on design, assumptions, and the structure of the available data [6].

The organizing principle used here is decision utility. A biomarker is useful only relative to a specified decision: whether a target is engaged, whether exposure is sufficient, whether a pathway is perturbed, whether a dose should advance, or whether a clinical signal is credible enough to continue development. Early discovery frameworks increasingly emphasize explicit uncertainty and falsification rather than accumulation of confirmatory-looking observations [7]. On that basis, this review treats translational biomarker failure as a break in a chain of inference rather than as a property intrinsic to the marker itself. This distinction is important because the same biomarker may fail for one context of use while remaining informative for another.

Biological validity in preclinical models

The first translational boundary precedes the biomarker assay itself: the preclinical model must contain the biological state that the marker is assumed to represent. Oncology provides a clear example. The predictive value of preclinical tumor models depends on how well the model reproduces the relevant tumor biology, microenvironment, treatment context, and patient heterogeneity rather than on the nominal sophistication of the model platform [8]. In psychiatric research, model validity is similarly construct dependent. Behavioral paradigms can be reproducible and sensitive while still capturing only a partial or nonhomologous component of the human phenotype [9]. Translational neuroscience therefore illustrates a central problem for biomarker interpretation: species differences in neuroanatomy, circuitry, metabolism, and behavior can alter the meaning of an apparently homologous readout [10].

The response to these limitations has often been to increase model complexity. Emerging preclinical technologies can improve human relevance, but their predictive value still requires validation against known pharmacology and clinically meaningful outcomes [11]. Three-dimensional systems, for example, can reproduce tissue architecture and cellular interactions that are absent in simpler models, yet complexity alone does not establish that a drug response is more representative of the human condition [12]. Human-centric methodological strategies may reduce particular cross-species assumptions, but they introduce their own requirements for benchmark selection, reproducibility, mechanistic interpretability, and integration into development workflows [13].

Accordingly, biological validity should be treated as question-specific. The relevant standard is not whether a model is “good,” but whether it contains the causal or mechanistically relevant features needed for the particular biomarker inference. If a marker is generated by a compensatory pathway that is exaggerated in the model, or by a cell population that is absent or altered in the target patient group, analytical precision can reinforce a biologically incorrect conclusion. Preclinical biomarker interpretation should therefore begin with an explicit statement of which biological feature is assumed to transfer and what evidence would falsify that assumption.

Species and disease-context transfer

Even when a model contains the intended biological process, the next boundary is transfer of that process across species and disease contexts. Cross-species paradigms are most informative when they preserve a construct or

neurobiological operation rather than merely reproduce a superficially similar phenotype [14]. A movement, circulating analyte, transcriptional response, or imaging signal can look comparable while arising from different regulatory architectures. The translational unit should therefore be the mechanistic relationship of interest, not the surface similarity of the readout.

Pharmacological integration can reduce this uncertainty. In the development of an afucosylated anti-CCR8 antibody, preclinical PK/PD, target biology, and regulatory T-cell depletion were combined to inform translational pharmacology rather than interpreted as isolated observations [15]. Such examples show how a coherent bridge can be strengthened when exposure, target engagement, and downstream biological effect are assessed together. They do not, however, establish clinical efficacy. Broader oncology-development analyses similarly argue that asset-level decisions require pharmacology, translational medicine, and clinical context to be considered jointly [16].

A useful counterpoint is the development of DKK3 as a pharmacodynamic biomarker for HtrA1 inhibition in geographic atrophy. The value of the marker came from its connection to the target pathway and relevant ocular context, not from generic biomarker performance [17]. This illustrates a recurring translational principle: disease context and compartment can determine whether the same molecular readout is informative, ambiguous, or misleading. Cross-species transfer is therefore strongest when mechanism, assay, tissue, and disease state remain aligned; it weakens when any of those are assumed rather than demonstrated.

Assay transferability

Assay transferability is often treated as an analytical harmonization problem, but translational equivalence requires more. A nonclinical assay can have excellent precision, sensitivity, and reproducibility while still failing to represent the human biological event that matters. Pharma experience with nonclinical assays emphasizes that analytical performance, biological relevance, and context of use must be considered together when judging translational fidelity [18]. The practical boundary is therefore between measuring the same analyte and measuring the same biological meaning.

Direct in vivo methods can narrow this gap when they interrogate the relevant pharmacology. Positron emission tomography can support drug development by measuring biodistribution, receptor occupancy, or target engagement in vivo, thereby reducing reliance on indirect systemic surrogates [19]. Bioanalytical development can serve a similar role. Ultra-sensitive assays for free and total IL-11 were designed to support target-engagement assessment and mechanistic PK/PD modeling for an anti-IL-11 therapeutic across development contexts [20]. In both examples, assay value arises from the relationship between the measured signal and a defined pharmacological question.

That relationship can be disrupted by assay architecture. Kinase programs illustrate how different activity assays can capture different aspects of enzymatic or pathway function, making method selection part of the biological interpretation rather than a neutral technical choice [21]. Functional imaging provides another caution. fMRI can reveal treatment-related changes at the systems level, but acquisition, analysis, physiological noise, and limited mechanistic specificity can complicate the interpretation of a sensitive signal as evidence of target engagement or disease modification [22]. Disease heterogeneity compounds the problem: osteoarthritis biomarker research shows that biochemical markers can shift in meaning across phenotypes, tissue processes, and stages of disease [23].

The translational question is therefore not “Can the assay be reproduced in humans?” but “Does the human assay preserve the same measured entity, biological relationship, dynamic range, timing, and decision meaning as the preclinical assay?” **Table 1** is placed here because those dependencies are difficult to compare in prose without obscuring where transfer can fail.

Table 1. Cross-scale conditions that determine whether a preclinical biomarker assay remains interpretable in humans

Manuscript-derived assay state	What must already be established	Failure criterion at transfer	Development consequence	Transfer boundary that must remain explicit	Next validation step	Permissible development claim	Proposed framework endpoint
Same analyte, different	Identity of the measured molecular	Human signal is analytically comparable	Apparent replication may be	Model-to-human	Demonstrate pathway relevance in	Analytical comparability only	Biological -validity failure

biological context	species and its pathway role	but reflects different disease biology	biologically misleading	biological validity	the target population		
Same biological process, non-equivalent assay architecture	Mechanistic relevance of the process	Platform differences alter sensitivity, specificity, or functional meaning	Exposure–response relationships become non-comparable	Measurement-to-inference boundary	Cross-platform bridging with shared reference samples or orthogonal readout	Assays interrogate related biology	Assay-transfer failure
Direct target-engagement measurement	Target accessibility and pharmacological specificity	Signal cannot distinguish binding or occupancy from biologically effective engagement	Dose escalation may be based on a proximal but incomplete readout	Target binding-to-functional activity boundary	Add downstream functional or pathway readout	Target access or occupancy demonstrated	Engagement sufficiency unresolved
Indirect functional or imaging biomarker	Link between signal and target-mediated physiology	Signal changes despite uncertain pharmacological specificity	Mechanistic interpretation becomes ambiguous	Signal-to-mechanism boundary	Orthogonal pharmacological or mechanistic validation	Functional response observed	Mechanistic attribution unresolved
Disease-heterogeneous biomarker response	Relevant phenotype or molecular subgroup	Aggregate assay response obscures opposing or subgroup-specific patterns	Trial enrichment or dose interpretation may be distorted	Population-transfer boundary	Stratified analysis tied to disease biology	Context-limited biomarker activity	Population-context failure

The same logic can be represented more compactly as a decision field rather than a linear validation pipeline. **Figure 1** is needed because assay transferability depends on feedback among model validity, measurement equivalence, target engagement, population context, and the intended development decision.

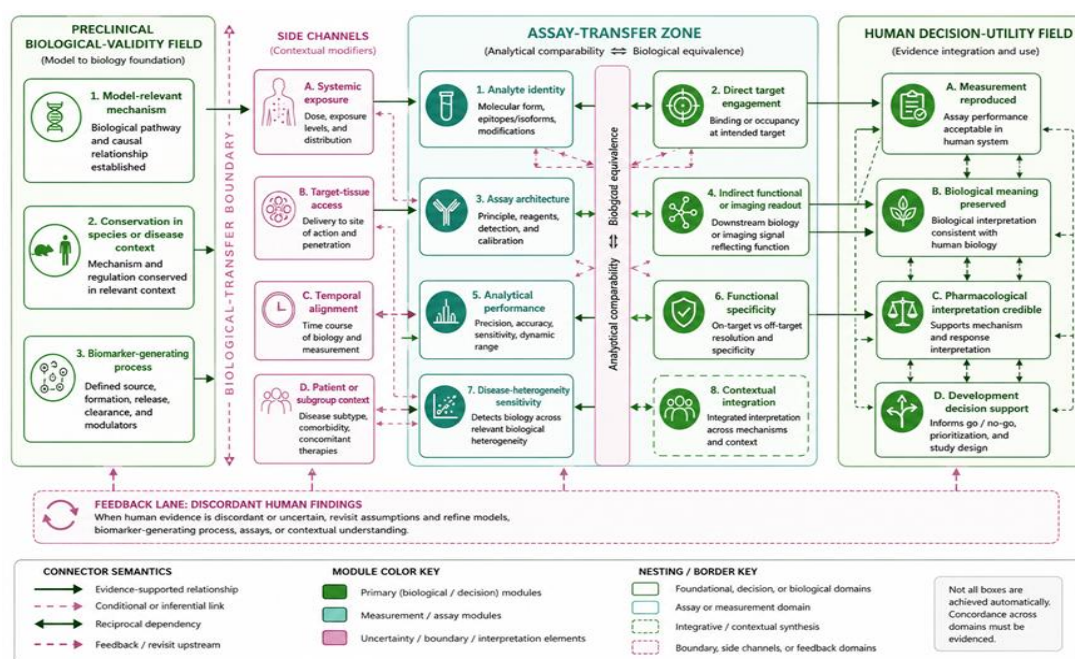


Figure 1. Assay transfer becomes decision-credible only when biological meaning survives each cross-scale boundary

Exposure–biomarker disconnect

The next failure boundary appears after an assay has transferred successfully: the measured biomarker may still not track the pharmacologically relevant exposure. Retrospective analyses of active human dose prediction show that translation from preclinical pharmacology to clinically active exposure is variable across programs and can fail for reasons that include pharmacokinetic behavior, pharmacodynamic assumptions, and incomplete understanding of the relevant biological system [24]. A biomarker therefore cannot be interpreted independently of the exposure metric used to contextualize it.

The ziritaxestat program provides an unusually direct illustration. In the ISABELA studies, plasma exposure and evidence of target engagement did not explain the absence of clinical efficacy in idiopathic pulmonary fibrosis [25]. The correct inference is not that target engagement was meaningless. Rather, proximal pharmacological evidence was insufficient to establish that modulating the target would produce the required downstream disease effect. This is a distinct failure state: the drug–target relationship can be credible while the target–clinical-effect relationship remains unsupported.

Not every apparent exposure–biomarker disconnect represents failure. Inclisiran demonstrates that pharmacodynamic effects can persist after systemic concentrations decline because the relevant pharmacology is determined by tissue uptake and intracellular persistence in the liver [26]. Physiologically based pharmacokinetic models can help formalize such exposure differences and support dose optimization, but their usefulness depends on parameter quality, physiological assumptions, and validation against observed data [27]. Drug-delivery strategies further show that target-site exposure and engagement can be altered independently of plasma concentration [28]. Declaring a biomarker “nonresponsive” from systemic PK alone can therefore be premature.

Table 2 is positioned here to distinguish true failure of the exposure-to-biomarker relationship from biologically plausible temporal or compartmental decoupling.

Table 2. Sequence states that distinguish exposure failure from delayed or compartment-specific biomarker pharmacology

Translational state	Precursor condition	Transition trigger	Observable readout	Downstream interpretation	Condition that interrupts or reverses the sequence	Proposed framework endpoint
Systemic exposure without target-site adequacy	Plasma exposure reaches expected range	Distribution is insufficient at the disease compartment	Weak or absent local engagement despite adequate plasma PK	Systemic PK overstates pharmacological adequacy	Improved tissue delivery or direct tissue measurement	Exposure-location failure
Target engagement without clinical effect	Drug reaches and modulates intended target	Proximal pathway response occurs	Engagement or pharmacodynamic biomarker changes	Target modulation is real but not sufficient for benefit	Downstream disease biology does not depend sufficiently on the modulated process	Target-to-outcome failure
Short plasma exposure with persistent pharmacodynamics	Drug is delivered to a retaining or durable-action compartment	Tissue uptake or intracellular persistence	Biomarker effect outlasts plasma concentration	Apparent PK/PD mismatch is mechanistically plausible	Loss of tissue retention or pathway persistence	Temporal-decoupling state, not failure
Model-predicted exposure support	Mechanistic PK model captures relevant physiology	Simulation bridges dose and target compartment	Predicted exposure or occupancy	Can inform dose selection if model credibility is adequate	Parameter misspecification or unmodeled population biology	Model-credibility boundary
Delivery-mediated engagement shift	Formulation or delivery changes	Target-site concentration rises	Increased local engagement or	Plasma concentration becomes a	Delivery heterogeneity or inaccessible	Compartment-aware

local distribution	relative to plasma	functional response	weaker proxy for pharmacology	target compartment	exposure state
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Tissue compartment mismatch

Compartment mismatch is the spatial counterpart of exposure–biomarker disconnect. A circulating marker may be easy to measure yet poorly represent what occurs in the tissue where the mechanism operates. Early clinical development of apilimod in C9orf72 amyotrophic lateral sclerosis illustrates why systemic exposure, cerebrospinal-fluid measurements, and pharmacodynamic evidence must be interpreted as separate layers rather than collapsed into a single statement of drug activity [29]. In central nervous system development more broadly, Tau-antibody programs have highlighted the difficulty of inferring therapeutically meaningful target engagement from peripheral exposure or binding when access to pathological Tau in the brain remains uncertain [30].

The implication is not that peripheral or surrogate compartments are intrinsically unreliable. They become credible when their relationship to the disease compartment is demonstrated. In phase III aducanumab studies, cerebrospinal-fluid amyloid biomarkers showed meaningful concordance with amyloid PET under a defined Alzheimer disease context [31]. Such evidence supports a validated cross-compartment relationship; it does not establish that cerebrospinal fluid universally substitutes for brain measurements or that concordance in one biomarker system transfers to another.

Compartment validity should therefore be treated as an empirical claim. The relevant questions are whether the sampled compartment receives the drug, whether the biomarker is generated or cleared in a way that tracks the target tissue, whether the time courses are aligned, and whether disease or treatment changes the relationship between compartments. When these conditions are unknown, a precise peripheral biomarker can still support the wrong pharmacological inference. When they are demonstrated, a surrogate compartment may provide a practical and scientifically defensible bridge.

Biomarkers without clinical endpoint linkage

A biomarker can be biologically credible, analytically transferable, exposure responsive, and appropriately compartmentalized yet still fail to answer the development question for which it is being used. This final inferential boundary concerns context of use. Neurofilament light chain in amyotrophic lateral sclerosis illustrates that evidentiary requirements depend on the specific purpose assigned to a biomarker rather than on a universal standard of “validation” [32]. A pharmacodynamic marker intended to demonstrate biological response is not required to perform the same task as a prognostic, predictive, monitoring, or surrogate endpoint.

This distinction prevents an important overcorrection. In biosimilar development, sensitive pharmacodynamic biomarkers may support comparative assessment without demonstrating a direct relationship to a clinical efficacy endpoint, provided that they are fit for the intended regulatory purpose [33]. Absence of clinical-endpoint linkage therefore does not automatically constitute biomarker failure. Failure occurs when a marker is used to support a decision that requires such linkage but the necessary relationship has not been demonstrated.

Conversely, when continuation or dose-selection decisions depend on anticipated patient benefit, proximal pharmacological evidence alone can be insufficient. Alzheimer disease development illustrates why biomarker and cognitive evidence must be interpreted together when constructing go/no-go criteria [34]. Companion-diagnostic development adds another boundary: implementation depends on alignment among the biomarker assay, medicinal product, intended population, and regulatory context [35].

Table 3 distinguishes these contexts because the same absence of outcome correlation can indicate either a genuine evidentiary deficit or a perfectly acceptable biomarker state, depending on the decision being supported.

Table 3. Decision-space constraints that determine when absent clinical-endpoint linkage constitutes translational biomarker failure

Biomarker decision state	Required patient or model context	Exposure support required	Target-engagement requirement	Biomarker readout must establish	Clinical-endpoint relationship required?	Proposed article-specific interpretation
Pharmacodynamic response marker	Population in which the target pathway is	Sufficient to interpret the observed response	Usually desirable when	That treatment perturbs the intended	Not necessarily	Valid PD state if context of use is restricted accordingly

	pharmacologically active		mechanistically proximal	biological process		
Dose-selection biomarker	Population and disease stage representative of the intended dose decision	Essential	Usually required	That increasing or maintaining exposure produces interpretable pharmacology	Depends on whether clinical benefit is being inferred	Incomplete if used beyond pharmacological dose justification
Predictive or enrichment biomarker	Defined patient subgroup and assay-positive population	Treatment-specific	Mechanistic support strengthens interpretation	Differential probability of treatment response or relevant biology	Usually necessary at the intended decision level	Population-transfer failure if subgroup relevance is assumed rather than demonstrated
Candidate surrogate	Clinical population matching the proposed use	Required	Helpful but insufficient alone	A biomarker change that reliably represents treatment effect on the clinical outcome	Yes	Endpoint-linkage failure until the required relationship is established
Regulatory comparability biomarker	Product-development context in which sensitive pharmacology is the intended evidentiary target	Required for interpretable comparison	Usually central	Comparative pharmacodynamic similarity	Not necessarily	Lack of direct outcome linkage is not itself failure

The relationships among these states are nonlinear. **Figure 2** therefore treats early biomarker interpretation as a series of falsification gates separated by uncertainty corridors rather than as a simple progression from biomarker response to clinical success.

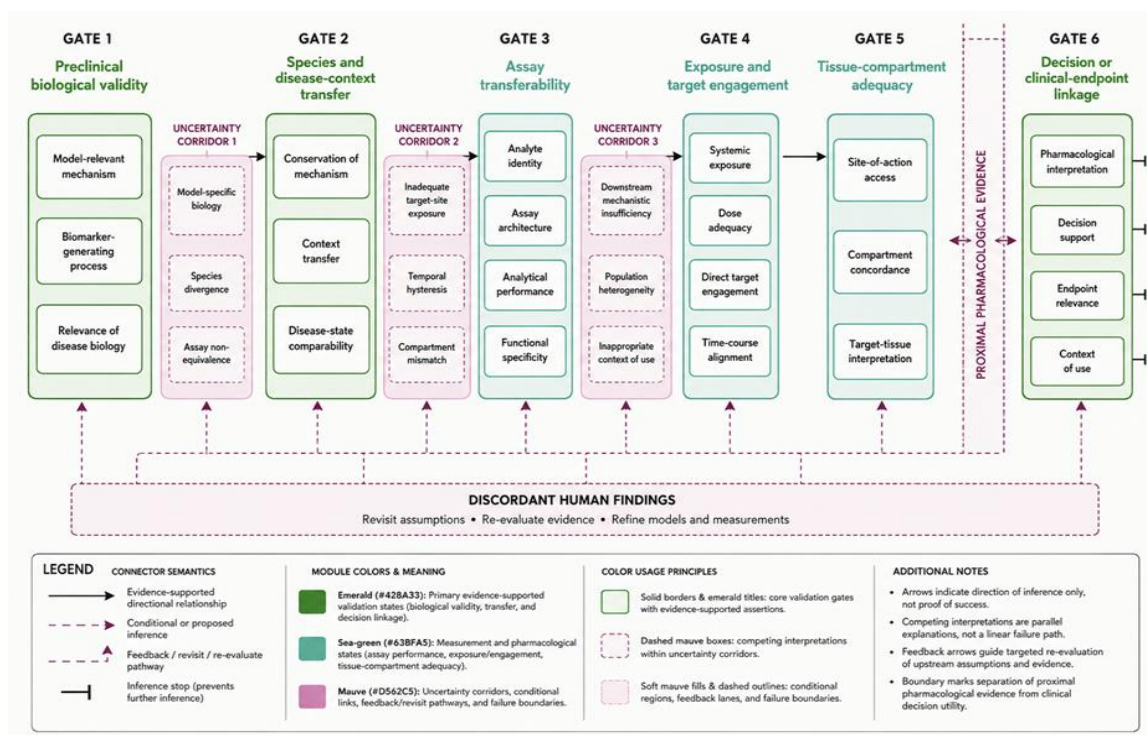


Figure 2. Early-development biomarker confidence depends on surviving distinct falsification gates rather than accumulating positive signals

A taxonomy of translational biomarker failure

The evidence reviewed above supports a proposed taxonomy organized by where an inference fails rather than by biomarker technology. Clinical proof-of-concept analyses have long emphasized that dose, exposure, pharmacodynamics, mechanism, timing, and endpoints must form a coherent chain if an early signal is to support a development decision [36]. The present synthesis separates six break points within that chain: biological-validity failure, species or disease-context transfer failure, assay-transfer failure, exposure–biomarker failure, compartment failure, and endpoint- or decision-linkage failure.

These states are not mutually exclusive. The same negative clinical observation can arise from adequate target engagement with an ineffective therapeutic mechanism, inadequate exposure at the disease site, a valid peripheral measurement that poorly tracks the target compartment, or an endpoint relationship that was never established. The taxonomy should therefore be used diagnostically rather than causally: it identifies which assumptions require falsification, not which mechanism has already been proven responsible.

Rescue and qualification strategies

Rescue should be matched to the failed inferential link. Weak model validity requires model benchmarking or reverse translation; assay ambiguity requires cross-platform bridging or orthogonal functional measurement; uncertain target-site pharmacology may require imaging, compartment-specific sampling, or mechanistic PK/PD modeling; and uncertain context of use requires explicit qualification against the development decision being made.

Accumulating additional measurements of the same type is less informative when competing explanations remain unresolved. Orthogonal evidence is valuable because it tests different assumptions. A tissue biomarker and an imaging measure, for example, can provide stronger evidence when they interrogate the same disease process through independent measurement routes. Even then, concordance should reduce uncertainty rather than be described as proof of mechanism.

Future directions

Future biomarker programs should specify transfer assumptions prospectively. Assay-development plans should distinguish analyte comparability from biological equivalence, exposure models should specify the relevant compartment and time scale, and clinical plans should define the context of use before biomarker results are interpreted as decision evidence.

Greater use of human-relevant experimental systems, causal methods, data standards, mechanistic modeling, and compartment-aware measurements may improve translation, but none eliminates the need for validation. The most useful future biomarker strategies will therefore be those that make uncertainty explicit and design measurements to discriminate among competing explanations before pivotal development decisions depend on them.

CONCLUSION

Translational biomarkers fail not because biomarkers are inherently unreliable, but because development programs often ask a measurement to carry more inference than its evidence supports. Biological validity, species transfer, assay equivalence, exposure, tissue access, target engagement, and clinical decision utility are separate requirements. Success at one does not guarantee success at the next.

A more defensible approach is to define the precise decision a biomarker is intended to support, identify each boundary crossed by that inference, and test those boundaries directly. The proposed failure taxonomy and falsification-gate architecture provide a structured way to locate uncertainty without converting association into mechanism or pharmacodynamic activity into assumed clinical benefit. In early development, the strongest biomarker is therefore not simply the most sensitive measurement, but the one whose biological meaning, pharmacological context, compartment, timing, and decision role remain demonstrably aligned.

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